CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

209092Orig1s001

Trade Name:	KISQALI
Generic or Proper Name:	ribociclib tablets
Sponsor:	Novartis Pharmaceuticals Corporation
Approval Date:	July 18, 2018
Indication:	KISQALI is a kinase inhibitor indicated in combination with: • an aromatase inhibitor for the treatment of pre/perimenopausal or postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer, as initial endocrine-based therapy; or • fulvestrant for the treatment of postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer, as initial endocrine based therapy or following disease progression on endocrine therapy.

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209092Orig1s001

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209092/S-001

SUPPLEMENT APPROVAL

Novartis Pharmaceuticals Corporation
Attention: Jiten Rana, PharmD
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Rana:

Please refer to your Supplemental New Drug Application (sNDA) dated June 28, 2018, received June 28, 2018, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for KISQALI® (ribociclib) tablets.

This Prior Approval supplemental new drug application expands the approved indication of KISQALI for the treatment of women with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative advanced or metastatic breast cancer. The expanded approved indication is for KISQALI in combination with:

- an aromatase inhibitor for the treatment of pre/perimenopausal or postmenopausal women, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer, as initial endocrine-based therapy; or
- fulvestrant for the treatment of postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer, as initial endocrine based therapy or following disease progression on endocrine therapy.

APPROVAL & LABELING

We have completed our review of this supplemental application. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the prescribing information, text for the patient package insert), with the addition of any labeling changes in pending "Changes

Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3453-1 Submit the interim overall survival (OS) report with data and analysis; the final OS report with data and analysis from clinical trial MONALEESA-7 entitled: "A phase III randomized, double-blind, placebo-controlled study of LEE011 or placebo in combination with tamoxifen and goserelin or a non-steroidal aromatase inhibitor (NSAI) and goserelin for the treatment of premenopausal women with HR+, HER2 negative advanced breast cancer".

The timetable you submitted on July 13, 2018, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 04/2017

Trial Completion: 12/2020
Interim OS Report Submission: 12/2019
Final OS Report Submission: 06/2021

3453-2 Submit the interim overall survival (OS) report with data and analysis; the final OS report with data and analysis, from clinical trial MONALEESA-3 entitled: "A randomized, double-blind, placebo-controlled study of ribociclib in combination with fulvestrant for the treatment of men and postmenopausal women with HR+, HER2 negative advanced breast cancer who have received no or only one line of prior endocrine treatment".

The timetable you submitted on July 13, 2018, states that you will conduct this study according to the following schedule:

Final protocol submission: 09/2016
Trial Completion: 09/2022
Interim OS report Submission: 09/2020
Final OS Report Submission: 03/2023

Submit clinical protocols to your IND 117796 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled **"Postmarketing Commitment Protocol," "Postmarketing Commitment Final Report," or "Postmarketing Commitment Correspondence."**

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the prescribing information to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft

Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

You must submit final promotional materials and prescribing information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Sakar Wahby, Regulatory Project Manager, at (240) 402-5364.

Sincerely,

{See appended electronic signature page}

Julia Beaver, MD
Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JULIA A BEAVER
07/18/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209092Orig1s001

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use KISQALI safely and effectively. See full prescribing information for KISQALI.

KISQALI® (ribociclib) tablets, for oral use
Initial U.S. Approval: 2017

----------RECENT MAJOR CHANGES----------

Indication and Usage (1)	07/2018
Dosage and Administration (2.1, 2.2)	07/2018
Warnings and Precautions (5.1, 5.2, 5.3, 5.4)	07/2018

----------INDICATIONS AND USAGE----------

KISQALI is a kinase inhibitor indicated in combination with:
- an aromatase inhibitor for the treatment of pre/perimenopausal or postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer, as initial endocrine-based therapy; or
- fulvestrant for the treatment of postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer, as initial endocrine based therapy or following disease progression on endocrine therapy. (1)

----------DOSAGE AND ADMINISTRATION----------

KISQALI tablets are taken orally with or without food in combination with an aromatase inhibitor or fulvestrant. (2)
- Recommended starting dose: 600 mg orally (three 200 mg tablets) taken once daily with or without food for 21 consecutive days followed by 7 days off treatment. (2.1)
- Dose interruption, reduction, and/or discontinuation may be required based on individual safety and tolerability. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

- Tablets: 200 mg (3)

----------CONTRAINDICATIONS----------

None. (4)

----------WARNINGS AND PRECAUTIONS----------

- QT interval prolongation: Monitor electrocardiograms (ECGs) and electrolytes prior to initiation of treatment with KISQALI. Repeat ECGs at approximately Day 14 of the first cycle and at the beginning of the second cycle, and as clinically indicated. Monitor electrolytes at the beginning of each cycle for 6 cycles, and as clinically indicated. Avoid using KISQALI with drugs known to prolong QT interval and/or strong CYP3A inhibitors. (2.2, 5.1, 7.1, 7.4)
- Increased QT Prolongation with Concomitant Use of Tamoxifen; KISQALI is not indicated for concomitant use with tamoxifen. (5.2)
- Hepatobiliary toxicity: Increases in serum transaminase levels have been observed. Perform Liver Function Tests (LFTs) before initiating treatment with KISQALI. Monitor LFTs every 2 weeks for the first 2 cycles, at the beginning of each subsequent 4 cycles, and as clinically indicated. (2.2, 5 3)
- Neutropenia: Perform Complete Blood Count (CBC) before initiating therapy with KISQALI. Monitor CBC every 2 weeks for the first 2 cycles, at the beginning of each subsequent 4 cycles, and as clinically indicated. (2.2, 5.4)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise patients of potential risk to a fetus and to use effective contraception during therapy. (5.5, 8.1, 8.3)

----------ADVERSE REACTIONS----------

Most common adverse reactions (incidence ≥20%) are neutropenia, nausea, infections, fatigue, diarrhea, leukopenia, vomiting, alopecia, headache, constipation, rash and cough. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- CYP3A4 Inhibitors: Avoid concomitant use of KISQALI with strong CYP3A inhibitors. If strong inhibitors cannot be avoided, reduce KISQALI dose. (2.2, 7.1)
- CYP3A4 Inducers: Avoid concomitant use of KISQALI with strong CYP3A inducers. (7.2)
- CYP3A substrates: The dose of sensitive CYP3A substrates with narrow therapeutic indices may need to be reduced when given concurrently with KISQALI. (7.3)
- Drugs known to prolong QT interval: Avoid concomitant use of drugs known to prolong QT interval such as anti-arrhythmic medicines. (7.4)

----------USE IN SPECIFIC POPULATIONS----------

Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 07/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

KISQALI is indicated in combination with:

- an aromatase inhibitor for the treatment of pre/perimenopausal or postmenopausal women, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer, as initial endocrine-based therapy; or
- fulvestrant for the treatment of postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer, as initial endocrine based therapy or following disease progression on endocrine therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing and Administration

The recommended dose of KISQALI is 600 mg (three 200 mg film-coated tablets) taken orally, once daily for 21 consecutive days followed by 7 days off treatment resulting in a complete cycle of 28 days. KISQALI can be taken with or without food *[see Clinical Pharmacology (12.3)]*.

When given with KISQALI, refer to the Full Prescribing Information for the recommended dose of the aromatase inhibitor being used.

When given with KISQALI, the recommended dose of fulvestrant is 500 mg administered on Days 1, 15, 29, and once monthly thereafter. Please refer to the Full Prescribing Information of fulvestrant.

Pre/perimenopausal women treated with the combination KISQALI 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 KISQALI 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. KISQALI 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.

2.2 Dose Modifications

Dose 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	**KISQALI**	
	Dose	**Number of Tablets**
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 further dose reduction below 200 mg/day is required, discontinue the treatment.

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

Table 2: 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	No dose adjustment is required.	Dose interruption until recovery to Grade ≤ 2. Resume KISQALI at the same dose level. If toxicity recurs at Grade 3, dose interruption until recovery, then resume KISQALI at the next lower dose level.	Dose interruption until recovery of neutropenia to Grade ≤ 2. Resume KISQALI at the next lower dose level.	Dose interruption until recovery to Grade ≤ 2. Resume KISQALI at the next lower dose level.
	Perform Complete Blood Counts (CBC) before initiating treatment with KISQALI. Monitor CBC every 2 weeks for the first 2 cycles, at the beginning of each subsequent 4 cycles, and as clinically indicated.			

*Grade 3 neutropenia with single episode of fever >38.3°C (or) above 38°C for more than one hour and/or concurrent infection.
Grading according to CTCAE Version 4.03. CTCAE=Common Terminology Criteria for Adverse Events.
ANC = absolute neutrophil count; LLN = lower limit of normal

Table 3: 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	No dose adjustment is required.	Baseline* at < Grade 2: Dose interruption until recovery to ≤ baseline grade, then resume KISQALI at same dose level. If Grade 2 recurs, resume KISQALI at next lower dose level. --- Baseline* at Grade 2: No dose interruption.	Dose interruption until recovery to ≤ baseline* grade, then resume at next lower dose level. If Grade 3 recurs, discontinue KISQALI.	Discontinue KISQALI
Combined elevations in AST and/or ALT WITH total bilirubin increase, in the absence of cholestasis	If patients develop ALT and/or AST > 3 x ULN along with total bilirubin > 2 x ULN irrespective of baseline grade, discontinue KISQALI.			
Perform Liver Function Tests (LFTs) before initiating treatment with KISQALI. 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, more frequent monitoring is recommended.				

*Baseline = prior to treatment initiation.
Grading according to CTCAE Version 4.03.
ULN = upper limit of normal
AST = aspartate aminotransferase; ALT = alanine aminotransferase

Table 4: Dose Modification and Management for QT Prolongation

ECGs with QTcF* > 480 ms	• Interrupt KISQALI Treatment • If QTcF prolongation resolves to < 481 ms, resume treatment at the next lower dose level; • If QTcF ≥ 481 ms recurs, interrupt dose until QTcF resolves to < 481 ms; then resume KISQALI at next lower dose level.
ECGs with QTcF > 500 ms	• Interrupt KISQALI treatment if QTcF greater than 500 ms. • If QTcF prolongation resolves to < 481 ms, resume treatment at the next lower dose level Permanently discontinue KISQALI if QTcF interval prolongation is either greater than 500 ms or greater than 60 ms change from baseline AND associated with any of the following: Torsades de Pointes, polymorphic ventricular tachycardia, unexplained syncope, or signs/symptoms of serious arrhythmia.

Electrocardiograms (ECGs) should be assessed prior to initiation of treatment.
Repeat ECGs at approximately Day 14 of the first cycle and at the beginning of the second cycle, and as clinically indicated.
In case of (QTcF) prolongation at any given time during treatment, more frequent ECG monitoring is recommended.
*QTcF = QT interval corrected by Fridericia's formula

Table 5: 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 KISQALI at same dose level. If Grade 3 recurs, resume KISQALI at the next lower dose level.	Discontinue KISQALI.

*Excluding neutropenia, hepatobiliary toxicity and QT interval prolongation.
Grading according to 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 KISQALI 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 KISQALI dose to 400 mg once daily. If the strong inhibitor is discontinued, change the KISQALI 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) and Clinical Pharmacology (12.3)]*.

Dose Modification for Hepatic Impairment

No dose adjustment is necessary in patients with mild hepatic impairment (Child-Pugh class A). The recommended starting dose is 400 mg KISQALI once daily for patients with moderate (Child-Pugh class B) and severe hepatic impairment (Child-Pugh class C) *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

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

Dose Modification for Renal Impairment

No dose adjustment is necessary in patients with mild or moderate renal impairment. The recommended starting dose is 200 mg KISQALI once daily for patients with severe renal impairment *[see Use in Specific Populations (8.7) and 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 QT Interval Prolongation

KISQALI has been shown to prolong the QT interval in a concentration-dependent manner *[see Clinical Pharmacology (12.2)]*. Based on the observed QT prolongation during treatment, KISQALI may require dose interruption, reduction or discontinuation as described in Table 4 *[see Dosage and Administration (2.2) and Drug Interactions (7.4)]*.

Across MONALEESA-2, MONALEESA-7, and MONALEESA-3 in patients with advanced or metastatic breast cancer who received the combination of KISQALI plus an aromatase inhibitor or fulvestrant, 14 out of 1054 patients (1%) had >500 ms post-baseline QTcF value, and 59 out of 1054 patients (6%) had a >60 ms increase from baseline in QTcF intervals.

These ECG changes were reversible with dose interruption and the majority occurred within the first four weeks of treatment. There were no reported cases of Torsades de Pointes.

In MONALEESA-2, on the KISQALI 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)]*.

Assess ECG prior to initiation of treatment. Initiate treatment with KISQALI only in patients with QTcF values less than 450 ms. Repeat ECG at approximately Day 14 of the first cycle and the beginning of the second cycle, and as clinically indicated.

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

Avoid the use of KISQALI in patients who already have or who are at significant risk of developing QT prolongation, including patients with:

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

Avoid using KISQALI with drugs known to prolong QT interval and/or strong CYP3A inhibitors as this may lead to prolongation of the QTcF interval.

5.2 Increased QT Prolongation with Concomitant Use of Tamoxifen

KISQALI is not indicated for concomitant use with tamoxifen. In MONALEESA-7, the observed mean QTcF increase from baseline was >10 ms higher in the tamoxifen plus placebo subgroup compared with the NSAI 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 KISQALI and tamoxifen combination and in 18/245 (7%) of patients receiving KISQALI plus an NSAI *[see Clinical Pharmacology (12.2)]*.

5.3 Hepatobiliary Toxicity

In MONALEESA-2, MONALEESA-7 and MONALEESA-3, increases in transaminases were observed. Across all studies, Grade 3 or 4 increases in ALT (10% versus 2%) and AST (7% versus 2%) were reported in the KISQALI and placebo arms, respectively.

Among the patients who had Grade ≥3 ALT/AST elevation, the median time-to-onset was 85 days for the KISQALI plus aromatase inhibitor or fulvestrant treatment group. The median time to resolution to Grade ≤ 2 was 22 days in the KISQALI plus aromatase inhibitor or fulvestrant treatment group. 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 occurred in 6 (1%) patients and all patients recovered after discontinuation of KISQALI. No cases occurred in MONALEESA-7.

Perform LFTs before initiating therapy with KISQALI. Monitor LFTs every 2 weeks for first 2 cycles, at the beginning of each subsequent 4 cycles, and as clinically indicated *[see Dosage and Administration (2.2)]*.

Based on the severity of the transaminase elevations, KISQALI may require dose interruption, reduction, or discontinuation as described in Table 3 (Dose Modification and Management for Hepatobiliary Toxicity) *[see Dosage and Administration (2.2)]*. Recommendations for patients who have elevated AST/ALT Grade ≥3 at baseline have not been established.

5.4 Neutropenia

In MONALEESA-2, MONALEESA-7 and MONALEESA-3, neutropenia was the most frequently reported adverse reaction (74%) and a Grade 3/4 decrease in neutrophil count (based on laboratory findings) was reported in 58% of patients receiving KISQALI plus an aromatase inhibitor or fulvestrant. Among the patients who had Grade 2, 3, or 4 neutropenia, the median time to Grade ≥2 neutropenia was 16 days. The median time to resolution of Grade ≥3 (to normalization or Grade <3) was 12 days in the KISQALI plus aromatase inhibitor or fulvestrant treatment group. Febrile neutropenia was reported in 1% of patients receiving KISQALI plus an aromatase inhibitor or fulvestrant. Treatment discontinuation due to neutropenia was 0.8%.

Perform CBC before initiating therapy with KISQALI. 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, KISQALI may require dose interruption, reduction or discontinuation as described in Table 2 *[see Dosage and Administration (2.2)]*.

5.5 Embryo-Fetal Toxicity

Based on findings from animal studies and the mechanism of action, KISQALI 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 KISQALI and for at least 3 weeks after the last dose *[see Use in Specific Population (8.1, 8.3) and Clinical Pharmacology (12.1)]*.

6 ADVERSE REACTIONS

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

- QT Interval Prolongation *[see Warnings and Precautions (5.1, 5.2)]*
- Hepatobiliary Toxicity *[see Warnings and Precautions (5.3)]*
- Neutropenia *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trial 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.

MONALEESA-2: KISQALI in combination with Letrozole

Postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine based therapy

The safety data reported below are based on MONALEESA-2, a clinical study of 668 postmenopausal women receiving KISQALI plus letrozole or placebo plus letrozole. The median duration of exposure to KISQALI plus letrozole was 13 months with 58% of patients exposed for ≥12 months.

Dose reductions due to adverse reactions (ARs) occurred in 45% of patients receiving KISQALI plus letrozole and in 3% of patients receiving placebo plus letrozole. Among patients receiving KISQALI plus letrozole, 7% were reported to have permanently discontinued both KISQALI and letrozole and 7% were reported to have permanently discontinued KISQALI alone due to ARs. Among patients receiving placebo plus letrozole, 2% were reported to have permanently discontinued both and 0.9% were reported to have permanently discontinued placebo alone due to ARs. Adverse reactions leading to treatment discontinuation of KISQALI in patients receiving KISQALI plus letrozole were ALT increased (4%), AST increased (3%), vomiting (2%). Antiemetics and antidiarrhea medications were used to manage symptoms as clinically indicated.

On-treatment deaths, regardless of causality, were reported in three cases (0.9%) of KISQALI plus letrozole treated patients vs. one case (0.3%) of placebo plus letrozole treated patients. Causes of death on KISQALI plus letrozole included one case each of the following: progressive disease, death (cause unknown), and sudden death (in the setting of Grade 3 hypokalemia and Grade 2 QT prolongation).

The most common ARs (reported at a frequency ≥ 20% on the KISQALI arm and ≥ 2% higher than placebo) were neutropenia, nausea, fatigue, diarrhea, leukopenia, alopecia, vomiting, constipation, headache, and back pain.

The most common Grade 3/4 ARs (reported at a frequency ≥ 5%) were neutropenia, leukopenia, abnormal liver function tests, and lymphopenia.

In MONALEESA-2, syncope occurred in 9 patients (3%) in the KISQALI plus letrozole arm versus 3 (1%) in placebo plus letrozole arm.

ARs and laboratory abnormalities occurring in patients in MONALEESA-2 are listed in Table 6 and Table 7, respectively.

Table 6: Adverse Reactions Occurring in ≥10% and ≥2% higher than Placebo Arm in MONALEESA-2 (All Grades)

	KISQALI + letrozole			Placebo + letrozole		
	N=334			N=330		
Adverse drug reactions	**All Grades %**	**Grade 3 %**	**Grade 4 %**	**All Grades %**	**Grade 3 %**	**Grade 4 %**
Infections and Infestations						
Urinary tract infection	11	1	0	8	0	0
Blood and lymphatic system disorders						
Neutropenia	75	50	10	5	1	0
Leukopenia	33	20	1	1	<1	0
Anemia	18	1	<1	5	1	0
Lymphopenia	11	6	1	2	1	0
Metabolism and nutrition disorders						
Decreased appetite	19	2	0	15	<1	0
Nervous system disorders						
Headache	22	<1	0	19	<1	0
Insomnia	12	<1	0	9	0	0
Respiratory, thoracic and mediastinal disorders						
Dyspnea	12	1	0	9	1	0
Musculoskeletal and connective tissue disorders						
Back pain	20	2	0	18	<1	0
Gastrointestinal disorders						
Nausea	52	2	0	29	1	0
Diarrhea	35	1	0	22	1	0
Vomiting	29	4	0	16	1	0
Constipation	25	1	0	19	0	0
Stomatitis	12	<1	0	7	0	0
Abdominal pain	11	1	0	8	0	0

Skin and subcutaneous tissue disorders						
Alopecia	33	0	0	16	0	0
Rash	17	1	0	8	0	0
Pruritus	14	1	0	6	0	0
General disorders and administration site conditions						
Fatigue	37	2	<1	30	1	0
Pyrexia	13	<1	0	6	0	0
Edema peripheral	12	0	0	10	0	0
Investigations						
Abnormal liver function tests[1]	18	8	2	6	2	0

Grading according to CTCAE 4.03 (Common Terminology Criteria for Adverse Events)
[1]abnormal liver function tests: ALT increased, AST increased, blood bilirubin increased

Table 7: Laboratory Abnormalities Occurring in ≥10% of Patients in MONALEESA-2

	KISQALI + letrozole N=334			Placebo + letrozole N=330		
Laboratory parameters	**All Grades %**	**Grade 3 %**	**Grade 4 %**	**All Grades %**	**Grade 3 %**	**Grade 4 %**
HEMATOLOGY						
Leukocyte count decreased	93	31	3	29	1	< 1
Neutrophil count decreased	93	49	11	24	1	< 1
Hemoglobin decreased	57	2	0	26	1	0
Lymphocyte count decreased	51	12	2	22	3	1
Platelet count decreased	29	1	< 1	6	0	< 1
CHEMISTRY						
Alanine aminotransferase increased	46	8	2	36	1	0
Aspartate aminotransferase increased	44	6	1	32	2	0
Creatinine increased	20	1	0	6	0	0
Phosphorous decreased	13	5	1	4	1	0
Potassium decreased	11	1	1	7	1	0

MONALEESA-7: KISQALI in combination with an Aromatase Inhibitor

Pre/perimenopausal patients with HR-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine based therapy

MONALEESA-7 was conducted in 672 pre/perimenopausal patients with HR-positive, HER2-negative advanced or metastatic breast cancer receiving either KISQALI plus a non-steroidal aromatase inhibitors (NSAI) or tamoxifen plus goserelin or placebo plus NSAI or tamoxifen plus goserelin. The median duration of exposure on the KISQALI 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 KISQALI plus NSAI plus goserelin or placebo plus NSAI plus goserelin.
Dose reductions due to adverse reactions (ARs) occurred in 33% of patients receiving KISQALI plus NSAI plus goserelin and in 4% of patients receiving placebo plus NSAI plus goserelin. Among patients receiving KISQALI plus NSAI, 3% were reported to have permanently discontinued both KISQALI and NSAI and 3% were reported to have permanently discontinued KISQALI alone due to ARs. Among patients receiving placebo plus NSAI, 2% were reported to have permanently discontinued both and 0.8% were reported to have permanently discontinued placebo alone due to ARs.
Adverse reactions leading to treatment discontinuation on KISQALI in patients receiving KISQALI plus NSAI (as compared to the placebo arm) were ALT increased (2% vs. 0.8%), AST increased (2% vs 0.8%), drug-induced liver injury (1% vs. 0.4%).

The most common ARs (reported at a frequency ≥20% on the KISQALI arm and ≥2% higher than placebo) were neutropenia, infections, leukopenia, arthralgia, nausea, and alopecia. The most common Grade 3/4 ARs (reported at a frequency ≥ 5%) were neutropenia, leukopenia, and abnormal liver function tests. See Table 8 below.

Adverse reactions and laboratory abnormalities occurring in patients in MONALEESA-7 are listed in Table 8 and Table 9, respectively.

Table 8: Adverse Reactions Occurring in ≥10% and ≥2% higher than Placebo Arm in MONALEESA-7 (NSAI) (All Grades)

	KISQALI + NSAI + goserelin N=248			Placebo + NSAI + goserelin N=247		
Adverse drug reactions	**All Grades %**	**Grade 3 %**	**Grade 4 %**	**All Grades %**	**Grade 3 %**	**Grade 4 %**
Infections and Infestations						
Infections[1]	35	2	0	24	< 1	0
Blood and lymphatic system disorders						
Neutropenia	78	55	10	7	2	< 1
Leukopenia	29	13	< 1	3	< 1	0
Anemia	19	3	0	8	1	0
Respiratory, thoracic and mediastinal disorders						
Cough	15	0	0	10	0	0
Musculoskeletal and connective tissue disorders						
Arthralgia	33	< 1	0	29	1	0
Gastrointestinal disorders						
Nausea	31	0	0	20	0	0
Constipation	16	0	0	12	0	0
Stomatitis	10	0	0	8	< 1	0
Skin and subcutaneous tissue disorders						
Alopecia	21	0	0	13	0	0
Rash	17	< 1	0	9	0	0
Pruritus	10	0	0	4	0	0
General disorders and administration site conditions						
Pyrexia	17	< 1	0	6	0	0
Pain in extremity	10	0	0	8	1	0
Investigations						
Alanine aminotransferase increased	13	5	0	9	1	0
Aspartate aminotransferase increased	13	4	0	10	1	0

Grading according to CTCAE 4.03 (Common Terminology Criteria for Adverse Events)
[1] Infections: urinary tract infections; respiratory tract infections; gastroenteritis; sepsis (<1%).

Additional adverse reactions in MONALEESA-7 for patients receiving KISQALI plus NSAI included asthenia (12%), thrombocytopenia (9%), dry skin (8%), oropharyngeal pain (7%), dyspepsia (5%), lacrimation increased (4%), dry eye (4%), vitiligo (3%), hypocalcemia, (2%), blood bilirubin increased (1%) and syncope (0.4%).

Table 9: Laboratory Abnormalities Occurring in ≥10% of Patients in MONALEESA-7

	KISQALI + NSAI + goserelin N=248			Placebo + NSAI + goserelin N=247		
Laboratory parameters	**All Grades %**	**Grade 3 %**	**Grade 4 %**	**All Grades %**	**Grade 3 %**	**Grade 4 %**
HEMATOLOGY						
Leukocyte count decreased	93	34	2	30	< 1	< 1
Neutrophil count decreased	92	54	9	27	2	0
Hemoglobin decreased	84	2	0	51	< 1	0
Lymphocyte count decreased	55	12	2	18	2	< 1
Platelet count decreased	26	< 1	0	9	0	< 1
CHEMISTRY						
Alanine aminotransferase increased	33	6	0	31	1	< 1
Aspartate aminotransferase increased	37	5	0	35	1	< 1
Creatinine increased	21	2	< 1	20	< 1	< 1
Phosphorous decreased	14	2	0	11	< 1	< 1
Potassium decreased	11	< 1	< 1	14	< 1	< 1
Gamma-glutamyl transferase increased	42	5	2	42	8	1
Glucose serum decreased	10	< 1	0	10	< 1	0

MONALEESA-3: KISQALI 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 data reported below are based on MONALEESA-3, a clinical study of 724 postmenopausal women receiving KISQALI plus fulvestrant or placebo plus fulvestrant. The median duration of exposure to KISQALI plus fulvestrant was 15.8 months with 58% of patients exposed for ≥ 12 months.
Dose reductions due to adverse reactions (ARs) occurred in 32% of patients receiving KISQALI plus fulvestrant and in 3% of patients receiving placebo plus fulvestrant. Among patients receiving KISQALI plus fulvestrant, 8% were reported to have permanently discontinued both KISQALI and fulvestrant and 9% were reported to have discontinued KISQALI alone due to ARs. Among patients receiving placebo plus fulvestrant, 4% were reported to have permanently discontinued both and 2% were reported to have discontinued placebo alone due to ARs. Adverse reactions leading to treatment discontinuation of KISQALI in patients receiving KISQALI plus fulvestrant (as compared to the placebo arm) were ALT increased (5% vs 0%), AST increased (3% vs 0.6%), and vomiting (1% vs 0%).

The most common ARs (reported at a frequency ≥ 20% on the KISQALI arm and ≥ 2% higher than placebo) were neutropenia, infections, leukopenia, cough, nausea, diarrhea, vomiting, constipation, pruritus, and rash. The most common Grade 3/4 ARs (reported at a frequency ≥ 5%) were neutropenia, leukopenia, infections, and abnormal liver function tests, See Table 10.

Adverse reactions and laboratory abnormalities occurring in patients in MONALEESA-3 are listed in Table 10 and Table 11, respectively.

Table 10: Adverse Reactions Occurring in ≥10% and ≥2% higher than Placebo Arm in MONALEESA-3 (All Grades)

	KISQALI + fulvestrant N=483			Placebo + fulvestrant N=241		
Adverse drug reactions	**All Grades %**	**Grade 3 %**	**Grade 4 %**	**All Grades %**	**Grade 3 %**	**Grade 4 %**

Infections and Infestations						
Infections[1]	42	5	0	30	2	0
Blood and lymphatic system disorders						
Neutropenia	69	46	7	2	0	0
Leukopenia	27	12	< 1	< 1	0	0
Anemia	17	3	0	5	2	0
Metabolism and nutrition disorders						
Decreased appetite	16	< 1	0	13	0	0
Nervous system disorders						
Dizziness	13	<1	0	8	0	0
Respiratory, thoracic and mediastinal disorders						
Cough	22	0	0	15	0	0
Dyspnea	15	1	< 1	12	2	0
Gastrointestinal disorders						
Nausea	45	1	0	28	< 1	0
Diarrhea	29	< 1	0	20	< 1	0
Vomiting	27	1	0	13	0	0
Constipation	25	< 1	0	12	0	0
Abdominal pain	17	1	0	13	< 1	0
Skin and subcutaneous tissue disorders						
Alopecia	19	0	0	5	0	0
Pruritus	20	< 1	0	7	0	0
Rash	23	< 1	0	7	0	0
General disorders and administration site conditions						
Edema peripheral	15	0	0	7	0	0
Pyrexia	11	< 1	0	7	0	0
Investigations						
Alanine aminotransferase increased	15	7	2	5	< 1	0
Aspartate aminotransferase increased	13	5	1	5	< 1	0

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

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

Additional adverse reactions in MONALEESA-3 for patients receiving KISQALI plus fulvestrant included asthenia (14%), dyspepsia (10%), 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%), and syncope (1%).

Table 11: Laboratory Abnormalities Occurring in ≥10% of Patients in MONALEESA-3

	KISQALI + fulvestrant N=483			**Placebo + fulvestrant N=241**		
Laboratory parameters	**All Grades %**	**Grade 3 %**	**Grade 4 %**	**All Grades %**	**Grade 3 %**	**Grade 4 %**
HEMATOLOGY						
Leukocyte count decreased	95	25	< 1	26	< 1	0
Neutrophil count decreased	92	46	7	21	< 1	0
Hemoglobin decreased	60	4	0	35	3	0
Lymphocyte count decreased	69	14	1	35	4	< 1
Platelet count decreased	33	< 1	1	11	0	0
CHEMISTRY						
Creatinine increased	65	< 1	< 1	33	< 1	0

	KISQALI + fulvestrant N=483			Placebo + fulvestrant N=241		
Laboratory parameters	**All Grades %**	**Grade 3 %**	**Grade 4 %**	**All Grades %**	**Grade 3 %**	**Grade 4 %**
Gamma-glutamyl transferase increased	52	6	1	49	8	2
Aspartate aminotransferase increased	49	5	2	43	3	0
Alanine aminotransferase increased	44	8	3	37	2	0
Glucose serum decreased	23	0	0	18	0	0
Phosphorous decreased	18	5	0	8	< 1	0
Albumin decreased	12	0	0	8	0	0

7 DRUG INTERACTIONS

7.1 Drugs That May Increase Ribociclib Plasma Concentrations

CYP3A4 Inhibitors

Coadministration of a strong CYP3A4 inhibitor (ritonavir) increased ribociclib exposure in healthy subjects by 3.2-fold *[see Clinical Pharmacology (12.3)]*. Avoid concomitant use of strong CYP3A inhibitors (e.g., boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, and voriconazole) and consider alternative concomitant medications with less potential for CYP3A inhibition.

If coadministration of KISQALI with a strong CYP3A inhibitor cannot be avoided, reduce the dose of KISQALI to 400 mg once daily *[see Dosage and Administration (2.2)]*.

Instruct patients to avoid grapefruit or grapefruit juice, which are known to inhibit cytochrome CYP3A enzymes and may increase the exposure to ribociclib *[see Patient Counseling Information (17)]*.

7.2 Drugs That May Decrease Ribociclib Plasma Concentrations

CYP3A4 Inducers

Coadministration of a strong CYP3A4 inducer (rifampin) decreased the plasma exposure of ribociclib in healthy subjects by 89% *[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 (e.g., phenytoin, rifampin, carbamazepine and St John's Wort (Hypericum perforatum)).

7.3 Effect of KISQALI on Other Drugs

CYP3A substrates with narrow therapeutic index

Coadministration of midazolam (a sensitive CYP3A4 substrate) with multiple doses of KISQALI (400 mg) increased the midazolam exposure by 3.8-fold in healthy subjects, compared with administration of midazolam alone *[see Clinical Pharmacology (12.3)]*. KISQALI given at the clinically relevant dose of 600 mg is predicted to increase the midazolam AUC by 5.2-fold. Therefore, caution is recommended when KISQALI is administered with CYP3A substrates with a narrow therapeutic index. The dose of a sensitive CYP3A substrate with a narrow therapeutic index, including but not limited to alfentanil, cyclosporine, dihydroergotamine, ergotamine, everolimus, fentanyl, pimozide, quinidine, sirolimus and tacrolimus, may need to be reduced as ribociclib can increase their exposure.

7.4 Drugs That Prolong the QT Interval

Avoid coadministration of KISQALI with medicinal products with a known potential to prolong QT such as antiarrhythmic medicines(including, but not limited to amiodarone, disopyramide, procainamide, quinidine and sotalol), and other drugs that are known to prolong the QT interval (including, but not limited to, chloroquine, halofantrine, clarithromycin, haloperidol, methadone, moxifloxacin, bepridil, pimozide and ondansetron) *[see Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies and the mechanism of action, KISQALI 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 postimplantation 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 13^{th} 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 KISQALI, advise lactating women not to breastfeed while taking KISQALI 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

Pregnancy Testing

Based on animal studies, KISQALI can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Females of reproductive potential should have a pregnancy test prior to starting treatment with KISQALI.

Contraception

Females

Based on animal studies, KISQALI can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception (methods that result in less than 1% pregnancy rates) during treatment with KISQALI and for at least 3 weeks after the last dose.

Infertility

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

8.4 Pediatric Use

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

8.5 Geriatric Use

Of 334 patients who received KISQALI in MONALEESA-2, 150 patients (45%) were ≥65 years of age and 35 patients (11%) were ≥75 years of age. Of 484 patients who received KISQALI in MONALEESA-3, 226 patients (47%) were ≥65 years of age and 65 patients (14%) were ≥75 years of age. No overall differences in safety or effectiveness of KISQALI were observed between these patients and younger patients.

8.6 Hepatic Impairment

No dose adjustment is necessary in patients with mild hepatic impairment (Child-Pugh A). A reduced starting dose of 400 mg is recommended in patients with moderate (Child-Pugh B) and severe hepatic impairment (Child-Pugh C) *[see Dosage and Administration (2.2)]*. Based on a pharmacokinetic trial in patients with hepatic impairment, mild hepatic impairment had no effect on the exposure of ribociclib. The mean exposure for ribociclib was increased less than 2-fold in patients with moderate (geometric mean ratio [GMR]: 1.44 for C_{max}; 1.28 for AUC_{inf}) and severe (GMR: 1.32 for C_{max}; 1.29 for AUC_{inf}) hepatic impairment *[see Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

Based on a population pharmacokinetic analysis, no dose adjustment is necessary in patients with mild (60 mL/min/1.73m^2 ≤ estimated glomerular filtration rate (eGFR) < 90 mL/min/1.73m^2) or moderate (30 mL/min/1.73m^2 ≤ eGFR < 60 mL/min/1.73m^2) renal impairment. Based on a renal impairment study in healthy subjects and non-cancer subjects with severe renal impairment (eGFR 15 to < 30 mL/min/1.73m^2), a starting dose of 200 mg is recommended. KISQALI has not been studied in breast cancer patients with severe renal impairment *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

There is limited experience with reported cases of overdose with KISQALI in humans. General symptomatic and supportive measures should be initiated in all cases of overdose where necessary.

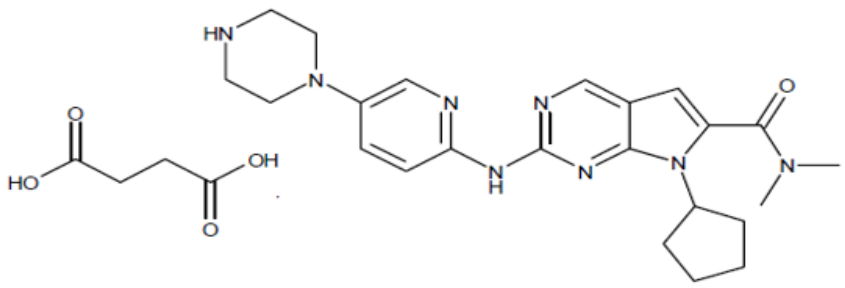
11 DESCRIPTION

KISQALI (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 $C_{23}H_{30}N_8O \cdot C_4H_6O_4$ and the molecular weight is 552.64 g/mol *(Free base: 434.55 g/mol)*.

The chemical structure of ribociclib is shown below:



KISQALI 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 play a crucial role in signaling pathways which lead to cell cycle progression and cellular proliferation. The cyclin D-CDK4/6 complex regulates cell cycle progression through phosphorylation of the retinoblastoma protein (pRb).

In vitro, ribociclib decreased pRb phosphorylation leading to arrest in the G1 phase of the cell cycle and reduced cell proliferation in breast cancer cell lines. *In vivo*, treatment with single agent ribociclib 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) 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

Cardiac Electrophysiology

Serial, triplicate ECGs were collected following a single dose and at steady-state to evaluate the effect of ribociclib on the QTcF interval in patients with advanced cancer. A pharmacokinetic-pharmacodynamic analysis included a total of 997 patients treated with ribociclib at doses ranging from 50 to 1200 mg. The analysis suggested that ribociclib causes concentration-dependent increases in the QTcF interval. The estimated mean change from baseline in QTcF for KISQALI 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 geometric mean C_{max} at steady-state *[see Warnings and Precautions (5.1, 5.2)]*.

12.3 Pharmacokinetics

Ribociclib exhibited over-proportional increases in exposure (peak plasma concentrations (C_{max}) and area under the time concentration curve (AUC)) across the dose range of 50 mg to 1200 mg following both single dose and repeated doses. Following repeated 600 mg once daily administration, steady-state was generally achieved after 8 days and ribociclib accumulated with a geometric mean accumulation ratio of 2.51 (range: 0.972 to 6.40).

Absorption

The time to reach C_{max} (T_{max}) following ribociclib administration was between 1 and 4 hours.

Food Effect: Compared to the fasted state, oral administration of a single 600 mg dose of KISQALI film-coated tablet with a high-fat, high-calorie meal (approximately 800 to 1000 calories with ~50% calories from fat, ~35% calories from carbohydrates, and ~15% calories from protein) had no effect on the rate and extent of absorption of ribociclib (C_{max} GMR: 1.00; 90% CI: 0.898, 1.11; AUC_{inf} GMR: 1.06; 90% CI: 1.01, 1.12).

Distribution

Binding of ribociclib to human plasma proteins *in vitro* was approximately 70% and independent of concentration (10 to 10,000 ng/mL). Ribociclib was equally distributed between red blood cells and plasma with a mean in vivo blood-to-plasma ratio of 1.04. The apparent volume of distribution at steady-state (Vss/F) was 1090 L based on population PK analysis.

Metabolism

In vitro and in vivo studies indicated ribociclib undergoes extensive hepatic metabolism mainly via CYP3A4 in humans. Following oral administration of a single 600 mg dose of radio-labeled 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 (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 (pharmacological and safety) 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 was a significant metabolite in excreta and represented approximately 14% and 4% of the administered dose in feces and urine, respectively. Numerous other metabolites were detected in both feces and urine in minor amounts (≤ 3% of the administered dose).

Elimination

The geometric mean plasma effective half-life (based on accumulation ratio) was 32.0 hours (63% CV) and the geometric mean apparent oral clearance (CL/F) was 25.5 L/hr (66% CV) at steady-state at 600 mg in patients with advanced cancer. The geometric mean apparent plasma terminal half-life (T1/2) of ribociclib ranged from 29.7 to 54.7 hours and geometric mean CL/F of ribociclib ranged from 39.9 to 77.5 L/hr at 600 mg across studies in healthy subjects.

Ribociclib is eliminated mainly via feces, with a small contribution of the renal route. In 6 healthy male subjects, following a single oral dose of radio-labeled ribociclib, 92% of the total administered radioactive dose was recovered within 22 days; feces was the major route of excretion (69%), with 23% of the dose recovered in urine.

Specific Populations

Patients with Hepatic Impairment

Based on a pharmacokinetic trial in patients with hepatic impairment, mild (Child-Pugh class A) hepatic impairment had no effect on the exposure of ribociclib. The mean exposure for ribociclib was increased less than 2-fold in patients with moderate (Child-Pugh class B; geometric mean ratio [GMR]: 1.44 for C_{max}; 1.28 for AUC_{inf}) and severe (Child-Pugh class C; GMR: 1.32 for C_{max}; 1.29 for AUC_{inf}) hepatic impairment. Based on a population pharmacokinetic analysis that included 160 patients with normal hepatic function and 47 patients with mild hepatic impairment, mild hepatic impairment had no effect on the exposure of ribociclib, further supporting the findings from the dedicated hepatic impairment study.

Patients with Renal Impairment

Mild (60 mL/min/1.73m^2 ≤ eGFR < 90 mL/min/1.73m^2) and moderate (30 mL/min/1.73m^2 ≤ eGFR < 60 mL/min/1.73m^2) renal impairment had no effect on the exposure of ribociclib based on a population PK analysis.

The effect of renal impairment on the pharmacokinetics of ribociclib was assessed in a renal impairment study in non-cancer subjects with normal renal function (eGFR ≥90 mL/min/1.73 m^2), severe renal impairment (eGFR 15 to <30 mL/min/1.73 m^2), and End Stage Renal Disease (ESRD; eGFR <15 mL/min/1.73 m^2). In subjects with severe renal impairment, AUC_{inf} increased by 1.96 fold, and C_{max} increased by 1.51 fold compared to subjects with normal renal function.

Effect of Age, Weight, Gender, and Race

Population PK analysis showed that there are no clinically relevant effects of age, body weight, gender, or race on the systemic exposure of ribociclib.

Drug Interaction Studies

Drugs That Affect Ribociclib Plasma Concentrations

CYP3A inhibitors: A drug interaction trial in healthy subjects was conducted with ritonavir (a strong CYP3A inhibitor). Compared to ribociclib alone, 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, following a single 400 mg ribociclib dose. C_{max} and AUC for LEQ803 (a prominent metabolite of LEE011, accounting for less than 10% of parent exposure) decreased by 96% and 98%, respectively. A moderate CYP3A4 inhibitor (erythromycin) is predicted to increase ribociclib C_{max} and AUC by 1.3-fold and 1.9-fold, respectively.

CYP3A inducers: A drug interaction trial in healthy subjects was conducted with rifampicin (a strong CYP3A4 inducer). Compared to ribociclib alone, rifampicin (600 mg daily for 14 days) decreased ribociclib C_{max} and AUC_{inf} by 81% and 89%, respectively, following a single 600 mg ribociclib dose. LEQ803 C_{max} increased 1.7-fold and AUC_{inf} decreased by 27%, respectively. A moderate CYP3A inducer (efavirenz) is predicted to decrease ribociclib C_{max} and AUC by 37% and 60%, respectively.

Drugs That Are Affected By KISQALI

CYP3A4 and CYP1A2 substrates: A drug interaction trial in healthy subjects was conducted as a cocktail study with midazolam (sensitive CYP3A4 substrate) and caffeine (sensitive CYP1A2 substrate). Compared to midazolam and caffeine alone, multiple doses of ribociclib (400 mg once daily for 8 days) increased midazolam C_{max} and AUC_{inf} by 2.1-fold and 3.8-fold, respectively. Administration of ribociclib at 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 was minimal, with C_{max} decreased by 10% and AUC_{inf} increased slightly by 20%. Only weak inhibitory effects on CYP1A2 substrates are predicted at 600 mg ribociclib once daily dose.

Gastric pH-elevating agents: Coadministration of ribociclib with drugs that elevate the gastric pH was not evaluated in a clinical trial; however, altered ribociclib absorption was not identified in a population PK analysis and was not predicted using physiology based PK models.

Letrozole: Data from a clinical trial in patients with breast cancer and population PK analysis 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: KISQALI 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 600 mg ribociclib.

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 KISQALI 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 KISQALI has a low potential to inhibit the activities of drug transporters P-gp, OATP1B1/B3, OCT1, MATEK2 at clinically relevant concentrations. KISQALI 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 OCT-1 in vitro.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis studies have not been conducted with ribociclib.

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

MONALEESA-2: KISQALI in Combination with Letrozole

Postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine based therapy

MONALEESA-2 was a randomized, double-blind, placebo-controlled, multicenter clinical study of KISQALI plus letrozole versus placebo plus letrozole conducted in postmenopausal women with HR-positive, HER2-negative, advanced breast cancer who received no prior therapy for advanced disease.

A total of 668 patients were randomized to receive either KISQALI plus letrozole (n= 334) or placebo plus letrozole (n= 334), 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 KISQALI 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.

Patients enrolled in MONALEESA-2 had a median age of 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.

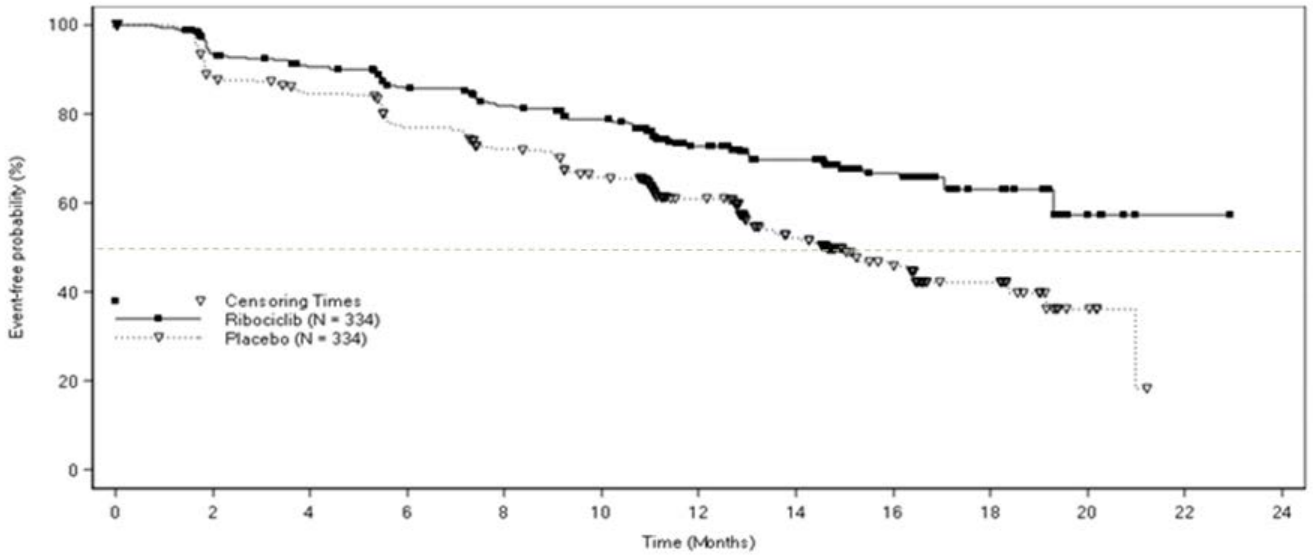
The efficacy results from MONALEESA-2 are summarized in Table 12 and Figure 1. The results shown are from a pre-planned interim efficacy analysis of PFS. Results were consistent across patient subgroups of prior adjuvant or neoadjuvant chemotherapy or hormonal therapies, liver and/or lung involvement, and bone-only metastatic disease. The PFS assessment based on a blinded independent central radiological review was consistent with investigator assessment. At the time of the PFS analysis, 6.5% of patients had died, and overall survival data were immature.

Table 12: Efficacy Results – MONALEESA-2 (Investigator Assessment, Intent-to-Treat Population)

	KISQALI + letrozole	**Placebo + letrozole**
Progression-free survival	**N = 334**	**N = 334**
Events (%)	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 to 0.720)	
p-value	< 0.0001[a]	
Overall Response Rate	**N=256**	**N=245**
Patients with measurable disease (95% CI)	52.7 (46.6, 58.9)	37.1 (31.1, 43.2)

[a]p-value estimated from one-sided log-rank test
NR = not reached

Figure 1 Kaplan-Meier Progression Free Survival Curves – MONALEESA-2 (Intent-to-Treat Population)



MONALEESA-7: KISQALI in Combination with an Aromatase Inhibitor

Pre/perimenopausal patients with HR-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine based therapy

MONALEESA-7 was a randomized, double-blind, placebo-controlled study of KISQALI plus either a non-steroidal aromatase inhibitor (NSAI) or tamoxifen and goserelin versus placebo plus either a NSAI or tamoxifen and goserelin conducted in pre/perimenopausal women with HR-positive, HER2-negative, advanced breast cancer who received no prior endocrine therapy for advanced disease.

A total of 672 patients were randomized to receive KISQALI plus NSAI or tamoxifen plus goserelin (n= 335) or placebo plus NSAI or tamoxifen plus goserelin (n= 337), stratified according to the presence of liver and/or lung metastases, prior chemotherapy for advanced disease and endocrine combination partner (tamoxifen and goserelin vs NSAI and goserelin). NSAI (letrozole 2.5 mg or anastrozole 1 mg) or tamoxifen 20 mg or 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 KISQALI 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.

Patients enrolled in MONALEESA-7 had a median age of 44 years (range 25 to 58) and were primarily Caucasian (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.

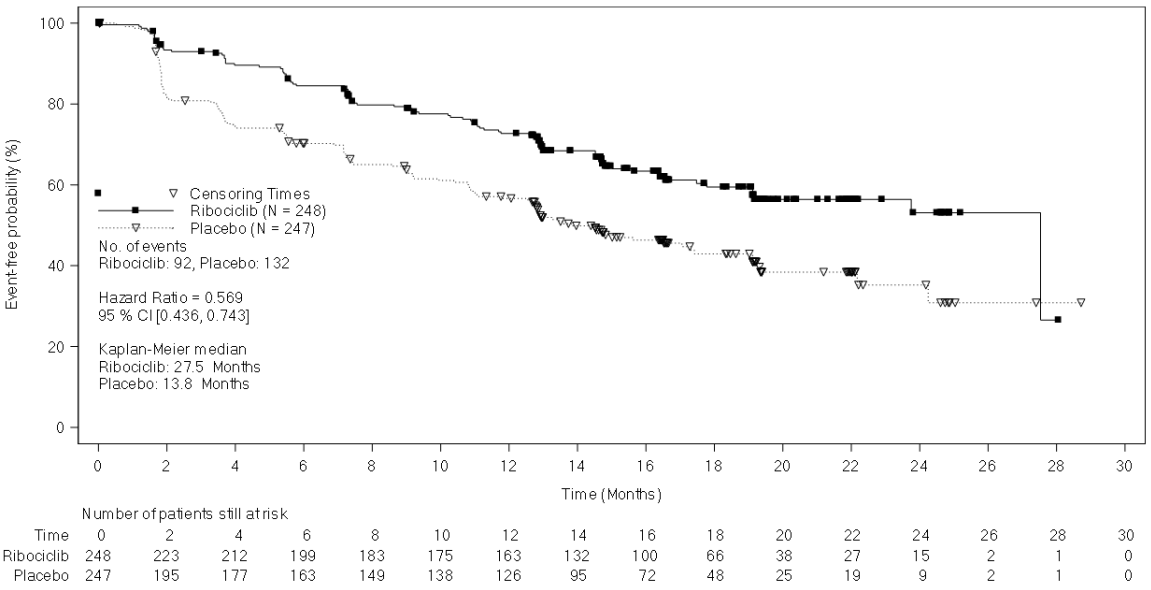
The efficacy results from a pre-specified subgroup analysis of 495 patients who had received KISQALI or placebo with NSAI plus goserelin are summarized in Table 13 and Figure 2. Consistent results were observed in stratification factor subgroups of disease site and prior chemotherapy for advanced disease. Overall survival data were immature with 13% deaths.

Table 13: Efficacy Results – MONALEESA-7 (NSAI, Investigator Assessment)

	KISQALI + NSAI + goserelin	**Placebo + NSAI + goserelin**
Progression-free survival	**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 Response Rate*	**N=192**	**N=199**

Patients with measurable disease (95% CI)	50.5 (43.4, 57.6)	36.2 (29.5, 42.9)
NR = not reached * Based on confirmed responses		

Figure 2 Kaplan-Meier Progression Free Survival Curves – MONALEESA-7 (NSAI, Investigator Assessment)



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

A total of 726 patients were randomized in a 2:1 ratio to receive KISQALI 600 mg and fulvestrant (n= 484) or placebo and fulvestrant (n= 242), stratified according to the presence of liver and/or lung metastases and prior endocrine therapy for advanced or metastatic disease. Fulvestrant 500 mg was administered intramuscularly on days 1, 15, 29, and once monthly thereafter, with either KISQALI 600 mg or placebo given orally once daily for 21 consecutive days followed by 7 days off until disease progression or unacceptable toxicity. 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.

Patients enrolled in this study had a median age of 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 Caucasian (85%), Asian (9%), and Black (0.7%). Nearly all patients (99.7%) had an ECOG performance status of 0 or 1. First and second line patients were enrolled in this study (of which 19% 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 14 and Figure 3. Consistent results were observed in stratification factor subgroups of disease site and prior endocrine treatment for advanced disease. At the time of the PFS analysis, 17% of patients had died, and overall survival data were immature.

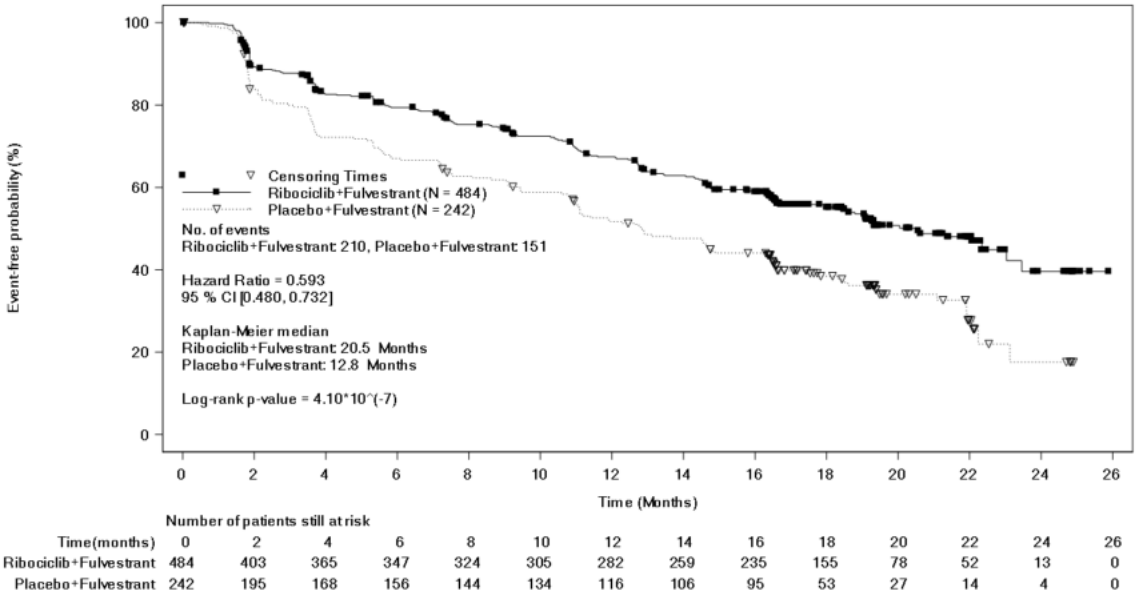
Table 14: Efficacy Results – MONALEESA-3 (Investigator Assessment, Intent-to-Treat Population)

	KISQALI + Fulvestrant	**Placebo + Fulvestrant**
Progression-free survival	**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 to 0.732)	
p-value[a]	<0.0001	
Overall Response Rate*	**N=379**	**N=181**
Patients with measurable disease (95% CI)	40.9 (35.9, 45.8)	28.7 (22.1, 35.3)

[a] p-value is obtained from the one-sided log-rank
* Based on confirmed responses

Figure 3 Kaplan-Meier Progression Free Survival Curves – MONALEESA-3 (Investigator assessment)



16 HOW SUPPLIED/STORAGE AND HANDLING

KISQALI (ribociclib) Tablets

Each film-coated tablet contains 200 mg of ribociclib free base.

Light greyish violet, round, curved with beveled edge, debossed with “RIC” on one side and “NVR” on the other side; available in:

Blister pack (21 tablets) – each blister pack contains 21 tablets (200 mg per tablet) (600 mg daily dose)
Outer container - 3 Blister packs per outer container NDC 0078-0874-63

Blister pack (14 tablets) – each blister pack contains 14 tablets (200 mg per tablet) (400 mg daily dose)
Outer container - 3 Blisters packs per outer container NDC 0078-0867-42

Blister pack (21 tablets) – each blister pack contains 21 tablets (200 mg per tablet) (200 mg daily dose)
Outer container – 1 Blister pack per outer container NDC 0078-0860-01

Store at 20ºC to 25°C (68ºF to 77°F). Store in the original package.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

QT Prolongation

Inform patients of the signs and symptoms of QT prolongation. Advise patients to contact their healthcare provider immediately for signs or symptoms of QT prolongation *[see Warnings and Precautions (5.1, 5.2)]*.

Hepatobiliary Toxicity

Inform patients of the signs and symptoms of hepatobiliary toxicity. Advise patients to contact their healthcare provider immediately for signs or symptoms of hepatobiliary toxicity *[see Warnings and Precautions (5.3)]*.

Neutropenia

Advise patients of the possibility of developing neutropenia and to immediately contact their healthcare provider should they develop a fever, particularly in association with any suggestion of infection *[see Warnings and Precautions (5.4)]*.

Embryo-Fetal Toxicity

Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception during KISQALI therapy and for at least 3 weeks after the last dose. Advise females to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, during treatment with KISQALI *[see Warnings and Precautions (5.5) and Use in Specific Populations (8.1, 8.3)]*.

Lactation

Advise lactating women not to breastfeed during treatment with KISQALI and for at least 3 weeks after the last dose *[see Use in Specific Populations (8.2)]*.

Drug Interactions

- Inform patients to avoid grapefruit or grapefruit juice while taking KISQALI *[see Drug Interactions (7.1)]*.
- Inform patients to avoid strong CYP3A inhibitors, strong CYP3A inducers, and drugs known to prolong the QT interval *[see Drug Interactions (7.1, 7.2, 7.4)]*.

Dosing

- Instruct patients to take the doses of KISQALI at approximately the same time every day and to swallow whole (do not chew, crush, or split them prior to swallowing) *[see Dosage and Administration (2.1)]*.
- If patient vomits or misses a dose, advise the patient to take the next prescribed dose at the usual time *[see Dosage and Administration (2.1)]*.
- Advise the patient that KISQALI may be taken with or without food *[see Dosage and Administration (2.1)]*.

Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

T2018-XX
July-2018

PATIENT INFORMATION
KISQALI® (kis kah' lee)
(ribociclib)
tablets

What is the most important information I should know about KISQALI?
KISQALI may cause serious side effects, including:

Heart rhythm problems (QT prolongation). KISQALI can cause a heart problem known as QT prolongation. This condition can cause an abnormal heartbeat and may lead to death. Your healthcare provider should check your heart and do blood tests before and during treatment with KISQALI. Tell your healthcare provider right away if you have a change in your heartbeat (a fast or irregular heartbeat), or if you feel dizzy or faint.

Liver problems. KISQALI can cause serious liver problems. Your healthcare provider should do blood tests to check your liver before and during treatment with KISQALI. Tell your healthcare provider right away if you get any of the following signs and symptoms of liver problems:

- yellowing of your skin or the whites of your eyes (jaundice)
- dark or brown (tea-colored) urine
- feeling very tired
- loss of appetite
- pain on the upper right side of your stomach area (abdomen)
- bleeding or bruising more easily than normal

Low white blood cell counts (neutropenia). Low white blood cell counts are very common when taking KISQALI and may result in infections that may be severe. Your healthcare provider should check your white blood cell counts before and during treatment with KISQALI. Tell your healthcare provider right away if you have signs and symptoms of low white blood cell counts or infections such as fever and chills.

Your healthcare provider may tell you to decrease your dose, temporarily stop or completely stop taking KISQALI if you develop certain serious side effects during treatment with KISQALI.

See **"What are the possible side effects of KISQALI?"** for more information about side effects.

What is KISQALI?

KISQALI is a prescription medicine used in combination with:

- an aromatase inhibitor to treat pre/perimenopausal or postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer that has spread to other parts of the body (metastatic), as the first endocrine based therapy; or
- fulvestrant to treat postmenopausal women with HR-positive, HER2-negative metastatic breast cancer as the first endocrine based therapy or with disease progression following endocrine therapy.

It is not known if KISQALI is safe and effective in children.

What should I tell my healthcare provider before taking KISQALI?
Before you take KISQALI, tell your healthcare provider if you:

- have any heart problems, including heart failure, irregular heartbeats, and QT prolongation
- have ever had a heart attack
- have a slow heartbeat (bradycardia)
- have problems with the amount of potassium, calcium, phosphorus, or magnesium in your blood
- have fever, chills, or any other signs or symptoms of infection
- have liver problems
- have any other medical conditions
- are pregnant, or plan to become pregnant. KISQALI can harm your unborn baby.
  - If you are able to become pregnant, your healthcare provider should do a pregnancy test before you start treatment with KISQALI.
  - Females who are able to become pregnant and who take KISQALI should use effective birth control during treatment and for at least 3 weeks after the last dose of KISQALI.
  - Talk to your healthcare provider about birth control methods that may be right for you during this time.
  - If you become pregnant or think you are pregnant, tell your healthcare provider right away.
- are breastfeeding or plan to breastfeed. It is not known if KISQALI passes into your breast milk. Do not breastfeed during treatment with KISQALI and for at least 3 weeks after the last dose of KISQALI.

Tell your healthcare provider about all of the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. KISQALI and other medicines may affect each other causing side effects. Know the medicines you take. Keep a list of them to show your healthcare provider or pharmacist when you get a new medicine.

How should I take KISQALI?

- Take KISQALI exactly as your healthcare provider tells you.
- Do not change your dose or stop taking KISQALI unless your healthcare provider tells you.
- Take KISQALI each day at about the same time, preferably in the morning.

- You may take KISQALI with or without food.
- Swallow KISQALI tablets whole. Do not chew, crush, or split KISQALI tablets before swallowing them.
- Do not take any KISQALI tablets that are broken, cracked, or that look damaged. If you miss a dose of KISQALI or vomit after taking a dose of KISQALI, do not take another dose on that day. Take your next dose at your regular time.
- If you take too much KISQALI, call your healthcare provider right away or go to the nearest hospital emergency room.
- Inform your healthcare provider if you are pre- or peri-menopausal.

What should I avoid while taking KISQALI?

Avoid eating grapefruit and drinking grapefruit juice during treatment with KISQALI since these may increase the amount of KISQALI in your blood.

What are the possible side effects of KISQALI?

KISQALI may cause serious side effects, including:

See **"What is the most important information I should know about KISQALI?"**

The most common side effects of KISQALI include:

neutropenia	nausea	infections	fatigue
diarrhea	leukopenia	vomiting	hair loss
headache	constipation	rash	cough

KISQALI may cause fertility problems if you are male and take KISQALI. This may affect your ability to father a child. Talk to your healthcare provider if this is a concern for you.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all of the possible side effects of KISQALI. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store KISQALI?

Store KISQALI at 68°F to 77°F (20°C to 25°C).
Keep KISQALI in the original container.

Keep KISQALI and all medicines out of the reach of children.

General information about the safe and effective use of KISQALI.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use KISQALI for a condition for which it was not prescribed. Do not give KISQALI to other people, even if they have the same symptoms you have. It may harm them. You can ask your pharmacist or healthcare provider for more information about KISQALI that is written for health professionals.

What are the ingredients in KISQALI?

Active ingredient: ribociclib

Inactive ingredients: 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 hydrolyzed), talc, titanium dioxide, and xanthan gum.

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T2018X-XX

For more information, go to www.KISQALI.COM or call 1-844-KISQALI (1-844-547-7254).

This Patient Information has been approved by the U.S. Food and Drug Administration. Issued: July 2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209092Orig1s001

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-disciplinary Review and Evaluation

Application Type	sNDA
Application Number(s)	209092, Supplement-1
Priority or Standard	Priority
Submit Date(s)	June 28, 2018
Received Date(s)	June 28, 2018
PDUFA Goal Date	December 28, 2018
Division/Office	DOP1/OHOP/OND
Review Completion Date	July 17, 2018
Established Name	Ribociclib
(Proposed) Trade Name	KISQALI
Pharmacologic Class	Kinase Inhibitor
Code name	LEE011
Applicant	Novartis
Formulation(s)	200 mg tablet
Dosing Regimen	600 mg orally (three 200 mg tablets) taken once daily with or without food for 21 consecutive days followed by 7 days off treatment.
Applicant Proposed Indication(s)/Population(s)	(b) (4)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	KISQALI is a kinase inhibitor indicated in combination with: • an aromatase inhibitor for the treatment of pre/perimenopausal or postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer, as initial endocrine-based therapy; or • fulvestrant for the treatment of postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer, as initial endocrine based

	therapy or following disease progression on endocrine therapy.

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Reviewers of Multi-Disciplinary Review and Evaluation

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Clinical Data Analyst	Jinzhong Liu
Clinical Reviewer	Jennifer Gao
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Additional Reviewers of Application

OPQ	Not applicable for this sNDA
Microbiology	Not applicable for this sNDA
OPDP	Not applicable for this sNDA
OSI	Not applicable for this sNDA
OSE/DEPI	Not applicable for this sNDA
OSE/DMEPA	Not applicable for this sNDA
OSE/DRISK	Not applicable for this sNDA
Other	Not applicable for this sNDA

OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality

OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

Section 1 Executive Summary includes only FDA's assessment.

1.1. Product Introduction

Ribociclib (KISQALI) is an inhibitor of cyclin-dependent kinase (CDK) 4 and 6 that is currently approved in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2) negative advanced or metastatic breast cancer. CDK 4 and 6 are activated upon binding to D-cyclins and play a key role in signaling pathways which lead to cell cycle progression and cellular proliferation.

The applicant proposed the following supplemental indications for the ribociclib label:

(b) (4)

1.2. Conclusions on the Substantial Evidence of Effectiveness

The review team recommends approval of KISQALI (ribociclib), according to 21 Code of Federal Regulations (CFR) 314.126(a)(b), for the following indications:

"KISQALI is a kinase inhibitor indicated in combination with:

- *an aromatase inhibitor for the treatment of pre/perimenopausal or postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer, as initial endocrine-based therapy; or*
- *fulvestrant for the treatment of postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer, as initial endocrine based therapy or following disease progression on endocrine therapy.*

Ribociclib is currently approved in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer. The basis of expanding the current indication with aromatase inhibitors to include pre- and perimenopausal women is a favorable benefit-risk profile based on results from Study E2301 (MONALEESA-7). MONALEESA-7 was a phase 3, randomized, double-blind, placebo-controlled trial of ribociclib plus goserelin plus tamoxifen or a non-steroidal aromatase inhibitor (NSAI) in pre- and perimenopausal women. The study met the primary endpoint for the intention-to-treat (ITT) population. In the NSAI subgroup, there

was a statistically significant and clinically meaningful improvement in progression-free survival (PFS) that favored the ribociclib plus non-steroidal aromatase inhibitor (NSAI) treatment arm for pre- and perimenopausal women. The estimated median PFS in the ribociclib plus NSAI arm was 27.5 months compared to 13.8 months in the placebo plus NSAI arm (HR 0.569; 95% CI (0.436, 0.743), p <0.0001). Results of blinded independent central review (BICR), subgroup analyses, and sensitivity analyses all support the results of the primary efficacy endpoint. In the tamoxifen subgroup, there was increased QT prolongation observed compared to the NSAI subgroup and as a result, given the QT safety concerns, the applicant decided not to seek an indication with tamoxifen.

The basis of expanding the current indication to include treatment with fulvestrant for postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer as initial endocrine-based therapy or following disease progression on endocrine therapy is a favorable benefit-risk profile based on results from Study F2301 (MONALEESA-3). MONALEESA-3 was a randomized, double-blind, placebo-controlled phase 3 trial of ribociclib plus fulvestrant in postmenopausal and men. There were no pre- or perimenopausal women on the study. While men were allowed on the study, no men were randomized. Results of MONALEESA-3 showed there was a statistically significant and clinically meaningful improvement in progression-free survival (PFS) that favored the ribociclib plus fulvestrant treatment arm. The estimated median PFS in the ribociclib plus fulvestrant arm was 20.5 months compared to 12.8 months in the placebo plus fulvestrant arm (HR 0.593; 95% CI (0.480, 0.732), p <0.0001). Results of blinded independent central review (BICR), subgroup analyses, and sensitivity analyses all support the results of the primary efficacy endpoint. (b) (4)

Across MONALEESA-3 and MONALEESA-7, ribociclib was generally tolerable with adverse reactions managed with dose reductions, temporary treatment discontinuations, supportive therapies, and/or standard medical care. The most common adverse reaction across the clinical program was neutropenia, occurring in >70% of patients. There were very few cases of neutropenia fever and neutropenic sepsis. The number of QT interval prolongation events and increases in transaminases (AST and/or ALT) was higher in patients who received ribociclib across the clinical program. QT interval prolongation and hepatobiliary toxicity are currently labelled as Warnings and Precautions. Additional common adverse reactions with ribociclib include infections, leukopenia, headache, cough, nausea, fatigue, diarrhea, vomiting, constipation, alopecia, and rash. Except for neutropenia, AST/ALT increase, leukopenia, and hypertension, most adverse reactions were Grade 1 or 2 and the rates of treatment discontinuation due to adverse reactions ranged from 7-17%. The safety profile of this agent is acceptable for this patient population with a serious and life-threatening disease.

1.3. **Benefit-Risk Assessment**

Benefit-Risk Summary and Assessment

Breast cancer is the most common cancer diagnosed in women and the second leading cause of cancer related death in women in the US, with more than 260,000 new cases and more than 40,000 patients dying from breast cancer in the US in 2018.[1] Approximately 75% of patients experience a relapse after initial diagnosis of stage I-III disease.[2] It is projected that there will be more than 165,000 women living with MBC in the year 2020. Breast cancer in male patients is rare, with fewer than 1% of breast cancer diagnoses in male patients.

Metastatic breast cancer is categorized into different histopathological subtypes based on the expression of the estrogen receptor (ER), progesterone receptor (PR), and the human epidermal growth factor receptor 2 (HER2). Hormone receptor (HR)-positive, HER2-negative breast cancer is the most common subtype of breast cancer in both females and males. Many patients are diagnosed and treated at an early stage with a combination of surgery and endocrine therapy, with or without radiation and/or chemotherapy.

Despite treatment of early-stage disease, approximately one-third of patients develop recurrent disease, including metastatic disease.[3] The initial therapy for HR-positive, HER2-negative metastatic disease is endocrine-based, typically with an aromatase inhibitor with or without a CDK4/6 inhibitor, tamoxifen for premenopausal women, or fulvestrant. However, not all patients respond to first-line therapy due to primary or *de novo* resistance. In the second-line setting, fulvestrant with or without a CDK4/6 inhibitor or chemotherapy are commonly used treatment options. Metastatic breast cancer is incurable and has a 5-year survival rate of approximately 25%.[4] Improving the outcomes of patients with metastatic disease is an unmet medical need.

The applicant submitted a supplemental new drug application (sNDA) for ribociclib for a proposed indication (b) (4) [redacted]

Ribociclib is an oral selective small molecule inhibitor of cyclin dependent kinase 4 (CDK4) and cyclin dependent kinase 6 (CDK6). Ribociclib inhibits Rb phosphorylation and blocks the progression from G1 to the S phase in the cell cycle leading to inhibition of tumor growth in preclinical models in the short term and with sustained target inhibition, the rebound of Rb phosphorylation is inhibited preventing cell cycle re-entry and leads to tumor senescence and apoptosis.

The benefit-risk assessment in this sNDA is primarily based on two phase 3 studies E2301 (MONALEESA-7) of ribociclib in combination with an

NSAI and goserelin in pre/perimenopausal women and MONALEESA-3 of ribociclib in combination with fulvestrant. Study E2301 (MONALEESA-7) was a randomized, double-blind, placebo-controlled trial in pre/peri-menopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer with no prior systemic therapy in this disease setting. This was a well-designed trial with an appropriate comparator arm. The primary endpoint was investigator-assessed progression-free survival (PFS) using RECIST 1.1 criteria. The estimated median PFS in the ribociclib plus NSAI plus goserelin arm was 27.5 months compared with 13.8 months in the placebo plus NSAI plus goserelin arm (HR=0.569, 95% CI: 0.436-0.743). Results from a BICR audit, subgroup analyses, and sensitivity analyses all supported the primary efficacy endpoint results. Overall survival (OS) data are immature. Analyses of the safety profile of ribociclib in combination with tamoxifen and goserelin in E2301 showed the mean QTcF increase from baseline was $\geq$10 msec in the tamoxifen plus placebo subgroup compared with the NSAI plus placebo subgroup. An increase of >60 msec from baseline in the QTcF interval was observed in 14/87 (16 %) of patients in the ribociclib and tamoxifen combination and in 18/245 (7%) of patients receiving ribociclib plus an NSAI. In the placebo arm, an increase of >60 msec from baseline occurred in 6/90 (7%) of patients receiving tamoxifen, and in no patients receiving an NSAI. Given the QT prolongation safety signal, the risk outweighed the benefit in this study arm and the applicant chose not to seek an indication with tamoxifen.

Study F2301 (MONALEESA-3) was a randomized, double-blind, placebo-controlled trial in patients with HR-positive, HER2-negative advanced or metastatic breast cancer who have received no or only one line of prior endocrine treatment. This was a well-designed trial with an appropriate comparator arm. The primary endpoint was investigator-assessed PFS using RECIST 1.1 criteria. The estimated median PFS in the ribociclib plus fulvestrant arm was 20.5 months compared with 12.8 months in the placebo plus fulvestrant arm (HR=0.593, 95% CI: 0.480-0.732, p<0.0001). Results from a BICR audit, subgroup analyses, and sensitivity analyses all supported the primary efficacy endpoint results. Overall survival (OS) data are immature. The applicant requested further extension of the indication to also include ribociclib in combination with fulvestrant for initial endocrine-based therapy in the metastatic setting, based on the 575 endocrine-naïve patients (in the metastatic setting) that enrolled in the study. The estimated median PFS in the ribociclib plus fulvestrant arm for this subgroup of patients was 20.7 months compared with 12.9 months in the placebo plus fulvestrant arm (HR 0.616., 95% CI: 0.487 - 0.780).

Overall, ribociclib was generally tolerable with adverse reactions that were managed by dose reductions, temporary treatment discontinuations, and/or supportive medications and standard medical care. Neutropenia was the most common adverse event across the clinical program with 78% of patients on the NSAI arm experiencing neutropenia in study E2301 and 69% of patients in study F2301. Neutropenia is listed as a Warnings and Precautions in the USPI.

The number of QT interval prolongation events and increases in transaminases (AST and/or ALT) was higher in patients who received ribociclib across the clinical program. QT interval prolongation and hepatobiliary toxicity are currently labeled as Warnings and Precautions. Additional common adverse reactions with ribociclib include infections, leukopenia, headache, cough, nausea, fatigue, diarrhea, vomiting, constipation,

alopecia, and rash.

(b) (4)

In conclusion, ribociclib in combination with NSAI and goserelin in pre/perimenopausal women demonstrated a statistically significant improvement in PFS in a large, randomized, double blind study. The indication was broadened to include the class of aromatase inhibitor agents as these agents are used interchangeably in clinical practice and did not demonstrate any new safety signal or drug interaction when used with ribociclib. Ribociclib in combination with fulvestrant also demonstrated a statistically significant improvement in PFS in a large, randomized, double blind study in the first line setting and following disease progression on endocrine therapy in postmenopausal women. Therefore, the benefit-risk profile is favorable to support approval of:

KISQALI is a kinase inhibitor indicated in combination with:

- *an aromatase inhibitor for the treatment of pre/perimenopausal or postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer, as initial endocrine-based therapy; or*
- *fulvestrant for the treatment of postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer, as initial endocrine based therapy or following disease progression on endocrine therapy.*

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• In 2018 it is estimated that there are over 260,000 new cases of breast cancer in the US. MBC is incurable and has a 5-year survival of approximately 25%.	**Locally advanced and metastatic breast cancer are serious and life-threatening conditions.**
Current Treatment Options	• The goals of treating MBC and locally advanced unresectable breast cancer are palliative in nature with the aim to prolong survival and to reduce cancer-related symptoms. Endocrine therapy options for postmenopausal women with HR-positive, HER2-negative MBC include aromatase inhibitors (AIs) such as anastrozole, letrozole, and	**There is an unmet medical need to improve the outcomes of patients with HR-positive, HER2-negative advanced or metastatic breast cancer.**

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	exemestane, and the estrogen receptor downregulator fulvestrant. For pre/perimenopausal women tamoxifen or ovarian suppression with an AI are treatment options.	
Benefit	• Study E2301 (MONALEESA-7) was a randomized, double-blind, placebo-controlled trial in pre/peri-menopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer with no prior systemic therapy in this disease setting. The primary endpoint was investigator-assessed progression-free survival (PFS). The estimated median PFS in the ribociclib plus NSAI plus goserelin arm was 27.5 months compared with 13.8 months in the placebo plus NSAI plus goserelin arm (HR=0.569, 95% CI: 0.436-0.743). Overall survival (OS) data are immature. • Study F2301 (MONALEESA-3) was a randomized, double-blind, placebo-controlled trial in patients with HR-positive, HER2-negative advanced or metastatic breast cancer who have received no or only one line of prior endocrine treatment. The primary endpoint was investigator-assessed progression-free survival (PFS). The estimated median PFS in the ribociclib plus fulvestrant arm was 20.5 months compared with 12.8 months in the placebo plus fulvestrant arm (HR=0.593, 95% CI: 0.480-0.732, p<0.0001). Overall survival (OS) data are immature. There were 575 endocrine-naïve patients that enrolled in the MONALEESA-3 study. The estimated median PFS in the ribociclib plus fulvestrant arm for this subgroup of patients was 20.7 months compared with 12.9 in the placebo plus fulvestrant arm (HR 0.616, 95% CI 0.487 - 0.780).	**Evidence of effectiveness was supported by a statistically significant and clinically meaningful PFS improvement with the addition of ribociclib to NSAI plus goserelin for pre/perimenopausal women in MONALEESA-7 and ribociclib to fulvestrant in MONALEESA-3, which were both large, double-blind, randomized, placebo-controlled trials. Additionally, ribociclib previously demonstrated a statistically significant and clinically meaningful improvement in PFS in the MONALEESA-2 trial as well, further supporting the evidence of benefit of the addition of this agent to endocrine based therapy. Supportive ORR, blinded independent central review (BICR)-assessed PFS, and subgroup analyses further substantiate the evidence of ribociclib benefit. Despite immature OS, in this population, the substantial improvement in PFS represents a clinically meaningful benefit due to the delay of progression and postponement of subsequent toxic therapies.**

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• Neutropenia was the most common adverse event across the clinical program with 78% of patients on the NSAI arm experiencing neutropenia in MONALEESA-7 and 69% of patients in MONALEESA-3. • Risk of QT prolongation in patients who received tamoxifen and ribociclib. • Men were eligible on MONALEESA-3 but no men were randomized. (b) (4) • There is no proposal or indication for a risk management plan.	**The safety profile of ribociclib in combination with NSAI or fulvestrant is acceptable for the intended population. Toxicities were manageable with appropriate treatment interruption and/or dose modifications which are clearly delineated in labeling. Warnings and Precautions in labeling detail the serious risks of the drug.** **Ribociclib is not indicated for concomitant use with tamoxifen. Warnings and precausions details the potential QT risk of ribociclib and tamoxifen.** **The safe use of ribociclib plus NSAI or fulvestrant can be managed through accurate labeling and routine oncology care. No REMS is indicated.**

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

x	The patient experience data that was submitted as part of the application, include:				Section where discussed, if applicable
	x	Clinical outcome assessment (COA) data, such as			[e.g., Section 6.1 Study endpoints]
			x	Patient reported outcome (PRO)	7.1.2
			□	Observer reported outcome (ObsRO)	

			□	Clinician reported outcome (ClinRO)	
			□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)			
	□	Patient-focused drug development or other stakeholder meeting summary reports			[e.g., Section 2.1 Analysis of Condition]
	□	Observational survey studies designed to capture patient experience data			
	□	Natural history studies			
	□	Patient preference studies (e.g., submitted studies or scientific publications)			
	□	Other: (Please specify)			
□	Patient experience data that was not submitted in the application, but was considered in this review.				

Laleh Amiri-Kordestani, MD

Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

Breast cancer is the most common form of cancer affecting women, accounting globally for 25% of all cancers and approximately 15% of all cancer deaths (Ferlay et al 2015). Conversely, breast cancer in men is relatively rare, with approximately 1% of all breast cancers in the US and globally occurring in men (Giordano et al 2004, Sasco et al 1993).

Breast cancer is currently the second most common cause of cancer death in more developed regions, following lung cancer (GLOBOCAN 2012). In 2018 in the United States, it was estimated that 40,920 women would die of breast cancer, and 266,120 new cases would be diagnosed (SEER Cancer Statistics Factsheet 2018). Worldwide, the number of new cases of breast cancer per year is estimated to be 1.67 million; of those, 494,076 are in Europe (GLOBOCAN 2012).

Breast cancer is a phenotypically diverse disease, the predominant subtype being the one whose tumor cells overexpress estrogen and/or progesterone receptors. Expression of the estrogen receptor (ER) and/or progesterone receptor (PgR) is one of the most important prognostic factors in invasive breast cancer (Dunnwald et al 2007, Bae et al 2015).

Approximately 70% of invasive breast cancers in women >45 years of age express ER and/or PgR, but not HER2, and are termed hormone receptor-positive (HR-positive), Human epidermal growth factor receptor 2 (HER2-negative) (Huang et al 2005). The biology of male breast cancer resembles that of postmenopausal female breast cancer, i.e., it occurs later in life with tumors that are typically HR-positive and HER2-negative (Anderson et al 2004, Anderson et al 2006, Ottini et al 2010).

Breast cancer is strongly related to age, and the highest incidence rates are found in older, postmenopausal women. Locally advanced and metastatic diseases are more frequently diagnosed in women at older ages. In the EU in 2008-2012 the incidence rate per 100,000 population-years among women of HR-positive, HER2-negative advanced breast cancer (aBC) was 6.6 in premenopausal women and 24.0 in postmenopausal women. The 5-year prevalence per 100,000 of HR-positive, HER2-negative in the EU was 13.9 in premenopausal women and 39.6 postmenopausal women (Jemal et al 2011).

Younger women with breast cancer have poorer survival despite receiving more intensive treatment as compared to older women (Anders et al 2008). This seeming contradiction may be related to differences in tumor biology and/or host differences between younger and older women. In fact, it has been reported that HR-positive breast cancer in premenopausal women is molecularly distinct and a more aggressive disease than HR-positive breast cancer in postmenopausal women, including changes in gene expression and somatic mutation patterns (Liao et al 2015), and is the leading cause of cancer death in women 20 to 59 years old (Benz 2008).

The FDA's Assessment:
FDA agrees with the applicant's assessment of breast cancer.

2.2. **Analysis of Current Treatment Options**

The Applicant's Position:
Advanced breast cancer is incurable, and therefore is considered a serious and life-threatening condition. The treatment goals in patients with aBC are to reduce tumor size, slow or delay progression and metastasis, prolong overall survival (OS), reduce complications, and optimize quality of life (QoL). Endocrine therapy is the core treatment modality for patients with HR-positive aBC and chemotherapy is recommended for cases that rapidly progressed or proven endocrine- resistance disease. However, the usefulness of estrogen deprivation is limited (median PFS benefit is only approximately 10-14 months in first line setting and approximately 5 to 6 months with second line treatment), since eventually resistance to therapy develops and poses serious clinical challenges. Thus, there is an unmet medical need to develop new therapies for the treatment of aBC.

Sequential endocrine therapy with alternative endocrine regimens or combination regimens with target agents aimed at multiple pathways is the preferred treatment for women with HR-positive, HER2-negative metastatic breast cancer. Cyclin-dependent kinase 4/6 inhibitors, which affect cell cycle progression by halting tumor growth, are an exciting new direction for the treatment of HR-positive breast cancer. To date, there are three approved CDK 4/6 inhibitors for the treatment of HR-positive, HER2-negative advanced or metastatic breast cancer: palbociclib, ribociclib, and abemaciclib.

Based on current treatment guidelines, tamoxifen is an approved standard endocrine therapy for use as initial therapy in pre- and perimenopausal women with HR positive, HER2 negative, aBC, often in combination with ovarian function suppression (OFS) agents (NCCN breast cancer guidelines Ver. 1.2018). Premenopausal women with advanced HR-positive breast cancer can also be treated with aromatase inhibitors (AIs) (e.g. letrozole, anastrozole, or exemestane).

Treatment options for postmenopausal women with HR-positive, HER2-negative aBC include selective estrogen receptor modulators (e.g. tamoxifen), estrogen receptor antagonists (e.g. fulvestrant), selective non-steroidal aromatase inhibitors (NSAIs; e.g. letrozole and anastrozole), steroidal AIs (e.g. exemestane), mTOR inhibitor combined with an endocrine agent (e.g. everolimus plus exemestane) and CDK4/6 inhibitors in combination with an endocrine agent (Cardoso et al 2017). The preferred first-line and second-line endocrine therapy for postmenopausal women with HR-positive, HER2-negative aBC depends on the previous disease presentation and treatment, including type and duration of adjuvant endocrine therapy or agent used in the advanced setting.

There are infrequent published prospective therapeutic studies of breast cancer treatments in men and consequently, treatment for metastatic breast cancer is based on the same principles

as in women, relying primarily on the extrapolation of clinical trial data from female patients.

Table 2-1: Summary of Treatment Armamentarium Relevant to Proposed Indication

Product(s) Name	Relevant Indication	Year of Approval And Type of Approval*	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
CDK 4/6 inhibitors						
Palbociclib (IBRANCE)	IBRANCE is a kinase inhibitor indicated for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with: an aromatase inhibitor as initial endocrine based therapy in postmenopausal women; or fulvestrant in women with disease progression following endocrine therapy.	2015,2016, 2017	Recommended starting dose: 125 mg once daily taken with food for 21 days followed by 7 days off treatment Capsules are taken orally with food in combination with an aromatase inhibitor or fulvestrant	Palbociclib plus letrozole vs. placebo plus letrozole PFS 24.8 vs. 14.5 months HR 0.576 (p<0.0001) vs. placebo plus fulvestrant (+ goserelin in pre- and perimenopausal patients) PFS 9.5 vs. 4.6 months; HR 0.461 (p<0.0001)	Most common adverse reactions (incidence ≥10%) were neutropenia, infections, leukopenia, fatigue, nausea, stomatitis, anemia, alopecia, diarrhea, thrombocytopenia, rash, vomiting, decreased appetite, asthenia, and pyrexia.	
Ribociclib (KISQALI)	Proposed indication: (b) (4)	2017	Recommended starting dose: 600 mg orally (three 200 mg tablets) taken once daily with or without food for 21 consecutive days followed by 7 days off treatment. KISQALI tablets are taken orally with or without food in combination with an aromatase inhibitor or fulvestrant.	Ribociclib plus letrozole vs. placebo plus letrozole PFS: 25.3 vs. 16 months HR 0.556 ($p = 1.07\times10^{-4}$)	Most common adverse reactions (incidence ≥ 20%) are neutropenia, nausea, infections, fatigue, diarrhea, leukopenia, vomiting, alopecia, headache, constipation, rash, and cough	

	(b) (4)					
Abemaciclib (VERZENIO)	VERZENIO is a kinase inhibitor indicated: • in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer. • In combination with fulvestrant for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2) negative advanced or metastatic breast cancer with disease progression following endorcrine therapy • as monotherapy for the treatment of adult patients with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting	2018	VERZENIO tablets are taken orally with or without food Recommended starting dose in combination with fulvestrant or an aromatase inhibitor: 150 mg twice daily. Recommended starting dose as monotherapy: 200 mg twice daily	Abemaciclib plus fulvestrant vs. placebo plus fulvestrant PFS: 16.4 vs. 9.3 months HR 0.553 (p<0.0001) Abemaciclib as a monotherapy ORR 19.7%, DoR 8.6 months Abemaciclib plus AI (anastrozole or letrozole) vs. placebo plus AI PFS: 28.2 vs. 14.8 months HR 0.540 (p<0.0001)	Most common adverse reactions (incidence ≥20%) were diarrhea, neutropenia, nausea, abdominal pain, infections, fatigue, anemia, leukopenia, decreased appetite, vomiting, headache, alopecia, and thrombocytopenia	
Other Treatments – Aromatase inhibitors						
Letrozole (Femara)	Femara is an aromatase inhibitor indicated for:	1997	Recommended dose: 2.5.mg	vs. tamoxifen TTP: 9.4 vs.	The most common adverse	

	Adjuvant treatment of postmenopausal women with hormone receptor positive early breast cancer Extended adjuvant treatment of postmenopausal women with early breast cancer who have received prior standard adjuvant tamoxifen therapy First and second-line treatment of postmenopausal women with hormone receptor positive or unknown advanced breast cancer		once daily Femara tablets are taken orally without regard to meals	6.0 months – HR 0.72 (p<0.0001) OS: 35 vs. 32 months (p=0.5136)	reactions (greater than 20%) were hot flashes, arthralgia; flushing, asthenia, edema, arthralgia, headache, dizziness, hypercholesterolemia, sweating increased, bone pain; and musculoskeletal	
Anastrozole (Arimidex)	ARIMIDEX is an aromatase inhibitor indicated for: • Adjuvant treatment of postmenopausal women with hormone receptor-positive early breast cancer • First-line treatment of postmenopausal women with hormone receptor-positive or hormone receptor unknown locally advanced or metastatic breast cancer • Treatment of advanced breast cancer in postmenopausal women with disease progression following tamoxifen therapy. Patients with ER-negative disease and patients who did not respond to previous tamoxifen therapy	1995	One 1 mg tablet taken once daily	vs. tamoxifen TTP: 11.1 vs. 5.6 months (p=0.006) and TTP: 8.2 vs. 8.3 months (p=0.92)	In the early breast cancer (ATAC) study, the most common (occurring with an incidence of ≥10%) side effects occurring in women taking ARIMIDEX included: hot flashes, asthenia, arthritis, pain, arthralgia, pharyngitis, hypertension, depression, nausea and vomiting, rash, osteoporosis, fractures, back pain, insomnia, headache, peripheral edema and lymphedema, regardless of causality. In the advanced breast cancer studies, the most common (occurring with an incidence of >10%) side effects occurring	

	rarely responded to ARIMIDEX				in women taking ARIMIDEX included: hot flashes, nausea, asthenia, pain, headache, back pain, bone pain, increased cough, dyspnea, pharyngitis and peripheral edema.	
Exemestane (Aromasin)	AROMASIN is an aromatase inhibitor indicated for: • adjuvant treatment of postmenopausal women with estrogen-receptor positive early breast cancer who have received two to three years of tamoxifen and are switched to AROMASIN for completion of a total of five consecutive years of adjuvant hormonal therapy • treatment of advanced breast cancer in postmenopausal women whose disease has progressed following tamoxifen therapy	1999	Recommended Dose: One 25 mg tablet once daily after a meal	vs. megestrol acetate TTP: 20.3 vs. 16.6 weeks (HR 0.84)	Early breast cancer: Adverse reactions occurring in ≥10% of patients in any treatment group (AROMASIN vs. tamoxifen) were hot flushes (21.2% vs. 19.9%), fatigue (16.1% vs. 14.7%), arthralgia (14.6% vs. 8.6%), headache (13.1% vs. 10.8%), insomnia (12.4% vs. 8.9%), and increased sweating (11.8% vs. 10.4%). Advanced breast cancer: Most common adverse reactions were mild to moderate and included hot flushes (13% vs. 5%), nausea (9% vs. 5%), fatigue (8% vs. 10%), increased sweating (4% vs. 8%), and increased appetite (3% vs. 6%) for AROMASIN and megestrol acetate, respectively	
mTOR inhibitor						

Everolimus (Afinitor)	AFINITOR is a kinase inhibitor indicated for the treatment of: • postmenopausal women with advanced hormone receptor-positive, HER2-negative breast cancer (advanced HR+ BC) in combination with exemestane after failure of treatment with letrozole or anastrozole	2009	10 mg once daily with or without food.	vs. placebo plus exemestane PFS: 7.8 vs. 3.2 months HR 0.45 (p<0.001)	The most common adverse reactions (incidence ≥ 30%) were: stomatitis, infections, rash, fatigue, diarrhea, and decreased appetite.	
Estrogen receptor modulator						
Fulvestrant (Faslodex)	FASLODEX is an estrogen receptor antagonist indicated for the: Treatment of hormone receptor (HR)-positive, human epidermal growth receptor 2 (HER2)-negative advanced breast cancer in postmenopausal women not previously treated with endocrine therapy. Treatment of HR-positive advanced breast cancer in postmenopausal women with disease progression following endocrine therapy. Treatment of HR-positive, HER2-negative advanced or metastatic breast cancer in combination with palbociclib in women with disease progression after endocrine therapy.	2002	FASLODEX 500 mg should be administered intramuscularly into the buttocks (gluteal area) slowly (1 - 2 minutes per injection) as two 5 mL injections, one in each buttock, on days 1, 15, 29 and once monthly thereafter. A dose of 250 mg is recommended in patients with moderate hepatic impairment to be administered intramuscularly into the buttock (gluteal area) slowly (1 - 2 minutes) as one 5 mL injection on days 1, 15, 29 and once monthly thereafter	vs. anastrozole PFS: 16.6 vs. 13.8 HR 0.797 (0.049)	The most common adverse reactions occurring in ≥5% of patients receiving FASLODEX 500 mg were: injection site pain, nausea, bone pain, arthralgia, headache, back pain, fatigue, pain in extremity, hot flash, vomiting, anorexia, asthenia, musculoskeletal pain, cough, dyspnea, and constipation	

Tamoxifen (Nalvadex)	Metastatic Breast Cancer: NOLVADEX is effective in the treatment of metastatic breast cancer in women and men. Adjuvant Treatment of Breast Cancer: NOLVADEX is indicated for the treatment of node-positive breast cancer in postmenopausal women following total mastectomy or segmental mastectomy, axillary dissection, and breast irradiation. NOLVADEX is indicated for the treatment of axillary node-negative breast cancer in women following total mastectomy or segmental mastectomy, axillary dissection, and breast irradiation.	1977	For patients with breast cancer, the recommended daily dose is 20-40 mg. Dosages greater than 20 mg per day should be given in divided doses (morning and evening).	Response rate in 14 Phase II studies and 9 literature reports. Overall database included 1164 patients	Most frequent ADRs: nausea, fluid retention, vaginal bleeding/discharge, skin rash, hot flashes, and fatigue Other concerns: ischemic cerebrovascular and thromboembolic events	

The FDA's Assessment:

FDA agrees with the applicant's assessment of current treatment options for HR+, HER2-negative advanced/metastatic breast cancer.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:
KISQALI (ribociclib) was approved by the FDA on March 13, 2017 for use in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer.

Kisqali Femara CO-PACK was approved on May 4, 2017 as initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer.

The FDA's Assessment:
FDA agrees with the applicant's history of the approval of ribociclib (NDA 209092) and the Kisqali Femara CO-PACK (NDA 209935).

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:
July 27, 2010: (b) (4)

May 31, 2013: IND 117796 for LEE011 was submitted to FDA for the treatment of adult women with locally advanced or metastatic ER+/HER2- breast cancer.

October 2, 2014: An End-of-Phase 2 meeting was held between Novartis and FDA to discuss the design of pivotal study CLEE011E2301.

October 8, 2014: The protocol for study CLEE011E2301 (MONALEESA-7) was submitted to IND 117,796 (Seq No. 0328).

March 26, 2015: An End-of-Phase 2 meeting was held between Novartis and FDA to discuss the design of pivotal study CLEE011F2301.

March 30, 2015: The protocol for study CLEE011F2301 (MONALEESA-3) was submitted to IND 117,796 (Seq No. 0463).

August 2, 2016: FDA granted breakthrough therapy designation based on the fact that breast cancer meets the criteria for a serious or life-threating disease and the preliminary clinical evidence generated by Study A2301 appeared to demonstrate substantial improvement in PFS compared with existing therapies.

August 29, 2016: NDA 209092 was submitted to FDA.

March 13, 2017: KISQALI (ribociclib) was approved for use in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer.

04-May-2017: Kisqali Femara co-pack was approved as initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor –positive, human epidermal growth factor receptor 2-negative advanced or metastatic breast cancer.

June 30, 2017: FDA provided responses to questions contained in the Type C Meeting background packaged dated June 9, 2017. The purpose of the requested meeting was to discuss and obtain agreement on the overall strategy for a dossier to support an expanded indication ribociclib based on the pivotal studies CLEE011E2301 and CLEE011F2301. Briefly, FDA agreed to the content of the submission package, the proposed clinical package, statistical methodology and proposed analyses for both pivotal studies, pooling strategy for the summaries of clinical efficacy and safety, the proposed clinical pharmacology package, proposal for submission of patient narratives and CRFs, proposal for electronic dataset submission, and provided further guidance on the OSI requests needed to support potential FDA inspections of clinical sites. The scheduled Type C meeting for July 14, 2017 was subsequently cancelled.

December 8, 2017: Breakthrough therapy designation was granted as FDA determined that Kisqali® (ribociclib) as initial endocrine-based therapy for the treatment of pre- or perimenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with tamoxifen or an aromatase inhibitor.

January 18, 2018: A Type B Pre-NDA meeting was held between Novartis and the FDA. The purpose of the meeting was to share the results of study CLEE011E2301 and obtain agreement from the FDA that the data analyses and overall presentation of data were adequate to support a supplemental NDA based on study CLEE011E2301. FDA agreed with a majority of points raised by Novartis and provided further guidance on the necessity of a 90/120 day safety update. FDA also agreed with presentation of further QTc information.

April 6, 2018: Kisqali sNDA based on studies E2301/F2301 considered for Real-time Review pilot program with the Division of Oncology Products 1. Novartis accepts participation in Real-time Review; schedule for submissions and FDA/sponsor teleconference schedule established.

April 17, 2018: FDA provided responses to questions contained in the Type B Meeting background package dated March 24, 2018. The purpose of the meeting was to share the results of study CLEE011F2301 and obtain agreement from the FDA that the data analyses and overall presentation of data were adequate to support a supplemental NDA based on studies CLEE011E2301 and CLEE011F2301.

April 27, 2018: [redacted] (b) (4).

June 28, 2018: Complete sNDA submission based on studies E2301/F2301 completed.

Real-time review initiative- NDA 209092 Supplement submission

This efficacy supplement to NDA 209092 participated in the Real-time Review FDA pilot program with submission of dossier components provided prior to the full sNDA submission. Teleconferences were scheduled every two weeks starting May 14, 2018 until July 2, 2018 and a schedule for submission of dossier components was also established. The first set of materials was sent to FDA on April 30, 2018, followed by additional information on May 18 and May 31, 2018.

The FDA's Assessment:

FDA agrees with the pre-submission regulatory activity from August 2, 2016 onward, as stated by the applicant above. FDA did not independently verify the information/dates for regulatory activity before August 2, 2016 listed above.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The FDA's Assessment:

No clinical sites were inspected for this sNDA.

4.2. Product Quality

The FDA's Assessment:

Not applicable

4.3. Clinical Microbiology

The FDA's Assessment:

Not applicable

4.4. Devices and Companion Diagnostic Issues

The FDA's Assessment:

Not applicable

5 Clinical Pharmacology

5.1. Executive Summary

The FDA's Assessment:

The proposed ribociclib dosing regimen is 600 mg (200 mg × 3 tablets) orally once daily with or without food for 21 consecutive days followed by 7 days off treatment in combination with an aromatase inhibitor or fulvestrant in a complete treatment cycle of 28 days. The evidence of efficacy was supported by three phase 3, randomized double-blind, placebo-controlled trials: Study F2301 (MONALEESA-3), E2301 (MONALEESA-7) and A2301 (MONALEESA-2). This review will only cover Study F2301 (in combination with fulvestrant) and Study E2301 (in combination with a non-steroidal aromatase inhibitor (NSAI) or tamoxifen and goserelin). Study A2301 (in combination with letrozole) was reviewed with the original NDA submission. The key review questions focus on the appropriateness of ribociclib dose in the general patient population and the recommendations for ribociclib dose in patients with severe renal impairment.

Recommendations

The Office of Clinical Pharmacology has reviewed the information contained in sNDA 209092 Supplement 1. This sNDA is approvable from a clinical pharmacology perspective. The key review issues with the specific recommendations/comments are summarized below:

Review Issue	Recommendations and Comments
Pivotal and Supportive evidence of effectiveness	The primary evidence of effectiveness comes from a phase 3 Study F2301 (ribociclib + fulvestrant) and a phase 3 Study E2301 (ribociclib + NSAI).
General dosing instructions	Only ribociclib 600 mg starting dose was studied in the phase 3 Studies. The proposed ribociclib dosing regimen of 600 mg orally once daily is efficacious and appears to have a manageable safety profile.
Dosing in patient subgroups (intrinsic and extrinsic factors)	A starting dose reduction to 200 mg is recommended for patients with severe renal impairment.
Coadministrated fulvestrant or tamoxifen	Ribociclib was administrated in combination with fulvestrant. There is no clinically relevant drug interaction between fulvestrant and ribociclib. No dose adjustment is recommended. Ribociclib was administrated in combination with tamoxifen. Tamoxifen Cmax and AUC increased approximately 2-fold following coadministration with ribociclib. Ribociclib is not indicated for concomitant use with tamoxifen due to prolongation of the QTcF interval.
Labeling	Generally acceptable. The review team has specific content and formatting change recommendations.

5.2. **Summary of Clinical Pharmacology Assessment**

5.2.1. **Pharmacology and Clinical Pharmacokinetics**

The Applicant's Position:

The clinical pharmacology of ribociclib has been well characterized and results were submitted in the initial New Drug Application. The data in the original submission included data of single-dose pharmacokinetics (PK) in healthy subjects, multiple-dose PK in patients with advanced solid tumors, including patients with HR-positive, HER2-negative aBC, mass balance (absorption, distribution, metabolism, and excretion), drug-drug interactions (DDIs), exposure-response/safety relationships, bioequivalence and relative bioavailability of formulations, cardiac safety, food effects on PK, PK in special populations (hepatic and renal impairment), and population PK in patients. Refer to the original NDA submission for ribociclib PK characterization. The NDA supplement includes clinical pharmacology data supporting the proposed dose regimen in the general population, PK characterization in special poulations (moderate/severe hepatic and severe renal impairment) and the dose recommendation, updated population PK in patients, updated food-drug interaction, and DDI with combination partners.

The FDA's Assessment:

FDA agrees with the applicant's ribociclib PK and ADME characterization. The information provided in this sNDA submission is the same as that from the original NDA 209092 (SDN 1) submission. Please refer to the original NDA multi-disciplinary review and evaluation for the FDA's assessment.

5.2.2. **General Dosing and Therapeutic Individualization**

5.2.2.1. General Dosing

The Applicant's Position:

Two Phase III studies (E2301 and F2301) evaluated ribociclib 600 mg. Selection of the ribociclib dose and regimen (600 mg daily on Days 1 to 21 of a 28-day cycle) was based on results from the first inhuman study of single agent ribociclib (Study X2101) and was also consistent with the previously approved dosing schedule used in combination with letrozole in the registration Study A2301 in patients with advanced breast cancer.

The recommended dose of ribociclib is 600 mg (3 x 200 mg film-coated tablets) taken orally, once daily for 21 consecutive days followed by 7 days off treatment resulting in a complete cycle of 28 days. Kisqali can be taken with or without food.

The FDA's Assessment:

FDA agrees with the applicant's proposed starting dose. The efficacy of ribociclib was only studied at the 600 mg QD starting dose. The proposed dose is effective and has a manageable safety profile. PMR 3168-1 was proposed to the applicant under the original NDA 209092 to evaluate an alternative dosing regimen in a future trial. See the original NDA 209092 multi-disciplinary review and evaluation as well as the applicant's outstanding issue PMR-3168-1 in this review for details.

5.2.2.2. Therapeutic Individualization

The Applicant's Position:

Specific populations:

Patients with hepatic impairment: Ribociclib was evaluated in subjects with hepatic impairment in study A2109. The results from this study indicate no ribociclib dose adjustment is warranted for patients with mild hepatic impairment (Child-Pugh A), while a dose reduction to 400 mg in patients with moderate (Child-Pugh B) and severe hepatic impairment (Child-Pugh C) is recommended

Results of an interim analysis of this study was submitted in the original NDA. The results of the final analysis indicated that ribociclib exposure was similar in subjects with mild hepatic impairment and those with normal hepatic function. Ribociclib AUClast and AUCinf were approximately 30% higher in subjects with moderate and severe hepatic impairment compared to subjects with normal hepatic function. Ribociclib at a dose of 400 mg was generally well tolerated in subjects with varying degrees of hepatic impairment.

Patients with renal impairment: There is no dose recommendation change for mild and moderate renal impairment since the original NDA submission which was based on population PK analysis.

In Study A2116, the pharmacokinetics and safety of a single 400 mg oral dose of ribociclib is being evaluated in non-cancer subjects with varying degrees of impaired renal function compared to matched healthy volunteers with normal renal function. Results from Part I (severe renal impairment compared to normal renal function) of the study demonstrated that ribociclib exposure was significantly higher in subjects with severe renal impairment (1.96-fold increase in AUCinf and 1.51-fold increase in Cmax) compared to exposure in subjects with normal renal function. Considering the approximately 2-fold increase in exposure, a reduced dose of 200 mg ribociclib is recommended in patients with severe renal impairment.

Drug-drug interactions:

Co-administration of ribociclib and its combination partners - anastrozole, letrozole, fulvestrant and tamoxifen:

Ribociclib was co-administered with anstrazole and letrozole or tamoxifen in study E2301 and with fulvestrant in study F2301. No DDI was apparent when ribociclib was concomitantly used with anastrozole or letrozole. Ribociclib exposure was consistent with historical single-agent data. Anastrozole and letrozole exposure data were comparable between the ribociclib 600-mg and the placebo arm. Fulvestrant showed no effect on ribociclib PK based on data in Study F2301, which was consistent with historical single-agent data. There are no known drug interactions with fulvestrant. Therefore, DDI was not anticipated between ribociclib and fulvestrant. Based on the population PK analysis, concomitant use of letrozole, anastrozole, or fulvestrant had no statistically significant or clinically relevant impact on ribociclib exposure.

For ribociclib and tamoxifen combination, ribociclib exposure (AUC) was estimated to be reduced by 26.7% (95% CI: 16.6, 35.2) in combination with 20 mg tamoxifen based on population PK analysis, and tamoxifen exposure (AUC and Cmax) was approximately 2-fold higher when administered with 600 mg ribociclib as compared to placebo in Study E2301. However, the changes in ribociclib exposure was not considered to be clinically relevant as patients who were dose reduced from the starting dose of 600 mg to lower doses had a PFS benefit and dose reduction had no impact on the response rate.

Based on both ΔQTcF and PK data observed in Study E2301, the higher ΔQTcF values in patients receiving ribociclib plus tamoxifen compared to NSAI or fulvestrant can be contributed by the QTcF prolongation effect of tamoxifen. Based on an imbalance in increased QTcF values and higher ΔQTcF observed in the ribociclib plus tamoxifen subgroup, Novartis does not propose to include the ribociclib and tamoxifen combination in the proposed indication (please see details in Section 0).

The FDA's Assessment:

FDA agrees with the applicant's proposed starting dose adjustments in patients with hepatic or renal impairment. The applicant submitted Study A2116 results in non-cancer subjects with severe renal impairment. The proposed 200 mg ribociclib starting dose is acceptable based on the clinical study outcome (approximately 2-fold increase in AUC in subjects with severe renal impairment comparing to that from subject with normal renal function) and ribociclib tablets strength of 200 mg. For patients with mild or moderate renal impairment or patients with hepatic impairment, the proposed dose adjustment is the same as the original NDA submission. The applicant updated the Study A2109 interim analysis in the original NDA with the final analysis in this submission. There are no clinical relevant differences between the results of the interim analysis and the final analysis. FDA conducted its own analyses and agrees with the applicant's DDI evaluation between ribociclib and its combination partners (anastrozole, letrozole, fulvestrant and tamoxifen). FDA agrees with the applicant's proposal of not including the ribociclib and tamoxifen combination in the proposed indication due to QTcF prolongation.

5.2.2.3. Outstanding Issues

The Applicant's Position:

Per original NDA approval, the following PMR/PMCs (b) (4)

PMR 3168-1 for studying alternate dosing regimen to mitigate QT prolongation risk after evaluation of Monaleesa-7 and 3 study results is (b) (4)

PMR 3168-1 (below): the protocol design will be discussed with the FDA.

Conduct a clinical trial to assess the efficacy and safety of an alternative dosing regimen for ribociclib after evaluation of ECG, PK and efficacy data from ongoing MONALEESA-3 (CLEE011F2301) and MONALEESA-7 (CLEE011E2301) studies. The objective of studying an alternative dosing regimen is to mitigate the risks for QT prolongation without compromising

efficacy. The primary safety assessments should include QT prolongation, hepatobiliary toxicities, and neutropenia. The primary efficacy endpoint should be objective response rate (ORR).

PMR 3168-2 for Part I of Study 2116 in subjects with severe renal impairment was submitted to the FDA in April 2018. (b) (4)

The FDA's Assessment:

FDA concludes that the PMR 3168-2 above is fulfilled by the clinical study report of Part I of Study 2116 under NDA209092 (SDN 346). The applicant plans to discuss with FDA on a study protocol to fulfil the PMR 3168-1 on July 16, 2018.

5.3. Comprehensive Clinical Pharmacology Review

5.3.1. General Pharmacology and Pharmacokinetic Characteristics

The Applicant's Position:

Comprehensive pharmacokinetic data on ribociclib were provided in the original NDA 209092 submission.

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 KISQALI 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. Ribociclib is not a substrate for hepatic uptake transporters OATP1B1/1B3 or OCT-1 in vitro.

The FDA's Assessment:

FDA agrees with the applicant's conclusion that ribociclib is not a substrate for OATP1B1/1B3 or OCT-1 in vitro based on the updated in vitro transport study reports. The other information provided by sponsor above is the same as the original NDA submission. See the original NDA 209092 multi-disciplinary review and evaluation for details.

5.3.2. Clinical Pharmacology Questions

5.3.2.1. Does the clinical pharmacology program provide supportive evidence of effectiveness?

The Applicant's Position:

Yes. The evidence of effectiveness of ribociclib was demonstrated in the original NDA 209092 submission based on study A2301. The results from the two new Phase III studies: E2301 and F2301 are consistent with previously observed efficacy results.

Study E2301 is the first randomized placebo-controlled Phase III clinical study evaluating a CDK4/6 inhibitor, ribociclib, in combination with the standard of care initial endocrine treatment backbone (i.e. tamoxifen or an NSAI and ovarian suppression with GnRH analogs), specifically in pre- or perimenopausal patients with HR-positive, HER2-negative advanced breast cancer. Study

E2301 met its primary objective by demonstrating statistically significant improvement in Investigator-assessed PFS in pre- or perimenopausal women with HR-positive, HER2-negative, advanced/metastatic breast cancer in the ribociclib arm. An estimated 43.1% relative risk reduction in the hazard rate of death or progression (HR = 0.569; 95% CI: 0.436, 0.743) occurred in the ribociclib arm over placebo. Median PFS per Investigator assessment was longer in the ribociclib arm (27.5 months; 95% CI: 19.1, NE) versus the placebo arm (13.8 months; 95% CI: 12.6, 17.4). The efficacy-exposure relationship showed no clear relationship between ribociclib average steady state Ctrough and PFS.

Study F2301 is a randomized (2:1), double-blind, placebo-controlled, international, multicenter Phase III study designed to evaluate the efficacy and safety of treatment with ribociclib plus fulvestrant versus placebo plus fulvestrant in men and postmenopausal women with HR-positive, HER2-negative advanced breast cancer who had received no prior therapy or only one line of prior endocrine treatment for advanced disease. The study met its primary objective, with an estimated 40.7% relative reduction in the risk of death or progression (HR=0.593; 95% CI: 0.480, 0.732) in the ribociclib plus fulvestrant arm compared with the placebo plus fulvestrant arm, which was statistically significant at a one-sided 2.5% level of significance (p = 4.10 × 10-7).

Median PFS was prolonged by a clinically meaningful 7.7 months, from 12.8 months (95% CI: 10.9, 16.3) in the placebo plus fulvestrant arm to 20.5 months in the ribociclib plus fulvestrant arm (95% CI: 18.5, 23.5). The efficacy-exposure relationship showed no clear relationship between average ribociclib Ctrough concentrations and PFS (Table 5-1).

Table 5-1 Analysis of PFS per Investigator assessment using log-rank test, Cox regression, and Kaplan-Meier method – Study F2301 (FAS)

	Ribociclib + Fulvestrant N = 484	**Placebo + Fulvestrant N = 242**
Category	**n (%)**	**n (%)**
Number of events - n (%)	210 (43.4)	151 (62.4)
Progression	200 (41.3)	143 (59.1)
Death [1]	10 (2.1)	8 (3.3)
Number censored - n (%)	274 (56.6)	91 (37.6)
P-value ribociclib + fulvestrant vs. placebo + fulvestrant [2]	4.10x10^($^{-7}$)	
Hazard ratio (95% CI) ribociclib + fulvestrant vs. placebo + fulvestrant [3]	0.593 (0.480, 0.732)	
Percentiles (95% CI)		
25th percentile	8.6 (6.5, 10.8)	3.6 (2.5, 5.5)
Median	20.5 (18.5, 23.5)	12.8 (10.9, 16.3)
75th percentile	NE (NE, NE)	22.2 (21.9, NE)
Kaplan-Meier estimate (95% CI)		
6 months	79.4 (75.4, 82.8)	67.0 (60.6, 72.7)
12 months	67.4 (62.8, 71.6)	51.7 (45.1, 57.9)
18 months	55.5 (50.6, 60.1)	38.4 (31.9, 44.9)

Category	Ribociclib + Fulvestrant N = 484 n (%)	Placebo + Fulvestrant N = 242 n (%)
24 months	39.6 (30.4, 48.6)	17.6 (8.3, 29.7)

NE: Not estimable.
[1] Death before progression
[2] P-value is obtained from the one-sided stratified log-rank test.
[3] Hazard ratio is obtained from Cox PH model stratified by lung and/or liver metastasis and previous endocrine therapy per IRT
Source: [Study F2301-Table 14.2-1.1], [Study F2301-Table 14.2-1.13], [Study F2301-Table 14.2-1.15], [Study F2301-Table 14.2-1.19], [Study F2301-Table 11-6] (data cut-off 03-Nov-2017)

There was no clear relationship between ribociclib exposure and efficacy endpoints based on exposure-efficacy analysis in Study E2301 and Study F2301 as well as pooled analysis of Study A2301, E2301, and F2301. This is consistent with the observation that patients across the ribociclib exposure range studied, including patients who started on 600 mg and dose reduced to 400 mg or further to 200 mg, continued to benefit from treatment. The results of the relationship between ribociclib exposure and efficacy were consistent with findings from the original NDA.

The FDA's Assessment:
FDA agrees with the applicant's conclusion that clinical pharmacology program provides supportive evidence of effectiveness. FDA agrees with the applicant's conclusions regarding E-R relationships for neutropenia.

5.3.2.2. Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The Applicant's Position:
Yes. The proposed dose 600 mg is effective, the drug was generally well tolerated, no new safety signals were identified, and AEs were effectively managed by dose interruption and/or reduction. To reduce the risk of subsequent QTcF prolongation, Kisqali at the next lower dose level after the resolution of the first occurrence of QTcF > 480 ms is recommended.

QT prolongation: QT prolongation is an important identified risk for ribociclib as described in the previous submission. Concentration-dependent change in the QTc interval were observed in patients with cancer and healthy subjects treated with ribociclib. Updated PK QTcF analysis showed that the combination partner was a significant covariate. At the ribociclib dose of 600 mg, the estimated ΔQTcF at the geometric mean of Cmax at steady state were similar for ribociclib in combination with NSAI or fulvestrant, and was 22.00 ms (90% CI: 20.56, 23.44) and 23.7 ms (90% CI: 22.31, 25.08), respectively. However, the estimated mean delta QTcF for ribociclib in combination with tamoxifen was considerably higher, and was 34.7 ms (90% CI: 31.64, 37.78). The model-estimated mean ΔQTcF values with the combination partners were consistent with the observed data.

In Study E2301, observed mean ΔQTcF values in patients in tamoxifen plus placebo subgroup was approximately 10 ms higher compared to patients in the NSAI plus placebo subgroup, suggesting that tamoxifen had a QTcF prolongation effect. Ribociclib 600 mg increased tamoxifen exposure approximately 2-fold. Tamoxifen is estimated to reduce the ribociclib steady-state exposure (AUC) by 26.7%. No apparent DDI between ribociclib and NSAI was observed.

Based on both ΔQTcF and PK data observed in Study E2301, the higher QTcF values in patients receiving ribociclib plus tamoxifen compared to NSAI can be contributed by the QTcF prolongation effect of tamoxifen. Based on an imbalance in increased QTcF values and higher ΔQTcF observed in the ribociclib plus tamoxifen subgroup, Novartis does not propose to include the ribociclib and tamoxifen combination in the proposed indication.

To reduce the risk of subsequent QTcF prolongation while maintaining efficacy, Novartis is proposing to update the Kisqali label in this submission to provide modified guidance for patients who experience QTcF > 480 ms which includes recommendations for restarting Kisqali at the next lower dose level after the resolution of the first occurrence of QTcF > 480 ms versus resuming at the same dose level (as currently stated in the Kisqali label).

Table 5-2: Dose modification and management- QT prolongation

ECGs with QTcF* > 480 msec	• Interrupt KISQALI Treatment • If QTcF prolongation resolves to < 481 msec, resume treatment at the next lower dose level; • If QTcF ≥ 481 msec recurs, interrupt dose until QTcF resolves to < 481 msec; then resume KISQALI at next lower dose level.
ECGs with QTcF > 500 msec	• Interrupt KISQALI treatment if QTcF greater than 500 msec. • If QTcF prolongation resolves to < 481 msec, resume treatment at the next lower dose level Permanently discontinue KISQALI if QTcF interval prolongation is either greater than 500 msec or greater than 60 msec change from baseline AND associated with any of the following: Torsades de Pointes, polymorphic ventricular tachycardia, unexplained syncope, or signs/symptoms of serious arrhythmia.
Electrocardiograms (ECGs) should be assessed prior to initiation of treatment. Repeat ECGs at approximately Day 14 of the first cycle and at the beginning of the second cycle, and as clinically indicated. In case of (QTcF) prolongation at any given time during treatment, more frequent ECG monitoring is recommended. *QTcF = QT interval corrected by Fridericia's formula	

Neutropenia: The relationship between ribociclib exposure and neutropenia has been well characterized in the previous submission. Consistent with the previous analysis, patients with grade 3 or worse neutropenia had higher geometric mean steady-state ribociclib Ctrough than those without grade 3 or worse neutropenia.

A longitudinal population ANC Exposure-response (E-R) analysis was conducted to characterize the relationship between ribociclib PK and ANC time course and evaluated the covariate effects of combination partners (i.e. tamoxifen, anastrozole, letrozole, and fulvestrant) and other factors of interest (e.g. age, race), on ribociclib ANC E-R relationship. The combination partners were found to have no statistically significant or clinically relevant effect on the ANC E-R relationship.

Figure 5-1 Boxplot of geometric mean SS ribociclib Ctrough (ng/mL) up to the event by occurrence of newly occurring grade 3 or worse neutropenia (PK-Neutropenia set)

APPEARS THIS WAY ON ORIGINAL

Diamonds represent the mean and circles represent values outside of 1.5*IQR.Lower and upper whiskers extend to most extreme points within 1.5*IQR of Q1 and Q3, respectively.

Hepatobiliary toxicity: Based on the original NDA submission, evaluation of the exposure-response relationship of grade 3 or 4 liver function tests (LFTs) was limited by the low number of events, and as such, no correlation between ribociclib exposure and LFT increase was observed and no meaningful conclusion could be drawn on the risks for hepatobiliary toxicity at alternative dosing regimen.

Collectively, the exposure-efficacy, and exposure-safety data based on studies E2301 (NSAI subgroup) and F2301 support the use of ribociclib 600 mg in combination with an AI or fulvestrant (b) (4)

The FDA's Assessment:

FDA agrees with the applicant's conclusion that the proposed starting dose of 600mg QD is efficacious and appears to have a manageable safety profile. FDA agrees with the applicant proposed updated dose modification plan in Table 5-2 to reduce the risk of QTcF prolongation as well as the applicant's proposal of not including the ribociclib and tamoxifen combination in the proposed indication due to QTcF prolongation. FDA conducted its own analyses and concluded that the applicant's analyses for QT prolongation and neutropenia are acceptable. Refer to the June 26, 2018 QT-IRT consult review in DARRTs for the QT prolongation analysis and the OCP Appendix in Section 17.3 for the neutropenia analysis.

5.3.2.3. Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

The Applicant's Position:

Yes. The recommendation for alternative dosing regimen for subpopulation based on intrinisic patient factors has no change since the original NDA approval except for patients with severe renal impairment.

Hepatic Impairment: Final analysis from Study A2109 conducted in subjects with hepatic impairment indicated that the mild hepatic impairment cohort had similar ribociclib exposure (AUCinf and AUClast), while moderate hepatic impairment and severe hepatic impairment cohort had approximately 30% higher AUCinf as compared to normal hepatic function cohort. Cmax was similar in mild hepatic impairment cohort compared to normal hepatic function cohort. Moderate hepatic impairment and severe hepatic impairment cohorts had 44% and 32% increase in Cmax compared to normal hepatic function cohort.

The results of the final analysis from Study A2109 are consistent with the results from the interim analysis in the original NDA. The results from this study indicate no ribociclib dose adjustment is warranted for patients with mild hepatic impairment (Child-Pugh A), while a dose reduction to 400 mg in patients with moderate (Child-Pugh B) and severe hepatic impairment (Child-Pugh C) is recommended.

Renal Impairment: Mild and moderate renal impairment was found to have no clinically important effect on ribociclib PK based on population PK analysis and hence does not warrant dose adjustment. The PopPK dataset included subjects with normal renal function (eGFR ≥ 90 mL/min/1.73m^2, N=438), mild impairment (60 ≤ eGFR<90 mL/min/1.73m^2, N=488), and moderate impairment (30 ≤ eGFR<60 mL/min/1.73m^2, N=113). The eGFR effect on ribociclib apparent clearance was estimated to have a 95% CI of 0.894, 1.080 (mean=0.991), indicating no clinical importance of renal function on ribociclib PK for patients with mild and moderate renal impairment. This conclusion is consistent with the earlier result from a smaller population presented in the previous submission.

Based on the dedicated renal impairment study, severe renal impairment was found to significantly increase ribociclib exposure. Subjects with severe renal impairment had 96% higher ribociclib exposure (AUCinf and AUClast). Cmax was also 51% higher in the severe renal impairment cohort compared to the normal renal function cohort. Based on higher ribociclib exposure in subjects with severe renal impairment, a starting dose of 200 mg is recommended for patients with severe renal impairment.

Intrinsic factors: Race, age, body weight and renal function were evaluated as intrinsic factors for the effect on ribociclib PK in the updated population PK analysis. The effects of age, race (Asian, or Others, vs. Caucasian), eGFR and body weight on ribociclib apparent clearance (CL/F) were found to be negligible. Body weight was found to be a significant covariate on the inter-compartmental clearance and peripheral volume, however, it is not clinically relevant as there is no impact on the exposure (AUC) of ribociclib. Gender was not evaluated in the updated population PK analysis as it was previously found have no impact on the PK of ribociclib.
No apparent differences in exposure parameters were observed between Asian versus non-Asian

patients in both studies E2301 and F2301.

The FDA's Assessment:

FDA agrees with the applicant's alternative dosing regimen for subpopulation. In this submission, the only new proposed regimen was the proposed starting dose of 200 mg ribociclib for patients with severe renal impairment. The proposed 200 mg starting dose is acceptable based on the clinical study results and ribociclib tablets strength of 200 mg. The applicant updated the population PK analysis for patients with mild or moderate renal impairment to include more patients. The conclusion of no clinical relevant PK difference in patients with mild and moderate renal impairment is consistent with the previous conclusion from a smaller population (77 patients with normal renal function, 76 patients with mild renal impairment and 35 with moderate renal impairment) in the original NDA submission. The applicant updated the Study A2109 interim analysis in the original NDA with the final analysis in this submission. There are no clinically relevant differences between the results of the interim analysis and the final analysis.

The population PK analysis was updated using the Studies E2301 and F2301 dataset. FDA conducted its own analyses and concluded that the applicant's population PK analysis is acceptable. The population PK analysis reached the same conclusion as the previous population PK analysis in the original NDA submission.

5.3.2.4. Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

The Applicant's Position:

As submitted in the original NDA, no clinically relevant food effect was observed with ribociclib - capsule and tablet formulation. In the original NDA based on PK, population PK and PBPK analysis, altered ribociclib absorption was not identified when ribociclib was coadministrated with proton pump inhibitors (PPIs).

Results of drug-drug interaction were detailed in the previous submission. Fulvestrant showed no effect on ribociclib PK based on data in Study F2301, which was consistent with historical single-agent data. There are no known drug interactions with fulvestrant. Therefore, DDI was not anticipated between ribociclib and fulvestrant. No DDI was apparent when ribociclib was concomitantly used with anastrozole or letrozole.

Refer to the original NDA submission for the detailed information on CYP enzymes related DDIs and management strategy. Ribociclib is a CYP3A4 substrate. Concomitant use of Kisqali should be avoided with strong CYP3A inhibitors. The applicant proposes to remove the languages of avoiding pomegranate or pomegranate juice as a CYP3A4 inhibitor while taking Kisqali from the US Prescribing Information. Although, in vitro experiments showed that pomegranate juice inhibited CYP3A; clinical studies have revealed that consumption of pomegranate juice does not modify the activity of CYP3A in humans (Farkas et al 2007, Misaka et al 2011, Park et al 2016). Therefore, it is unlikely that coadministration of pomegranate or pomegranate juice would have

any clinically meaningful increase in ribociclib exposure.

The FDA's Assessment:

FDA agrees with the applicant's conclusion that coadministration of pomegranate or pomegranate juice would unlikely have any clinically meaningful increase in ribociclib exposure. The other information provide by the sponsor is the same as the original NDA submission. See the original NDA 209092 multi-disciplinary review and evaluation for details.

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6 Sources of Clinical Data

6.1. Table of Clinical Studies

The Applicant's Position:

Table 6-1: Listing of Clinical Trials Relevant to this sNDA

Trial Identity NCT no.		Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Studies to Support Efficacy and Safety of ribociclib plus NSAI in premenopausal women with HR-positive, HER2-negative, advanced breast cancer								
LEE011E2301 (MONALEESA7) NCT02278120		Randomized, double-blind, placebo-controlled, international, multicenter Phase III study	**Ribociclib arm:** Ribociclib 600 mg per once daily, Days 1-21 of each 28-day cycle; plus tamoxifen 20 mg/NSAI (letrozole 2.5 mg or anastrozole 1 mg) once daily, Days 1-28 of each 28-day cycle per oral; plus goserelin 3.6 mg sc on Day 1 of each 28-day cycle **Placebo arm:** Placebo once daily, Days 1-21 of each 28-day cycle; plus tamoxifen 20 mg/NSAI (letrozole 2.5 mg or anastrozole 1 mg) once daily, Days 1-28 of each 28-day cycle; plus goserelin 3.6 mg sc on Day 1 of each 28-day cycle	**Primary endpoint**: PFS by Investigator assessment **Secondary endpoints:** OS**,** ORR; CBR; TTR; DoR; ECOG performance status; Time to 10% deterioration in the global health status/QOL scale score of the EORTC QLQ-C30; Change from baseline in the global health status/QOL scale score of the EORTC QLQ-C30; Safety and tolerability endpoints. **Exploratory endpoints:** PK; Biomarkers; PFS2.	At the time of the primary analysis, median duration of exposure to the study treatment was 15.2 months in the ribociclib group and was 12 months in the placebo group Median duration of exposure to ribociclib was 15.1 months	Total: 672 Ribociclib arm: 335 Placebo arm: 337 NSAI subgroup: 248 ribociclib arm; 247 placebo arm Tamoxifen subgroup: 87 ribociclib arm; 90 placebo arm	premenopausal women with HR-positive, HER2-negative, advanced breast cancer who received no prior hormonal therapy for advanced disease	A total of 188 centers, across 30 countries
Studies to Support Efficacy and Safety of ribociclib plus fulvestrant in postmenopausal women with HR-positive, HER2-								

Trial Identity NCT no.		Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
negative advanced breast cancer								
LEE011F2301 (MONALEESA3) NCT02422615		Randomized, double-blind, placebo-controlled, international, multi-center Phase III	Ribociclib (600 mg once daily, on Days 1-21 of a 28-day cycle) plus fulvestrant (500 mg [two 5-mL intra-muscular injections]) every 28 days on the first day of each cycle with an additional dose on Day 15 of Cycle 1) Placebo (once daily, Days 1 to 21 of a 28-day cycle) + fulvestrant (500 mg [two 5-mL intra-muscular injections]) every 28 days on the first day of each cycle with an additional dose on Day 15 of Cycle 1)	**Primary endpoint:** PFS by Investigator assessment **Secondary endpoints:** OS, ORR and CBR, TTR, DoR, Time to deterioration of ECOG PS, PROs (EORTC QLQ-C30, EQ-5D-5L and BPI-SF questionnaires), Safety and tolerability endpoints, PK concentrations **Exploratory:** PFS2, Biomarkers	At the time of the primary analysis, median duration of exposure to study treatment was 15.8 months in the ribociclib group vs 12.0 months placebo group	726 (2:1 randomization: 484 in ribociclib plus fulvestrant arm, 242 in placebo plus fulvestrant arm)	postmenopausal women with HR-positive, HER2-negative advanced breast cancer who received no or only one prior endocrine therapy for advanced breast cancer	A total of 175 sites across 30 countries
LEE011X2108 NCT02088684		Phase 1b	Ribociclib 600 mg once daily (on Days 1-21 of a 28-day cycle) plus fulvestrant 500 mg (dosed on Days 1 and 15 in Cycle 1, and Day 1 of each subsequent cycle).	**Primary endpoint:** Incidence of Dose Limiting Toxicities (DLTs) in Cycle 1 **Secondary endpoint:** ORR, DoR and CBR PFS, Safety and tolerability endpoints, PK concentrations and parameters **Exploratory:** Biomarkers	median duration of exposure to study treatment was 7.4 months	13 patients	postmenopausal women with locally advanced or metastatic HR-positive, HER2-negative breast cancer who had failed or progressed on AI treatment	

The FDA's Assessment:

FDA agrees with the summary of MONALEESA-7 and MONALEESA-3 study designs as presented in the table above. FDA reviewed the applicant's position on study LEE011X2108 above. Study X2108 is not designed as a registration trial and is not being used to support a labeling indication.

7 Statistical and Clinical Evaluation

7.1. Review of Relevant Individual Trials Used to Support Efficacy

The Applicant's Position:

Efficacy claims for use of ribociclib 600 mg in combination with an AI and LHRH agonist as initial endocrine-based therapy for the treatment of pre- or perimenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer are mainly based on the primary analysis results from the Phase III Study E2301 (data cut-off date: 20Aug2017).

Efficacy claims for use of ribociclib 600 mg in combination with fulvestrant are mainly based on the primary analysis results from the Phase III from Study F2301 (data cut-off-date: 03Nov2017). In addition, supportive interim results are provided based on Arm 3 of Study X2108 (data cut-off date: 10-Feb-2017).

Additional support for efficacy of ribociclib in combination with endocrine therapy in patients with no prior endocrine therapy for advanced disease is also provided based on pooled (N=1738) efficacy data from Study F2301 (only patients with no prior endocrine therapy for advanced disease), Study LEE011E2301 (only patients assigned to combination treatment with an NSAI in the treatment assignment eCRF), and Study A2301.

The FDA's Assessment:

The efficacy claims for ribociclib with an AI+LHRH agonist as initial endocrine-based therapy for pre- and perimenopausal women are based off results from MONALEESA-7. Efficacy claims for ribociclib with fulvestrant in the 1st and 2nd line settings are based off results from MONALEESA-3). FDA did not review interim results of study X2108 as this is not a registration trial. FDA did not review the pooled efficacy analyses for MONALEESA-3, MONALEESA-7, and MONALEESA-2 (study A2301) as the patient population, eligibility criteria, and hormonal therapy backbone are different across the studies.

7.1.1. Study E2301 (MONALEESA-7)

Study Design

This is a Phase III, randomized, double-blind, placebo-controlled global study comparing ribociclib plus goserelin plus either tamoxifen or a NSAI (letrozole or anastrozole), (henceforth ribociclib arm) versus placebo plus goserelin plus either tamoxifen or a NSAI (letrozole or anastrozole)

(henceforth placebo arm), in premenopausal women with HR-positive, HER2-negative advanced breast cancer who received no prior hormonal therapy for advanced breast cancer.

Approximately 660 patients were planned to be randomized in a 1:1 ratio to one of the following treatment arms:

- Ribociclib arm: Ribociclib (600 mg orally once daily, on Days 1-21 of a 28-Day cycle) plus goserelin (3.6 mg subcutaneous implant on Day 1 of 28day Cycle) plus either tamoxifen (20 mg orally once daily) or a NSAI (either letrozole 2.5 mg orally once daily or anastrozole 1 mg orally once daily).
- Placebo arm: Placebo (orally daily, on Days 1-21 of a 28day cycle) plus goserelin (3.6 mg subcutaneous implant on Day 1 of 28day Cycle) plus either tamoxifen (20 mg orally once daily) or a NSAI (letrozole 2.5 mg orally once daily or anastrozole 1 mg orally once daily).

Randomization was stratified by the following factors:

- Presence of lung or liver metastases: (yes vs. no)
- Prior chemotherapy for advanced disease (yes vs. no)
- Endocrine combination partner (tamoxifen and goserelin vs. a NSAI (letrozole or anastrozole) and goserelin).

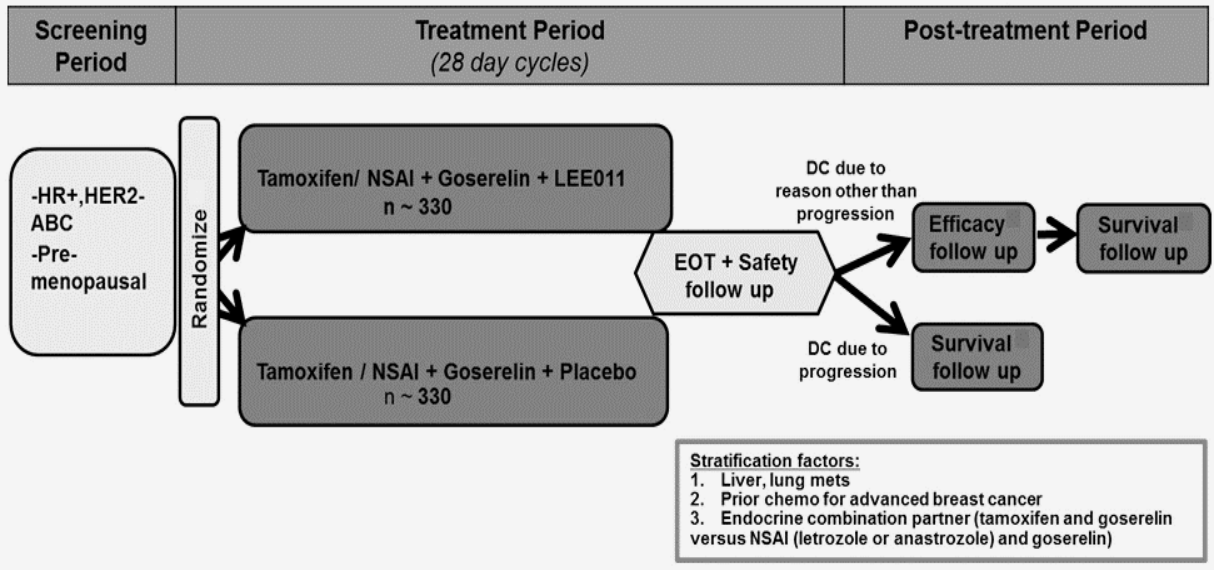
Treatment assignment with tamoxifen or NSAI was based on the patient's prior (neo) adjuvant therapy for breast cancer.

Efficacy assessments were deemed appropriate for evaluating the key elements of aBC in terms of currently used methodologies. The primary efficacy endpoint was PFS based on local Investigator/radiologist assessment. Progression-free survival (PFS), OS, ORR, and CBR are all accepted and well-recognized endpoints for oncology trials. Progression-free survival is less affected by biases introduced by subsequent therapies than OS and may provide a more biologically relevant measure of the effect of new treatments on the disease process. Clinically meaningful improvements in PFS have been used as the basis for regulatory approval of therapies for patient populations with breast cancer.

The study consisted of four phases: Screening (up to 28 days), randomized treatment phase, post-treatment efficacy follow-up, and survival follow-up.

The Figure 7-1 below demonstrates the MONALEESA 7 study schema.

Figure 7-1 Study design



The study consisted of four phases: Screening (up to 28 days), randomized treatment phase, post-treatment efficacy follow-up, and survival follow-up:

Screening phase

Premenopausal women with HR-positive, HER2-negative advanced breast cancer were screened for eligibility during the period up to 28 days prior to starting the combination of ribociclib plus goserelin plus either tamoxifen or a NSAI or placebo plus goserelin plus either tamoxifen or a NSAI on study Day 1. During this time, the inclusion and exclusion criteria were assessed and all screening assessments, laboratory tests, and procedures were performed.

Randomized treatment phase

All eligible randomized patients were to continue study treatment until disease progression, unacceptable toxicity, withdrawal of consent, or until patient was lost to follow-up. Patients were followed for survival regardless of treatment discontinuation for any reason, and regardless of achieving the primary endpoint, until the planned number deaths for final OS analysis occurred (except if consent was withdrawn or patient was lost to follow-up).

Safety follow-up

After discontinuation of study treatment, all patients were to be followed for safety for at least 30 days except in case of death, loss to follow-up, or withdrawal of consent.

Efficacy follow-up

Patients who discontinued study treatment for reasons other than disease progression were followed up every eight weeks for efficacy during the first 18 months, and every 12 weeks thereafter until disease progression, death, loss to follow-up, patient/guardian decision or withdrawal of consent. If a patient started a new antineoplastic treatment without withdrawing consent, the patient was followed for efficacy according to above specified protocol schedule

until disease progression, death, withdrawal of consent, loss to follow-up, or patient/guardian decision. The reason for study completion was recorded on the End of Post Treatment Follow-up Phase Disposition CRF page.

Survival follow-up

All patients were to be followed for survival once they discontinued study treatment and tumor evaluations until reaching the final number of OS events or if the study was stopped for other reasons. Survival follow-up was to be conducted every 12 weeks or earlier if a survival update was required to meet safety or regulatory needs. Survival information was to be obtained until death, lost to follow up, or the patient withdrew consent for survival follow-up.

During the survival follow up, in addition to vital status, all subsequent anti-neoplastic therapies initiated after study treatment discontinuation were collected along with the start/end date and date of disease progression on subsequent therapies to assess time to progression on next-line therapy (PFS2). PFS2 is defined as the time from date of randomization to the first documented progression on next-line therapy or death from any cause, whichever occurred first. Disease progression was determined based on Investigator assessment of progression on next-line therapy.

Study Design

The randomized, double-blind, placebo-controlled, multicenter, parallel-group study design is the gold standard design for Phase III studies as it minimized allocation bias, balancing both known and unknown prognostic factors in the assignment of treatments. This study was designed with the objective to evaluate the therapeutic effect of adding ribociclib to tamoxifen and goserelin or a NSAI and goserelin in premenopausal patients with advanced breast cancer. The choice of control group (tamoxifen and or NSAI plus goserelin endocrine therapy) was based on its use as standard of care in premenopausal patients with advanced breast cancer.

The standard daily doses of NSAIs were used (2.5 mg letrozole or 1 mg anastrozole). Results from patients treated with the combination of ribociclib at 600 mg and letrozole at 2.5 mg in [Study A2301] suggested that this combination is tolerable.

The standard dose of goserelin of 3.6 mg subcutaneously every 28 days was used, as goserelin was not expected to affect the metabolism of nor be affected by co-administration of other drugs.

Diagnostic Criteria

The study included pre- or perimenopausal women with HR-positive, HER2-negative advanced breast cancer who received no prior hormonal therapy for their advanced disease and were eligible for endocrine therapy. Patients had histologically and/or cytologically confirmed diagnosis of estrogen-receptor and/or progesterone receptor positive breast cancer by local laboratory.

Inclusion criteria

1. An adult female patient (≥ 18 years and < 60 years old at the time of informed consent) who signed informed consent before any study-related activities and according to local guidelines.
2. Confirmed negative serum pregnancy test (β-hCG) before starting study treatment or patient had a hysterectomy.
3. Patient was either pre- or perimenopausal at the time of study entry.
   - Premenopausal status was defined as either:
     - Patient had last menstrual period within the last 12 months.
     - If on tamoxifen or toremifene within the past 14 days, plasma estradiol, and follicle stimulating hormone (FSH) was to be in the premenopausal range per local normal range.
     - In case of therapy induced amenorrhea, plasma estradiol and/or FSH was to be in the premenopausal range per local normal range.
   - Patient who had bilateral oophorectomy was not eligible
   - Perimenopausal status was defined as neither pre- nor postmenopausal (see exclusion criteria 3)
4. Patients had advanced (locoregionally recurrent or metastatic) breast cancer not amenable to curative therapy (e.g. surgery and/or radiotherapy).
5. Patients who received (neo) adjuvant therapy for breast cancer were eligible:
   - If the patient never received any prior endocrine therapy OR if ≥ 12 months had elapsed since the patient's last dose of adjuvant therapy, then the patient was eligible to receive tamoxifen plus goserelin or a NSAI plus goserelin for advanced breast cancer based on the investigator's choice.
   - If tamoxifen or fulvestrant was the last prior (neo) adjuvant therapy and the last dose was given < 12 months prior to randomization, then the patient was eligible to receive a NSAI (letrozole or anastrozole) plus goserelin for advanced breast cancer.
   - If letrozole, anastrozole, or exemestane was the last prior (neo) adjuvant therapy and the last dose was given < 12 months prior to randomization, then the patient was eligible to receive tamoxifen plus goserelin for advanced breast cancer.
6. Patients who received ≤ 14 days of tamoxifen or a NSAI (letrozole or anastrozole) with or without goserelin or only goserelin ≤ 28 days for advanced breast cancer prior to randomization were allowed. Patients were to continue treatment with the same hormonal agent plus goserelin during the study. No treatment interruption was required for these patients prior to randomization.

   Note: Patient's receiving goserelin for reasons other than for advanced breast cancer treatment were eligible (e.g. endometriosis). Patient who received ≤ 28 days of goserelin for advanced breast cancer were eligible.
7. Patients who received up to one line of chemotherapy for advanced breast cancer and discontinued 28 days before randomization.
8. Histological and/or cytological confirmation of estrogen receptor (ER)-positive and/or progesterone receptor-positive breast cancer by local laboratory.
9. Patients diagnosed with HER2-negative breast cancer defined as a negative in situ hybridization test or an immunohistochemistry (IHC) status of 0, 1+, or 2+. If IHC was 2+, a

negative in situ hybridization (fluorescent in situ hybridization [FISH], chromosome in situ hybridization [CISH], or silver-enhanced in situ hybridization [SISH]) test was required by local laboratory testing.

10. Patients had either:
    - Measurable disease, i.e. at least one measurable lesion as per Response Evaluation Criteria In Solid Tumors RECIST v1.1 criteria

    OR

    - If no measurable disease was evident at least one predominantly lytic bone lesion was to be present (patients with no measurable disease and only one predominantly lytic bone lesion that was previously irradiated were eligible if there was documented evidence of disease progression of the bone lesion after irradiation).
11. Patient had ECOG performance status 0 or 1.
12. Patient had adequate bone marrow and organ function as defined by the following laboratory values (as assessed by central laboratory):
    - Absolute neutrophil count ≥ 1.5×10^9/L
    - Platelets ≥ 100×10^9/L
    - Hemoglobin ≥ 9.0 g/dL
    - Potassium, sodium, calcium (corrected for serum albumin), and magnesium within normal limits of the central laboratory or corrected to within normal limits with supplements before the first dose of study medication.
    - International Normalized Ratio (INR) ≤ 1.5
    - Serum creatinine <1.5 mg/dL
    - In absence of liver metastases, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) had to be <2.5×ULN. If the patient had liver metastases, ALT and AST had to be < 5×ULN.
    - Total serum bilirubin < ULN; or total bilirubin ≤ 3.0×ULN with direct bilirubin <1.5ULN per central laboratory in patients with well documented Gilbert's Syndrome.
13. Patient was to be able to swallow study therapy.
14. Patient was to be able to communicate with the Investigator and comply with the requirements of the study procedures.
15. Patient willing to remain at the clinical site as required by the visit evaluation schedule in the protocol.

Exclusion criteria

1. Patients who received prior CDK4/6 inhibitor therapy.
2. Patients with known hypersensitivity to any of the excipients of ribociclib or goserelin or hormonal treatment assigned (tamoxifen or a NSAI [letrozole or anastrozole]).
3. Patients were postmenopausal. Postmenopausal status was defined either by:
    - Prior bilateral oophorectomy
    - Age ≥ 60
    - Age < 60 and amenorrhea for 12 or more months (in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression) and FSH and estradiol in the postmenopausal range per local normal range.

- If taking tamoxifen or toremifene, and age < 60, then FSH and plasma estradiol level in postmenopausal ranges per local laboratory normal range.
    - For women with therapy-induced amenorrhea, serial measurements of FSH and/or estradiol are needed to ensure menopausal status (NCCN breast cancer guidelines Ver. 1.2018)

4. Patients with inflammatory breast cancer at Screening.
5. Patients who received any prior hormonal anti-cancer therapy for advanced breast cancer, except for ≤ 14 days of tamoxifen or NSAI or goserelin ≤ 28 days for advanced breast cancer prior to randomization.
6. Patients who had not had resolution of all acute toxic effects of prior anti-cancer therapy to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 grade ≤1 (except alopecia or other toxicities not considered a safety risk for the patient at investigator's discretion).
7. Patients with a concurrent malignancy or malignancy within 3 years of randomization, with the exception of adequately treated basal cell skin carcinoma, squamous cell skin carcinoma, non-melanomatous skin cancer, or curatively resected cervical cancer.
8. Patients with CNS metastases.
   Note: CNS involvement was to be ruled out by assessments if a patient had any signs or symptoms indicating potential CNS metastases.
9. Patients with impairment of gastrointestinal (GI) function or GI disease that significantly alter the absorption of the study drugs (e.g. ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection).
10. Patients with a known history of human Immunodeficiency virus infection (HIV) (testing not mandatory).
11. Patients with any other concurrent severe and/or uncontrolled medical condition that would, in the investigator's judgment, contraindicate patient participation in the clinical study (e.g. chronic pancreatitis, chronic active hepatitis, etc.)
12. Patients who had clinically significant, uncontrolled heart disease and/or cardiac repolarization abnormality including any of the following:
    - History of angina pectoris, symptomatic pericarditis, myocardial infarction or coronary artery bypass graft (CABG) within 6 months prior to study entry
    - Documented cardiomyopathy
    - Left Ventricular Ejection Fraction (LVEF) < 50% as determined by Multiple Gated acquisition (MUGA) scan or echocardiogram (ECHO)
    - Clinically significant cardiac arrhythmias (e.g. ventricular tachycardia), complete left bundle branch block, high-grade AV block (e.g. bifascicular block, Mobitz type II and third degree AV block).
    - Long QT syndrome or family history of idiopathic sudden death or congenital long QT syndrome, or any of the following:
        - Risk factors for Torsades de Pointes (TdP) including uncorrected hypokalemia or hypomagnesemia, history of cardiac failure, or history of clinically significant/symptomatic bradycardia
        - Resting heart rate < 50 beats per minute (bpm) at rest by triplicate ECG

- Resting heart rate > 90 beats per minute (bpm) at rest by triplicate ECG
- Systolic blood pressure > 160 or < 90 mmHg
- On screening, inability to determine the QTcF interval on the ECG (inability to read or interpret the QTcF interval on the ECG) or QTcF > 450 ms (using Fridericia's correction). All as determined by the average of the triplicate screening ECG, per central review.

13. Patients currently receiving any of the following substances and where use could not be discontinued seven days prior to the start of the treatment:
    - Known strong inducers or inhibitors of CYP3A4/5, including grapefruit, grapefruit hybrids, pummelos, star-fruit, and Seville oranges.
    - Medications with a known risk to prolong the QT interval or induce Torsades de Pointes that cannot be discontinued or replaced by safe alternative medication
    - Medications with a narrow therapeutic window and which are predominantly metabolized through CYP3A4/5.
    - For patients receiving tamoxifen: known strong inducers or inhibitors of CYP2D6
    - Herbal preparations/medications and dietary supplements (except vitamins)
14. Patient who had major surgery within 14 days prior to starting study drug or had not recovered from major side effects.
15. Patients who were currently receiving warfarin or other Coumadin-derived anti-coagulant, for treatment, prophylaxis or otherwise. Therapy with heparin, low molecular weight heparin (LMWH), or fondaparinux was allowed.
16. Patients who were currently receiving or those who had received systemic corticosteroids ≤ 2 weeks prior to starting study drug, or who had not fully recovered from the side effects of such treatment.

    Note: The following uses of corticosteroids were permitted: single doses, topical applications (e.g., for rash), inhaled sprays (e.g., for obstructive airways diseases), eye drops or local injections (e.g., intra-articular).
17. Patients were concurrently using other antineoplastic agents (except for patients who received ≤ 14 days of tamoxifen or NSAI or goserelin ≤ 28 days for advanced breast cancer prior to randomization).
18. Patients who received radiotherapy ≤ 4 weeks or limited field radiation for palliation ≤ 2 weeks prior to randomization, and who had not recovered to grade ≤ 1 from related side effects of such therapy (with the exception of alopecia) and/or if ≥ 25% of the bone marrow was irradiated.
19. Pregnant or nursing (lactating) women, where pregnancy was defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
20. Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, unless they were using highly effective methods of contraception during dosing of study treatment and for 21 days after stopping study medication. Highly effective contraception methods included:

- Total abstinence (when this was in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal were not acceptable methods of contraception.
- Total hysterectomy or tubal ligation at least six weeks before taking study treatment.
- Male sterilization (at least six months prior to screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient.
- Combination of the following:
    a. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
    b. Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/ vaginal suppository.

21. Participation on a prior investigational study within 30 days prior to enrollment or within five half-lives of the investigational product (whichever was longer).
22. Unable to understand and comply with study instructions and requirements.
23. Patients with symptomatic visceral disease or any disease burden that made the patient ineligible for endocrine therapy per the Investigator's best judgment.

Study treatments

Patients were randomly assigned to one of the following treatment arms in a 1:1 ratio to either ribociclib or placebo arm:

- Ribociclib plus tamoxifen or a NSAI (letrozole or anastrozole) plus goserelin (ribociclib arm)
- Placebo plus tamoxifen or a NSAI (letrozole or anastrozole) plus goserelin (placebo arm)

Administrative structure

The administrative structure of the study, including internal and external participants, is described in Appendix 16.1.4-Section 1 of the Clinical Study Report. A list of investigators, their affiliations and their qualifications, plus that of other important staff, as well as members of the independent Data Monitoring Committee (DMC), is provided in Appendix 16.1.4-Section 2 of the Clinical Study Report.

Study endpoints

Efficacy: The primary efficacy endpoint was PFS based on local radiology assessment using RECIST v1.1 criteria. PFS was defined as the time from the date of randomization to the date of the first documented disease progression or death due to any cause.

The key secondary efficacy endpoint was OS, defined as the time from date of randomization to date of death due to any cause. Other secondary efficacy endpoints were: Overall response rate (ORR), Clinical benefit rate (CBR), time to response, duration of response and time to definitive deterioration of Eastern Cooperative Oncology Group performance status (ECOG PS). ORR was defined as the proportion of patients with best overall response (BOR) of confirmed CR or PR according to RECIST v1.1, and CBR was defined as the proportion of patients with a BOR of confirmed CR or PR, or stable disease lasting 24 weeks or longer, according to RECIST v1.1. Time to response was defined as the time between date of randomization and the first documented response (CR or PR, which had to be confirmed subsequently). Duration of response was defined

as the time from first documentatied tumor response to the first documented progression or death due to underlying cancer. Deterioration of ECOG PS was defined as an increase in ECOG PS by at least one category from baseline or death due to any cause. Deterioration was considered definitive if ECOG PS had no subsequent return to baseline or better during the treatment period.

Patient reported outcomes: Time to definitive 10% deterioration in quality of life, including the global health scale score of EORTC QLQ-C30, were assessed. Definitive 10% deterioration was defined as a worsening in score by at least 10% compared to baseline, with no later improvement above this threshold during the treatment period, or death due to any cause.

Safety: Safety was assessed by monitoring AEs, ECGs, and laboratory abnormalities.

Statistical analysis plan

The primary PFS analysis was planned to be assessed after approximately 329 PFS events have been documented. The primary efficacy analysis was the comparison of PFS between the two treatment arms using a stratified log-rank test at one-sided 2.5% level of significance, with strata as defined by the IRT.

The study was originally designed to ensure 90% power to detect a hazard ratio of 0.67 (median PFS 9 months vs. 13.4 months) including an interim futility analysis at 50% information fraction (164 events), an interim analysis for superiority at 80% information fraction (263 events), and a final analysis after approximately 329 PFS events. The interim analyses were subsequently eliminated in protocol amendments 3 and 4 respectively (see below). The elimination of the futility analyses resulted in increasing the power for the primary endpoint to 95% based on the targeted 329 PFS events.

Overall survival (OS) was the key secondary endpoint. A hierarchical testing strategy, where OS was to be statistically tested only if the primary efficacy endpoint of PFS was significantly different between the two treatment arms, was used to control the overall type-I error rate. OS was to be compared using a stratified log-rank test at overall one-sided 2.5% level of significance. A maximum of three analyses were planned for OS: at the time of the PFS analysis (provided PFS was significant); after approximately 189 deaths (75% of OS events) were documented; and a final analysis after approximately 252 deaths. The Type I error rate was controlled using a 3-look group sequential design with Lan-DeMets (O'Brien- Fleming) alpha spending function and using the hierarchical testing approach.

Protocol amendments

SAP amendments

The SAP was amended twice before sponsor unblinding, as outlined below, to reflect amendments to the study protocol.

Amendment 1 (finalized 5-Jun-2017) removed the interim futility and efficacy analyses for PFS, updated the PFS analyses based on BIRC assessment to reflect the change to an audit-based approach, and incorporated PFS2 as an exploratory endpoint, all based on the corresponding amendments to the study protocol.

Amendment 2 (finalized 27-Sep-2017) further clarified some analysis conventions, including the definition of baseline for RECIST-based endpoints and subgroup definitions.

The FDA's Assessment:
The applicant has described protocol amendments and the statistical analysis plan above. The SAP is acceptable.

7.1.2. Study E2301 (MONALEESA-7) Results

The Applicant's Position:

Compliance with Good Clinical Practice

According to the Applicant, the study was conducted in full conformance with the ethical principles of Good Clinical Practice (GCP) as required by the major regulatory authorities, and in conformance with the principles of the Declaration of Helsinki. Written informed consent was obtained from each participant in the study. The study protocol and four amendments were approved by local Independent Ethics Committees (IEC) or Institutional Review Boards (IRB).

Study E2301 was conducted at 188 sites across 30 countries as follows: Argentina (3), Australia (5), Belgium (4), Brazil (7), Bulgaria (3), Canada (6), Colombia (2), France (8), Germany (12), Greece (2), Hong Kong (3), Hungary (6),India (4), Italy (21), Republic of Korea (6), Lebanon (6), Malaysia (2), Mexico (3),Poland (2), Portugal (5), Russian Federation (2), Saudi Arabia (1), Singapore (2), Spain (17), Switzerland (1), Taiwan province of China (8), Thailand (2), Turkey (6), United Arab Emirates (1) and United States (38).

Table 7-1 Analysis Population for Study E2301

	Ribociclib 600 mg N (%)	Placebo N (%)
All randomized patients	**335 (100)**	**337 (100)**
ITT Population (Full Analysis Set)	**335 (100)**	**337 (100)**
Safety Set	**335 (100)**	**337 (100)**

Patient disposition

Six-hundred and seventy-two patients were randomized between 17-Dec-2014 and 01Aug2016 in a 1:1 ratio to receive treatment with either ribociclib plus goserelin plus either tamoxifen or a NSAI (letrozole or anastrozole) (n = 335) or placebo plus goserelin plus either tamoxifen or a NSAI (letrozole or anastrozole) (n = 337). All randomized patients received study treatment.

As of the 20Aug2017 data cut-off date, a greater proportion of patients continued to receive treatment in the ribociclib arm (174 patients; 51.9%) compared to the placebo arm (121 patients; 35.9%) (Table 7-2).

Table 7-2 Patient disposition-Study E2301

Disposition	Ribociclib 600 mg	Placebo	All patients
	N = 335	N = 337	N = 672

	n (%)	n (%)	n (%)
Patients randomized			
Treated	335 (100)	337 (100)	672 (100)
Patients treated			
Treatment ongoing[1]	174 (51.9)	121 (35.9)	295 (43.9)
End of treatment	161 (48.1)	216 (64.1)	377 (56.1)
Reason for end of treatment			
Progressive disease	122 (36.4)	174 (51.6)	296 (44.0)
Patient/guardian decision	14 (4.2)	8 (2.4)	22 (3.3)
Adverse event	12 (3.6)	10 (3.0)	22 (3.3)
Physician decision	8 (2.4)	19 (5.6)	27 (4.0)
Death	3 (0.9)	3 (0.9)	6 (0.9)
Lost to follow-up	2 (0.6)	0	2 (0.3)
Protocol deviation	0	2 (0.6)	2 (0.3)
Entered post-treatment follow-up[2]	12 (7.5)	9 (4.2)	21 (5.6)
No longer being followed in post-treatment follow-up	8 (5.0)	6 (2.8)	14 (3.7)
Continued to be followed in post-treatment follow-up	4 (2.5)	3 (1.4)	7 (1.9)
Reason for end of post-treatment follow-up[3]			
Progressive disease	6 (50.0)	3 (33.3)	9 (42.9)
Patient/guardian decision	2 (16.7)	1 (11.1)	3 (14.3)
Death	0	1 (11.1)	1 (4.8)
Physician decision	0	1 (11.1)	1 (4.8)
Entered survival follow-up[2]	133 (82.6)	195 (90.3)	328 (87.0)

[1]Patients continue study treatment at the time of the cut-off 20 AUG 2017.
[2]The percentages of patients who entered post-treatment follow-up and the percentage of patients who entered survival follow-up use the number discontinued from treatment as the denominator.
[3]Patients who enter and then discontinue from the post-treatment follow-up phase at the end of post-treatment follow-up. In this section the denominator=the number of patients who entered post-treatment follow-up.
Source: Study E2301-Table 14.1-1.3

Protocol Violations/Deviations

Overall, the number of major protocol deviations (deviations leading to exclusion from the per-protocol set) was low (1.3%), with no imbalance evident across the two treatment arms. Given the size of the study, these deviations did not impact the overall results (Table 7-3).

Table 7-3 Protocol deviations leading to exclusion from the Per-protocol set – Study E2301

Protocol deviation	Ribociclib 600 mg	Placebo	All patients

	N = 335	N = 337	N = 672
	n (%)	n (%)	n (%)
Any protocol deviation	5 (1.5)	4 (1.2)	9 (1.3)
Selection criteria not met	5 (1.5)	4 (1.2)	9 (1.3)
Criteria for measureable disease not met	3 (0.9)	1 (0.3)	4 (0.6)
Menopausal status not met (patient is neither pre- nor perimenopausal)	2 (0.6)	2 (0.6)	4 (0.6)
Criteria for prior therapy for advanced breast cancer not met	0	1 (0.3)	1 (0.1)
A patient with multiple protocol deviations within a category is counted only once in the category. Patients may have protocol deviations in more than one protocol deviation category Source Study E2301-Table 14.1-1.7			

The FDA's Assessment:

The FDA agrees with the results presented in this section.

Demographic Characteristics

Demographic and baseline disease characteristics were balanced between the two treatment arms. The median age of patients was 44 years (range: 25 to 58 years), within the age limit specified in the inclusion criteria of the study. Overall, 672 patients were enrolled from 30 countries and 205 sites, with a broad representation of race and ethnicities (30.1% were of other ethnicities, 19.5% were east Asian, 13.7 were Hispanic or Latino, and in 11.6% patients ethnicity was not reported) reflecting the countries and regions that participated in the study (Table 7-4).

Table 7-4 Demographic and baseline characteristics – Study E2301

	Ribociclib 600 mg	Placebo	All patients
	N = 335	N = 337	N = 672
Demographic variable			
Age (years)			
Mean (standard deviation)	42.6 (6.6)	43.7 (6.17)	43.1 (6.4)
Median (min-max)	43 (25 - 58)	45 (29 -58)	44 (25 -58)
Age category (years) - n (%)			
<40	98 (29.3)	88 (26.1)	186 (27.7)
≥ 40	237 (70.7)	249 (73.9)	486 (72.3)
Race - n (%)			
Caucasian	187 (55.8)	201 (59.6)	388 (57.7)
Asian	99 (29.6)	99 (29.4)	198 (29.5)
Black	10 (3.0)	9 (2.7)	19 (2.8)
Native American	3 (0.9)	3 (0.9)	6 (0.9)
Other	16 (4.8)	7 (2.1)	23 (3.4)
Unknown	20 (6.0)	18 (5.3)	38 (5.7)

	Ribociclib 600 mg	Placebo	All patients
	N = 335	N = 337	N = 672
Demographic variable			
Ethnicity - n (%)			
East Asian	62 (18.5)	69 (20.5)	131 (19.5)
Hispanic or Latino	49 (14.6)	43 (12.8)	92 (13.7)
West Asian	26 (7.8)	27 (8.0)	53 (7.9)
Southeast Asian	19 (5.7)	16 (4.7)	35 (5.2)
South Asian	9 (2.7)	8 (2.4)	17 (2.5)
Russian	5 (1.5)	3 (0.9)	8 (1.2)
Mixed ethnicity	1 (0.3)	2 (0.6)	3 (0.4)
Other	99 (29.6)	103 (30.6)	202 (30.1)
Not Reported	42 (12.5)	36 (10.7)	78 (11.6)
Unknown	23 (6.9)	30 (8.9)	53 (7.9)
Region - n (%)			
Europe and Australia	136 (40.6)	139 (41.2)	275 (40.9)
Asia	92 (27.5)	88 (26.1)	180 (26.8)
North America	47 (14.0)	50 (14.8)	97 (14.4)
Latin America	31 (9.3)	25 (7.4)	56 (8.3)
Other	29 (8.7)	35 (10.4)	64 (9.5)
ECOG performance status – n (%) at baseline			
0	245 (73.1)	255 (75.7)	500 (74.4)
1	87 (26.0)	78 (23.1)	165 (24.6)
2	0	1 (0.3)	1 (0.1)
Missing	3 (0.9)	3 (0.9)	6 (0.9)
Source: Study E2301-Table 14.1-3.1			

Other baseline characteristics (e.g., disease characteristics, important concomitant drugs)
Randomization was stratified according to the presence of liver and/or lung metastases (yes/no), prior chemotherapy for advanced disease (yes/no), and endocrine combination partner (tamoxifen/NSAI). Stratification factors per IRT are summarized in Table 7-5.

Table 7-5: Randomization by stratification factor – Study E2301

Stratification factor at randomization	Ribociclib 600 mg N=335 n (%)	Placebo N=337 n (%)	All Patients N=672 n (%)
Lung and/or liver metastases			
Yes	171 (51.0)	173 (51.3)	344 (51.2)
No	164 (49.0)	164 (48.7)	328 (48.8)
Prior chemotherapy for advanced disease			
Yes	60 (17.9)	60 (17.8)	120 (17.9)
No	275 (82.1)	277 (82.2)	552 (82.1)
Endocrine combination partner			
Tamoxifen and goserelin	90 (26.9)	89 (26.4)	179 (26.6)
NSAI and goserelin	245 (73.1)	248 (73.6)	493 (73.4)

- Strata as entered in the IRT during randomization
Source: Study E2301 - Table 14.1-1.4

The FDA's Assessment:

The FDA agrees with the results presented. The variables were well balanced across the arms.

Patients enrolled in Study 2 had a median age of 44 years (range 25 to 58) and were primarily Caucasian (58%), Asian (30%), 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 (Table 7-4, Table 7-5, Table 7-6, Table 7-7, Table 7-8).

Table 7-6: Disease history – Study E2301

Disease characteristics	Ribociclib 600 mg N = 335 n (%)	Placebo N = 337 n (%)	All patients N = 672 n (%)
Primary site of cancer – n (%)			
Breast	335 (100.0)	337 (100.0)	672 (100.0)
Histological grade – n (%)			
Well differentiated	28 (8.4)	26 (7.7)	54 (8.0)
Moderately differentiated	146 (43.6)	145 (43.0)	291 (43.3)
Poorly differentiated	91 (27.2)	92 (27.3)	183 (27.2)
Undifferentiated	1 (0.3)	4 (1.2)	5 (0.7)
Unknown	68 (20.3)	70 (20.8)	138 (20.5)
Missing	1 (0.3)	0	1 (0.1)

Disease characteristics	Ribociclib 600 mg	Placebo	All patients
	N = 335	N = 337	N = 672
	n (%)	n (%)	n (%)
Stage at initial diagnosis – n (%)			
0	4 (1.2)	3 (0.9)	7 (1.0)
I	24 (7.2)	30 (8.9)	54 (8.0)
II	91 (27.2)	89 (26.4)	180 (26.8)
III	69 (20.6)	66 (19.6)	135 (20.1)
IV	140 (41.8)	135 (40.1)	275 (40.9)
Unknown	7 (2.1)	14 (4.2)	21 (3.1)
Disease status at study entry– n (%)			
Locally advanced	1 (0.3)	1 (0.3)	2 (0.3)
Distant metastatic	334 (99.7)	336 (99.7)	670 (99.7)
Disease free interval - n (%) [1]			
De novo	136 (40.6)	134 (39.8)	270 (40.2)
Non de novo	199 (59.4)	203 (60.2)	402 (59.8)
≤ 12 months	23 (6.9)	13 (3.9)	36 (5.4)
>12 months	176 (52.5)	190 (56.4)	366 (54.5)
Types of lesions at baseline-n (%)			
Both target and non-target	244 (72.8)	247 (73.3)	491 (73.1)
Non-target only	66 (19.7)	62 (18.4)	128 (19.0)
Target only	25 (7.5)	28 (8.3)	53 (7.9)
Current extent of disease (metastatic sites) – n (%)			
Bone	251 (74.9)	247 (73.3)	498 (74.1)
Bone only metastasis	81 (24.2)	78 (23.1)	159 (23.7)
Visceral	193 (57.6)	188 (55.8)	381 (56.7)
Lung or Liver	173 (51.6)	170 (50.4)	343 (51.0)
Liver	105 (31.3)	115 (34.1)	220 (32.7)
Lung	106 (31.6)	88 (26.1)	194 (28.9)
Other [2]	53 (15.8)	42 (12.5)	95 (14.1)
Lymph nodes	142 (42.4)	158 (46.9)	300 (44.6)
Soft Tissue	25 (7.5)	21 (6.2)	46 (6.8)
Skin	8 (2.4)	8 (2.4)	16 (2.4)
None	1 (0.3)	0	1 (0.1)
Number of metastatic sites - n (%)			
0	1 (0.3)	0	1 (0.1)
1	112 (33.4)	117 (34.7)	229 (34.1)
2	106 (31.6)	99 (29.4)	205 (30.5)
3	61 (18.2)	75 (22.3)	136 (20.2)
4	41 (12.2)	32 (9.5)	73 (10.9)
≥ 5	14 (4.2)	14 (4.2)	28 (4.2)

Disease characteristics	Ribociclib 600 mg	Placebo	All patients
	N = 335	N = 337	N = 672
	n (%)	n (%)	n (%)
[1] De novo includes patients with no first recurrence/progression or first recurrence/progression within 90 days of diagnosis with no prior antineoplastic medication. For non-de novo patients, DFI is the time from initial diagnosis to first recurrence/progression. [2] Other visceral includes any metastatic site other than soft tissue, bone, lung, liver, skin, and lymph nodes Source: Study E2301-Table 14.1-3.2			

Table 7-7: Endocrine therapy and receptor status (FAS) – Study E2301

Disease history	Ribociclib 600 mg N = 335	Placebo N = 337	All patients N = 672
(Neo-) adjuvant endocrine therapy – (n%)			
No prior (neo-) adjuvant endocrine therapy	208 (62.1)	196 (58.2)	404 (60.1)
Progression on or within 12 months of end of endocrine therapy	100 (29.9)	105 (31.2)	205 (30.5)
Progression >12 months after end of endocrine therapy	25 (7.5)	35 (10.4)	60 (8.9)
Missing[1]	2 (0.6)	1 (0.3)	3 (0.4)
HER2 receptor status – n (%)			
Negative	335 (100.0)	337 (100.0)	672 (100.0)
Estrogen receptor status – n (%)			
Positive	331 (98.8)	335 (99.4)	666 (99.1)
Negative	4 (1.2)	2 (0.6)	6 (0.9)
Progesterone receptor status – n (%)			
Positive	290 (86.6)	288 (85.5)	578 (86.0)
Negative	45 (13.4)	49 (14.5)	94 (14.0)
Estrogen and/or progesterone receptor status – n (%)			
At least one positive	335 (100.0)	337 (100.0)	672 (100.0)
Source: [Study E2301-Table 14.1-3.2]			

Table 7-8: Prior antineoplastic therapy – Study E2301

Characteristics	Ribociclib 600 mg N = 335 n (%)	Placebo N = 337 n (%)	All patients N = 672 n (%)
Surgery (biopsy)			
Yes	195 (58.2)	213 (63.2)	408 (60.7)
No	140 (41.8)	124 (36.8)	264 (39.3)

Characteristics	Ribociclib 600 mg N = 335 n (%)	Placebo N = 337 n (%)	All patients N = 672 n (%)
Radiotherapy			
Yes	161 (48.1)	183 (54.3)	344 (51.2)
No	174 (51.9)	154 (45.7)	328 (48.8)
Medication (systemic therapy)			
Yes	206 (61.5)	205 (60.8)	411 (61.2)
No	129 (38.5)	132 (39.2)	261 (38.8)
Medication setting[1]			
Adjuvant	157 (46.9)	158 (46.9)	315 (46.9)
Neoadjuvant	62 (18.5)	62 (18.4)	124 (18.5)
Therapeutic	49 (14.6)	49 (14.5)	98 (14.6)
Medication: chemotherapy setting[1]			
Adjuvant	109 (32.5)	110 (32.6)	219 (32.6)
Neoadjuvant	60 (17.9)	61 (18.1)	121 (18.0)
Therapeutic	47 (14.0)	47 (13.9)	94 (14.0)
Medication: hormonal therapy setting1			
Adjuvant	126 (37.6)	140 (41.5)	266 (39.6)
Neoadjuvant	2 (0.6)	3 (0.9)	5 (0.7)
Therapeutic	1 (0.3)	3 (0.9)	4 (0.6)
Type of last therapy			
Radiotherapy	103 (30.7)	105 (31.2)	208 (31.0)
Hormonal therapy	60 (17.9)	62 (18.4)	122 (18.2)
Chemotherapy	42 (12.5)	52 (15.4)	94 (14.0)
Surgery	48 (14.3)	30 (8.9)	78 (11.6)
Other	8 (2.4)	6 (1.8)	14 (2.1)
Setting of last therapy			
Adjuvant	118 (35.2)	128 (38.0)	246 (36.6)
Neoadjuvant	0	2 (0.6)	2 (0.3)
Palliative	50 (14.9)	47 (13.9)	97 (14.4)
Therapeutic	38 (11.3)	43 (12.8)	81 (12.1)
Not applicable	48 (14.3)	30 (8.9)	78 (11.6)

[1]A patient may have multiple settings
Metastatic setting is any antineoplastic agent given to treat the cancer except in the adjuvant and neo-adjuvant setting
Biopsies are excluded when identifying last therapy; last therapy is identified based on start date;
Setting at last therapy and best response at last therapy was set to 'Not applicable' if the type of last therapy is surgery (non-biopsy)
Source: Study E2301-Table 14.1-3.6

The FDA's Assessment:

The FDA agrees with the baseline characteristics presented by the applicant. The results were well balanced across the two treatment arms.

Prior hormonal therapy for advanced disease

Patients were allowed to have received ≤ 14 days of tamoxifen or NSAI, or goserelin ≤ 28 days for advanced breast cancer prior to randomization. Endocrine therapies received by patients as their prior hormonal therapy for advanced disease are summarized in Study E2301-Table 14.1-3.8.

Treatment compliance, concomitant medications and rescue medication

Treatment compliance

No formal treatment compliance measurements for ribociclib plus NSAI and placebo plus either NSAI were performed. The Investigator assessed the compliance by examining the records of drug administration and the numbers of boxes as well as the tablets/capsules dispensed, received, and returned.

Concomitant medications

Anilides (42.1% in both treatment groups) and non-steroidal anti-inflammatories (approximately 36% in both treatment groups) were the most commonly prescribed concomitant medication in both treatment groups. Concomitant use of bisphosphonates was also similar between ribociclib and placebo groups (24.8% vs. 24.9%, respectively) Study E2301-Table 14.32.1.

Rescue medication

Not applicable as no rescue medication were allowed in the study.

The FDA's Assessment:

The FDA agrees with the results in this section.

Efficacy results-Primary endpoint (Including Sensitivity Analyses)

Progression Free Survival

The ribociclib arm demonstrated clear superiority over the placebo arm for the primary endpoint of PFS per investigator assessment. A 44.7% estimated relative risk reduction was evident in the PFS endpoint per Investigator assessment in favor of the ribociclib arm (HR = 0.553; 95% CI: 0.441, 0.694; one sided p-value <0.0001). Median PFS was prolonged by 10.8 months, from 13.0 months (95% CI: 11.0, 16.4) for patients in the placebo arm to 23.8 months (95% CI: 19.2, NE) for patients in the ribociclib arm (Table 7-9 and Figure 7-2).

Robustness of the primary analysis was confirmed by results of the PFS analysis per central BIRC review. The imaging data from approximately 40% of total randomized patients (n = 267) in study were reviewed using the BIRC audit-based approach. Results of the PFS analysis per BIRC yielded a 57.3% relative risk reduction (HR = 0.427; 95% CI: 0.288, 0.633) was evident in the PFS

endpoint in favor of the ribociclib arm, verifying the results of the Investigator-assessed PFS (Table 7-9 and Figure 7-3).

Two methods were used to determine whether a 100% BIRC review should be conducted (NCI method (Study E2301-Table 14.2-1.3); and the PhRMA method (Study E2301-Table 14.2-1.4). Based on the results, the pre-specified thresholds that would have triggered a full BIRC review of all patients' data were not met and the full central review was therefore not performed.

Table 7-9: Progression free survival – Study E2301

	Investigator assessment		**BIRC assessment**	
	Ribociclib plus NSAI/Tamoxifen	**Placebo plus NSAI/Tamoxifen**	**Ribociclib plus NSAI/Tamoxifen**	**Placebo plus NSAI/Tamoxifen**
	N = 335	**N = 337**	**N = 133**	**N = 134**
Category	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Number of events - n (%)	**131 (39.1)**	**187 (55.5)**	40 (30.1)	72 (53.7)
Progression	128 (38.2)	183 (54.3)	39 (29.3)	71 (53.0)
Death[1]	3 (0.9)	4 (1.2)	1 (0.8)	1 (0.7)
Number censored - n (%)	204 (60.9)	150 (44.5)	93 (69.9)	62 (46.3)
P-value ribociclib + NSAI/Tamoxifen vs. placebo + NSAI/Tamoxifen [2]	**<0.0001**		-	
Hazard ratio (95% CI) ribociclib + NSAI/Tamoxifen vs. placebo + NSAI/Tamoxifen [3]	**0.553 (0.441, 0.694)**		**0.427 (0.288, 0.633)**	

	Investigator assessment		BIRC assessment	
	Ribociclib plus NSAI/Tamoxifen	Placebo plus NSAI/Tamoxifen	Ribociclib plus NSAI/Tamoxifen	Placebo plus NSAI/Tamoxifen
	N = 335	N = 337	N = 133	N = 134
Category	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Percentiles (95% CI)				
25th percentile	10.6 (7.4, 12.8)	5.6 (3.6, 7.2)	12.8 (7.2, 17.4)	3.7 (2.0, 5.5)
Median	23.8 (19.2, NE)	13.0 (11.0, 16.4)	NE (19.9, NE)	11.1 (7.4, 16.9)
75th percentile	NE (27.5, NE)	NE (24.2, NE)	NE (NE, NE)	NE (22.1, NE)

BIRC=Blinded Independent Review Committee, CI=confidence interval, NE=not estimable, [1] Death before progression

[2] One-sided p-value obtained from log-rank test stratified by liver and/or lung metastases, prior chemotherapy for advanced disease, and endocrine combination partner per IRT

[3] Hazard ratio obtained from Cox PH model stratified by liver and/or lung metastases, prior chemotherapy for advanced disease, and endocrine combination partner per IRT

Source: Study E2301-Table 14.2-1.1, Study E2301-Table 14.2-1.13, Study E2301-Table 14.2-1.2, Study E2301-Table 14.2-1.14, Study E2301-Table 14.2-1.19, Study E2301-Table 14.2-1.20.

Figure 7-2: Progression-free survival per Investigator – Study E2301 (FAS)

Source: Study E2301-Figure 14.2-1.1

Figure 7-3: Progression-free survival per BIRC assessment – Study E2301 (FAS)

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Source: Study E2301- Figure 14.2-1.2

The FDA's Assessment:
The FDA agrees with the results and conclusions presented by the applicant.

PFS analysis based on endocrine partner
The addition of ribociclib to NSAI treatment resulted in a 43.1% relative risk reduction (HR = 0.569; 95% CI 0.436, 0.743) in the hazard rate of progression/death was observed, with a 13.7-month prolongation in median PFS. The median PFS was 27.5 months (95% CI: 19.1, NE) and 13.8 months (95% CI: 12.6, 17.4) in the ribociclib and placebo arms, respectively. The K-M PFS curves diverged early at two months indicating the early consistent separation favoring the ribociclib arm. This trend was as observed for the full population (Table 7-10 and Figure 7-4).

Table 7-10: PFS per Investigator assessment by subgroups of endocrine combination partner – Study E2301 (FAS)

	Combination partner: NSAI and goserelin		**Combination partner: tamoxifen and goserelin**	
	Ribociclib	**Placebo**	**Ribociclib**	**Placebo**
	N=248	**N=247**	**N=87**	**N=90**
Number of events – n (%)	**92 (37.1)**	**132 (53.4)**	**39 (44.8)**	**55 (61.1)**
Progression	92 (37.1)	129 (52.2)	36 (41.4)	54 (60.0)
Death [1]	0	3 (1.2)	3 (3.4)	1 (1.1)
Number censored – n (%)	**156 (62.9)**	**115 (46.6)**	**48 (55.2)**	**35 (38.9)**

	Combination partner: NSAI and goserelin		Combination partner: tamoxifen and goserelin	
	Ribociclib	**Placebo**	**Ribociclib**	**Placebo**
	N=248	**N=247**	**N=87**	**N=90**
Hazard ratio (95% CI) ribociclib vs. placebo [2]	**0.569 (0.436, 0.743)**		**0.585 (0.387, 0.884)**	
Percentiles (95% CI)				
25th percentile	11.0 (7.5, 13.0)	3.8 (3.3, 7.2)	7.5 (3.9, 12.8)	7.4 (5.6, 9.0)
Median	27.5 (19.1, NE)	13.8 (12.6, 17.4)	22.1 (16.6, 24.7)	11.0 (9.1, 16.4)
75th percentile	NE (27.5, NE)	NE (24.2, NE)	24.7 (23.0, NE)	19.4 (16.9, NE)

NE=Not estimable
N is the number of patients in each treatment arm assigned to the corresponding combination partner in the CRF.
[1] Death before progression
[2] Hazard ratio is obtained from unstratified Cox PH model
Source: Study E2301-Table 14.2-1.35

Figure 7-4: Kaplan-Meier plot of progression-free survival per Investigator assessment by endocrine combination partner-NSAI – Study E2301 (FAS)

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Source: Study E2301-Figure 14.2-1.1a

The FDA's Assessment:
The FDA agrees with the results presented by the applicant.

Sensitivity and supportive analyses

Several supportive and sensitivity analyses were performed to assess the overall robustness of the primary efficacy results. Supportive analysis included repeating the primary efficacy analysis using the data obtained through blinded independent central review (BIRC) of tumor assessment based on an audit-based approach.

Sensitivity analyses conducted included repeating the primary PFS analysis using the Per Protocol Set (PPS), different censoring rules, and using an unstratified log-rank test to compare the two treatment arms.

Supportive analysis of PFS

PFS assessed by blinded independent review committee (BIRC) was used in this study as a supportive analysis of the primary endpoint. Study protocol Amendment 3 (dated 24-Jun-2016) included the change of approach for BIRC assessment of PFS from a full read to an audit (sample) based approach, and this audit-based methodology for Study E2301 was agreed upon per health authority correspondence.

The two methods used to determine whether a 100% BIRC review should be conducted were the NCI method and the PhRMA method. The NCI method HR estimate was 0.465 (90% CI: 0.36, 0.61), while the differential discordance of early and late discrepancy rates based on the PhRMA method were 10.5% and -14.7% respectively. Based on these results, the pre-specified triggers for a full BIRC review of all patients' data were not met, and therefore, a full BIRC review was not conducted.

Robustness of the primary analysis was confirmed by results of the PFS analysis per central BIRC review. Results of the PFS analysis per the BIRC review yielded a 57.3% relative risk reduction (HR = 0.427; 95% CI: 0.288, 0.633) in favor of the ribociclib arm, verifying the results of the Investigator-assessed PFS.

Sensitivity analysis of PFS

Multiple sensitivity and supportive analyses demonstrated the observed PFS benefit was robust and consistent across relevant prognostic categories, with HRs ranging from 0.516 (95% CI: 0.410, 0.651) to 0.573 (95% CI: 0.458, 0.716) (Table 7-11).

Table 7-11: Sensitivity analyses of PFS per Investigator assessment – Study E2301(FAS)

Sensitivity analysis	Median PFS (95% CI)	p-value	Hazard ratio (95% CI)
Primary analysis			
Ribociclib 600 mg	23.8 (19.2, NE)	9.83×10^{-8}	0.553 (0.441, 0.694)
Placebo	13.0 (11.0, 16.4)		
Unstratified log-rank test and Cox model			

Ribociclib 600 mg	23.8 (19.2, NE)	3.85×10^{-7}	0.573 (0.458, 0.716)
Placebo	13.0 (11.0, 16.4)		
Stratified Cox model, adjusting for baseline covariates [1]			
Ribociclib 600 mg	23.8 (19.2, NE)	9.83×10^{-8}	0.516 (0.410, 0.651)
Placebo	13.0 (11.0, 16.4)		
'Actual event' [2]			
Ribociclib 600 mg	23.8 (19.2, NE)	1.62×10^{-7}	0.562 (0.449, 0.703)
Placebo	12.9 (11.0, 16.4)		
'Backdating' [3]			
Ribociclib 600 mg	23.8 (19.2, NE)	7.36×10^{-8}	0.553 (0.442, 0.692)
Placebo	12.9 (10.9, 15.6)		
'Censoring for antineoplastic therapy' [4]			
Ribociclib 600 mg	23.8 (19.4, NE)	1.21×10^{-7}	0.551 (0.438, 0.693)
Placebo	13.3 (11.1, 16.5)		

CI Confidence interval; PFS Progression-free survival

[1] Baseline covariates included in the Cox proportional hazard model are ECOG performance status (0 vs. ≥ 1), bone only lesion at baseline (yes vs. no), age (< 40 vs. ≥ 40 years), and prior (neo-)adjuvant endocrine therapy (ET) (none; yes – progression while on or within 12 months of end of (neo-)adjuvant ET; yes –progression > 12 months after end of (neo-)adjuvant ET)

[2] Analysis includes the event whenever it occurred even after ≥ 2 missing tumor assessments

[3] Analysis uses the date of the next scheduled assessment for events occurring after ≥ 1 missing assessment

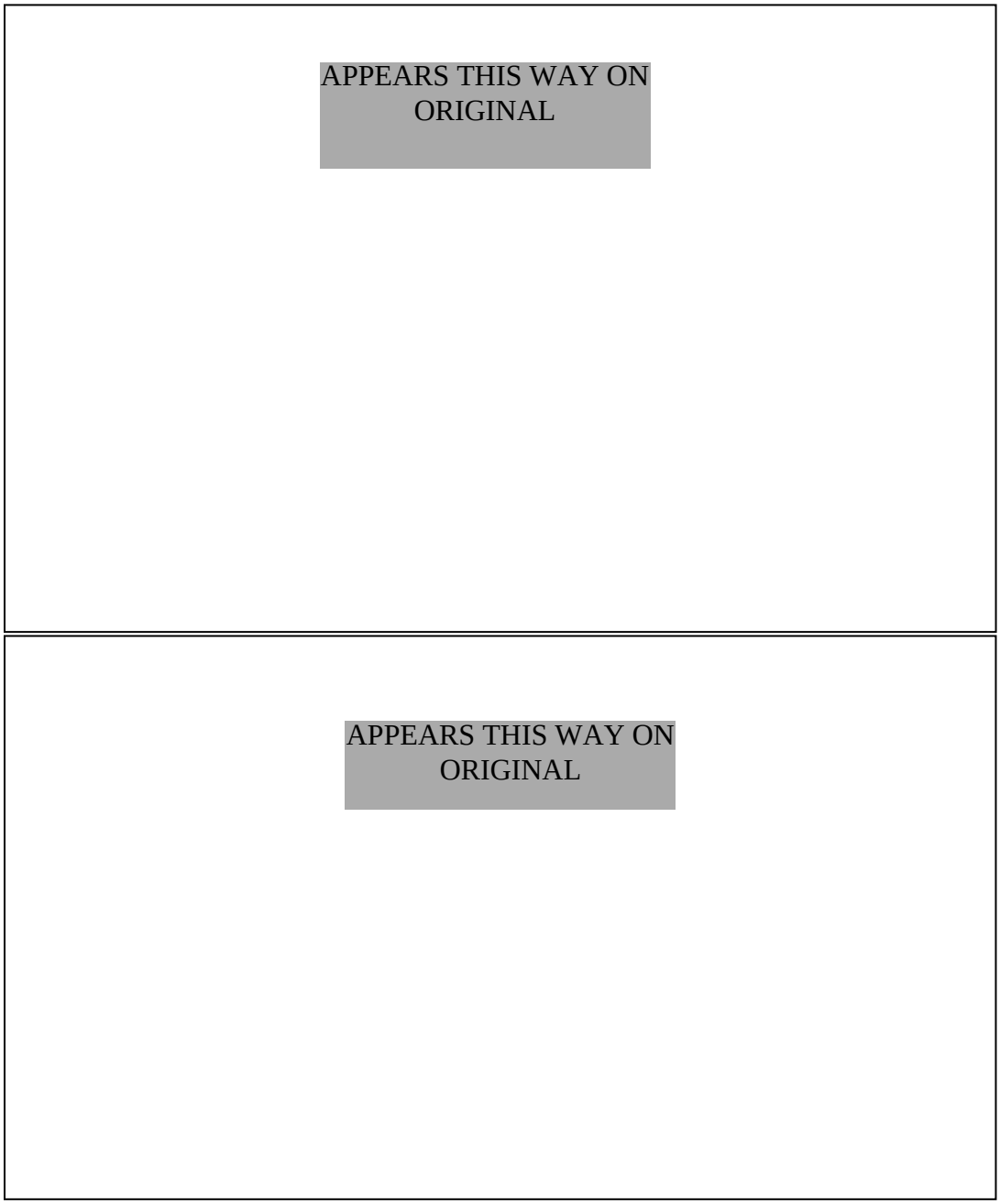
[4] Analysis performed by censoring patients at start of new antineoplastic therapy- p-values make no adjustment for multiple testing

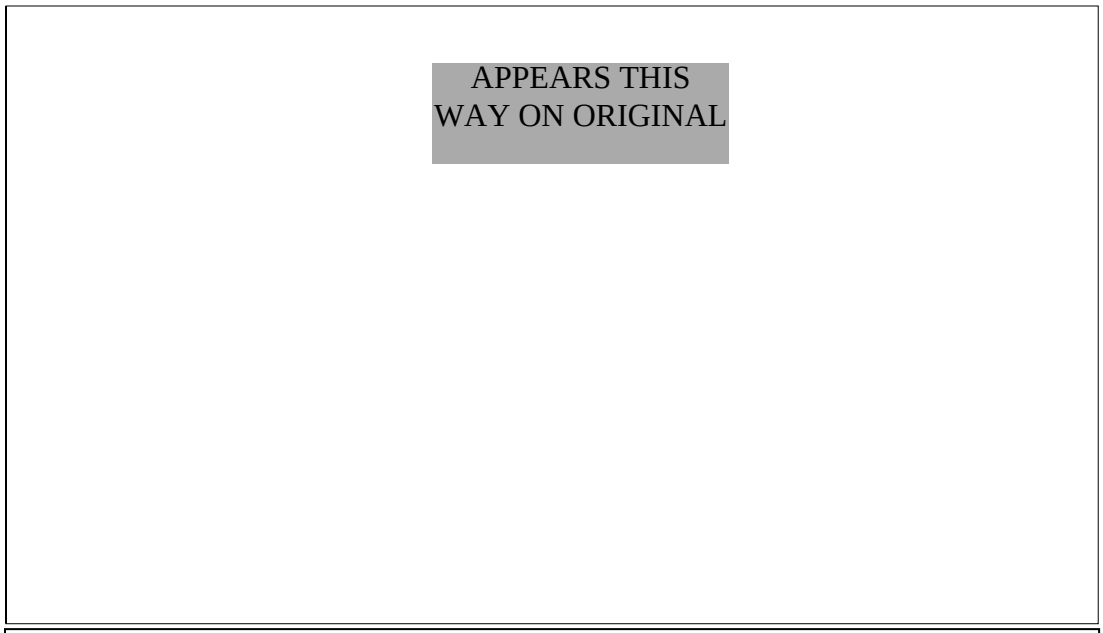
Source: Study E2301-Table 11-12, Study E2301-Table 14.2-1.1, Study E2301-Table 14.2-1.6, Study E2301-Table 14.2-1.7, Study E2301-Table 14.2-1.8, Study E2301-Table 14.2-1.11, and Study E2301-Table 14.21.12.

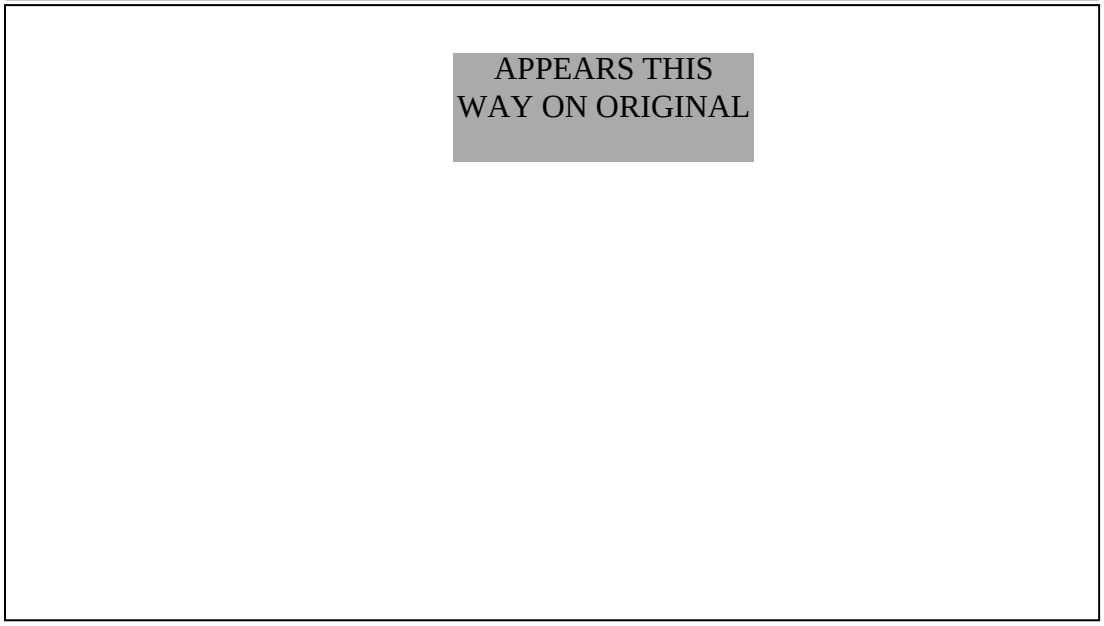
PFS subgroup analyses

Subgroup analyses of PFS were repeated within the NSAI subgroup, and homogeneity and consistency of PFS was evident across most of the subgroups assessed, with HRs favoring the ribociclib arm (Figure 7-5).

Figure 7-5: PFS by subgroups per Investigator assessment - ribociclib plus NSAI subgroup (Study E2301-FAS)







1] Prior chemotherapy in metastatic setting; [2] Adjuvant or neo-adjuvant chemotherapy in patients with no prior chemotherapy in metastatic setting.
Source: Study E2301-Figure 14.2-1.3b.

The FDA's Assessment:

The FDA agrees with the results presented by the applicant, except for the presentation of the p-values. Since these are exploratory analyses, these p-values should be considered nominal only. For patients in the USA (N=45), the hazard ratio was 0.468 (95% CI: 0.173, 1.267) in favor of the ribociclib arm.

Secondary efficacy results

Overall survival-key secondary endpoint

Overall survival (OS) data were immature with 89 deaths (of the 252 deaths planned for the final OS analysis) occurring up to the data cut-off date, 43/335 (12.8%) in the ribociclib arm and 46/337 (13.6%) in the placebo arm.

The FDA's Assessment:

The FDA agrees with the applicant that the OS data is immature at the time of the final PFS analysis. Nevertheless, the data do not indicate any harm or detriment to survival at this juncture. In the NSAI group (the one for which the indication is given), the estimated hazard ratio for OS is 0.798 (95% CI: 0.491, 1.295) in favor of the ribociclib arm. In the ITT analysis set (N=672), the estimated hazard ratio for OS is 0.916 (95% CI: 0.601, 1.396) in favor of the ribociclib arm. At the time of this review, there were only 66 deaths reported in the NSAI subgroup (13.3%) and 89 deaths in the full ITT population (13.2%).

Efficacy Results – other Secondary and other relevant endpoints

Overall response rate and clinical benefit rate

Ribociclib combination was associated with improved ORR and CBR in all patients and also in patients with measurable disease at baseline. Ribociclib treatment was associated with earlier and durable responses. Numerical trends in favor of a shorter time to response and durable responses in the ribociclib arm were also seen in the subgroup of patients receiving NSAI (Table 7-11).

Table 7-12: Secondary efficacy results (Study E2301)

	Overall study population	**NSAI subgroup (N=248 ribociclib arm; 247 placebo arm)**
N	FAS = 335 ribociclib arm; 337 placebo arm Patients with measurable disease at baseline = 269 ribociclib arm; 275 placebo arm	All NSAI=248 ribociclib arm; 247 placebo arm Patients with measurable disease at baseline = 192 ribociclib arm; 199 placebo arm
ORR	All patients: 40.9% (95% CI: 35.6, 46.2) vs. 29.7% (95% CI: 24.8, 34.6) Patients with measurable disease at baseline: 50.9% (95% CI: 45.0, 56.9) vs. 36.4%.(95% CI: 30.7, 42.0)	All patients: 39.1% vs. 29.1% Patients with measurable disease at baseline: 50.5% vs. 36.2%
CBR	All patients: 79.1% (95% CI: 74.8, 83.5) vs. 69.7% (95% CI: 64.8, 74.6) Patients with measurable disease at baseline: 79.9% (95% CI: 75.1, 84.7) vs. 67.3% (95% CI: 61.7, 72.8)	All patients: 80.2% vs. 67.2% Patients with measurable disease at baseline: 81.8% vs. 63.8%.

TTR	Estimated probability of a response by 2 months: 18.4% (95% CI: 14.6, 23.1) vs. 10.5% (95% CI: 7.6, 14.3)	Estimated probability of a response by 2 months: 19.7% (95% CI: 15.2, 25.3) vs. 10.5% (95% CI: 7.2, 15.1)
DOR	Median duration of response 21.3 months (95% CI: 18.3, NE) vs. 17.5 months (95% CI: 12.0, NE)	Median duration of response in the ribociclib arm was not reached (95% CI: 18.3, NE) and was 17.5 months (95% CI: 12.0, NE) in the placebo arm
Source: SCE Study E2301-Table 3-17, SCE Study E2301-Table 3-18, Study E2301-Table 14.2-1.25, Study E2301-Table 14.2-1.25a, Study E2301-Figure 14.2-1.6, Study E2301-Figure 14.2-1.6a, Study E2301-Table 14.2-1.28, Study E2301-Table 14.2-1.28b, Study E2301-Table 14.2-1.29		

The FDA's Assessment:

The FDA agrees with the results presented by applicant; however, the FDA does not concur with the interpretation of the results (ORR, CBR, TTR, DOR) in the paragraph directly above Table 7-12. To be specific, the FDA does not concur with the use of the phrases "improved ORR and CBR," "earlier and durable responses," and "shorter time to response and durable responses."

Time to deterioration of ECOG PS

Time to definitive deterioration in overall study population in Eastern Cooperative Oncology Group performance status (ECOG PS) showed no differences between the two treatment arms with an HR of 0.781 (95% CI: 0.524, 1.166; one-sided p = 0.113). Median time to definitive deterioration in ECOG performance status by one category of the score was not reached in both the treatment arms (Study E2301-Table 11-17 and Study E2301-Table 14.2-3.18).

Patient-reported outcomes

Results of QoL analyses in overall study population, with regard to the time to definitive 10% deterioration of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) global health scale score favored the ribociclib arm with an HR of 0.699 (95% CI: 0.533, 0.916: p = 0.004). Median time to definitive 10% deterioration of the EORTC QLQ-C30 global health score was not reached for the ribociclib arm and was 21.2 months in the placebo arm (Study E2301-Table 14.2-3.8a).

A numerical trend in favor of ribociclib was seen in the time to definitive 10% deterioration of the physical functioning scale and emotional functioning scale of the QLQ-C30, with HRs of 0.742 (95% CI: 0.542, 1.017; p=0.031) and 0.723 (95% CI: 0.551, 0.951; p=0.010), respectively. Trends in the social functioning scale were comparable between the arms (HR=0.912; 95% CI 0.679, 1.226; p=0.274) (Study E2301-Figure 14.2-3.1b, Study E2301-Figure 14.2-3.1c, Study E2301-Figure 14.2-3.1d, Study E2301-Table 14.2-3.8b, Study E2301-Table 14.2-3.8c, Study E2301-Table 14.2-3.8d).

A numerical trend in favor of the ribociclib arm was seen in the measure of time to definitive 10% deterioration in the breast symptoms sub-scale of the QLQ-BR23 with an HR of 0.678 (95% CI: 0.446, 1.031: p = 0.034). A numerical trend in favor of the ribociclib arm was seen in the time to definitive 10% deterioration in the VAS scale score of the EORTC- EuroQoL 5-dimension questionnaire-5D-5L (EQ-5D-5L) (of overall health) with an HR of 0.675 (95% CI: 0.514, 0.888: p = 0.002) (Study E2301-Table 14.2-3.7e, Study E2301-Table 14.2-3.8e ,Study E2301-Figure 14 2-3.1e, Study E2301-Table 14.2-3.8f, Study E2301-Table 14.23.7f and Study E2301-Figure 14 23.1f). EQ-5D-5L measures the health status in five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). No relevant differences were observed in each of the five measures between the two treatment arms. Analyses of functional scales and symptom scales/items of WPAI-GH suggest no clinically meaningful changes from Baseline and no meaningful differences between treatment arms.

Overall, results of QoL analyses were not worse with ribociclib as compared with to placebo. In some instances, ribociclib combinations trended towards increased QoL as compared with NSAI and placebo.

The FDA's Assessment:

The applicant's position on the PRO data presented above was reviewed. FDA did not conduct separate analyses of the PROs. The applicant did not seek a PRO labeling indication.

7.1.3. Study F2301 (MONALEESA-3)

Study Design

This is an international, multicenter, randomized, double-blind, placebo-controlled Phase III trial designed to determine the efficacy and safety of treatment of ribociclib with fulvestrant versus fulvestrant with placebo.

Men and postmenopausal women with HR-positive HER2-negative advanced breast cancer were randomized in a 2:1 ratio to one of the following treatment arms:

- Ribociclib (600 mg orally once daily on Days 1-21 of a 28-day cycle) plus fulvestrant (500 mg intramuscular [im] injection on Cycle 1 Days 1 and 15 and on Day 1 of subsequent cycles).
- Placebo (orally once daily on Days 1-21 of a 28-day cycle) plus fulvestrant (500 mg im injection on Cycle 1 Days 1 and 15 and on Day 1 of subsequent cycles).

Randomization was stratified by the following factors:

1. Presence of lung and/or liver metastases (yes versus no).
2. Previous endocrine therapy defined as:

A) Patients treatment naive for metastatic/advanced disease include:

i. Patients whose disease relapsed >12 months after completion of (neo)adjuvant endocrine therapy with no subsequent treatment for advanced/metastatic disease,

OR

ii. Patients with de novo advanced/metastatic disease (no prior exposure to endocrine therapy).

B) Patients who received up to 1 line of treatment for metastatic/advanced disease include:

i. Patients whose disease relapsed on or within 12 months from completion of (neo) adjuvant endocrine therapy, with no subsequent treatment for advanced/metastatic disease,

OR

ii. Patients whose disease relapsed > 12 months from completion of (neo) adjuvant endocrine therapy, and progressed on or after subsequent endocrine treatment for advanced/metastatic disease,

OR

iii. Patients with advanced/metastatic disease at the time of diagnosis that progressed on or after endocrine therapy for advanced/metastatic disease with no prior (neo) adjuvant treatment for early disease.

The study consisted of four phases: the Screening phase (up to 28 days), treatment phase, efficacy follow-up, and survival follow-up (including progression on next-line therapy (PFS2) (Figure 7-7).

Screening phase: Men and postmenopausal women with HR-positive, HER2-negative advanced breast cancer were screened for eligibility during the period up to 28 days immediately prior to starting the combination of ribociclib plus fulvestrant or placebo plus fulvestrant on Study Day 1. During this time, the inclusion and exclusion criteria were assessed and all screening assessments, laboratory tests, and procedures were performed.

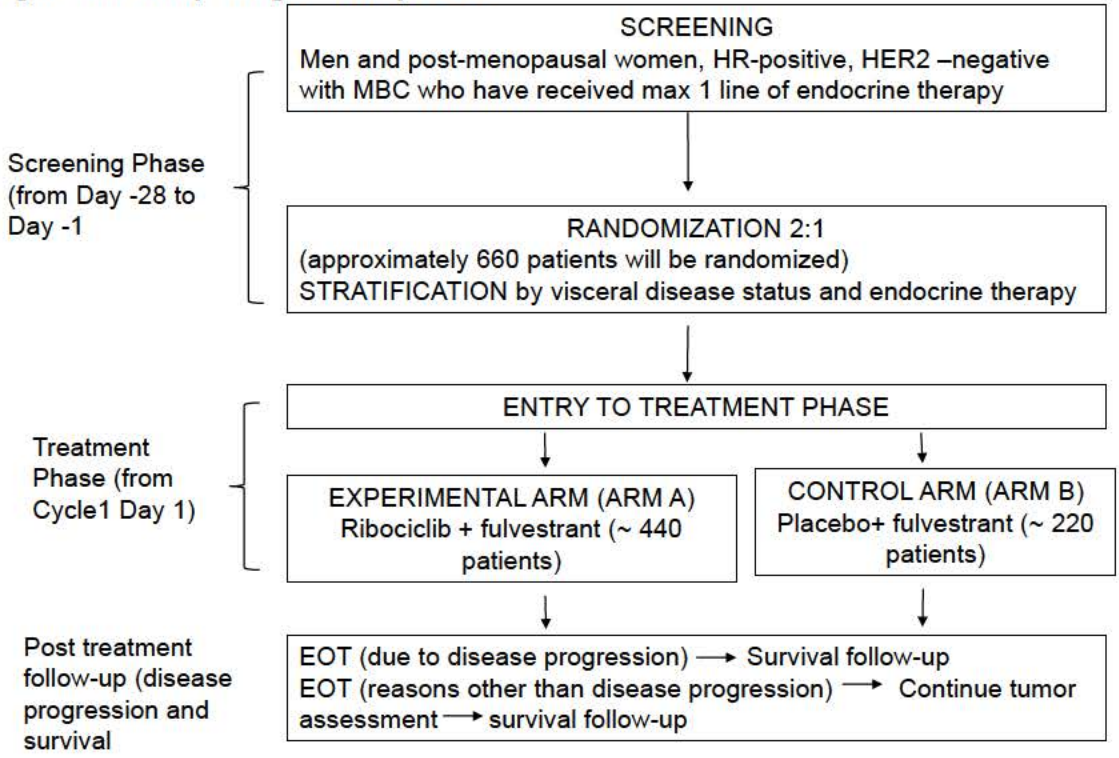
Treatment phase: Study treatment continued until disease progression, occurrence of unacceptable toxicity, withdrawal of consent by the patient, loss to follow-up, or termination of the study by the Sponsor.

Safety follow-up: All patients were followed-up for safety up to 30 days after the last dose of study treatment. For patients who discontinued due to an adverse event (AE) or an abnormal laboratory value were followed until resolution or stabilization of the event, whichever came first.

Efficacy follow-up: In this phase, patients who discontinued study treatment for reasons other than disease progression, death, withdrawal of consent, or loss to follow-up, were followed for efficacy (tumor assessments and PROs) every 8 weeks during the first 18 months and every 12 weeks thereafter (until disease progression, death, loss to follow-up, or any other reasons).

PFS2 and survival follow-up: In this phase, patients were followed for survival status every 12 weeks regardless of new antineoplastic therapy or any other treatment discontinuation reason, until death, loss to follow-up, or withdrawal of consent. In addition, information regarding the subsequent antineoplastic therapies initiated after study treatment discontinuation were collected to assess time to PFS2. Progression free survival 2 was defined as the time from the date of randomization to the first documented disease progression (clinical or radiologic) on next-line therapy or death from any cause, whichever occurred first.

Figure 7-6 Study Design – Study F2301



Study Design

The randomized, double-blind, placebo-controlled, multicenter, parallel-group design is the gold standard for Phase III trials as it minimizes allocation bias, balancing both known and unknown prognostic factors in the assignment of treatments. The efficacy and safety of fulvestrant is well characterized, so a randomization ratio of 2:1 (ribociclib plus fulvestrant versus placebo plus fulvestrant) was selected to allow better evaluation of the efficacy and safety of the ribociclib plus fulvestrant combination. The stratification factors (presence or absence of lung/liver metastases and previous endocrine therapy) were selected because of their well-recognized prognostic value.

Diagnostic Criteria

The patient population consisted of men and women with HR–positive, HER2-negative advanced breast cancer who received no or only one line of prior endocrine therapy.

Inclusion criteria

Patients eligible for inclusion in this study were required to meet **all** of the following criteria:

1. Adult male/female ≥ 18 years old at the time of informed consent and who signed the informed consent before any trial-related activities and according to local guidelines.
2. Female patients had to be postmenopausal. Postmenopausal status was defined either by
   - Prior surgical bilateral oophorectomy (with or without hysterectomy)
   - Age ≥ 60

- Age < 60 and amenorrheic for 12 or more months in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression, and follicle stimulating hormone and estradiol in the postmenopausal range per local normal range.

3. Patients with histologically and/or cytologically confirmed diagnosis of ER-positive and/or PgR-positive breast cancer by local laboratory (based on most recent analyzed biopsy).
4. Patients with HER2-negative breast cancer (based on most recent analyzed biopsy) defined as a negative in situ hybridization test or an immunohistochemistry (IHC) status of 0, 1+, or 2+. If IHC was 2+, a negative in situ hybridization (fluorescent in situ hybridization, chromosome in situ hybridization, or silver-enhanced in situ hybridization) test was required by local laboratory testing.
5. Patients with either
   - Measurable disease i.e. at least one measurable lesion per Response Evaluation Criteria In Solid Tumors (RECIST 1.1) (a lesion at a previously irradiated site was only counted as a target lesion if there was a clear sign of progression since the irradiation).

     OR
   - If no measurable disease was evident then at least one predominantly lytic bone lesion was to be present (patients with no measurable disease and only one predominantly lytic bone lesion that was previously irradiated were eligible if there was documented evidence of disease progression of the bone lesion after irradiation).
6. Patients with advanced (loco regionally recurrent not amenable to curative therapy (e.g. surgery and/or radiotherapy) or metastatic) breast cancer. Patient could be:
   - Newly diagnosed advanced/metastatic breast cancer, treatment naïve.
   - Relapsed with documented evidence of relapse more than 12 months from completion of (neo) adjuvant endocrine therapy with no treatment for advanced/metastatic disease.
   - Relapsed with documented evidence of relapse on or within 12 months from completion of (neo) adjuvant endocrine therapy with no treatment for advanced/metastatic disease.
   - Relapsed with documented evidence of relapse more than 12 months from completion of (neo) adjuvant endocrine therapy and then subsequently progressed with documented evidence of progression after one line of endocrine therapy (with either an anti-estrogen or an AI) for advanced/metastatic disease.
   - Advanced/metastatic breast cancer at diagnosis that progressed with documented evidence of progression after one line of endocrine therapy (with either an anti-estrogen or an AI).
     a. Note: Patients who relapsed with documented evidence of relapse on/or within 12 months from completion of (neo) adjuvant endocrine therapy and then subsequently progressed with documented evidence of progression after one line of endocrine therapy (with either an anti-estrogen or an AI) for metastatic/advanced disease were not included in the study.
7. Patients with ECOG PS 0 or 1.
8. Patients with adequate bone marrow and organ function as defined by the following laboratory values (as assessed by the central laboratory for eligibility):

- Absolute neutrophil count ≥ 1.5×10^9 /L
- Platelets ≥ 100×10^9 /L
- Hemoglobin ≥ 9.0 g/dL
- International normalized ratio of ≤ 1.5
- Serum creatinine < 1.5 mg/dL
- Total bilirubin less than the upper limit of normal (ULN) except for patients with Gilbert's syndrome who were to be included if the total bilirubin was ≤ 3.0×ULN or direct bilirubin ≤ 1.5×ULN
- Aspartate aminotransferase (AST) < 2.5×ULN, except for patients with liver metastasis, who were only included if the AST was < 5×ULN
- Alanine aminotransferase (ALT) < 2.5×ULN, except for patients with liver metastasis, who were only included if the ALT was < 5×ULN.

9. Patients with the following laboratory values within normal limits or corrected to within normal limits with supplements before the first dose of study medication: sodium, potassium, magnesium, and total calcium (corrected for serum albumin).

Exclusion criteria

Patients eligible for this study did **not** meet **any** of the following criteria:

1. Patients with symptomatic visceral disease or any disease burden that made the patient ineligible for endocrine therapy per the Investigator's best judgment.
2. Patients who received prior treatment with chemotherapy (except for neoadjuvant/adjuvant chemotherapy), fulvestrant, or any CDK4/6 inhibitor.
3. Patients who received prior neoadjuvant/adjuvant treatment with anthracyclines at cumulative doses of 450 mg/m² or more for doxorubicin or 900 mg/m² or more for epirubicin.
4. Patients with a known hypersensitivity to any of the excipients of ribociclib or fulvestrant.
5. Patients with inflammatory breast cancer at Screening.
6. Patients who were concurrently using other anticancer therapy.
7. Patients who had major surgery within 14 days prior to starting study drug or had not recovered from major side effects.
8. Patients with Child-Pugh score B or C.
9. Patients who were currently receiving warfarin or other coumarin-derived anticoagulants, for treatment, prophylaxis, or otherwise. Therapy with heparin, low molecular weight heparin, or fondaparinux was allowed.
10. Patients who did not recover from all toxicities related to prior anticancer therapies to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 grade ≤ 1. Exception to this criterion: patients with any grade of alopecia were allowed to enter the study.
11. Patients who received radiotherapy ≤ 4 weeks or limited field radiation for palliation ≤ 2 weeks prior to randomization, and who had not recovered to grade 1 or better from related side effects of such therapy (with the exception of alopecia) and/or from whom ≥ 25% of the bone marrow was irradiated.

12. Patients with a concurrent malignancy or malignancy within 3 years of randomization, with the exception of adequately treated, basal or squamous cell skin carcinoma or curatively resected cervical cancer.
13. Patients with central nervous system (CNS) involvement unless they met ALL of the following criteria:
    - At least 4 weeks from prior therapy completion (including radiation and/or surgery) to starting the study treatment.
    - Clinically stable CNS tumor at the time of screening and not receiving steroids and/or enzyme inducing anti-epileptic medications for brain metastases.
14. Patients with impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of the study drugs (e.g. ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection).
15. Patients with a known history of Human Immunodeficiency Virus infection (testing not mandatory).
16. Patients with any other concurrent severe and/or uncontrolled medical condition that would, in the Investigator's judgment, cause unacceptable safety risks, contraindicate patient participation in the clinical study, or compromise compliance with the protocol (e.g. chronic pancreatitis, chronic active hepatitis, active untreated or uncontrolled fungal, bacterial, or viral infections, etc.).
    - Clinically significant, uncontrolled heart disease and/or cardiac repolarization abnormality including any of the following:
    - History of angina pectoris, symptomatic pericarditis, or coronary artery bypass graft, or myocardial infarction within 6 months prior to study entry
    - Documented cardiomyopathy
    - Left Ventricular Ejection Fraction < 50% as determined by multiple gated acquisition (MUGA) scan or echocardiogram (ECHO)
    - Long QT syndrome or family history of idiopathic sudden death or congenital long QT syndrome, or any of the following:
    - Risk factors for Torsades de Pointe (TdP) including uncorrected hypokalemia or hypomagnesemia, history of cardiac failure, or history of clinically significant/symptomatic bradycardia
    - Concomitant medication(s) with a known risk to prolong the QT interval and/or known to cause TdP that cannot be discontinued or replaced by safe alternative medication (e.g. within 5 half-lives or 7 days prior to starting study drug)
    - Inability to determine the QTcF interval
    - Clinically significant cardiac arrhythmias including but not limited to ventricular tachycardia, complete left bundle branch block, high-grade AV block (e.g. bifascicular block, Mobitz type II and third-degree AV block)
    - Systolic blood pressure > 160 mm Hg or < 90 mm Hg
    - Bradycardia (heart rate < 50 beats per minute [bpm] at rest), by electrocardiogram (ECG) (mean of triplicate) and pulse
    - Tachycardia (heart rate > 90 bpm at rest), by ECG (mean of triplicate) and pulse

- On screening, inability to determine the QTcF interval on the ECG (i.e. unreadable or not interpretable) or QTcF > 450 ms (using Fridericia's correction). All as determined by screening ECG (mean of triplicate ECGs).

17. Patients who were currently receiving any of the following substances and cannot be discontinued 7 days prior to Cycle 1 Day 1:
    - Known strong inducers or inhibitors of cytochrome P450 (CYP) 3A4/5, including grapefruit, grapefruit hybrids, pummelos, star-fruit, and Seville oranges.
    - Medications with a narrow therapeutic window and that are predominantly metabolized through CYP3A4/5.
    - Herbal preparations/medications, dietary supplements (except vitamins).
18. Patients who were currently receiving or had received systemic corticosteroids ≤ 2 weeks prior to starting study drug, or who had not fully recovered from side effects of such treatment. **Note:** The following uses of corticosteroids were permitted: single doses, topical applications (e.g. for rash), inhaled sprays (e.g. for obstructive airways diseases), eye drops, or local injections (e.g. intra-articular).
19. Patients who participated in a prior investigational study within 30 days prior to enrollment or within 5-half-lives of the investigational product, whichever was longer.
20. Patients who were not able to understand and to comply with study instructions and requirements.

Dose selection

Selection of the 600 mg daily dosing schedule for ribociclib (on Days 1-21 of a 28-day cycle) was based on the results from the single-agent first in human study of ribociclib (Study CLEE011X2101). This dose showed an acceptable safety profile, adequate exposure, and preliminary evidence of disease stabilization as a single agent. The activity of this dosing regimen in combination with letrozole 2.5 mg was demonstrated in postmenopausal women. In another study of ribociclib with fulvestrant (Study CLEE011X2108), the results showed that the combination was tolerable and a drug-drug interaction between ribociclib and fulvestrant was unlikely. Thus, these doses were used in the study.

Fulvestrant was administered in accordance with its approved label.

Study treatments

Patients were randomly assigned to one of the following treatment arms in a 2:1 ratio:

- Ribociclib plus fulvestrant
- Placebo plus fulvestrant

Administrative structure

The administrative structure of the study, including internal and external participants, is described in Appendix 16.1.4-Section 1 of the Clinical Study Report

A list of investigators, their affiliations and their qualifications, plus that of other important staff, as well as members of the independent Data Monitoring Committee (DMC), is provided in Appendix 16.1.4-Section 2 of the Clinical Study Report.

Study endpoints

Efficacy: The primary efficacy endpoint was PFS based on local radiology assessment using RECIST v1.1 criteria. PFS was defined as the time from the date of randomization to the date of the first documented disease progression or death due to any cause.

One of the secondary efficacy endpoints was OS, defined as the time from date of randomization to date of death due to any cause. Other secondary efficacy endpoints were: Overall response rate (ORR), Clinical benefit rate (CBR), time to response, duration of response and time to definitive deterioration of Eastern Cooperative Oncology Group performance status (ECOG PS). ORR was defined as the proportion of patients with best overall response (BOR) of confirmed CR or PR according to RECIST v1.1, and CBR was defined as the proportion of patients with a BOR of confirmed CR or PR, or stable disease lasting 24 weeks or longer, according to RECIST v1.1. Time to response was defined as the time between date of randomization and the first documented response (CR or PR, which had to be confirmed subsequently). Duration of response was defined as the time from first documentatied tumor response to the first documented progression or death due to underlying cancer. Deterioration of ECOG PS was defined as an increase in ECOG PS by at least one category from baseline or death due to any cause. Deterioration was considered definitive if ECOG PS had no subsequent return to baseline or better during the treatment period.

Patient reported outcomes: Time to definitive 10% deterioration in quality of life, including the global health scale score of EORTC QLQ-C30, were assessed. Definitive 10% deterioration was defined as a worsening in score by at least 10% compared to baseline, with no later improvement above this threshold during the treatment period, or death due to any cause.

Safety: Safety was assessed by monitoring AEs, ECGs, and laboratory abnormalities.

Statistical analysis plan

Efficacy analyses were based on data from the Full Analysis Set (FAS), which consisted of all randomized patients. Following the intent-to-treat principle, patients were analyzed according to the treatment and stratum they were assigned to at randomization. Safety analyses were based on the Safety Set, which included all patients who received at least one dose of any component of study treatment and had at least one post-baseline safety assessment.

The primary PFS analysis was to be conducted either once approximately 125 PFS events had occurred in patients treatment naïve in advanced metastatic breast cancer or after approximately 364 events in total had occurred across both treatment arms, whichever came later. The primary efficacy analysis was the comparison of PFS between the two treatment arms using a stratified log-rank test at one-sided 2.5% level of significance with strata as defined by the IRT.

The study was originally designed to ensure 90% power to detect a hazard ratio of 0.67 improvement in median PFS from 9 months vs. 13.4 months) including an interim futility analysis at 50% information fraction (182 events), an interim analysis for superiority at 80% information fraction (291 events), and a final analysis after approximately 364 PFS events. The interim

analyses were subsequently eliminated in protocol amendment 2 (see below). The eliminatiin of the futility analyses resulted in increasing the power for the primary endpoint to 95% based on the targeted 364 PFS events.

Overall survival (OS) was a secondary endpoint. A hierarchical testing strategy, where OS was to be statistically tested only if the primary efficacy endpoint of PFS was significantly different between the two treatment arms, was used to control the overall type-I error rate. OS was to be compared using a stratified log-rank test at overall one-sided 2.5% level of significance. A maximum of three analyses were planned for OS: at the time of the PFS analysis (provided PFS was significant), at which point a total of 161 deaths (46% of OS events) were expected; after 263 events (75% of OS events) were documented; and a final OS analysis after approximately 351 deaths (100% of OS events, expected 56 months from date of first patient to be randomized). The type I error rate was controlled using a 3-look group sequential design with Lan-DeMets (O'Brien- Fleming) alpha spending function.

Protocol amendments

SAP amendments

The SAP was amended twice before sponsor unblinding, as outlined below, to reflect amendments to the study protocol.

Amendment 1 (finalized 6-Jun-2017) removed the interim futility and efficacy analyses for PFS, updated the PFS analyses based on BIRC assessment to reflect the change to an audit-based approach, and incorporated PFS2 as an exploratory endpoint, all based on the corresponding amendments to the study protocol.

Amendment 2 (finalized 11-Oct-2017) further clarified some analysis conventions, including the definition of baseline for RECIST-based endpoints and subgroup definitions.

The FDA's Assessment:

The applicant has described the protocol amendments and SAP above. The SAP is acceptable to the FDA. Note that the hazard ratio is to be estimated using a stratified Cox-proportional hazards model.

7.1.4. Study F2301 (MONALEESA-3) Results

The Applicant's Position:

Compliance with Good Clinical Practice

According to the Applicant, the study was conducted in full conformance with the ethical principles of Good Clinical Practice (GCP) as required by the major regulatory authorities, and in conformance with the principles of the Declaration of Helsinki. Written informed consent was obtained from each participant in the study. The study protocol and four amendments were approved by local Independent Ethics Committees (IEC) or Institutional Review Boards (IRB).

Study F2301 was conducted at 175 sites across 30 countries as follows: Australia (4), , Austria (3), Belgium (6), Bulgaria (3), Canada (12), Colombia (2), Czech Republic (5), Denmark (6), France (14), Germany (26), Hungary (5), Italy (8), Jordan(1), Republic of Korea (3), Lebanon (2), Malaysia (2), Mexico (1), Netherlands (12), Norway (1), Poland (2), Portugal (2), Russian federation (2), Singapore (1), Spain (12), Sweden (3), Switzerland (3), Thailand (2), Turkey (4), United Kingdom (2), United States (26).

Table 7-13 Analysis Population for Study F2301

	Ribociclib + Fulvestrant N (%)	**Placebo + Fulvestrant N (%)**
All randomized patients	484(100.0)	242(100.0)
ITT Population (Full Analysis Set)	484(100.0)	242(100.0)
Safety Set	483 (99.8)	241 (99.6)

Patient disposition

As of the data cut-off, 280 patients (38.6%) continued to receive treatment with at least one study drug (ribociclib, matching placebo, or fulvestrant), while 444 patients (61.2%) had discontinued study treatment. At the time of data cut-off, treatment with at least one study drug was ongoing for a greater proportion of patients in the ribociclib plus fulvestrant arm relative to the placebo plus fulvestrant arm (42.1% vs. 31.4%, respectively). Disease progression was the primary reason for treatment discontinuation, and was less frequent in the ribociclib plus fulvestrant arm compared with the placebo plus fulvestrant arm (39.9% vs. 58.7%, respectively). Other reasons (in > 3% of all patients) were adverse event (8.5% vs. 4.1%), physician decision (4.5% vs. 2.9%), and subject/guardian decision (4.3% vs. 2.1%) (
Table 7-14).

Table 7-14: Patient disposition – Study F2301 (FAS)

Disposition Reason	**Ribociclib + Fulvestrant**	**Placebo + Fulvestrant**	**All Patients**
	N=484	**N=242**	**N=726**
	n (%)	**n (%)**	**n (%)**
Patients randomized			
Untreated	1 (0.2)	1 (0.4)	2 (0.3)
Treated	483 (99.8)	241 (99.6)	724 (99.7)
Patients treated			
Treatment ongoing [1]	204 (42.1)	76 (31.4)	280 (38.6)
End of treatment	279 (57.6)	165 (68.2)	444 (61.2)
Reason for end of treatment			
Progressive disease	193 (39.9)	142 (58.7)	335 (46.1)
Adverse event	41 (8.5)	10 (4.1)	51 (7.0)
Physician decision	22 (4.5)	7 (2.9)	29 (4.0)
Subject/guardian decision	21 (4.3)	5 (2.1)	26 (3.6)

Disposition Reason	Ribociclib + Fulvestrant	Placebo + Fulvestrant	All Patients
	N=484	N=242	N=726
	n (%)	n (%)	n (%)
Death	2 (0.4)	0	2 (0.3)
Protocol deviation	1 (0.2)	1 (0.4)	2 (0.3)
Technical problems	0	1 (0.4)	1 (0.1)
Entered post-treatment efficacy follow-up [2]	25 (9.0)	7 (4.2)	32 (7.2)
No longer being followed in post-treatment follow-up	15 (5.4)	5 (3.0)	20 (4.5)
Continue to be followed in post-treatment follow-up	10 (3.6)	2 (1.2)	12 (2.7)
Reason for end of post-treatment follow-up [3]	15 (60.0)	5 (71.4)	20 (62.5)
Progressive disease	9 (36.0)	3 (42.9)	12 (37.5)
Subject/guardian decision	4 (16.0)	1 (14.3)	5 (15.6)
Death	2 (8.0)	1 (14.3)	3 (9.4)
Entered survival follow-up [2]	223 (79.9)	146 (88.5)	369 (83.1)

[1] Patients continuing study treatment at the time of the cut-off 3-Nov-2017.
[2] The percentages of patients who entered post-treatment follow-up and the percentage of patients who entered survival follow-up use the number of patients with end of treatment as the denominator.
[3] Patients who enter and then discontinue from the post-treatment follow-up phase. In this section the denominator is equal to the number of patients who entered post-treatment follow-up.
Source: Study F2301-Table 14.1-1.3 (data cut-off 03-Nov-2017)

The FDA's Assessment:
The FDA agrees with the results presented in this section.

Protocol Violations/Deviations
The numbers of major protocol deviations leading to exclusion from the Per-protocol Set were low with no imbalance between the treatment arms. A total of 16 patients (2.2%) were excluded from the Per-protocol Set due to protocol deviations; all deviations were due to the selection criteria not being met and the most frequent one was the criterion for measurable disease or lytic bone lesion not met (Table 7-15).

Table 7-15: Protocol deviations leading to exclusion from the Per-protocol Set – Study F2301 (FAS)

	Ribociclib + Fulvestrant	Placebo + Fulvestrant	All Patients
	N=484	N=242	N=726
Protocol deviation	n (%)	n (%)	n (%)
Any protocol deviation	11 (2.3)	5 (2.1)	16 (2.2)

Protocol deviation	Ribociclib + Fulvestrant N=484 n (%)	Placebo + Fulvestrant N=242 n (%)	All Patients N=726 n (%)
Selection criteria not met	11 (2.3)	5 (2.1)	16 (2.2)
Criteria for measurable disease or lytic bone lesion not met	7 (1.4)	3 (1.2)	10 (1.4)
Postmenopausal status not met	4 (0.8)	1 (0.4)	5 (0.7)
Breast cancer type (HR status) not met	0	1 (0.4)	1 (0.1)
A patient with multiple occurrences of a protocol deviation category is counted only once in the protocol deviation category. Patients may have protocol deviations in more than one protocol deviation category. Source: Study F2301-Table 14.1-1.7			

The FDA's Assessment:

The FDA agrees with the results presented in this section.

Demographic Characteristics

Overall, patients reflected the broad population of postmenopausal women with HR-positive, HER2-negative, advanced breast cancer, and were therefore considered to be representative of the intended target population.

The median age was 63 years (range: 31 to 89) in both treatment arms; the proportions of patients aged ≥ 65 years were identical in both arms (46.7%), and the proportions of patients aged ≥ 75 years were similar in both arms (13.4% and 14.5% in the ribociclib plus fulvestrant and placebo plus fulvestrant arms, respectively). Although allowed per protocol, no male patients were enrolled. The majority of the patients were Caucasian (85.3%), and 8.7% were Asian (Table 7-16).

Table 7-16: Demographic and baseline characteristics – Study F2301 (FAS)

Demographic variable	Ribociclib + Fulvestrant N=484	Placebo + Fulvestrant N=242	All patients N=726
Age (years)			
n	484	242	726
Mean (standard deviation)	63.4 (9.78)	62.8 (10.59)	63.2 (10.05)
Median	63.0	63.0	63.0
Min, Max	31, 89	34, 86	31, 89
Age category 1 (years) – n (%)			
< 65	258 (53.3)	129 (53.3)	387 (53.3)
≥ 65	226 (46.7)	113 (46.7)	339 (46.7)
Age category 2 (years) – n (%)			

Demographic variable	Ribociclib + Fulvestrant	Placebo + Fulvestrant	All patients
	N=484	N=242	N=726
< 75	419 (86.6)	207 (85.5)	626 (86.2)
≥ 75	65 (13.4)	35 (14.5)	100 (13.8)
Sex -n (%)			
Female[1]	484 (100.0)	242 (100.0)	726 (100.0)
Race – n (%)			
Caucasian	406 (83.9)	213 (88.0)	619 (85.3)
Asian	45 (9.3)	18 (7.4)	63 (8.7)
Native American	5 (1.0)	1 (0.4)	6 (0.8)
Black	3 (0.6)	2 (0.8)	5 (0.7)
Other	10 (2.1)	3 (1.2)	13 (1.8)
Unknown	15 (3.1)	5 (2.1)	20 (2.8)
Region - n (%)			
Europe and Australia	347 (71.7)	173 (71.5)	520 (71.6)
North America	69 (14.3)	43 (17.8)	112 (15.4)
Asia	40 (8.3)	16 (6.6)	56 (7.7)
Latin America	6 (1.2)	3 (1.2)	9 (1.2)
Other	22 (4.5)	7 (2.9)	29 (4.0)
Body mass index (kg/m^2)			
n	474	231	705
Mean (standard deviation)	27.03 (5.487)	27.55 (6.111)	27.20 (5.700)
Median	26.30	26.30	26.30
Min-Max	16.1 -49.0	15.8 – 49.4	15.8 - 49.4
ECOG performance status - n (%)			
0	310 (64.0)	158 (65.3)	468 (64.5)
1	173 (35.7)	83 (34.3)	256 (35.3)
Missing	1 (0.2)	1 (0.4)	2 (0.3)

[1] No male patients were enrolled
Source: Study F2301-Table 14.1-3.1 (data cut-off 03-Nov-2017)

The FDA's Assessment:

The FDA agrees with the results the applicant presented. The two arms were well balanced across the treatment arms.

Other baseline characteristics (e.g., disease characteristics, important concomitant drugs)

Randomization was stratified according to the presence of liver and/or lung metastases (yes/no), previous endocrine therapy (A/B). Stratification factors per IRT are summarized in Table 18.

Table 7-17: Randomization by stratification factor – Study F2301

Stratification factor at randomization	Ribociclib + Fulvestrant N=484 n (%)	Placebo + Fulvestrant N=242 n (%)	All patients N=726 n (%)
Lung and/or liver metastases			
Yes	234 (48.3)	117 (48.3)	351 (48.3)
No	250 (51.7)	125 (51.7)	375 (51.7)
Previous endocrine therapy			
A	236 (48.8)	118 (48.8)	354 (48.8)
B	248 (51.2)	124 (51.2)	372 (51.2)

- Strata as entered in the IRT during randomization
Previous endocrine therapy (A vs B) is classified as: A) Treatment naïve for metastatic/advanced disease (aBC) include: i. Relapse >12 months after completion of (neo)adjuvant ET (endocrine therapy) with no subsequent treatment for aBC, OR ii. De novo aBC (no prior exposure to ET). B) Receiving up to 1 line ET for aBC include: i. Relapse on or within 12 months from completion of (neo) adjuvant ET, with no subsequent treatment for aBC, OR ii. Relapse > 12 months from completion of (neo) adjuvant ET, and progression on or after subsequent ET for aBC, OR iii. aBC at the time of diagnosis that progressed on or after ET for aBC with no prior (neo) adjuvant treatment for early disease.
Source: Study F2301 - Table 14.1-1.4

Nearly all patients (99.7%) had an ECOG performance status of 0 or 1. First and second line patients were enrolled in this study (of which 19% 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. 1.4% 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 (Table 7-16 and Table 7-18).

Table 7-18: Disease history – Study F2301 (FAS)

	Ribociclib + Fulvestrant	Placebo + Fulvestrant	All Patients
	N=484	N=242	N=726
Disease history	**n (%)**	**n (%)**	**n (%)**
Primary site of cancer - n (%)			
Breast	484 (100.0)	241 (99.6)	725 (99.9)
Missing	0	1 (0.4)	1 (0.1)
Histological grade - n (%)			
Well differentiated	45 (9.3)	30 (12.4)	75 (10.3)
Moderately differentiated	244 (50.4)	123 (50.8)	367 (50.6)
Poorly differentiated	107 (22.1)	53 (21.9)	160 (22.0)
Undifferentiated	9 (1.9)	4 (1.7)	13 (1.8)
Unknown	79 (16.3)	31 (12.8)	110 (15.2)
Missing	0	1 (0.4)	1 (0.1)
Stage at initial diagnosis - n (%)			
0	1 (0.2)	2 (0.8)	3 (0.4)
I	73 (15.1)	43 (17.8)	116 (16.0)
II	167 (34.5)	78 (32.2)	245 (33.7)
III	106 (21.9)	52 (21.5)	158 (21.8)
IV	132 (27.3)	58 (24.0)	190 (26.2)
Unknown	5 (1.0)	7 (2.9)	12 (1.7)
Missing	0	2 (0.8)	2 (0.3)
Stage at time of study entry - n (%)			
II	2 (0.4)	0	2 (0.3)
III	4 (0.8)	2 (0.8)	6 (0.8)
IV	478 (98.8)	239 (98.8)	717 (98.8)
Missing	0	1 (0.4)	1 (0.1)
Disease-free interval - n (%) [1]			
De novo	97 (20.0)	42 (17.4)	139 (19.1)
Non de novo	387 (80.0)	199 (82.2)	586 (80.7)
≤ 12 months	22 (4.5)	9 (3.7)	31 (4.3)
>12 months	365 (75.4)	190 (78.5)	555 (76.4)
Missing	0	1 (0.4)	1 (0.1)
Time since initial diagnosis of primary site (months) - n (%)			
≤ 3 months	82 (16.9)	38 (15.7)	120 (16.5)
>3 and ≤ 12 months	26 (5.4)	11 (4.5)	37 (5.1)
> 12 months	376 (77.7)	192 (79.3)	568 (78.2)
Missing	0	1 (0.4)	1 (0.1)
Time since initial diagnosis of primary site (months)			
n	484	241	725
Mean	83.67	94.82	87.38

	Ribociclib + Fulvestrant	Placebo + Fulvestrant	All Patients
	N=484	N=242	N=726
Disease history	**n (%)**	**n (%)**	**n (%)**
SD	80.424	85.258	82.172
Median	63.64	71.72	66.83
Minimum, Maximum	0.4, 396.5	0.6, 364.3	0.4, 396.5
Time from initial diagnosis to first recurrence/progression (months)			
n	392	205	597
Mean	89.61	97.76	92.41
SD	70.291	73.583	71.482
Median	75.65	85.36	78.13
Minimum, Maximum	0.0, 368.7	0.0, 363.9	0.0, 368.7
Prior endocrine treatment status - n (%)			
No prior ET [2]	138 (28.5)	74 (30.6)	212 (29.2)
Prior ET	346 (71.5)	167 (69.0)	513 (70.7)
Adjuvant treated patients	236 (48.8)	127 (52.5)	363 (50.0)
Progression on or within 12 months of end of (neo-)adjuvant ET[3]	138 (28.5)	72 (29.8)	210 (28.9)
Progression >12 months of end of (neo-)adjuvant ET	98 (20.2)	55 (22.7)	153 (21.1)
Second line patients[4]	110 (22.7)	40 (16.5)	150 (20.7)
Missing	0	1 (0.4)	1 (0.1)
HER2 receptor status - n (%)			
Negative	484 (100.0)	241 (99.6)	725 (99.9)
Missing	0	1 (0.4)	1 (0.1)
Estrogen receptor status - n (%)			
Positive	481 (99.4)	241 (99.6)	722 (99.4)
Negative	3 (0.6)	0	3 (0.4)
Missing	0	1 (0.4)	1 (0.1)
Progesterone receptor status - n (%)			
Positive	353 (72.9)	167 (69.0)	520 (71.6)
Negative	113 (23.3)	69 (28.5)	182 (25.1)
Unknown	18 (3.7)	5 (2.1)	23 (3.2)
Missing	0	1 (0.4)	1 (0.1)
Estrogen/progesterone receptor status - n (%)			
At least one positive	484 (100.0)	241 (99.6)	725 (99.9)
Both positive	350 (72.3)	167 (69.0)	517 (71.2)
ER positive / PR negative	113 (23.3)	69 (28.5)	182 (25.1)
ER negative / PR positive	3 (0.6)	0	3 (0.4)

	Ribociclib + Fulvestrant	Placebo + Fulvestrant	All Patients
	N=484	N=242	N=726
Disease history	**n (%)**	**n (%)**	**n (%)**
ER positive/ PR unknown	18 (3.7)	5 (2.1)	23 (3.2)
Both negative	0	0	0
Other (one negative and one unknown)	0	0	0
Missing	0	1 (0.4)	1 (0.1)
Types of lesions at baseline- n (%)			
Target only	52 (10.7)	23 (9.5)	75 (10.3)
Non-target only	105 (21.7)	60 (24.8)	165 (22.7)
Both target and non-target	327 (67.6)	158 (65.3)	485 (66.8)
Unknown	0	1 (0.4)	1 (0.1)
Current extent of disease (metastatic sites) - n (%)			
Bone	367 (75.8)	180 (74.4)	547 (75.3)
Bone only	103 (21.3)	51 (21.1)	154 (21.2)
Visceral	293 (60.5)	146 (60.3)	439 (60.5)
Lung or liver	242 (50.0)	121 (50.0)	363 (50.0)
Lung	146 (30.2)	72 (29.8)	218 (30.0)
Liver	134 (27.7)	63 (26.0)	197 (27.1)
CNS	6 (1.2)	2 (0.8)	8 (1.1)
Other[5]	102 (21.1)	51 (21.1)	153 (21.1)
Lymph nodes	199 (41.1)	115 (47.5)	314 (43.3)
Soft tissue	23 (4.8)	14 (5.8)	37 (5.1)
Skin	20 (4.1)	8 (3.3)	28 (3.9)
Breast	4 (0.8)	1 (0.4)	5 (0.7)
None	2 (0.4)	0	2 (0.3)
Missing	0	1 (0.4)	1 (0.1)
Number of metastatic sites - n (%)			
0	2 (0.4)	0	2 (0.3)
1	151 (31.2)	73 (30.2)	224 (30.9)
2	156 (32.2)	76 (31.4)	232 (32.0)
3	114 (23.6)	48 (19.8)	162 (22.3)
4	38 (7.9)	34 (14.0)	72 (9.9)
≥ 5	23 (4.8)	10 (4.1)	33 (4.5)
Missing	0	1 (0.4)	1 (0.1)

	Ribociclib + Fulvestrant	Placebo + Fulvestrant	All Patients
	N=484	N=242	N=726
Disease history	**n (%)**	**n (%)**	**n (%)**

DFI = disease-free interval; ET = endocrine therapy; SD = standard deviation.
[1] De novo includes patients with no first recurrence/progression or first recurrence/progression within 90 days of diagnosis with no prior antineoplastic medication. For non-de novo patients, DFI is the time from initial diagnosis to first recurrence/progression.
[2] No prior ET (endocrine therapy) include a. de novo patients and b. patients diagnosed with early stages of disease, treated with surgery and/ or radiation therapy and/ or chemotherapy (but no endocrine therapy) for that early setting and relapsed afterwards with advanced disease.
[3]One patient from placebo arm was included in progression on/within 12 months of end of ET but did not have documented ET end date.
[4] 3 patients from ribociclib arm were included in second line but did not have documented disease progression
[5] Other visceral includes any metastatic site other than soft tissue, breast, bone, lung, liver, CNS, skin, and lymph nodes.
Source: Study F2301-Table 14.1-3.2 (data cut-off 03-Nov-2017)

Table 7-19: Prior antineoplastic therapy – Study F2301 (FAS)

	Ribociclib + Fulvestrant	Placebo + Fulvestrant	All Patients
	N=484	N=242	N=726
Characteristic	**n (%)**	**n (%)**	**n (%)**
Surgery (biopsy)			
Yes	394 (81.4)	203 (83.9)	597 (82.2)
No	90 (18.6)	38 (15.7)	128 (17.6)
Missing	0	1 (0.4)	1 (0.1)
Radiotherapy			
Yes	302 (62.4)	160 (66.1)	462 (63.6)
No	182 (37.6)	81 (33.5)	263 (36.2)
Missing	0	1 (0.4)	1 (0.1)
Medication (systemic therapy)			
Yes	375 (77.5)	193 (79.8)	568 (78.2)
No	109 (22.5)	48 (19.8)	157 (21.6)
Missing	0	1 (0.4)	1 (0.1)
Medication setting [1,2]			
Adjuvant	314 (64.9)	162 (66.9)	476 (65.6)
Neoadjuvant	66 (13.6)	33 (13.6)	99 (13.6)
Prevention	1 (0.2)	0	1 (0.1)
Therapeutic/Metastatic	99 (20.5)	36 (14.9)	135 (18.6)

Characteristic	Ribociclib + Fulvestrant N=484 n (%)	Placebo + Fulvestrant N=242 n (%)	All Patients N=726 n (%)
Palliative/Metastatic	13 (2.7)	4 (1.7)	17 (2.3)
Medication: chemotherapy setting[1,2]			
Adjuvant	209 (43.2)	101 (41.7)	310 (42.7)
Neoadjuvant	65 (13.4)	30 (12.4)	95 (13.1)
Therapeutic/Metastatic	3 (0.6)	0	3 (0.4)
Palliative/Metastatic	1 (0.2)	0	1 (0.1)
Medication: hormonal therapy setting [1,2]			
Adjuvant	286 (59.1)	139 (57.4)	425 (58.5)
Neoadjuvant	4 (0.8)	6 (2.5)	10 (1.4)
Therapeutic/ Metastatic	97 (20.0)	36 (14.9)	133 (18.3)
Palliative/ Metastatic	13 (2.7)	4 (1.7)	17 (2.3)
Type of last therapy			
Hormonal therapy	206 (42.6)	100 (41.3)	306 (42.1)
Radiotherapy	133 (27.5)	74 (30.6)	207 (28.5)
Surgery excluding biopsy	65 (13.4)	37 (15.3)	102 (14.0)
Chemotherapy	14 (2.9)	14 (5.8)	28 (3.9)
PI3K/AKT/mTOR	3 (0.6)	1 (0.4)	4 (0.6)
Other	4 (0.8)	1 (0.4)	5 (0.7)
Setting at last therapy			
Adjuvant	200 (41.3)	111 (45.9)	311 (42.8)
Neoadjuvant	3 (0.6)	4 (1.7)	7 (1.0)
Therapeutic/Metastatic	82 (16.9)	34 (14.0)	116 (16.0)
Palliative/Metastatic	66 (13.6)	32 (13.2)	98 (13.5)
Not applicable	65 (13.4)	37 (15.3)	102 (14.0)

[1] A patient may have multiple settings.
[2] For data regarding all settings including Other therapy setting, see Study F2301-Table 11-5.
Therapeutic setting was any antineoplastic agent given to treat the cancer except in the adjuvant and neo-adjuvant setting
Last therapy was based on start date.
Setting at last therapy and best response at last therapy was set to 'Not applicable' if the type of last therapy was surgery (non-biopsy).
Source: Study F2301-Table 14.1-3.6 (data cut-off 03-Nov-2017)

The FDA's Assessment:

The FDA agrees with the results the applicant presented. The two arms were well balanced across the treatment arms.

Treatment compliance, concomitant medications and rescue medication

Treatment compliance

No formal treatment compliance measurement for ribociclib/placebo was performed. Compliance was assessed by Investigators examining the records of drug administration and the numbers of boxes as well as the tablets/capsules dispensed, received, and returned for ribociclib and placebo.

Concomitant medications

By treatment group, ATC classes were often similar in the frequency or type of medicine concomitantly administered. However, proton pump inhibitors (PPIs) were administered at a slightly higher frequency (37.1%) in the ribociclib plus fulvestrant group, as compared with that in the placebo plus fulvestrant treatment group (25.3%). Of these, pantoprazole and associated formulations were the primary PPI. most frequent type administered was anilides (43.7% versus 46.5%) in patients treated with ribociclib plus fulvestrant compared with placebo plus fulvestrant, respectively (Study F2301-Table 14.3-2.1).

Rescue medication

Not applicable as no rescue medication were allowed in the study.

Efficacy results-Primary endpoint (Including Sensitivity Analyses)

Investigator–assessed Progression Free Survival

The ribociclib plus fulvestrant arm demonstrated clear superiority over the placebo arm for the primary endpoint of PFS per investigator assessment. A 40.7% estimated relative risk reduction was evident in the PFS endpoint per investigator assessment in favor of the ribociclib plus fulvestrant arm (HR = 0.593, 95% CI: 0.480, 0.732); one sided p-value = < 0.0001). Median PFS was prolonged by 7.7 months, from 12.8 months (95% CI: 10.9, 16.3) for patients in the placebo arm to 20.5 months (95% CI: 18.5, 23.5) for patients in the ribociclib arm (Table 7-20 and

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Figure 7-7).

Robustness of this primary analysis was confirmed by results of the PFS analysis per central BIRC review. The imaging data from approximately 40% of total randomized patients (n = 290) in study were reviewed by BIRC based on an audit-based approach. Results of the PFS analysis per BIRC yielded a 50.8% relative risk reduction (HR = 0.492; 95% CI: 0.345, 0.703) in the PFS endpoint in

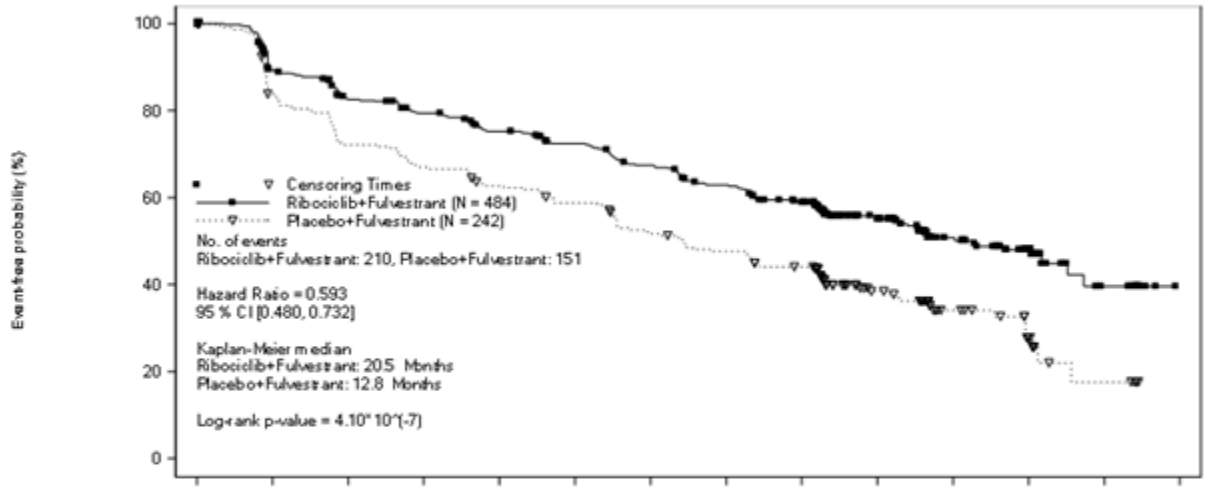
favor of the ribociclib arm, consistent with the results of the Investigator-assessed PFS (Table 7-21 and Figure 7-8).

Table 7-20: Progression-free survival analyses – Study F2301 (FAS)

	Investigator assessment		BIRC assessment	
	Ribociclib + Fulvestrant	**Placebo + Fulvestrant**	**Ribociclib + Fulvestrant**	**Placebo + Fulvestrant**
	N = 484	**N = 242**	**N = 193**	**N = 97**
Category	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Number of events - n (%)	210 (43.4)	151 (62.4)	72 (37.3)	54 (55.7)
Progression	200 (41.3)	143 (59.1)	62 (32.1)	52 (53.6)
Death[1]	10 (2.1)	8 (3.3)	10 (5.2)	2 (2.1)
Number censored - n (%)	274 (56.6)	91 (37.6)	121 (62.7)	43 (44.3)
P-value ribociclib + fulvestrant vs. placebo + fulvestrant [2]	< 0.0001		-	
Hazard ratio (95% CI) ribociclib + fulvestrant vs. placebo + fulvestrant[3]	0.593 (0.480, 0.732)		0.492 (0.345, 0.703)	
Percentiles (95% CI)				
25th percentile	8.6 (6.5, 10.8)	3.6 (2.5, 5.5)	9.2 (5.6, 11.0)	2.1 (1.8, 3.6)
Median	20.5 (18.5, 23.5)	12.8 (10.9, 16.3)	NE (18.2, NE)	10.9 (3.8, 17.2)
75th percentile	NE (NE, NE)	22.2 (21.9, NE)	NE (NE, NE)	22.2 (19.1, 22.2)

NE: Not estimable.
[1] Death before progression
[2] P-value is obtained from the one-sided stratified log-rank test.
[3] Hazard ratio is obtained from Cox PH model stratified by lung and/or liver metastasis and previous endocrine therapy per IRT
Source: Study F2301-Table 14.2-1.1, Study F2301-Table 14.2-1.13, Study F2301-Table 14.2-1.15. Study F2301-Table 14.2-1.2, Study F2301-Table 14.2-1.14, Study F2301-Table 14.2-1.16, Study F2301-Table 14.2-1.19
(data cut-off 03-Nov-2017)

Figure 7-7: Progression-free survival per Investigator assessment – Study F2301 (FAS)

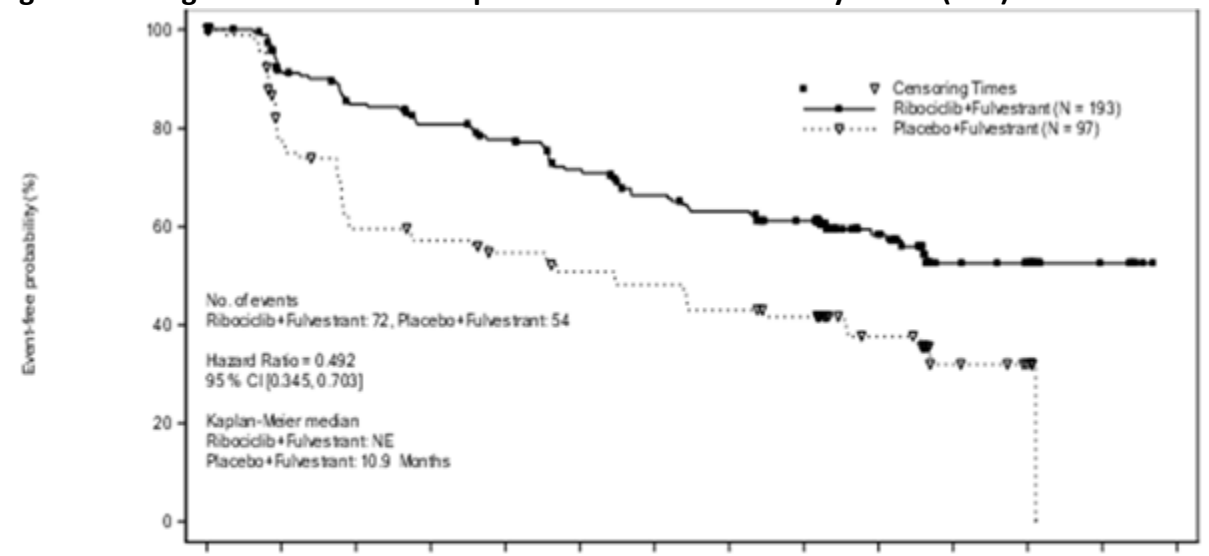


Number of patients still at risk

Time(months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26
Ribociclib+Fulvestrant	484	403	365	347	324	305	282	259	235	155	78	52	13	0
Placebo+Fulvestrant	242	195	168	156	144	134	116	106	95	53	27	14	4	0

Source: Study F2301-Figure 14.2-1.1

Figure 7-8 Progression-free survival per BIRC assessment - Study F2301 (FAS)



Number of patients still at risk

Time(months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26
Ribociclib+Fulvestrant	193	161	146	136	128	114	101	95	87	53	22	17	6	0
Placebo+Fulvestrant	97	66	50	47	43	39	37	33	30	18	8	4	0	0

Source: Study F2301-Figure 14.2-1.2

The FDA's Assessment:

The FDA agrees with the results and conclusions of this section.

Sensitivity and supportive analyses
Several supportive and sensitivity analyses were performed to assess the overall robustness of the primary efficacy results. Supportive analysis included repeating the primary efficacy analysis using the data obtained through blinded independent central review (BIRC) of tumor assessment based on an audit-based approach.

Sensitivity analyses conducted included repeating the primary PFS analysis using the Per Protocol Set (PPS), different censoring rules, and using an unstratified log-rank test to compare the two treatment arms.

Supportive analysis of PFS
Robustness of this primary analysis was confirmed by results of the PFS analysis per central BIRC review (Table 7-21).

Sensitivity analysis of PFS
Multiple sensitivity and supportive analyses (performed using different censoring rules and using an unstratified log-rank test) demonstrated the observed PFS benefit was robust and consistent across relevant prognostic categories, with HRs ranging from 0.576 (95% CI: 0.465, 0.713) to 0.617 (95% CI: 0.502, 0.759) (Table 7-21).

Table 7-21: Sensitivity analyses of PFS per Investigator assessment – Study F2301 (FAS)

Sensitivity analysis	Median PFS (95% CI)	p-value	Hazard ratio (95% CI)
Primary analysis			
Ribociclib+fulvestrant	20.5 (18.5,23.5)	4.10*10^(-7)	0.593 (0.480,0.732)
Placebo+fulvestrant	12.8 (10.9,16.3)		
Unstratified log-rank test and Cox model			
Ribociclib+fulvestrant	20.5 (18.5,23.5)	1.58*10^(-6)	0.611 (0.495,0.753)
Placebo+fulvestrant	12.8 (10.9,16.3)		
Stratified Cox model, adjusting for baseline covariates[1]			
Ribociclib+fulvestrant	20.5 (18.5,23.5)	4.10*10^(-7)	0.580 (0.470,0.717)
Placebo+fulvestrant	12.8 (10.9,16.3)		
Actual event [2]			
Ribociclib+fulvestrant	19.4 (17.6,22.3)	1.04*10^(-6)	0.610 (0.496,0.750)
Placebo+fulvestrant	12.8 (10.9,14.9)		
Backdating [3]			
Ribociclib+fulvestrant	19.3 (16.6,23.0)	1.88*10^(-6)	0.617 (0.502,0.759)

Sensitivity analysis	Median PFS (95% CI)	p-value	Hazard ratio (95% CI)
Placebo+fulvestrant	12.8 (10.9,14.9)		
Censoring for antineoplastic therapy [4]			
Ribociclib+fulvestrant	20.6 (18.6,23.5)	1.31*10^(-7)	0.576 (0.465,0.713)
Placebo+fulvestrant	12.8 (11.0,16.3)		

CI=Confidence interval; PFS=Progression-free survival
1 Baseline covariates included in the Cox proportional hazard model are age (≥ 65 vs <65), prior chemo therapy in (neo)adjuvant setting (yes vs no), ECOG performance status (0 vs. 1), and bone only lesion at baseline (yes or no).
2 Analysis included the event whenever it occurred even after ≥ 2 missing tumor assessments
3 Analysis used the date of the next scheduled assessment for events occurring after ≥ 1 missing assessment
4 Analysis was performed by censoring patients at start of new antineoplastic therapy
p-values make no adjustment for multiple testing
Source: Study F2301-Table 14.2-1.1, Study F2301-Table 14.2-1.6, Study F2301-Table 14.2-1.7, Study F2301-Table 14.2-1.8, Study F2301-Table 14.2-1.11 and Study F2301-Table 14.2-1.12. (data cut-off 03-Nov-2017).

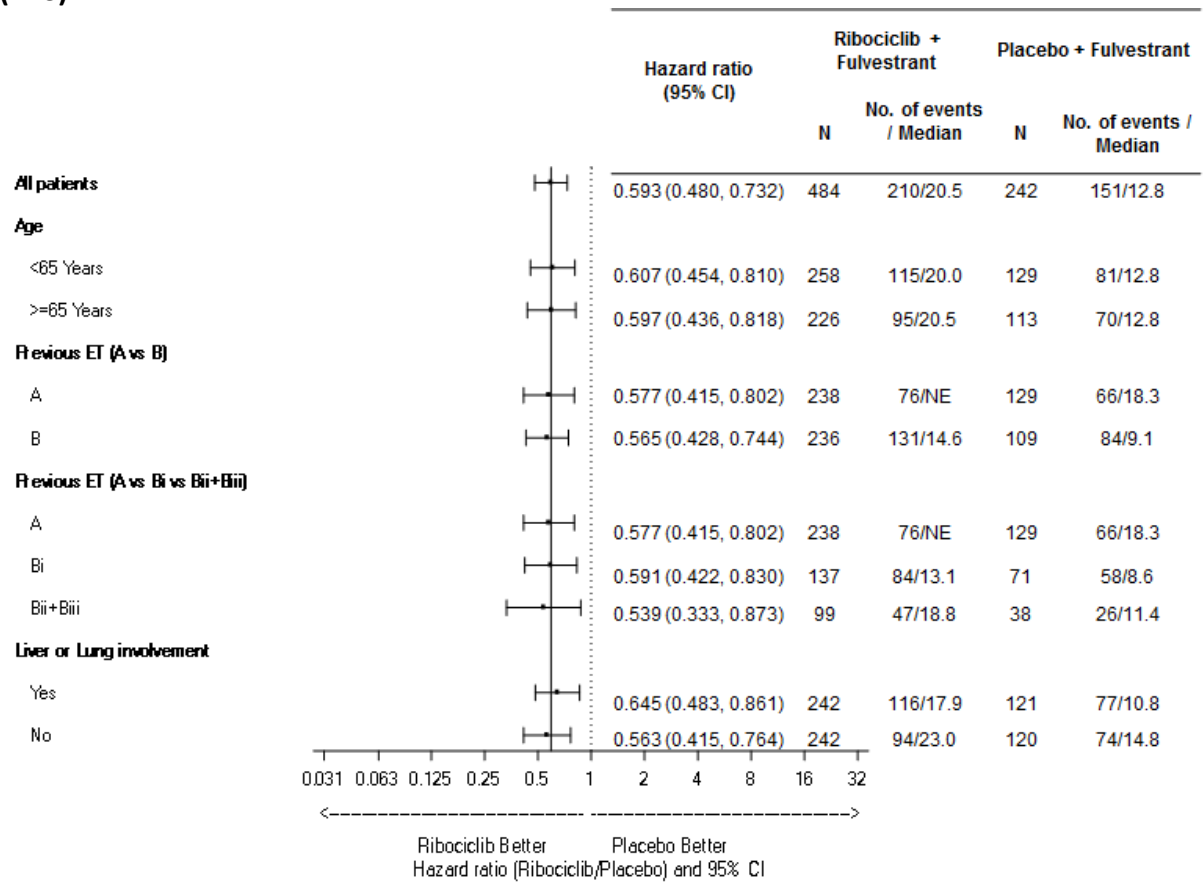
The FDA's Assessment:

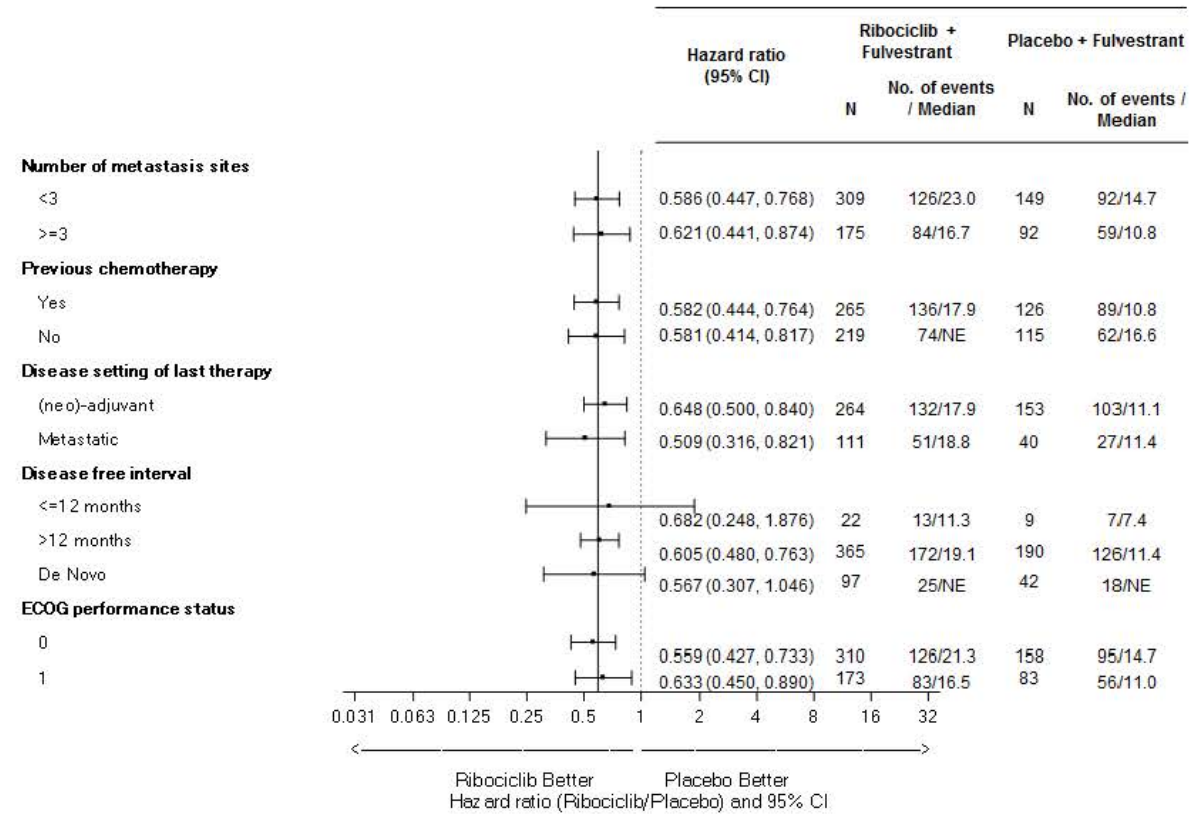
The FDA agrees with the estimates the applicant provided. These are all exploratory analyses and the p-values presented should be considered nominal only.

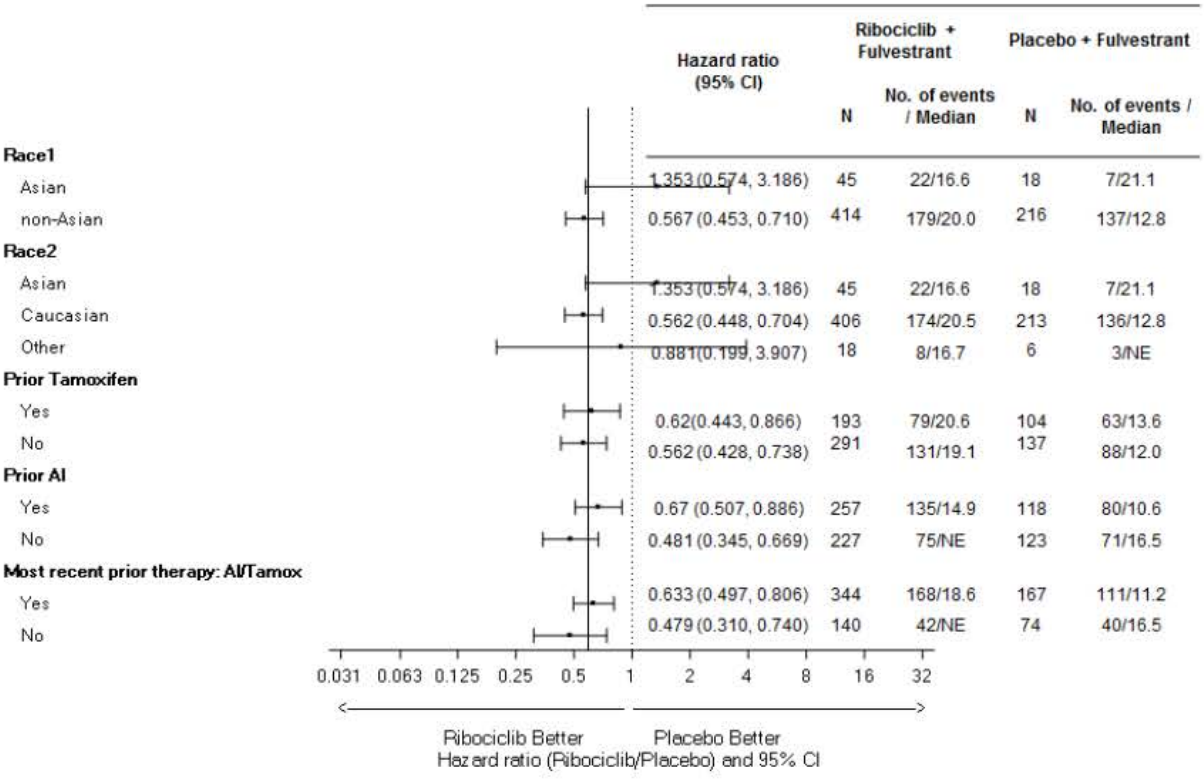
PFS subgroup analyses

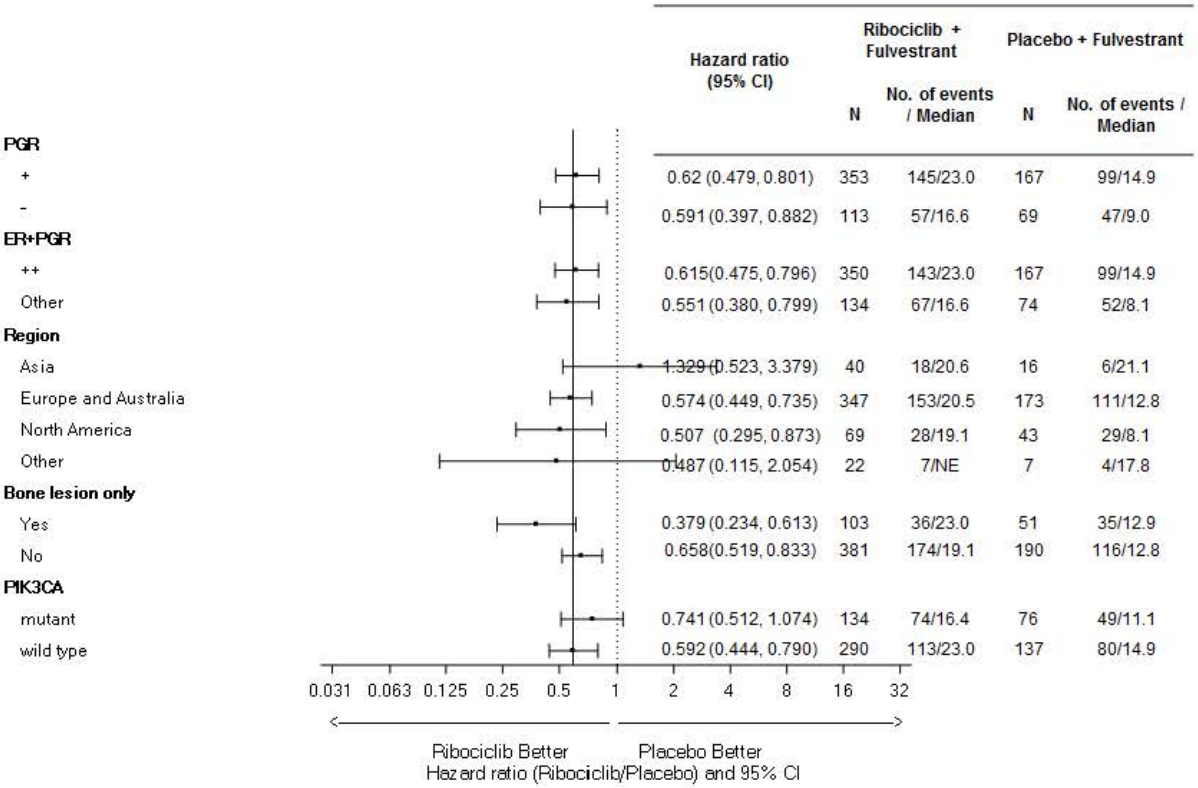
Homogeneity and consistency of the PFS benefit was generally evident across all predefined subgroups with hazard ratios in favor of treatment with ribociclib plus fulvestrant, including the baseline stratification factors of presence of liver and/or lung metastases and previous endocrine therapy (treatment naive or up to line of treatment for advanced disease). The only exception was the Asian subgroup, for which the number of PFS events and number of patients were too few to draw any meaningful conclusions. Excluding the Asian subgroups, HRs ranged from 0.379 (95% CI: 0.234, 0.613) to 0.881 (95% CI: 0.199, 3.907) (Figure 7-9).

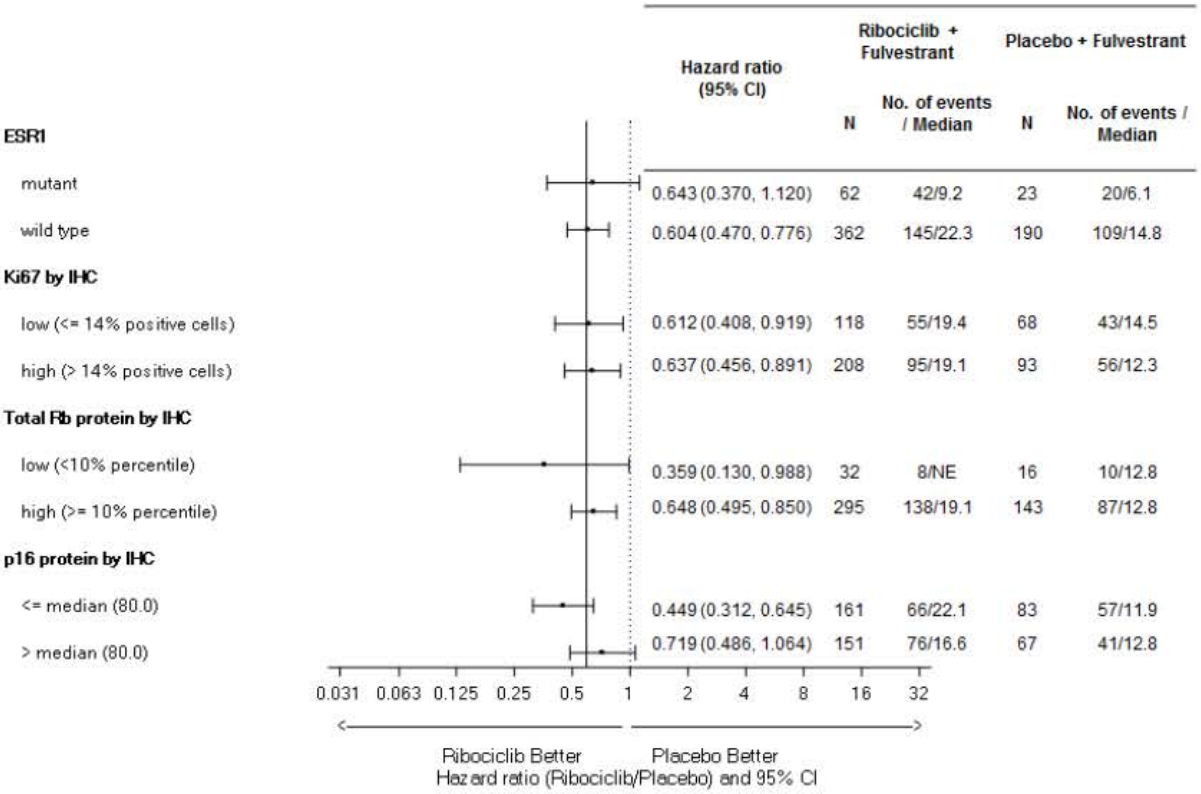
Figure 7-9: Forest plot of PFS subgroup analyses per Investigator assessment – Study F2301 (FAS)

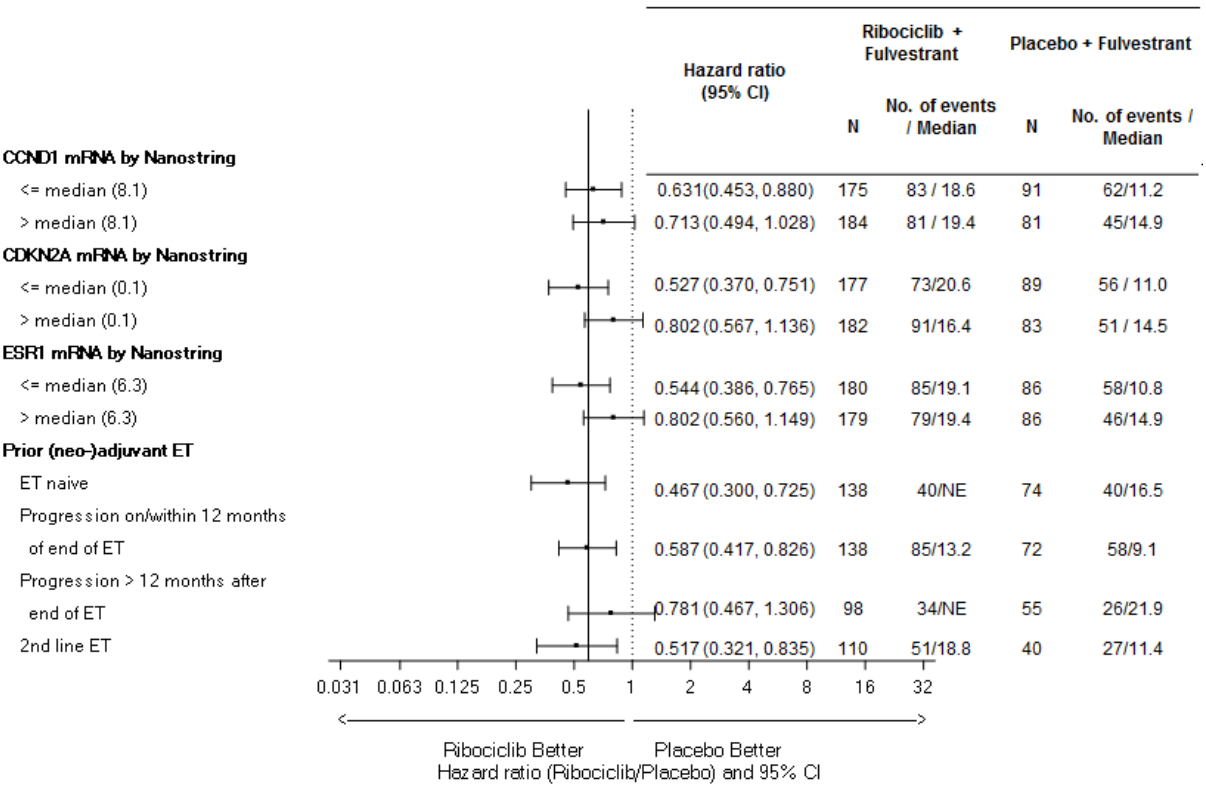







Hazard ratio (95% CI)
Ribociclib + Fulvestrant
Placebo + Fulvestrant
N
No. of events / Median
N
No. of events / Median
PGR
+ 0.62 (0.479, 0.801) 353 145/23.0 167 99/14.9
- 0.591 (0.397, 0.882) 113 57/16.6 69 47/9.0
ER+PGR
++ 0.615(0.475, 0.796) 350 143/23.0 167 99/14.9
Other 0.551 (0.380, 0.799) 134 67/16.6 74 52/8.1
Region
Asia 1.329 (0.523, 3.379) 40 18/20.6 16 6/21.1
Europe and Australia 0.574 (0.449, 0.735) 347 153/20.5 173 111/12.8
North America 0.507 (0.295, 0.873) 69 28/19.1 43 29/8.1
Other 0.487 (0.115, 2.054) 22 7/NE 7 4/17.8
Bone lesion only
Yes 0.379 (0.234, 0.613) 103 36/23.0 51 35/12.9
No 0.658(0.519, 0.833) 381 174/19.1 190 116/12.8
PIK3CA
mutant 0.741 (0.512, 1.074) 134 74/16.4 76 49/11.1
wild type 0.592 (0.444, 0.790) 290 113/23.0 137 80/14.9
0.031 0.063 0.125 0.25 0.5 1 2 4 8 16 32
Ribociclib Better
Placebo Better
Hazard ratio (Ribociclib/Placebo) and 95% CI


Hazard ratio (95% CI)
Ribociclib + Fulvestrant
Placebo + Fulvestrant
N
No. of events / Median
N
No. of events / Median
ESR1
mutant 0.643 (0.370, 1.120) 62 42/9.2 23 20/6.1
wild type 0.604 (0.470, 0.776) 362 145/22.3 190 109/14.8
Ki67 by IHC
low (<= 14% positive cells) 0.612 (0.408, 0.919) 118 55/19.4 68 43/14.5
high (> 14% positive cells) 0.637 (0.456, 0.891) 208 95/19.1 93 56/12.3
Total Rb protein by IHC
low (<10% percentile) 0.359 (0.130, 0.988) 32 8/NE 16 10/12.8
high (>= 10% percentile) 0.648 (0.495, 0.850) 295 138/19.1 143 87/12.8
p16 protein by IHC
<= median (80.0) 0.449 (0.312, 0.645) 161 66/22.1 83 57/11.9
> median (80.0) 0.719 (0.486, 1.064) 151 76/16.6 67 41/12.8
0.031 0.063 0.125 0.25 0.5 1 2 4 8 16 32
Ribociclib Better
Placebo Better
Hazard ratio (Ribociclib/Placebo) and 95% CI



Hazard ratio (95% CI) is based on stratified Cox PH model by lung and/or liver metastasis, and previous endocrine therapy per IRT.
Exception: for subgroup analyses related to stratification factors (lung/liver metastasis and previous endocrine therapy), unstratified Cox PH model is used.
Subgroups are derived based on eCRF and biomarker data.
Source: Study F2301-Figure 14.2-1.3, Study F2301-Table 14.2-1.21

The FDA's Assessment:

The FDA agrees with the results the applicant provided; however, these results are all exploratory and should be considered as such. On a final note, the study enrolled 71 patients in the United States and the hazard ratio for the subgroup of patients in the USA was 0.45 (95% CI: 0.22, 0.91).

Secondary efficacy results

Overall survival

Overall survival data were not mature at the time of the data cut-off date and collection of survival data is continuing, with a total of 120 deaths (34.2% information fraction) as of the 03-Nov-2017 data cut-off: 70 (14.5%) in the ribociclib plus fulvestrant arm and 50 (20.7%) in the placebo plus fulvestrant arm.

The FDA's Assessment:

The FDA agrees with the applicant that the OS data are immature at the time of the final PFS analysis. Nevertheless, the data do not indicate any harm or detriment to survival at this

juncture. In the ITT population, the estimate hazard ratio for OS is 0.670 (95% CI: 0.465, 0.964) in favor of the ribociclib arm. Note that the hazard ratio is consistent across prior endocrine therapy use (first-line vs second-line) in the metastatic setting.

Efficacy Results –other relevant endpoints

Overall response rate and clinical benefit rate

Ribociclib combination was associated with improved ORR and CBR in all patients and also in patients with measurable disease at baseline. Ribociclib treatment was associated with earlier and durable responses (Table 7-22).

Table 7-22 Secondary efficacy results (Study F2301)

	Overall study population
N	FAS = 484 ribociclib arm; 242 placebo arm Patients with measurable disease at baseline = 379 ribociclib arm; 181 placebo arm
ORR	FAS: 32.4% (95% CI: 28.3, 36.6) vs 21.5% (95% CI: 16.3, 26.7); Patients with measurable disease at baseline: 40.9% (95% CI: 35.9, 45.8) vs. 28.7% (95% CI: 22.1, 35.3) (p = 0.003).
CBR	All patients: 70.2% (95% CI: 66.2, 74.3) vs. 62.8% (95% CI: 56.7, 68.9); p = 0.020 Patients with measurable disease at baseline: 69.4% (95% CI: 64.8, 74.0) vs. 59.7% (95% CI: 52.5, 66.8)
TTR	The median time to response (CR or PR) was not reached for either arm. However, numerical trends were in favor of a more rapid response in the ribociclib plus fulvestrant arm. Estimated probability of achieving response by Month 6 was 26.6% (95% CI: 22.7, 31.0) for the ribociclib plus fulvestrant arm and 16.2% (95% CI: 12.0, 21.6) for the placebo plus fulvestrant arm.
DOR	Median duration of response was not reached in both the arms The estimated probability of maintaining response for at least 12 months was 78.3% (95% CI: 15.5, 30.0) in the ribociclib plus fulvestrant arm vs. 74.8% (95% CI: 15.1, 40.2) in the placebo plus fulvestrant arm.
Source: Study F2301-Table 14.2-1.22, Study F2301-Table 14.2-1.23, Study F2301-Table 14.2-1.26, Study F2301-Table 14.2-1.27	

The FDA's Assessment:

For ORR, the ribociclib+fulvestrant arm had 8 complete responses, and 148 partial responses in the FAS. The placebo + fulvestrant arm had 0 complete responses and 52 partial responses in the FAS. The FDA agrees with the results provided for the estimates; however, the FDA considers CBR and TTR to be exploratory measures only. The FDA does not concur with the language used to describe differences in these measures, specifically the phrases "improved ORR and CBR" and "earlier and durable responses."

Time to deterioration of ECOG PS
Time to definitive deterioration in ECOG PS showed minimal difference between the two treatment arms with an HR of 0.864 (95% CI: 0.628, 1.188; p = 0.184). The median time to definitive deterioration in ECOG performance status by one category of the score was not reached in either treatment arm (Study F2301-Table 14.2-3.9).

Patient-reported outcomes
Results of QoL analyses with regard to time to definitive 10% deterioration of the EORTC QLQ-C30 global health scale score demonstrated a numerical trend in favor of the ribociclib plus fulvestrant arm, with an HR of 0.795 (95% CI: 0.602, 1.050) and a one-sided p-value of 0.051. Of note, the median time to definitive 10% deterioration in global health status was not reached for the ribociclib plus fulvestrant arm, and was 19.4 months in the placebo plus fulvestrant arm (Study F2301-Table 14.2-3.4a).

No meaningful differences were observed between the treatment arms for time to definitive 10% deterioration in the physical functioning, emotional functioning, and social functioning scores. Results of QoL analyses with regard to time to definitive 10% deterioration in the VAS of the EQ-5D-5L were similar between the two treatment arms, with an HR of 0.874 (95% CI: 0.657, 1.162; p=0.178) (Study F2301-Table 14.2-3.4f).

Results of QoL analyses with regard to time to definitive 10% deterioration in the worst pain item for Brief Pain Inventory-Short form questionnaire (BPI-SF) were similar between the two treatment arms, with an HR of 0.809 (95% CI: 0.578, 1.131; p=0.108). Corresponding results of QoL analyses with regard to time to definitive 10% deterioration in the pain severity index for BPI-SF were also similar between the two treatment arms, with an HR of 0.813 (95% CI: 0.596, 1.110; p=0.099). Lastly, results with regard to time to definitive 10% deterioration in the pain interference index for BPI-SF were also similar between the two treatment arms, with an HR of 0.870 (95% CI: 0.625, 1.212; p=0.206) (Study F2301-Table 14.2-3.4g, Study F2301-Table 14.2-3.4h, Study F2301-Table 14.2-3.4i).

Persistence of Effect
No long-term efficacy data are available for ribociclib in combination with NSAI or fulvestrant at the time of this application, with the exception of those presented in the preceding sections.
In Study E2301, 32.2% patients in the ribociclib group and 22.6% of patients in the placebo group received ≥ 18 months of treatment, with longest duration of exposure being 30.1 months for both the groups (Study E2301-Table 12-1). In Study F2301, 39.1% patients in the ribociclib group and 30.7% of patients in the placebo group received ≥ 18 months of treatment, with longest duration of exposure being 27.4 months in the ribociclib group and 25.9 months in the placebo group (Study F2301-Table 12-1). The median duration of study follow-up was 19.2 months in Study E2301 and 20.4 months in Study F2301.

In Study A2301, the results from the updated PFS analysis (02-Jan-2017 data cut-off, with increased follow-up duration of 26.4 months compared to 15.3 months at the time of primary analysis) were consistent with the previously reported PFS primary analysis results and support

continuing efficacy of ribociclib. The median PFS with ribociclib was prolonged by 9.3 months, from 16.0 months (95% CI: 13.4-18.2) in the placebo with letrozole arm to 25.3 months (95% CI: 23.0-30.3) in the ribociclib with letrozole arm (HR=0.568; 95% CI: 0.457-0.704; $p=9.63\times10^{-8}$) (Kisqali-PSUR 22Aug2017-21Feb2018). These results indicate that the efficacy benefit persists with longer follow-up. With additional approximately 11 months of median follow up after the first interim analysis (median follow up time 15.3 months), no new or unexpected toxicities were observed and no new safety signals were identified in updated PFS analysis. Treatment with ribociclib should continue for as long as clinical benefit is evident, or until unacceptable toxicity occurs. Following discontinuation of therapy, the natural course of the disease can be expected. No information about withdrawal and rebound has been generated in support of this application.

The FDA's Assessment:

FDA reviewed the applicant's assessment of persistence of effect above. Overall survival data are currently immature from MONALEESA-2 and the final report is expected June 2022 as part of PMC 3168-3.

Pooled efficacy data

Study F2301 (only patients with no prior endocrine therapy for advanced disease), Study E2301 (only patients assigned to an NSAI in the treatment assignment CRF), and Study A2301 (FAS) were included in the first-line endocrine therapy pool. These analyses were performed for RECIST-based endpoints and were based on local radiology assessment. Overall, the results for the first-line endocrine therapy pool are consistent with efficacy results of individual registration studies included in the analyses and are in favor of using ribociclib in combination with endocrine therapy (fulvestrant or an NSAI) in HR-positive, HER2-negative, advanced or metastatic breast cancer who had received no prior hormonal therapy for advanced disease. Detailed results from these pooled analyses are provided in (SCE Study F2301-Section 3.3).

The ribociclib plus endocrine therapy and placebo plus endocrine therapy arms were well balanced with regard to demographics and baseline characteristics. Prognostic factors and risk groups were evenly distributed between the two arms. Patients were representative of the intended target population, with 99.9% in both arms having a negative HER2 receptor status, and 100% in both arms having an HR-positive receptor status (SCE Study F2301-Section 3.3).

For PFS based on the first-line endocrine therapy pool, a 41.6% relative risk reduction (HR=0.584; 95% CI: 0.510, 0.669) was evident in the hazard rate of progression/death in favor of ribociclib plus endocrine therapy. Median PFS in the first-line endocrine therapy pool was prolonged by a clinically meaningful 9.3 months, from 14.6 months (95% CI: 13.0, 16.5) for patients receiving placebo plus endocrine therapy to 23.9 months (95% CI: 22.1, 27.5) for ribociclib plus endocrine therapy-treated patients (SCE Study F2301-Section 3.3).

Overall response per Investigator assessment based on RECIST 1.1 was observed in 37.8% of patients (95% CI: 34.8, 40.9) receiving treatment with ribociclib plus endocrine therapy versus 27.4% (95% CI: 24.3, 30.5) in the placebo plus endocrine therapy arm. The corresponding CBRs

were 76.6% (95% CI: 73.9, 79.3) and 69.1% (95% CI: 65.9, 72.4) for patients receiving ribociclib plus endocrine therapy and placebo plus endocrine therapy, respectively (SCE Study F2301-Section 3.3).

The FDA's Assessment:

FDA reviewed the applicant's assessment of the pooled efficacy data for MONALEESA-2, MONALEESA-3, and MONALEESA-7 above. FDA did not conduct independent analyses of pooled efficacy data, as the patient population, menopausal status, and hormonal therapy backbone differed across these three studies and pooling results would be difficult to interpret as a result.

7.2. **Assessment of Efficacy Across Trials**

Not applicable as the primary efficacy evaluation for ribociclib plus NSAI combination as first line in pre, peri-menopausal women was based on one trial, MONELESSA-7 as described in Sections 7.1.2 and the primary efficacy evaluation for ribociclib plus fulvestrant combination in post-menopausal women was based on MONELESSA-3 as described in Sections 7.1.4.

The FDA's Assessment:

Not applicable since each study is supporting a different indication. As each study was conducted using a different hormonal therapy backbone and studied in different patient populations, the FDA did not assess pooled efficacy.

7.3. **Integrated Assessment of Effectiveness**

The Applicant's Position:

The magnitude of the observed benefit seen in Studies E2301 and F2301 are clinically meaningful and highly statistically significant. The addition of ribociclib to NSAI treatment in Stuy E2301 resulted in a 43.1% relative risk reduction (HR = 0.569; 95% CI 0.436, 0.743) in the hazard rate of progression/death was observed, with a 13.7-month prolongation in median PFS. The median PFS was 27.5 months (95% CI: 19.1, NE) and 13.8 months (95% CI: 12.6, 17.4) in the ribociclib and placebo arms, respectively. The K-M PFS curves diverged early at two months indicating the early consistent separation favoring the ribociclib arm. This trend was as observed for the full population. In Study F2301, the ribociclib plus fulvestrant arm demonstrated clear superiority over the placebo arm for the primary endpoint of PFS per investigator assessment. A 40.7% estimated relative risk reduction was evident in the PFS endpoint per investigator assessment in favor of the ribociclib plus fulvestrant arm (HR = 0.593, 95% CI: 0.480, 0.732); one sided p-value = >0.0001.). Median PFS was prolonged by 7.7 months, from 12.8 months (95% CI: 10.9, 16.3) for patients in the placebo arm to 20.5 months (95% CI: 18.5, 23.5) for patients in the ribociclib arm. Ribociclib in combination with an NSAI or fulvestrant (plus goserelin in premenopausal patients) has a manageable and acceptable safety profile for HR-positive, HER2-negative advanced breast cancer patients. The AE profile in registration studies (Study E2301 and Study F2301) is characterized by predictable, primarily low-grade events. These events are generally reversible and non-cumulative. Hence, ribociclib in combination with NSAI or fulvestrant offers a valuable

treatment optio (b) (4) Results from the pooled first-line endocrine therapy (based on subpopulations from Studies F2301, E2301, and A2301) further strengthen the use of ribociclib in this target indication.

The FDA's Assessment:

FDA's independent analysis of the efficacy results for MONALEESA-3 and MONALEESA-7 support an expansion of the proposed indication for ribociclib. The improvement in PFS demonstrated in MONALEESA-7 for pre- and perimenopausal women with the use of ribociclib in combination with an NSAI and goserelin and in MONALEESA-3 with the use of ribociclib in combination with fulvestrant are statistically significant and clinically meaningful. Overall survival data are immature, but there is no compelling evidence of harm to overall survival at this time.

While men were allowed on MONALEESA-3, no men were randomized. Men were not eligible for MONALEESA-7 (b) (4)

7.4. **Review of Safety**

The Applicant's Position:

Ribociclib in combination with an AI or fulvestrant (plus goserelin in premenopausal patients) has a manageable and acceptable safety profile for HR-positive, HER2-negative advanced breast cancer patients. The AE profile in registration studies (Study E2301 and Study F2301) is characterized by predictable, primarily low-grade events. These events were generally reversible and non-cumulative. Guidance for the management of AEs to reduce the clinical burden of these toxicities, and to improve QoL would remain the same as in the approved label based on original submission. No unknown or unexpected safety signals were observed although the higher frequency of QTc interval prolongation and higher ΔQTcF when administered in combination with tamoxifen precludes its use. Safety data from Studies E2301 and F2301 were consistent with those presented in the original submission.

The pooled safety data from Studies E2301, A2301, and X2107 further confirm the acceptable and manageable safety profile of the ribociclib plus AI combination therapy in the intended target population.

Neutropenia, hepatobiliary toxicity, and QTc interval prolongation continue to be considered as important identified risks, although each of these events can be effectively managed with ribociclib dose modifications.

Safety data from the subgroup of ribociclib plus goserelin and NSAI from Study E2301 and Study F2301 form the basis for the modified indication sought in this submission. The population

recruited in Study E2301 (pre- and perimenopausal women with HR-positive, HER2-negative aBC) and Study F2301 (postmenopausal women with HR-positive aBC), adequately represents the target population for expansion of indication. Demographic, disease, and other baseline characteristics in both the studies were representative of the intended patient population (b) (4) with the proposed indication.

The routine clinical and laboratory evaluations performed were adequate to assess the safety of ribociclib. The placebo control in combination with standard endocrine therapy highlights the comorbidities and underlying risks for patients with advanced breast cancer and thus provides an important context for assessing the safety of ribociclib.

Overall, the safety profile of ribociclib in combination with goserelin and NSAI treatment or fulvestrant has been well characterized in the intended target patient populations and was consistent with the results from previous studies. No new safety risks were identified. Neutropenia, hepatobiliary toxicity, and QTc interval prolongation continue to be considered as important identified risks, although each of these events can be effectively managed with ribociclib dose modifications. In view of the established clinical benefit in patients with HR-positive, HER2-negative disease, the safety and tolerability profiles of ribociclib in combination with NSAI or fulvestrant (and goserelin in premenopausal patients) are considered to be acceptable.

The FDA's Assessment:

For this sNDA, the applicant submitted safety data from MONALEESA-3, a phase 3 trial of ribociclib/placebo plus fulvestrant in the first- or second-line metastatic settings, and MONALEESA-7, a phase 3 trial of ribociclib/placebo + goserelin + NSAI/tamoxifen in pre- and perimenopausal women in the first-line metastatic setting. Additional updated safety data from MONALEESA-2, a phase 3 trial of ribociclib/placebo plus letrozole in the first-line metastatic setting were also submitted. FDA reviewed the applicant's position on study X2107 above but did not conduct independent analyses of this study, as it is not designed as a registration trial and is not being used to support the applicant's proposed labeling indication.

In MONALEESA-7, analyses of QT safety data from the ribociclib + tamoxifen + goserelin arm showed a mean QTcF increase from baseline that was more than 10 ms in the ribociclib+tamoxifen subgroup compared to the ribociclib+NSAI subgroup. A pharmacokinetic-pharmacodynamic analysis estimated mean changes from baseline in QTcF were 22.0 ms (90% CI: 20.6, 23.4) and 34.7 ms (90% CI: 31.64, 37.78) for ribociclib+ NSAI and ribociclib+tamoxifen, respectively, at the steady-state geometric mean Cmax. Furthermore, an QTcF interval increase of >60 ms from baseline was seen in 16% (14/87) in the ribociclib+tamoxifen subgroup, compared to 7% (18/245) in the ribociclib+NSAI subgroup. In the placebo+tamoxifen subgroup, a QTcF interval increase of >60 ms from baseline occurred in 7% (6/90) of patients, compared with no patients in the placebo+NSAI subgroup. Given this increase in QTcF in patients who received tamoxifen, ribociclib is not indicated for concomitant use with tamoxifen and the applicant is not seeking an indication for ribociclib

with tamoxifen. Therefore, FDA's safety analyses of MONALEESA-7 focused only on the ribociclib/placebo + NSAI + goserelin arms and only these results will be discussed.

7.4.4. **Safety Review Approach**

The Applicant's Position:

Key safety data in support of this application are the primary analyses from the two registration studies: Study E2301 (ribociclib in combination with NSAI; N = 495) and Study F2301 (ribociclib in combination with fulvestrant; N = 724). This safety population allows for an informed assessment of the safety profile of the ribociclib in combination with goserelin plus AI or fulvestrant and an evaluation of the overall benefit-risk in patients with HR-positive, HER2-negative advanced breast cancer. This population is also considered appropriate for the detection and characterization of common AEs and to provide guidance on toxicity management.

In addition, safety data from Study E2301 (NSAI subgroup; data cut-off date of 20-Aug-2017), A2301 (updated data cut-off date of 04-Jan-2017), and X2107 (updated data cut-off date of 02-May-2017) were pooled (N = 1206) to provide a more comprehensive evaluation of the safety profile of ribociclib in combination with NSAI in the first-line endocrine setting across a broader patient population that includes pre- or perimenopausal and postmenopausal women with HR-positive, HER2-negative locally advanced or metastatic breast cancer.

Cumulative review of all safety data from post marketing experience has not identified any new safety concerns.

Table 7-23 Studies contributing to safety data of ribociclib in combination with NSAI

Study	Study design, objectives and population	Dose and treatment duration	Safety assessments and analyses	Study status and patients in safety set
Registration study				
Study E2301(NSAI subgroup)	• Phase III, placebo-controlled, randomized, double-blind study • Efficacy and safety in adult, female, pre- or perimenopausal patients who were 18 years and older with HRpositive, HER2-negative, recurrent, or	• Ribociclib 600 mg once daily taken on Days 1-21 of a 28-day cycle + /NSAI (letrozole 2.5-mg daily or anastrozole 1-mg daily) taken on Days 128 of each 28-day cycle + goserelin 3.6 mg by sc implant on Day 1 of every 28day cycle	• Toxicity assessments per CTCAE version 4.03 • Reporting of AEs and SAEs • Routine ECGs, vital signs, and laboratory evaluations 30-day safety follow up Safety topics and subgroup analyses: • Deaths, SAEs, other significant AEs, ECGs, all AEs, clinical laboratory data	**Status**: Ongoing with cutoff date of 20-Aug-2017 **Total patients: N=495** Ribociclib 600 mg: 248 Placebo: 247

Study	Study design, objectives and population	Dose and treatment duration	Safety assessments and analyses	Study status and patients in safety set
	metastatic breast cancer who received no prior endocrine therapy for advanced or metastatic disease, and for whom endocrine therapy is intended.	• Until disease progression, unacceptable toxicity, death, or discontinuation from the study treatment for any other reason	• Subgroups: age, race, region, liver involvement (yes, no), and prior chemotherapy (yes, no), prior endocrine therapy within 12 months prior to study entry (yes vs. no), renal function, hepatic function	
Other studies contributing to safety assessments				
Study A2301	• Phase III, placebo-controlled, randomized, double-blind in adult, female, post-menopausal patients who were 18 years and older with HRpositive, HER2-negative, recurrent, or metastatic breast cancer who received no prior therapy for advanced disease • Efficacy and safety in patients with HRpositive, HER2-negative advanced breast cancer	• Once daily ribociclib 600 mg Days 1-21 of a 28-day cycle + letrozole 2.5 mg once daily • Until disease progression, unacceptable toxicity, death, or discontinuation from the study treatment for any other reason	• Toxicity assessments per CTCAE version 4.03 • Reporting of AEs and SAEs • Routine ECGs, vital signs, and laboratory evaluations 30-day safety follow up Safety topics and subgroup analyses: • Safety topics and subgroup analyses • Deaths, SAEs, other significant AEs, ECGs, all AEs, clinical laboratory data • Subgroups: age, race, region, liver metastasis (yes, no), and prior lines of chemotherapy (yes, no), prior chemotherapy(yes, no)	**Statu**s: Ongoing with cutoff date of 04-Jan-2017 **Total patients: N=664** Ribociclib 600 mg: 334 Placebo: 330
Study X2107	Phase Ib, open-label dose escalation and dose expansion study in adult postmenopausal	• Once daily ribociclib 600 mg Days 1-21 of a 28-day cycle +	• Toxicity assessments per CTCAE version 4.03 • Incidence of DLTs in Cycle 1 Deaths,	**Status**: Ongoing with cutoff date of 02-May-2017

Study	Study design, objectives and population	Dose and treatment duration	Safety assessments and analyses	Study status and patients in safety set
	women with locally advanced or metastatic HRpositive /HER2-negative breast cancer • Dose escalation: to estimate MTD/RP2D of ribociclib in combination with letrozole in patients who received prior treatment • Dose expansion: to characterize the safety and tolerability of ribociclib in combination with letrozole in patients who received no prior treatment	letrozole 2.5 mg once daily • Until disease progression, unacceptable toxicity, death, or discontinuation from the study treatment for any other reason	SAEs, other significant AEs, ECGs, all AEs, clinical laboratory data	**Total patients: N=47** Ribociclib 600 mg: Dose escalation: 19 Dose expansion: 28

AE=Adverse event; CTCAE=Common Terminology Criteria for Adverse Events; DLT=Dose-limiting toxicity; ECG=Electrocardiogram; HER2=Human epidermal growth factor receptor; HR=Hormone receptor; NSAI=Non-steroidal aromatase inhibitor; SAE=Serious AE; MTD=Maximum tolerated dose; RP2D=Recommended dose for Phase II

Source: Study E2301, Study A2301, Study X2107

Table 7-24: Phase-III controlled study that contributed key safety data of ribociclib in combination with fulvestrant

Study	Objective // population	Comment	No. of patients	Treatment, dosing schedule, and d in cycle	Safety data // endpoint	Status
Placebo-controlled combination clinical study						
F2301	Safety, efficacy, tolerability of ribociclib in combination with fulvestrant vs. placebo in combination with fulvestrant // Men[1] and postmenopausal women with HRpositive, HER2negative advanced breast, defined as loco-regionally not amendable to curative therapy or metastatic breast cancer, who received no or only one line of prior endocrine therapy	Registration clinical study	Safety set: 724[2] Ribociclib in combination with fulvestrant treatment group: **483** Placebo in combination with fulvestrant treatment group: **241**	Ribociclib: 600 mg orally once daily dosage on Days 1 to 21 within 28-d cycles. Fulvestrant: 500 mg dose (two 5-mL intramuscular (im) injections) every 28 d, with additional dose on Cycle 1 Day 15. Matching placebo: orally once daily, Days 1 to 21 within 28-d cycles.	AE, SAE, other significant AE, vital signs, ECG, clinical laboratory data, urinalysis // Frequency, severity of AEs; laboratory abnormalities [Predefined subgroups: prior endocrine therapy, prior chemotherapy, lung/liver metastasis, age, race, region.]	Study ongoing, as of data cut-off date: 03-Nov-2017 [Study F2301
Other study contributing to safety assessments						

Study	Objective // population	Comment	No. of patients	Treatment, dosing schedule, and d in cycle	Safety data // endpoint	Status
X2108	**Phase Ib**: Dose escalation to estimate MTD/RP2D of two triple combinations[2]; dose confirmation of ribociclib in combination with fulvestrant. **Phase II**: Randomized (1:1:1), safety, efficacy, tolerability // Postmenopausal women with locally advanced or HRpositive, HER2negative metastatic breast cancer whose disease recurred or progressed on an aromatase inhibitor therapy	Interventional clinical study	**Safety set**: 13[3] Arm 3 only Ribociclib in combination with fulvestrant treatment group: 13	**Phase Ib**:[3,4] Arm 3 only Ribociclib: 600 mg orally once daily dosage on Days 1 to 21 within 28-d cycles. Fulvestrant: 500 mg dose im on Day 1 and Day 15 only within Cycle 1. Day 1 only within all subsequent cycles. **Phase II**: terminated.	AE, SAE, other significant AE, vital signs, ECG, clinical laboratory data, urinalysis // AE, SAE, changes in clinical laboratory data, vital signs, ECG, dose interruption, reductions, intensity	Study ongoing, as of data cut-off 10-Feb-2017 Study X2108

[1] Although eligibility criterion included males, no male patient enrolled
[2] The total number of randomized patients who were treated Study F2301-Table 14.1-1.3
[3]Enrollment started with first cohort of female patients to Arm 3 of Phase Ib: no patient enrolled to Arm-3a Phase Ib (i.e. continuous ribociclib dosage regimen + fulvestrant)
[4] Results of triple combinations (Arm 1: ribociclib + buparlisib + fulvestrant; Arm 2: ribociclib + alpelisib + fulvestrant) will be presented when all patients discontinue study treatment and in a subsequent CSR
AE = adverse event; SAE = serious adverse event
Source: Synopses of Individual Studies, Tabular Listing of All Clinical Studies

The FDA's Assessment:

In MONALEESA-7, 495 pre- or perimenopausal patients received ribociclib/placebo + NSAI + goserelin in the safety population. In MONALEESA-3, 724 postmenopausal women received ribociclib/placebo + fulvestrant in the safety population. Adverse events were assessed at baseline and during the study treatment period and for at least 30 days after study completion. The incidence and severity of adverse events were compared to prior and ongoing trials with ribociclib and were placed in the context of other drugs in the same class. Laboratory studies were assessed at regular intervals as defined in the protocols. Hematology labs included a complete blood cell count with differential. Serum chemistries include liver function evaluation, renal function evaluation, and electrolytes. The applicant provided separate safety datasets for MONALEESA-7, MONALEESA-3, and an integrated safety dataset including safety information from MONALEESA-2. Data cut-offs and key safety data are

presented by the applicant above. The applicant's assessment of study X2108 was reviewed but FDA did not independently assess the data.

The applicant submitted updated safety datasets on July 13, 2018 to fulfill the 90-day Safety Update for MONALEESA-3 and MONALEESA-7, with a dataset cut-off date of April 1, 2018. An evaluation of deaths, serious AEs, AEs leading to permanent discontinuation of ribociclib, hepatobiliary toxicity, infections, neutropenia, and QT prolongation showed results consistent with the known safety findings of ribociclib and no new safety signals were identified.

7.4.5. **Review of the Safety Database**

The Applicant's Position:

For study E2301, the overall safety profile of ribociclib plus goserelin plus either tamoxifen or NSAI combination observed in the current study was consistent with prior ribociclib experience in postmenopausal women with advanced breast cancer, with the exception of an increased rate of QTcF prolongation in the ribociclib group compared with the placebo group. QTcF prolongation occurred more frequently in the tamoxifen subgroup compared to NSAI subgroup.

The safety data from Study E2301 in this review document are primarily focused on the Study E2301 (NSAI subgroup) and the NSAI pooled dataset. Safety data from ribociclib in combination with tamoxifen in Study E2301, are consistent in general with those reported from ribociclib in combination with other therapies, with the exception of QTc interval prolongation.

Overall Exposure

Exposure to treatment in Study E2301- NSAI subgroup

Total exposure was 297.7 patient-years and 241.1 patient-years for patients randomized to the ribociclib plus NSAI plus goserelin group (hereafter referred to as the ribociclib group) and placebo plus NSAI plus goserelin group (hereafter referred to as the placebo group), respectively. The median duration of exposure to the study treatment was longer in the ribociclib group (15.3 months: range: 0.0 to 30.0) compared to the placebo group (12.8 months; range: 1.0 to 30.0), with 167 patients (67.3%) exposed for ≥ 12 months in the ribociclib group compared to 126 patients (51.0%) in the placebo group (Table 7-25).

Table 7-25: Duration of exposure to study treatment Study E2301 (Safety set)

	RIBO + NSAI	PBO + NSAI
Duration of exposure (months)	**N = 248**	**N = 247**
Exposure categories (months) – n (%)		
< 3	28 (11.3)	53 (21.5)
3 - < 6	15 (6.0)	24 (9.7)
6 - < 9	17 (6.9)	22 (8.9)
9 - < 12	21 (8.5)	22 (8.9)
12 - < 15	39 (15.7)	33 (13.4)
15 - < 18	49 (19.8)	35 (14.2)
≥ 18	79 (31.9)	58 (23.5)
Exposure (months)		
Mean (SD)	14.4 (7.13)	11.7 (7.59)
Median	15.3	12.8
Min, Max	0, 30	1, 30
Patient-years	**297.7**	**241.1**

Min, Max=Minimum, Maximum; NSAI=non-steroidal aromatoase inhibitor; PBO=placebo; RIBO=ribociclib;
For Study E2301, only patients assigned to NSAI (letrozole or anastrozole) in treatment assignment CRF are included.
Study treatment includes any medication that is part of study treatment.
Patient-years is calculated as the sum of exposure (in years) across all patients.

The FDA's Assessment:

FDA's assessment of treatment exposure for MONALEESA-7 is shown in Table 7-26 below. The treatment duration and cumulative dose in the ribociclib arms were higher compared to the placebo. Actual and relative dose intensities were lower in the ribociclib arm compared to the placebo. Overall, these differences are expected given the known side effect profile of ribociclib. FDA's findings of median and mean treatment duration agree with the applicant's.

Table 7-26: FDA Analysis of Treatment Exposure for MONALEESA-7

	Ribociclib (N=248)	Placebo (N=247)
Treatment Duration (Months)		
Mean (SD)	14.4 (7.1)	11.7 (7.6)
Median (Min - Max)	15.3 (0 - 29.8)	12.8 (0.5 - 30.1)
Actual Dose Intensity (mg/day)		
Mean (SD)	503.3 (117.1)	587.4 (51.6)
Median (Min - Max)	561 (167.3 - 628.6)	600 (200 - 700)
Relative Dose Intensity (%)		
Mean (SD)	83.9 (19.5)	97.9 (8.6)
Median (Min - Max)	93.5 (27.9 - 104.8)	100 (33.3 - 116.7)
• Source ADaM dataset: adex.xpt. • Source SDTM dataset: ex.xpt.		

Overall Exposure- Study F2301

The Applicant's Position

Cumulative exposure to study treatment was 536.4 patient-years with ribociclib in combination with fulvestrant vs. 238.7 patient-years with placebo in combination with fulvestrant. The median duration of exposure to ribociclib and placebo was comparable (12.7 months and 11.1 months, respectively) (Table 7-27).

Table 7-27: Duration of exposure to study treatment - Study F2301 (Safety set)

	Study treatment	
	RIBO + FULV	**PBO + FULV**
	N=483	**N=241**
	n (%)	**n (%)**
Exposure (mo)		
Mean (SD)	13.33 (7.903)	11.88 (7.753)
Median	15.77	11.96
Minimum – maximum	0.9 – 27.4	0.9 – 25.9
Exposure category – n (%)		
< 3 mo	92 (19.0)	54 (22.4)
3 to < 6 mo	45 (9.3)	27 (11.2)
6 to < 9 mo	30 (6.2)	16 (6.6)
9 to < 12 mo	37 (7.7)	25 (10.4)
12 to < 15 mo	31 (6.4)	19 (7.9)
15 to < 18 mo	59 (12.2)	26 (10.8)

	Study treatment	
	RIBO + FULV	**PBO + FULV**
	N=483	**N=241**
	n (%)	**n (%)**
≥ 18 mo	189 (39.1)	74 (30.7)
Patient-years	**536.4**	**238.7**

FULV = fulvestrant; NA = not available; PBO = placebo; RIBO = ribociclib; SD = standard deviation.
Study treatment is defined as ribociclib in combination with fulvestrant or matching placebo in combination with fulvestrant.
Patient-years is calculated as the sum of exposure in years (y) across all patients.
Source: SCS Study F2301-Appendix 1-Table 3-2.1, SCS Study F2301-Appendix 1-Table 3-2.2, Study F2301-Table 14.3-1.1

The FDA's Assessment:

FDA's assessment of treatment exposure for MONALEESA-3 is shown in Table 7-28 below. The treatment duration and cumulative dose in the ribociclib arms were higher compared to the placebo. Actual and relative dose intensities were lower in the ribociclib arm compared to the placebo. Overall, these differences are expected given the known side effect profile of ribociclib. FDA's findings of median and mean treatment duration agree with the applicant's.

Table 7-28: FDA Analysis of Treatment Exposure for MONALEESA-3

	Ribociclib (N=483)	**Placebo (N=241)**
Treatment Duration (Months)		
Mean (SD)	13.3 (7.9)	11.9 (7.8)
Median (Min - Max)	15.8 (0.9 - 27.4)	12 (0.9 - 25.9)
Actual Dose Intensity (mg/day)		
Mean (SD)	511 (105.1)	589 (36.1)
Median (Min - Max)	552.4 (136.1 - 800)	600 (339.5 - 711.6)
Relative Dose Intensity (%)		
Mean (SD)	85.2 (17.5)	98.2 (6)
Median (Min - Max)	92.1 (22.7 - 133.3)	100 (56.6 - 118.6)

- Source ADaM dataset: adex.xpt.
- Source SDTM dataset: ex.xpt.

Relevant characteristics of the safety population: Study E2301

The Applicant's Position:

Baseline characteristics were well balanced between the ribociclib and placebo group, thereby providing assurance with regard to the interpretation of the treatment comparison and the validity of the safety conclusions. Overall, patients were representative of a broader population of pre- and perimenopausal women with HRpositive, HER2-negative, advanced or metastatic breast cancer who did not receive prior endocrine therapy for their advanced/metastatic disease, and for whom endocrine therapy is intended.

The FDA's Assessment:

FDA conducted its own analyses and agrees the safety population between the ribociclib and placebo arms for MONALEESA-7 show the baseline characteristics were well balanced and representative of a broader population of pre- and perimenopausal women.

Relevant characteristics of the safety population: Study F2301

The Applicant's Position:

Baseline characteristics were well balanced between the two treatment groups in Study F2301 and thereby, providing reassurance with regard to the interpretation of the treatment comparison and the validity of the safety conclusions. Differences in baseline characteristics between Study F2301 and Study X2108 were not clinically noteworthy. Overall, the study populations were representative of the target population.

The FDA's Assessment:

FDA conducted its own analyses and agrees the safety population between the ribociclib and placebo arms for MONALEESA-3 show the baseline characteristics were well balanced and representative of a broader population of pre- and perimenopausal women. No men or pre/perimenopausal women were enrolled on this study. Data from study X2108 were not evaluated by the FDA as this study is not being used to support a labeling indication.

Adequacy of the safety database

The Applicant's Position:

The population recruited in Study E2301 (pre- and perimenopausal women with HR-positive, HER2-negative aBC) and Study F2301 (postmenopausal women with HR-positive HER2-negative aBC), adequately represents the target population for expansion of indication. Demographic, disease, and other baseline characteristics in both the studies were representative of the intended patient population (b) (4) with the proposed indication.

Exposure to study treatment (ribociclib plus goserelin and NSAI from Study E2301 and ribociclib in combination with fulvestrant from Study F2301), was considered adequate in women with HR-positive, HER2-negative advanced or metastatic breast cancer. Overall, the routine clinical and laboratory evaluations performed were adequate to assess the safety of ribociclib. The placebo control in combination with standard endocrine therapy highlights the comorbidities and underlying risks for patients with advanced breast cancer and thus provides an important context for assessing the safety of ribociclib.

The FDA's Assessment:

FDA agrees with the applicant's assessment of the overall adequacy of the safety databases for MONAEESA-3 and MONALEESA-7.

7.4.6. **Adequacy of Applicant's Clinical Safety Assessments**

The Applicant's Position:

The safety of ribociclib in combination with an AI or fulvestrant (plus goserelin in premenopausal patients) was evaluated on the basis of the:

- Frequency, type, severity, and causal relationship of AEs to study treatment
  - AEs were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 for all studies used in this safety assessment.
- Frequency of deaths, serious adverse events (SAEs), and other clinically significant AEs (including AEs leading to discontinuation and AEs requiring dose interruption and/or reduction)
- Frequency and type of AEs in key demographic subgroups (age, and race,) and by Baseline disease characteristics
- Changes in laboratory variables, with particular attention to grade 3/4 laboratory abnormalities
- Electrocardiogram (ECG) changes

Adverse events were coded using different versions of MedDRA. Study E2301 used MedDRA version 20.0. Studies A2301 and X2107-used MedDRA version 18.1. In order to have 'SCS pool' datasets for these three studies, all AEs were mapped to MedDRA version 20.0. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 20.1 in Study F2301, and by MedDRA version 19.1 in Study X2108.

Adverse events of special interest (AESI) were selected based on the mechanism of action of ribociclib and biological plausibility, as well as nonclinical observations.

The FDA's Assessment:

FDA's independent analyses of safety for both MONALEESA-3 and MONALEESA-7 focused on deaths and treatment emergent AEs (TEAEs, defined as any AE beginning between the day of the first dose and 30 days after the last dose of any study drug), including serious TEAEs, TEAEs leading to study drug interruption/reduction or study discontinuation, and AEs of special interest such as neutropenia, hepatobiliary toxicity, and QT prolongation.

7.4.7. **Safety Results**

Results of Study E2301 (MONALEESA-7)

The Applicant's Position:

Deaths

On-treatment deaths (i.e. deaths occurring while receiving study treatment or within 30 days of the last dose of study treatment) were reported for 6 patients: 1 patient (0.4%) in the ribociclib

group and 5 patients (2.0%) in the placebo group. All the 6 deaths were attributed to progression of underlying breast cancer (Table 7-29).

Table 7-29: Deaths while on treatment by preferred term –Study E2301 (Safety set)

	RIBO+ NSAI	PBO+ NSAI
Primary reason for death	**N=248**	**N=247**
Preferred term	**n (%)**	**n (%)**
On-treatment deaths	**1 (0.4)**	**5 (2.0)**
Study indication	1 (0.4)	5 (2.0)
NSAI=non-steroidal aromatase inhibitor; PBO=placebo; RIBO=ribociclib [1] For study E2301, only patients assigned to NSAI in treatment assignment CRF are included. Source: SCS Study E2301Appendix 1Table 3-4.6		

The FDA's Assessment:

FDA's analyses agree with the applicant's for the number of patients that died within 30 days after the last dose of any study drug in MONALEESA-7. The numbers are overall low and within the expected range based on the known data from the current ribociclib USPI.

Serious adverse events

The Applicant's Position:

The proportion of patients in Study E2301 (NSAI subgroup) with SAEs was comparable between the ribociclib (16.9%) and placebo groups (13.4%). Serious AEs were infrequently reported in both treatment groups. In the ribociclib group, the most frequently occurring SAEs were drug induced liver injury (4 patients, 1.6%), abdominal pain, dyspnea, febrile neutropenia, and back pain (all occurred in 3 patients each) (Table 7-30).

Table 7-30: Serious adverse events by preferred term, irrespective of causality (with an incidence of at least 1% in either treatment group)–Study E2301 (Safety set)

	RIBO+ NSAI	PBO+ NSAI
	N=248	N=247
Preferred term	**n (%)**	**n (%)**
Total	**42 (16.9)**	**33 (13.4)**
Abdominal pain	3 (1.2)	0
Dyspnoea	3 (1.2)	2 (0.8)
Febrile neutropenia	3 (1.2)	1 (0.4)
Back pain	3 (1.2)	1 (0.4)
Constipation	0	0
Pleural effusion	2 (0.8)	4 (1.6)
Urinary tract infection	0	0
Pyrexia	2 (0.8)	2 (0.8)
Drug-induced liver injury	4 (1.6)	1 (0.4)

NSAI=non-steroidal aromatase inhibitor; PBO=placebo; RIBO=ribociclib
[1] For study E2301, only patients assigned to NSAI in treatment assignment CRF are included.
Preferred terms are sorted in descending order of frequency, as reported in pooled ribociclib column.
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
A patient with multiple adverse events is counted only once in the total row.
AEs up to 30 days after the last study treatment will be included.
MedDRA Version 20.0 has been used for coding of adverse events.
Source: SCS Study E2301Appendix 1Table 3-4.8

The FDA's Assessment:

FDA's analyses of serious TEAEs occurring in at least 1% of patients in any treatment arm agrees with the applicant's findings presented above. Overall serious TEAEs were low and well balanced between the treatment arms.

Dropouts and/or Discontinuations Due to Adverse Effects

The Applicant's Position:

Treatment discontinuations (of one or more study drugs) in Study E2301 (NSAI subgroup) as a result of AEs were reported in 6.5% of patients in the ribociclib group and 3.2% of patients in the placebo group. The most frequently reported AEs (> 1% of patients) leading to treatment discontinuation of ribociclib were alanine aminotransferase (ALT) increased (2.4%), aspartate aminotransferase (AST) increased (1.6%), and DILI (1.2%) (Table 7-31).

Table 7-31: Adverse events leading to discontinuation by preferred term, irrespective of causality –Study E2301 (Safety set)

	RIBO+ NSAI	PBO+ NSAI
	N=248	N=247
Preferred term	**n (%)**	**n (%)**
Total	**16 (6.5)**	**8 (3.2)**
ALT increased	6 (2.4)	2 (0.8)
AST increased	4 (1.6)	2 (0.8)
Vomiting	0	0
Drug-induced liver injury	3 (1.2)	1 (0.4)
Neutropenia	1 (0.4)	0

NSAI=non-steroidal aromatase inhibitor; PBO=placebo; RIBO=ribociclib
[1] For study E2301, only patients assigned to NSAI in treatment assignment CRF are included.
Peferred terms are sorted in descending order of frequency in pooled ribociclib column.
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
A patient with multiple adverse events is counted only once in the total row.
AEs up to 30 days after the last study treatment will be included.
MedDRA Version 20.0 has been used for coding of adverse events.
Source: SCS Study E2301Appendix 1Table 3-4.10

The FDA's Assessment:

FDA's analyses of treatment discontinuations due to TEAEs on MONALEESA-7 agree with the applicant's findings above, with 6.5% of patients on the ribociclib and 3.2% of patients on the placebo arms. Neutropenia as a cause was low overall with only 1 case in the ribociclib arm. QT prolongation was low with 1 patient in each arm (0.4% for both). DILI was also low with 1.2% in the ribociclib and 0.4% in the placebo arm. There were no reported cases of febrile neutropenia causing treatment discontinuation. Overall the TEAEs leading to treatment discontinuation were low, balanced between the treatment arms, and within the expected incidence range.

Laboratory Findings

The Applicant's Position

Clinical abnormalities

Postbaseline biochemical laboratory abnormalities of any grade occurred in similar proportions of patients in the ribociclib and placebo groups. Most of these clinical chemistry abnormalities were mild (grade 1 or 2) in both treatment groups.

The most commonly (≥ 5% of patients) occurring grade 3 biochemical laboratory abnormalities in the ribociclib group included: increases in ALT (6%) and GGT (5%). The grade 4 abnormalities

were low and were noted in less than 1% of patients, except for increased GGT which was noted in 2% of patients (Table 7-32).

Hematological abnormalities
The most frequent grade 3 hematological abnormalities noted in the ribociclib group were decreased absolute neutrophil count (54%) and decreased leukocyte count (34%). Decreased neutrophils (9%) was the most frequent grade 4 abnormality noted in patients in the ribociclib group (Table 7-32).

Table 7-32: Laboratory abnormalities occurring in ≥ 10% of patients in Study LEE011E2301

	KISQALI plus NSAI plus goserelin N=248			Placebo plus NSAI plus goserelin arm N=247		
Laboratory parameters	**All Grades %**	**Grade 3 %**	**Grade 4 %**	**All Grades %**	**Grade 3 %**	**Grade 4 %**
HEMATOLOGY						
Leukocyte count decreased	93	34	2	30	< 1	< 1
Neutrophil count decreased	92	54	9	27	2	0
Hemoglobin decreased	84	2	0	51	< 1	0
Lymphocyte count decreased	55	12	2	18	2	< 1
Platelet count decreased	26	< 1	0	9	0	< 1
CHEMISTRY						
Alanine aminotransferase increased	33	6	0	31	1	< 1
Aspartate aminotransferase increased	37	5	0	35	1	< 1
Creatinine increased	21	2	< 1	20	< 1	< 1
Phosphorous decreased	14	2	0	11	< 1	< 1
Potassium decreased	11	< 1	< 1	14	< 1	< 1
Gamma-glutamyl transferase increased	42	5	2	42	8	1
Glucose serum decreased	10	< 1	0	10	< 1	0

The FDA's Assessment:
FDA agrees with the applicant's assessment of laboratory abnormalities.

Vital Signs
The Applicant's Position:
Differences in vital signs and body weight between the ribociclib and placebo groups were not considered to be clinically noteworthy in Study E2301.

The FDA's Assessment:

FDA agrees with the applicant's position on vital signs for MONALEESA-7 above.

Electrocardiograms (ECGs)

The Applicant's Position:

Notable QTcF values in Study E2301 were noted in higher proportion of patients in ribociclib group compared to placebo group.

- In the ribociclib group, 13/245 patients (5.3%) had post-baseline QTcF > 480 ms, including 4/245 patients (1.6%) with QTcF > 500 ms. A > 60 ms increase from baseline in QTcF interval was observed in 18/245 patients (7.3%).
- In the placebo group, 3/245 patients (1.2%) had post-baseline QTcF > 480 ms. No patient had a post-baseline QTcF > 500 ms and none had a > 60 ms increase in QTcF from baseline. (Table 7-33).

Table 7-33: Notable QTcF values –Study E2301 (Safety set)

	RIBO+ NSAI N=248 n/m (%)	**PBO+ NSAI N=247 n/m (%)**
QTcF (ms)		
New >450	112/241 (46.5)	40/232 (17.2)
New >480	13/245 (5.3)	3/245 (1.2)
New >500	4/245 (1.6)	0/245
Increase from baseline >30	130/245 (53.1)	41/245 (16.7)
Increase from baseline >60	18/245 (7.3)	0/245
For study E2301, only patients assigned to NSAI in treatment assignment CRF were included. Baseline was defined as the average of last ECG measurements taken before start of study tre atment Source: SCS Study E2301-Appendix 1-Table 3-7.4		

The FDA's Assessment:

FDA agrees with the applicant's conclusion that there was a higher proportion of patients in ribociclib group compared to placebo group in Study E2301 with notable QTcF values.

QT

The Applicant's Position:

The frequency of notable QTcF values was higher in the Study E2301 (NSAI group) compared to that in Study A2301. In Study E2301, majority of the ECG assessments (approximately 80%) collected were single measurements and are subject to greater variation than those from averaging triplicate ECG assessments in Study A2301. Further, when the QTcF data based on the highest single post-baseline QTcF value of the replicates in Study A2301 was compared the

frequency of notable QTcF values appear to be consistent between Study E2301 (NSAI subgroup) and Study A2301 (SCS Study E2301-Appendix 1-Table 5-2.1 and Table 5-2.4).

Based on both ΔQTcF and PK data observed in Study E2301, the higher QTcF values in patients receiving ribociclib plus tamoxifen compared to NSAI or fulvestrant can be contributed by the QTcF prolongation effect of tamoxifen. Based on an imbalance in increased QTcF values and higher ΔQTcF observed in the ribociclib plus tamoxifen subgroup, Novartis does not propose to include the ribociclib and tamoxifen combination in the proposed indication (please see details in Section 5.3.2.2

The FDA's Assessment:
FDA agrees with the applicant's proposal of not including the ribociclib and tamoxifen combination in the proposed indication due to QTcF prolongation. The reviewers confirmed the sponsor's analysis that observed mean QTcF increase from baseline was approximately more than 10 ms higher in the tamoxifen plus placebo group compared with NSAI plus placebo group.

Immunogenicity
The Applicant's Position:
Not applicable as this was not assessed nor expected

The FDA's Assessment:
FDA agrees with the applicant's position on immunogenicity for MONALEESA-7 above.

Safety Results: Study F2301 (MONALEESA-3)
Deaths
Deaths 'on-treatment' were reported in similar proportions of patients (13 patients; 2.7% versus eight patients; 3.3%) in both treatment groups; the majority were attributed to the underlying condition. Of the 13 deaths in the ribociclib plus fulvestrant group, seven were due to study indication. None of the remaining 6 deaths were related to the study treatment except for death due to acute respiratory distress syndrome in a 80 year old patient who had lung metastasis prior to study entry: the Patient was hospitalized on Day 338 with acute respiratory distress; treatment with ribociclib and fulvestrant was discontinued; the patient died 17 days following discontinuation of ribociclib; following autopsy, it was diagnosed that the patient had acute respiratory distress syndrome (Table 7-34).

Table 7-34: On-treatment deaths by preferred term irrespective of causality - Study F2301 (Safety set)

	RIBO + FULV	PBO + FULV
	N=483	N=241
	n (%)	n (%)
Total	**13 (2.7)**	**8 (3.3)**
Study indication	7 (1.4)	7 (2.9)
Other	6 (1.2)	1 (0.4)
Pulmonary embolism	1 (0.2)	1 (0.4)
Acute respiratory distress syndrome	1 (0.2)	0
Cardiac failure	1 (0.2)	0
Pneumonia	1 (0.2)	0
Shock haemorrhagic	1 (0.2)	0
Ventricular arrhythmia	1 (0.2)	0

PTs are sorted by descending frequency, as reported in the ribociclib treatment column.
Deaths occurring up to 30 d, inclusive, after last dose of study treatment are included.
MedDRA Version 20.1 was used.
Source: Study F2301-Table 14.3.1-1.6, Study F2301-Listing 14.3.2-1.1

The FDA's Assessment:

FDA analyses of patients who died within 30 days after the last dose of any study drug agrees with the applicant's presented above, except FDA found 6 (2.5%) deaths in the placebo arm due to study indication while the applicant reported 7 (2.9%) deaths. However, this discrepancy is on the placebo arm (and not the ribociclib arm) and the numbers are overall low and within the expected range based on the known data from the current ribociclib USPI.

Serious adverse events

The Applicant's Position:

Serious AEs in Study F2301 were reported more frequently in the ribociclib group compared to the placebo group (28.6% vs. 16.6%). While the incidence of specific individual SAEs was low for both treatment groups, the most commonly reported SAE (≥ 1.5%) was pneumonia in 9 patients (1.9%) in the ribociclib group. A higher proportion of SAEs with suspected relationship to study treatment was reported in the ribociclib group (11.2%) compared to the placebo (2.5%) (Table 7-35).

Table 7-35: Serious adverse events by preferred term irrespective of causality (at least 1% in any group) – Study F2301 (Safety set)

	RIBO + FULV			PBO + FULV		
	N=483			N=241		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Total	**138 (28.6)**	**91 (18.8)**	**23 (4.8)**	**40 (16.6)**	**27 (11.2)**	**7 (2.9)**
Pneumonia	9 (1.9)	8 (1.7)	0	0	0	0
Nausea	7 (1.4)	5 (1.0)	0	0	0	0
Vomiting	7 (1.4)	5 (1.0)	0	1 (0.4)	0	0
Anaemia	6 (1.2)	3 (0.6)	0	0	0	0
Dyspnoea	6 (1.2)	5 (1.0)	0	5 (2.1)	4 (1.7)	0
Neutropenia	6 (1.2)	3 (0.6)	1 (0.2)	0	0	0
Pleural effusion	6 (1.2)	4 (0.8)	1 (0.2)	3 (1.2)	2 (0.8)	0
Abdominal pain	5 (1.0)	5 (1.0)	0	1 (0.4)	1 (0.4)	0
Acute kidney injury	5 (1.0)	4 (0.8)	0	0	0	0
Febrile neutropenia	5 (1.0)	5 (1.0)	0	0	0	0
Pyrexia	5 (1.0)	1 (0.2)	0	1 (0.4)	0	0

PTs are sorted in descending frequency of all grades column, as reported in the ribociclib treatment column.
A patient with multiple occurrences of an SAE under one treatment is counted only once in the SAE category for that treatment.
A patient with multiple events is counted only once in the total row.
MedDRA Version 20.1 was used.
Source: Study F2301-Table 14.3.1-1.9

The FDA's Assessment:

FDA's analysis of all grade serious AEs in MONALEESA-3 agree with the applicant's presented above. The incidence of serious AEs was higher in the ribociclib arm, but overall low and within the expected for ribociclib. The incidence of febrile neutropenia and neutropenia were low overall and within the expected for ribociclib.

A total of 9 patients experienced acute kidney injury/acute renal failure while on study (8 ribociclib+fulvestrant arm, 1 placebo+fulvestrant arm). All patients recovered from their AE. Refer to Table 7-36 below for individual patients, relation to study drug as assessed by the applicant, whether the AE was serious, AE grade, and study drug action.

Table 7-36: FDA Assessment of Acute Kidney Injury/Acute Renal Failure for MONALEESA-3

Patient ID	Treatment Arm	Relation to Study Drug	AE Serious	AE Grade	Study Drug Action
(b) (6)	Ribociclib	No	Y	3	Dose not changed
	Ribociclib	No	Y	3	Drug withdrawn
	Ribociclib	No	Y	3	Drug interrupted
	Ribociclib	Yes, investigational treatment	Y	2	Drug interrupted
	Ribociclib	Yes, investigational treatment	Y	3	Drug interrupted
	Ribociclib	Yes, investigational treatment	N	1	Dose not changed
	Ribociclib	Yes, both and/or indistinguishable	N	1	Dose not changed
	Ribociclib	Yes, investigational treatment	N	1	Drug interrupted
	Placebo	No	N	2	Dose not changed

The majority were grade 1-2 in severity. Study drug was withdrawn in one case in the ribociclib arm with an AE grade of 3. Study drug was interrupted in 4 cases in the ribociclib arm. Narratives for patients with drug interruption/withdrawn and AE grade 3 reviewed and summarized below:

- (b) (6): **70 year old Asian woman with metastases to lymph nodes, bone, skin, and paratracheal. On day 180, the patient was hospitalized with grade 1 nausea, vomiting, and grade 2 dizziness. She received an overdose of propafenone and diltiazem for atrial fibrillation, which developed while on study. The same day the patient had grade 3 acute kidney injury and bradycardia, grade 2 hyperkalemia with K=5.7, and creatinine at 2.33. The patient was treated and ribociclib held. AKI resolved on day 184. Afib resolved on day 199 and ribociclib was restarted on the same day. Study drug was permanently discontinued on day 239 due to disease progression. AKI could have been due to overdose of propafenone and diltiazem and is less likely due to ribociclib itself. However, the event of afib, which the patient did not have at baseline, could have been contributed by ribociclib.**
- (b) (6): **68 year old black woman with metastases to bone, liver, and lymph nodes at baseline and normal chemistries at baseline. On study day 141, the patient had grade 2 creatinine increase to 141.4 (reference range 45-81) and BUN increase to 9.8 (reference range 2.8-7.2). On day 156 the patient developed gastroenteritis, abdominal pain, and diarrhea – all grade 1. Ribociclib was held and the patient treated with antibiotics. Diarrhea resolved on day 162. On day 220 ribociclib was held due to a dispensing error. On day 225 the patient had a grade 1 creatinine increase and second episode of diarrhea. On day 227 she had grade 3 AKI with creatinine > 6 mg/dL. On day 228 she had grade 4 creatinine increase and admitted to the ICU for AKI. Ribociclib continue to be held and patient was treated with echo showing LVH but normal LVEF. AKI resolved on day 238 and patient discharged on day 239. Last dose of study drug was day 219. Patient eventually came off study for PD. Ribociclib, dehydration, diarrhea, and GI illness likely all contributed to the AKI.**
- (b) (6): **59 year old Caucasian female with metastases to bone, adrenal, ovary, and**

lymph nodes. On day 261 patient was on off week of ribociclib and developed polyuria and blood in the urine with shaking chills. On day 262 patient was hospitalized for urinary sepsis, had a temperature of 39C, grade 3 leukopenia, and grade 1 creatinine increase. She was diagnosed with grade 3 urosepsis. She received antibiotics and was discharged on day 266. On day 373 during the off week of ribociclib she developed grade 3 kidney infection, no creatinine reported. She received Cipro and protocol deviation was noted as ciprofloxacin is QT prolongation. Ultrasound unremarkable. Kidney infection resolved on day 391. Ribociclib was not interrupted. Planned Pigtail catheters were inserted on day 393 with complication of ureteral obstruction. Day 396 ureteral obstruction and grade 3 AKI noted and patient was hospitalized, ribociclib was held. She underwent bilateral nephrostomy during this admission and AKI resolved on day 403. Ribociclib was restarted at 600 mg on day 416. On day 455 the patient had a UTI and fever which was treated with antibiotics and ribociclib continued. The UTI waxed and waned while on treatment with ribociclib temporarily held multiple times. The patient continued on treatment. The sepsis was likely contributed by ribociclib, and the resulting AKI was due to sepsis.

- (b) (6): 75 year old Caucasian women with metastases to lung, bone, and pleural. On day 43 the patient developed AKI grade 2 with grade 2 creatinine elevation. She was hospitalize and ribociclib held. AKI resolved on day 47. Concomitant medications included rosuvastatin and lisinopril. AKI did not recur. Ribociclib could have contributed to the AKI, although Lisinopril is a confounding factor.
- (b) (6): 61 year old Caucasian woman with metastases to bone, colon, bladder, and lymph nodes. At baseline she had palpitations, hydronephrosis grade 2, intermittent bladder spasms grade 2, urinary incontinence grade 2, grade 1 dizziness, and grade 1 creatinine elevation. She had vomiting, nausea, diarrhea, dizziness, and asthenia leading up to day 34, when she was diagnosed with grade 2 hypotension, grade 3 AKI and hospitalized. Ribociclib was held and the patient treated for UTI and symptoms. Hydronephrosis was noted and ureteral stents placed. Ribociclib was restarted on day 42 at a reduced dose of 400 mg due to nausea and vomiting. Due to ongoing nausea, vomiting, fatigue, ribociclib was permanently discontinued on day 142 and patient taken off study day 166. The patient had many comorbidities at baseline and these, in addition to nausea and vomiting likely caused poor PO, leading to hypotension and contributing to the AKI.
- (b) (6): 72 year old Caucasian woman with metastases to lung, bone, and liver. On day 530 during the week off ribociclib, patient had grade 3 pancytopenia and grade 1 AKI. She was diagnosed with grade 3 pneumonia on XRT and hospitalized. Ribociclib was held and AKI resolved on day 533. Ribociclib likely contributed to pancytopenia and pneumonia which in turn contributed to AKI.

Overall review of AKI suggests ribociclib likely contributed to nausea, vomiting, diarrhea, and infections which then led to AKI. However, the overall incidence of AKI was low and patients recovered.

Dropouts and/or Discontinuations Due to Adverse Effects

The Applicant's Position:

In Study F2301, treatment discontinuation (of one or both study drugs) as a result of AEs was more frequent in the ribociclib group compared to the placebo group (17.2% vs. 6.2%). Increased ALT (4.6%), increased AST (2.7%), and vomiting (1.0%) were the most frequent AEs leading to discontinuation of study drug in ≥ 1% of patients. All other AEs that led to discontinuation of study drug were reported in < 1% of patients (Table 7-37).

Table 7-37: Adverse events leading to discontinuation by preferred term irrespective of causality (at least 1% in any group) – Study F2301 (Safety set)

	RIBO + FULV			PBO + FULV		
	N=483			N=241		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Total	83 (17.2)	36 (7.5)	12 (2.5)	15 (6.2)	9 (3.7)	1 (0.4)
Alanine aminotransferase increased	22 (4.6)	6 (1.2)	5 (1.0)	0	0	0
Aspartate aminotransferase increased	13 (2.7)	3 (0.6)	3 (0.6)	1 (0.4)	1 (0.4)	0
Vomiting	5 (1.0)	1 (0.2)	0	0	0	0

PTs are sorted in descending frequency of all grades column, as reported in the ribociclib treatment column.
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
A patient with multiple AEs is counted only once in the total row.
AEs leading to discontinuation refers to any component of study treatment.
MedDRA Version 20.1 was used.
Source: Study F2301-Table 14.3.1-1.11

The FDA's Assessment:

FDA's assessment of the TEAEs leading to treatment discontinuation for MONALEESA-3 occurring in at least 1% of patients in any arm agrees with the applicant's findings above.

Laboratory Findings

The Applicant's Position

Clinical abnormalities

The most frequently reported post-baseline clinical chemistry abnormalities (all grades) in the ribociclib plus fulvestrant group were increased creatinine (65%), GGT (52%), AST (49%) and ALT (44%). Elevations in ALT and GGT were frequent grade 3 abnormalities while grade 4 abnormalities were primarily due to elevated ALT (Table 7-38).

Hematological abnormalities

The most frequently reported post-baseline hematological abnormalities (all grades) in the ribociclib plus fulvestrant group (with a ≥ 10% difference relative to the placebo plus fulvestrant group) were decreased neutrophils (+71.0%), decreased leukocytes (+68.7%), decreased lymphocytes (+34.0%), and decreased hemoglobin (+25.3%). Decreased neutrophil and leukocyte counts formed the majority of grade 3 abnormalities, while grade 4 abnormalities were predominantly decreased neutrophil counts (Table 7-38).

Table 7-38: Laboratory abnormalities occuring in ≥ 10% of patients in Study F2301 (Safety set)

	KISQALI plus fulvestrant N=483			Placebo plus fulvestrant N=241		
Laboratory parameters	**All Grades %**	**Grade 3 %**	**Grade 4 %**	**All Grades %**	**Grade 3 %**	**Grade 4 %**
HEMATOLOGY						
Leukocyte count decreased	95	25	< 1	26	< 1	0
Neutrophil count decreased	92	46	7	21	< 1	0
Hemoglobin decreased	60	4	0	35	3	0
Lymphocyte count decreased	69	14	1	35	4	< 1
Platelet count decreased	33	< 1	1	11	0	0
CHEMISTRY						
Creatinine increased	65	< 1	< 1	33	< 1	0
Gamma-glutamyl transferase increased	52	6	1	49	8	2
Aspartate aminotransferase increased	49	5	2	43	3	0
Alanine aminotransferase increased	44	8	3	37	2	0
Glucose serum decreased	23	0	0	18	0	0
Phosphorous decreased	18	5	0	8	< 1	0
Albumin decreased	12	0	0	8	0	0

The FDA's Assessment:

FDA agrees with the applicant's assessment of laboratory abnormalities.

Vital Signs

Differences in vital signs and body weight between the ribociclib and placebo groups in Study F2301 were not considered to be clinically noteworthy.

The FDA's Assessment:

FDA agrees with the applicant's positions on vital signs and body weight above.

Electrocardiograms (ECGs)

The Applicant's Position:

Based on ECG data, notable ECG abnormalities related to QT prolongation in Study F2301 were more frequently reported with ribociclib in combination with fulvestrant treatment compared with placebo in combination with fulvestrant treatment (Table 7-39).

Table 7-39: Notable QTcF parameters by treatment group in Study F2301 (Safety set)

	RIBO + FULV	PBO + FULV
	N=483	N=241
	n/m (%)	n/m (%)
QTcF		
Increase from baseline > 30 ms	270/480 (56.3)	46/240 (19.2)
Increase from baseline > 60 ms	31/480 (6.5)	1/240 (0.4)
New > 450 ms	205/473 (43.3)	52/234 (22.2)
New > 480 ms	27/480 (5.6)	6/239 (2.5)
New > 500 ms	8/480 (1.7)	1/239 (0.4)

n = Number of patients who meet the designated criterion.
m = Number of patients at risk for a specific category. For new abnormality postbaseline, this is the number of patients with both baseline and postbaseline evaluations, and baseline not meeting the criteria. For abnormal change from baseline, it is the number of patients with both baseline and postbaseline evaluations.
N = Total number of patients in the treatment group in this analysis set.
All scheduled and unscheduled visits are included.
Source: Study F2301-Table 14.3-5.4

The FDA's Assessment:

FDA agrees with the applicant's analysis that there is a higher proportion of patients with notable QTcF values in ribociclib+ fulvestrant group compared to placebo+ fulvestrant group in MONALEESA-3.

Overall safety results of Study X2108 (Supportive study)

Overall, safety results in Study X2108 are consistent with the safety findings in Study F2301.
The median duration of exposure to ribociclib plus fulvestrant was 7.4 months (range: 1.8 to 13.8) SCS Study F2301-Table 1-7.

There were no deaths reported in the ribociclib in combination with fulvestrant treatment group (i.e. Arm 3) in Study X2108 -Listing 14.3.2-2.1.

Neutropenia related AEs were reported in 12 patients (92.3%), and all were suspected to be drug related, as assessed by the Investigator. Grade 3/4 AEs were reported in 10 patients (76.9%) and of these, 2 patients' (15.4%) events were serious. Five patients' (38.5%) events required dose adjustment or interruption. However, no patient discontinued study treatment due to this SEC Study X2108-Table 14.3.1-2.8, Study X21208-Listing 14.3.2-2.3.

One patient (7.7%) in Study X2108 had QTcF > 500ms and a further patient (7.7%) had QTcF > 480 ms. Four of 13 patients (30.8%) had a QTcF change from baseline (ΔQTcF) > 60 ms Study X2108-Table 14.3-5.4; No cardiac related AEs concurrent with the QTcF prolongations were reported.

Hepatobiliary toxicity related events were reported in 46.2% of patients, with grade 3/4 events reported in 15.4% of patients. One patient required dose adjustment or interruption and one had discontinued study drug due to increased ALT and abnormal hepatic function Study X2108-Section 12.4.3.3.

The FDA's Assessment:
The FDA did not review Study X2108 data and results, as this study is not a registration trial and is not used to support a labeling indication.

7.4.8. **Analysis of Submission-Specific Safety Issues**
Adverse events of special interest (Study E2301 - NSAI subgroup and Study F2301)

The Applicant's Position:
As a result of signals observed during the conduct of clinical studies with ribociclib, several groups of events, adverse events of special interest (AESI), are detailed and analyzed in these studies (Study E2301 and Study F2301). These groups consist of AEs for which there is a specific clinical interest in connection with inhibition of CDK4/cyclin-D1 and CDK6/ cyclin-D3 enzyme complexes. Overall results indicate that the AESI associated with the treatment of ribociclib plus NSAI and goserelin or ribociclib plus fulvestrant was consistent with the known safety profiles of ribociclib, goserelin, NSAI, and fulvestrant. Three categories of events are discussed here (neutropenia, QT prolongation, hepatobiliary toxicity); these are well characterized clinical issues associated with the use of ribociclib and which, in general, can be effectively managed in the clinical setting (with dose interruption and/or dose modification).

Commentary on the remaining AESI is provided in [SCS Study E2301Section 2.2.8], and [SCS Study F2301-Section 2.1.5].

Neutropenia
Neutropenia is a common adverse effect associated with CDK4/6 inhibition that is concentration dependent, transient, and reversible. Myelosuppression is suggestive of direct effect of the compound on hematopoiesis and may be related to the pharmacological inhibition of cell replication due to CDK4/6 inhibition. Neutropenia associated with ribociclib therapy can be clinically managed through dose modification and interruption.

In Study E2301 (NSAI subgroup), neutropenia related events were more frequent in the ribociclib group compared to the placebo group (78.2% vs 7.7%, respectively); the majority of these events were grade 3/4 in severity (66.6% vs. 3.6%, respectively). Dose interruptions/adjustments were

required for 62.9% of patients in the ribociclib group. However, discontinuation of study drug due to neutropenic events occurred in only 1 patient (0.4%), suggesting that these events are manageable with adequate monitoring and dose adjustments and ribociclib drug holiday from Day 22 to Day 28 [SCS Study E2301-Table 2-14]. Events of febrile neutropenia in association with ribociclib therapy were reported infrequently (6 patients; 2.4%, all grade 3 and related to study treatment). Dose adjustment/interruption was required for 5 patients (2.0%) and of these, all events were manageable and resolved, and no patient discontinued due to febrile neutropenia. None of these events led to discontinuation of study drug [SCS Study E2301-Table 2-13]. The Kaplan-Meier median time to first occurrence of grade 3/4 neutropenia related events was 1.9 months [SCS Study E2301-Figure 2-1].

In Study F2301, neutropenia related events were more frequent in the ribociclib plus fulvestrant group compared to placebo plus fulvestrant group (69.6% vs 2.1%, respectively); the majority of these events were grade 3/4 in severity (53.4% vs. 0%, respectively). In the ribociclib plus fulvestrant group, dose interruptions/adjustments were required for 51.8% of patients, primarily due to AEs of neutropenia and neutrophil count decreased. However, discontinuation of study drug due to neutropenic events occurred in only 4 patients (0.8%), suggesting that these events are manageable with adequate monitoring and dose adjustments and ribociclib drug holiday from Day 22 to Day 28 [SCS Study F2301-Table 2-22].

Events of febrile neutropenia in association with ribociclib plus fulvestrant therapy were reported infrequently (5 patients; 1.0%, all grade 3/4 and SAEs) and these events required dose interruption/adjustment in 4 patients. None of these events led to discontinuation of study drug [SCS Study F2301-Table 2-22]. Among patients with grade 2 or worse neutropenia (based on laboratory findings), the median time to onset was 2.43 weeks (range: 1.71 to 96.14) in the ribociclib plus fulvestrant group [Study F2301-Table 14.3-3.10]. The Kaplan-Meier median time to first occurrence of grade 3/4 neutropenia events was 4.1 weeks [SCS Study F2301-Figure 2-1].

The FDA's Assessment:

FDA conducted an independent assessment of neutropenia and the results are shown below in Table 7-40. Neutropenia is a known common side effect of the CDK 4/6 inhibitor class of drugs. There were more patients with neutropenia, but neutropenia as a cause of treatment discontinuation was low. Instances of grade 3-4 febrile neutropenia was also low. Neutropenia is listed in the Warnings and Precautions section of the label.

Table 7-40: FDA Analysis of Neutropenia

Study E2301	Ribociclib n=248	Placebo n=247
Neutropenia leading to Treatment Discontinuation	1 (0.4)	0
All grade neutropenia	194 (78.2)	19 (7.7)
Grade 3 neutropenia	133 (53.6)	8 (3.2)
Grade 4 neutropenia	25 (10.1)	1 (0.4)
Grade 3-4 febrile neutropenia	6 (2.4)	2 (0.8)
Study F2301	**Ribociclib n=483**	**Placebo n=241**
Neutropenia leading to Treatment Discontinuation	2 (0.4)	0
All grade neutropenia	335 (69.4)	5 (2.1)
Grade 3 neutropenia	213 (44.1)	0
Grade 4 neutropenia	33 (6.8)	0
Grade 3-4 febrile neutropenia	2 (0.4)	0

QT interval prolongation

QT prolongation is an important identified safety risk for ribociclib. As previously known, ribociclib prolongs the QT interval in a concentration-dependent manner. Results of detailed analyses and discussion for QT interval prolongation are available in the QT safety report [Study E2301/ Study F2301 QT/QTcF Safety Analysis Report].

In study E2301, a QTcF interval increase of > 60 ms from baseline was observed in 14/87 (16.1%) of the patients receiving ribociclib in combination with tamoxifen and in 18/245 (7.3%) of the patients receiving ribociclib in combination with NSAI. In the placebo group, a QTcF interval increase of > 60 ms from baseline occurred in 6/90 (6.7%) of the patients receiving tamoxifen and in no patients receiving a NSAI. In the ribociclib group, post-baseline QTcF > 480 ms was noted in 5.3% of patients including 1.6% of patients with QTcF > 500 ms. A > 60 ms increase from baseline in QTcF interval was observed in 7.3% of patients. A slightly higher frequency of notable QTcF values noted in Study E2301 (NSAI subgroup) compared to Study A2301 are likely due to the differences in the ECG collection methodology, and collection time points between these studies [Study E2301-Table 14.3-5.3], [SCS Study E2301-Appendix 1-Table 3-7.4], [Study E2301/ Study F2301 QT/QTcF Safety Analysis Report-Section 5].

In the ribociclib group in Study E2301 (NSAI subgroup), most of these events were mild (grade 1 or 2, in 8.1% of patients); grade 3 events were reported in 1.2% of patients. No grade 4 QT prolongation was reported. Dose adjustments or interruptions required in 3.2% of patients, and all were due to the AE of electrocardiogram QT prolonged. Syncope was reported in 1 patient (0.4%), and was of grade 2 severity; no action was taken and the event resolved on same day of occurrence [Study E2301-Listing 16.2.7-.1.1]. One patient (0.4%) discontinued study treatment due to event of electrocardiogram QT prolonged. None of the events were reported as SAEs. QTcF prolongation was not associated with cardiac SAEs or arrhythmias. No events of cardiac

arrest, sudden death, or Torsades de Pointes were reported [SCS-E2301-Appendix 1-Table 3-4.17].

In Study F2301, a slightly higher frequency of notable QTcF values were observed in Study F2301 compared to those in Study A2301. QTcF values of >500 ms were observed in eight patients (1.7%) in the ribociclib group and in one patient (0.4%) in the placebo group. A > 60 ms increase from Baseline in QTcF interval was observed in 31 patients (6.5%) in the ribociclib group and in one patient (0.4%) in the placebo group [Study F2301-Table 14.3-5.4]. Considering the differences in ECG collection methodology and collection at additional mid-cycle time points, the QTcF values in Study F2301 were consistent with that of values in Study A2301 [Study E2301/ Study F2301 QT/QTcF Safety Analysis Report-Section 5].

In Study F2301, 'QT interval prolongation' grouped events were reported more frequently in the ribociclib group compared to the placebo group (37/483 patients; 7.7% vs 5/241 patients; 2.1%; respectively). Electrocardiogram QT prolonged was the most frequent AE by PT reported in 30 patients (6.2%) in the ribociclib group. No events of sudden death, or Torsades de Pointes were reported [Study F2301-Table 14.3.1-1.18].

In the ribociclib group, AE of prolonged electrocardiogram QT was reported in 30 patients (6.2%) and most (27 patients; 5.6%) were suspected to be drug related, as assessed by the Investigator. The majority of these events were either grade 1 or 2 in severity, with grade 3 or 4 events reported in 7 patients (1.4%). In 2 patients, these events were reported as serious. AE of prolonged electrocardiogram QT leading to treatment discontinuation was reported in 3 patients (0.6%). Dose interruptions/adjustments were required for 12 patients (2.5%).

With ribociclib treatment, syncope was reported in 6 patients (1.2%) and none were suspected to be drug related. Grade 3/4 syncope were reported in 4 patients (0.8%) and of these, 1 patients' (0.2%) event was serious. Dose adjustment/interruption was not required [Study F2301-Table 14.3.1-1.18].

The FDA's Assessment:

FDA has reviewed and verified the sponsor's analysis, and the final values as negotiated with the sponsor are reflected in labeling edits (e.g., Values for QT interval prolongation with ribociclib + NSAI or ribociclib + fulvestrant and a higher QT prolongation effects for ribociclib + tamoxifen are listed in the label as Warnings and Precautions). Refer to QT-IRT review for more details.

Hepatobiliary toxicity

Hepatobiliary toxicity has been reported during treatment with ribociclib and therefore, should be closely monitored. The most plausible mechanism underlying the liver effects of ribociclib is immune-mediated. Additionally, it could be due to multifactorial etiology (e.g. contributions from BSEP inhibition and reactive metabolite formation potentially leading to protein adduct formation).

In Study E2301 (NSAI subgroup), the proportion of patients with hepatobiliary toxicity events were similar in ribociclib group and the placebo group (21.0% vs. 20.2%); likewise the proportion of patients with grade 3 (7.3% vs. 6.5%) and grade 4 events (0.8% in both the treatment group) were also similar in both the treatment group. The most frequently reported events in this AESI category included: ALT increased (13.3% vs. 8.9%), AST increased (12.9% vs. 10.1%) [SCS Study E2301-Table 2-18].

Eleven patients (4.4%) in the ribociclib group and 3 patients (1.2%) in the placebo group discontinued study treatment due to hepatobiliary events; of these 3 patients (1.2%) and 1 patient (0.4) in the ribociclib and placebo group, respectively discontinued treatment due to event of potential drug-induced liver injury. Four patients (1.6%) in the ribociclib group, and 1 patient (0.4%) in the placebo group had drug-induced liver injury reported as an AE. These events were considered as SAEs and were suspected to be related to study treatment by the Investigator [SCS Study E2301-Table 2-17]. Overall, the incidence of increased transaminases (> 3 × ULN) was higher in the ribociclib group compared to the placebo group (11.2% vs. 6.6%) [Study E2301-Table 14.3-3.9]. There were no cases of Hy's Law in Study E2301.

In Study F2301, the proportion of patients with hepatobiliary toxicity events was higher in ribociclib group compared to placebo group (21.7% vs. 14.9%); likewise the proportion of patients with grade 3/4 were also higher in ribociclib group compared to placebo group (12.8% vs. 5.4%). The two most frequent event types were increased ALT (14.5% vs. 4.6%) and increased AST (13.3% vs. 4.6%). Thirty three patients (6.8%) in the ribociclib group and 3 patients (1.2%) in the placebo group discontinued study treatment due to hepatobiliary events; primarily due to increased ALT or increased AST [Study F2301-Table 14.3.1-1.18].

The incidence of AST or ALT elevations (> 3×ULN) was higher in the ribociclib plus fulvestrant group compared to the placebo plus fulvestrant group (16.5% versus 7.1%, respectively) [Study F2301-Table 14.3-3.9]. There were 2 cases (Patient F2301-(b) (6), Patient F2301-(b) (6)) of confirmed Hy's Law in Study F2301. Elevated transaminases in both the cases were suspected to be related to study drug as assessed by the Investigator. Ribociclib was discontinued in both of these cases and these patients subsequently recovered after treatment discontinuation. Patient narratives for these two Hy's Law cases can be found in [Study F2301-Section 14.3.3].

The FDA's Assessment:

FDA conducted an independent assessment of hepatobiliary toxicity and the results are shown below in Table 7-41. Hepatobiliary toxicity is a known side effect of ribociclib. FDA agrees there were no instances of Hy's law in MONALEESA-7. The FDA reviewed the incidence and narratives for Hy's law cases occurring in MONALEESA-3—patients recovered after discontinuation of ribociclib. Hepatobiliary toxicity is listed in the label as a Warnings and Precautions.

Table 7-41: FDA Analysis of Hepatobiliary Toxicities

Study E2301	Ribociclib n=248	Placebo n=247
Hepatobiliary Toxicity	52 (21.0)	50 (20.2)
Hepatobiliary disorders leading to treatment discontinuation (DILI, hyperbilirubinemia, hypertransaminaemia)	4 (1.6)	2 (0.8)
Hepatobiliary laboratory abnormalities leading to treatment discontinuation	11 (4.4)	6 (2.4)
Study F2301	**Ribociclib n=483**	**Placebo n=241**
Hepatobiliary Toxicity	105 (21.7)	36 (14.9)
Death from hepatic failure	1 (0.2)	2 (0.8)
Death from hepatic enzyme increase	1 (0.2)	0
Hepatobiliary disorders leading to treatment discontinuation (acute hepatic failure, DILI, hepatocellular injury, hepatotoxicity)	5 (1.0)	2 (0.8)
Hepatobiliary laboratory abnormalities leading to treatment discontinuation	40 (8.3)	1 (0.4)

7.4.9. **Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability**

The Applicant's Position:

See clinical Pharmacology section.

The FDA's Assessment:

FDA reviewed the PRO data the applicant presented. No independent PRO data analysis was performed. The applicant is not seeking to include PRO in the proposed labeling.

7.4.10. **Safety Analyses by Demographic Subgroups**

The Applicant's Position:

Subgroup analyses were conducted to identify potential safety issues restricted to particular subpopulations; these typically demonstrated a pattern of events consistent with that reported for the overall study populations. No additional safety concerns were observed for subpopulations in these subgroup analyses.

Adverse events by age-Study E2301

Subgroup <65 and ≥ 65 years

In the ribociclib group, the incidence of AEs was generally similar for patients in different age subgroups (<65 years and ≥ 65years).

The incidence of AEs was generally similar for patients <65 years of age and those aged ≥ 65 years, with some differences in incidence for several events; however, no consistent trends were evident that could be perceived as being indicative of an increased risk for an event on

the basis of age other than those that might be expected. Differences (≥ 10% across the age groups) were observed for following AEs:

- Vomiting (+16.9%), diarrhea (+15.8%), hypertension (+14.4%), nausea (+13.7%), decreased appetite (+12.4%), fatigue (+11.9%), anaemia (+11.5%), blood creatinine increased (+10.2%), and oedema peripheral (+10.1%) were reported more frequently in the older patients (≥ 65 years) compared to those aged <65 years. Of note, few of these AEs were also reported higher in older patients in the placebo group, and the relative difference between the treatment groups was comparable between the two age subgroups: cough, decreased appetite, urinary tract infection, hypertension, and oedema peripheral.
- Neutrophil count decreased (-11.4%) and hot flush (-12.4%) were reported less frequently in the older patients (≥ 65 years) compared to those aged <65 years. Hot flush was also reported less in the older patients in placebo group, and the relative difference between the treatment groups was similar between the two age subgroups.

Subgroup <40 and ≥ 40 years: The incidence of AEs in the ribociclib group was generally similar for patients <40 years of age and those aged ≥ 40 years. Differences (≥ 10% across the age groups) were observed for few events including: back pain (+10.9%) and diarrhea (+10.4%) which were reported more frequently in patients aged <40 years compared to ≥ 40 years. However the relative difference between the ribociclib and placebo group for back pain was similar across the two age subgroups (1.4% and 0.8% for <40 years and ≥ 40 years subgroup, respectively.

Adverse events of special interest by race-Study E2301

Comparison was possible between the Caucasian and Asian subpopulations. Given the limited sample size for Blacks (n=4), and for whom race was recorded as 'other' (n=9), and 'unknown' no definitive conclusions can be drawn regarding AEs by race in this analysis, hence data are not displayed in the table (Table 7-23).

The incidence of AESIs in the ribociclib group was generally comparable across the two subpopulations. 'Infections'events (+16.4%) and 'leukopenia' events (+12.8%) were more prominent in Caucasians compared to Asian subpopulation. However, the relative difference between the two treatment groups for these events was comparable across the two subpopulations (Table 7-23).

Relative difference between the treatment groups:

- Infections: Caucasian (12.8%) vs. Asian (9.2%)
- Leukopenia: Caucasian (29.4%) vs. Asian (22.0%)

Adverse events of special interest by age –group category < 65 y vs. ≥ 65 y- Study F2301

The occurrence of hematological AESIs was comparable in patients < 65 y vs. ≥ 65 y, with the exception of neutropenia (72.4% in < 65 y vs. 66.4% in ≥ 65 y).

Among the neutropenia AEs, suspected AEs occurred higher in proportion in patients with <65 y compared with ≥ 65 y (71.6% vs. 66.4%). No differences were observed in the occurrence of grade 3/4 AEs, AEs leading to discontinuation, and AEs needing dose interruptions and adjustments.
The following nonhematological AESIs were higher in proportion in patients with < 65 y compared to ≥ 65 y: infections (57.6% vs. 48.7%) and hepatobiliary toxicities (24.1% vs. 19.0%).
Among the infection-related AEs, suspected AEs were higher in patients < 65 y compared with ≥ 65 y (11.3% vs. 8.8%), as well as SAEs (7.0% vs. 4.9%). No differences were observed in the occurrence of grade 3/4 AEs, AEs leading to discontinuation, and AEs needing dose adjustments or interruptions.

Among the hepatobiliary toxicity related AEs, higher proportion of patients < 65 y compared with ≥ 65 y had grade 3/4 AEs, (15.2% vs. 10.2%), suspected AEs (20.2% vs. 16.4%), and AEs needing dose adjustments or interruptions (16.7% vs. 9.3%).

The following nonhematological AESIs were higher in proportion in patients ≥ 65 y compared with < 65 years: pulmonary toxicities, respiratory disorders (38.5% vs. 28.8%) and renal toxicities (14.2% vs. 7.0%).

Among the pulmonary toxicity / respiratory disorder related AEs, higher proportion of patients ≥ 65 y compared with patients < 65 y had grade 3/4 AEs (3.5% vs. 0.4%), and SAEs (2.7% vs. 0.8%). No differences were observed in the occurrence of suspected AEs, AEs leading to discontinuation, AEs needing dose adjustments or interruptions.

Adverse events of special interest by race (Asian vs. non-Asian)- Study F2301
The number of Asian patients was low. Among the hematological AESIs, neutropenia and anemia were reported in more Asian patients relative to non-Asian patients (neutropenia: 73.3% vs. 69.2%; anemia: 20.0% vs. 16.5%).

Among the neutropenia related AEs, grade 3/4 AEs, and suspected AEs, and AEs that required dose interruption/adjustment were higher in Asian patients compared to non-Asian patients (grade 3/4: 64.4% vs. 52.3%; suspected AEs: 73.3% vs. 68.8%; dose interruption/adjustment: 64.4% vs. 51.3%). No differences were observed in the occurrence of AEs leading to discontinuation and AEs needing dose interruptions and adjustments.

Among the anemia related AEs, grade 3/4 AEs, suspected AEs, AEs leading to discontinuation, and AEs needing dose interruptions and adjustments were comparable in Asian and non-Asian patients.

Leukopenia was reported in higher proportion of the non-Asian patients compared to Asian patients (29.5% vs. 22.2%). Suspected AEs were higher in the non-Asian patients compared to Asian patients (29.1% vs. 22.2%). No differences were observed in the occurrence of grade 3/4 AEs, AEs leading to discontinuation and AEs needing dose interruptions and adjustments.
Thrombocytopenia was reported in higher proportion of the non-Asian patients compared to Asian patients (9.0% vs. 4.4%) and so were suspected AEs (8.7% vs. 2.2%).

The occurrence of nonhematological AESI were comparable in Asian and non-Asian patients (difference less than 3%).

The FDA's Assessment:
FDA did not conduct separate safety analyses by demographic subgroup. Safety is not expected to differ across demographic subgroups for ribociclib.

7.4.11. **Specific Safety Studies/Clinical Trials**
The Applicant's Position:
Not applicable

The FDA's Assessment:
Not applicable

7.4.12. **Additional Safety Explorations**
Human Carcinogenicity or Tumor Development
The Applicant's Position:
See Pharmacology/toxicology review.

The FDA's Assessment:
Carcinogenicity studies were not conducted or required to support this sNDA.

Human Reproduction and Pregnancy
The Applicant's Position:
Based on data from nonclinical studies, ribociclib was found to be embryofetotoxic and teratogenic. There were no reported pregnancies or lactation events reported in the ribociclib clinical development program in HR-positive, HER-negative advanced or metastatic breast cancer. Of relevance, for women of childbearing potential (WOCBP), pregnancy status should be verified prior to treatment with ribociclib. For sexually active WOCBP, effective contraception methods (i.e. results in < 1% pregnancy rate) should be used when using ribociclib during treatment and for 21 days after stopping treatment with ribociclib.

The FDA's Assessment:
Please refer to FDA's independent review of pharmacology/toxicology data performed by Dr. George Chang and Dr. Tiffany Ricks.

Pediatrics and Assessment of Effects on Growth
The Applicant's Position:
Not applicable.

The FDA's Assessment:
Not applicable.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Applicant's Position:
There are very few known cases of overdosage with ribociclib. General symptomatic and supportive measures should be initiated in all cases of overdosage as necessary.
No studies were conducted to assess withdrawal and rebound effects but no such effects were reported in clinical studies.

The FDA's Assessment:
FDA agrees with the applicant's position.

7.4.13. **Safety in the Postmarket Setting**
Safety Concerns Identified Through Postmarket Experience
The Applicant's Position:
Kisqali was first registered in United States on 13-Mar-2017 and 22-Aug-2017 in the EU. It is also available in the Unites States as Kisqali Femara CO-PACK approved on 04-May-2017. As of 21-Feb-2018, the cumulative estimated worldwide exposure to Kisqali is (b) (4). The post-marketing experience with ribociclib has been reviewed on an ongoing basis and the results available in PSURs, with the second PSUR covering the period of 22Aug2017 through 21Feb2018. Cumulative review of all the safety data from this postmarketing period has not identified any new safety concerns.

The algorithm used to derive postmarketing exposure is based on the active substance sold and the Defined Daily Dose (DDD). The DDD was based on a targeted therapeutic daily dose for ribociclib study drug, i.e. 600 mg, administered during a 21-d treatment period, followed by a 7-d no-treatment period, every 28-d treatment cycle. Therefore, Kisqali DDD was 450 mg.

The FDA's Assessment:
FDA receives periodic adverse event reports for NDA 209092 and has reviewed these with no new safety signals identified.

Expectations on Safety in the Postmarket Setting
The Applicant's Position:
Toxicities appear to have been adequately represented in both E2301 and F2301 studies.

The FDA's Assessment:
FDA agrees with the applicant's statement.

7.4.14. **Integrated Assessment of Safety**
The Applicant's Position:
As expected when adding to 'backbone therapy', the overall incidences of grade 3/4 AEs, SAEs, AEs leading to discontinuation, and AEs requiring dose adjustment were all higher for patients receiving treatment with ribociclib group relative to placebo group (Table 7-42). Rates of discontinuations due to AE (6.5% in Study E2301 NSAI subgroup, 17.2% in Study F2301) and on-treatment deaths (0.4% in Study E2301 NSAI subgroup, 2.7% in Study F2301) with the ribociclib

combination were within the spectrum of rates reported with current standard of care and investigational regimens. However, in the context of the significant clinical benefit observed for this patient population with limited therapeutic options, the tolerability of this combination regimen is considered to be acceptable. The overall safety profile appears to be manageable (based on the existing AE management guidance in ribociclib label) and, in general, is consistent with the toxicities reported for other CDK4/6 inhibitors.

Table 7-42: Clinically relevant differences (Study E2301-NSAI subgroup, Study F2301)

	Study E2301		Study F2301	
	Ribociclib + NSAI	**Placebo + NSAI**	**Ribociclib + Fulvestrant**	**Placebo + Fulvestrant**
	N=248	**N=247**	**N=483**	**N=241**
Median exposure (mo)	15.1	12.6	15.8	12.0
Minimum, maximum	0, 30	0.5, 30	0.9, 27.4	0.9, 25.9
On treatment deaths	1 (0.4)	5 (2.0)	13 (2.7)	8 (3.3)
Grade 3/4 adverse events (AEs) – n (%)	191 (77.0)	77 (31.2)	378 (78.3)	71 (29.5)
Serious adverse events – n (%)	42 (16.9)	33 (13.4)	138 (28.6)	40 (16.6)
AEs leading to discontinuation – n (%)	16 (6.5)	8 (3.2)	83 (17.2)	15 (6.2)
AEs leading to dose interruption – n (%)	180 (72.6)	47 (19.0)	347 (71.8)	53 (22.0)
AEs requiring dose adjustment – n (%)	83 (33.5)	11 (4.5)	154 (31.9)	7 (2.9)
Source: SCS Study E2301-Table 1-4, SCS Study E2301-Table 2-1, SCS Study E2301-Table 2-4, SCS Study F2301-Table 1-3, SCS Study F2301-Table 2-1, SCS Study F2301-Table 2-16, SCS Study F2301-Table 2-17				

On treatment deaths

On treatment deaths, regardless of causality, in the pooled data-set of phase III studies (Study A2301, Study E2301, Study F2301), were reported in 21 cases (2%) of patients treated with ribociclib plus any combination while 16 cases (2.0%) of patients treated with placebo plus any combination. The most frequent cause of death on treatment was disease progression in all treatment groups (SCS Study F2301 Appendix 4-Table 12-5).

Three treatment-related deaths due to acute respiratory distress syndrome, acute respiratory failure and sudden death were reported in patients on ribociclib with combination therapy. In these three cases a causal role of ribociclib in the events leading to death could not be excluded. The acute respiratory distress syndrome occurred in study CLEE011F2301 in the setting of lung metastases (Study F2301-Table 12-11). The acute respiratory failure occurred in study CLEE011A2301 in a setting of atypical pneumonia and a pre-existing pulmonary fibrosis (Study A2301-Section 12.3.1). The sudden death occurred in study CLEE011A2301 in a setting of Grade

3 hypokalemia and Grade 2 QT prolongation (CO Study A2301-Section 6.3). The review of these cases does not change the benefit risk of ribociclib.

Main adverse effects
In Study E2301 (NSAI subgroup), the most commonly reported AEs in the ribociclib group (in ≥ 30% of patients) included: neutropenia (56.5%), neutrophil count decreased (33.5%), arthralgia (33.5%), nausea (31.5%), and hot flush (31.0%). The most frequent grade 3 AEs (with incidence ≥ 20%) in the ribociclib group were neutropenia (39.1%) and decreased neutrophil count (23.4%). Neutropenia (6.0%) and decreased neutrophil count (4.4%) were the most frequently reported grade 4 AEs in the ribociclib group, other grade 4 events (leukopenia and lymphopenia) were reported in one patient (0.4%) each.

In Study F2301, the most common AEs reported in association with ribociclib plus fulvestrant (≥ 30% incidence) were neutropenia, nausea, and fatigue. The most frequent grade 3/4 AEs (in ≥ 10% of the patients) in the ribociclib plus fulvestrant group were neutropenia, and decreased neutrophil count.

These events are consistent with known safety profile of ribociclib and are tolerable, with only a small proportion of patients with complicated cases and/or discontinuing treatment as a result of these events. Several of the more frequently reported AEs are likely to be related, at least in part, to the underlying disease process and/or other comorbid conditions. Adverse events reported were, in general, consistent with the known safety and tolerability profiles of other CDK4/6 inhibitors. No new or unexpected safety signals were apparent.

Key safety topics
Neutropenia (with mostly uncomplicated cases), hepatobiliary toxicity (occurring predominantly within the initial 6 months of treatment), and QTc interval prolongation (observed uncommonly) continue to be considered as important identified risks, although each of these events can be effectively managed with ribociclib dose modifications.

Neutropenia
Neutropenia is a common side effect associated with CDK4/6 inhibition that is both transient and reversible; the severity of which is concentration-dependent.

While the incidence of grade 3-4 neutropenia in Study E2301 was 66.5% (based on the AESI pooled event category), there were 6 cases (2.4%) of febrile neutropenia. Neutropenia was the most common AE leading to dose interruption or reduction in ribociclib group (reported for 62.9% of patients based on the AESI pooled event category). However, AEs leading to discontinuation was relatively low (0.4%; only one patient) in the ribociclib group (SCS Study E2301-Table 2-13], [SCS Study E2301-Table 2-14).

Similarly, incidence of grade 3-4 neutropenia in Study F2301 was 53.4% (based on the AESI pooled event category), there were 5 cases (1.0%) of febrile neutropenia. Neutropenia was the most common AE leading to dose interruption or reduction in ribociclib group (reported for

51.8% of patients based on the AESI pooled event category). However, AEs leading to discontinuation was relatively low (0.8%; four patients) in the ribociclib group (SCS Study F2301-Table 2-22).

Febrile neutropenia events reported in these studies were managed by dose interruptions and adjustments and none of the patients with febrile neutropenia discontinued study treatment in these two studies. Of note, the consequences of neutropenia can be minimized with appropriate clinical management (regular monitoring, standard supportive therapy) and dose management guidelines available in product label (dose interruption and/or reduction).

QTc interval prolongation

QT prolongation is an important identified safety risk for ribociclib. As previously known, ribociclib prolongs the QT interval in a concentration-dependent manner. The QT/QTcF safety data of ribociclib in combination with endocrine therapy from Studies E2301 (NSAI) and Study F2301 (fulvestrant), and the model-estimated ΔQTcF values at steady state Cmax of ribociclib are consistent with the data reported in the original submission. No serious arrhythmias or Torsades de Pointes were observed at the time the abnormal QT intervals occurred. Results from the assessment of QT/QTc data suggest the ECG and serum electrolyte monitoring plan in the current label are considered adequate to minimize the risk (Study E2301/ Study F2301 QT/QTcF Safety Analysis Report).

The mean observed ΔQTcF on C1D15 2 h post-dose observed in Study E2301 (NSAI subgroup, 18.6 ms) was consistent with that of Study A2301 (19.6 ms), and the mean observed ΔQTcF on Cycle 3Day 15 2 h post-dose in Study E2301 (NSAI subgroup) was 19.5 ms.

QT interval prolongation AEs were reported in a similar proportion of patients treated with ribociclib in Study E2301 (NSAI subgroup), and Study F2301. Very few discontinuations of study drug due to QT prolongation related AEs occurred in Study E2301 (1 patient), Study F2301 (3 patients) indicating acceptable tolerability with the treatment. No events of Torsades de Pointes or sudden death were reported in Studies E2301 and F2301.

To optimize risk minimization measures of QT prolongation and allow patients to continue therapy while maintaining efficacy, Novartis proposes to modify the label to recommend restarting ribociclib at the next lower dose level after resolution of the first occurrence of QTcF >480 ms versus resuming at the same dose level (as currently stated in the ribociclib label).

Table 7-43: Dose modification and management - QT prolongation

	Dose modifications
ECGs with QTcF > 480 ms	Withhold ribociclib if QTcF is > 480 ms. If QTcF prolongation resolves to <481 ms, resume treatment at the next lower dose level. If QTcF ≥ 481 ms recurs, withhold until values return to <481 ms, and resume treatment at the next lower dose level.
ECGs with QTcF >500 ms	Withhold ribociclib if QTcF is >500 ms until values return to <481 ms; resume treatment with ribociclib at the next lower dose level Discontinue treatment with ribociclib if QTcF is >500 ms or >60 ms change from Baseline in combination with Torsade de Pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia

As similarly observed in Study A2301, among patients with QTcF > 480 ms in Study E2301 (NSAI subgroup) and Study F2301, the median time to first occurrence of grade 2 or worse QTcF prolongation event based on the ECG data was 2.1 weeks. Therefore, based on the assessment of QT data and considering that events, if they occur, are reversible and manageable, the current ECG monitoring schedule in the approved ribociclib label is adequate.

Hepatobiliary toxicity

Hepatobiliary toxicity has been reported during treatment with ribociclib and therefore, should be closely monitored. It is important to note that NSAI or fulvestrant as single agents are associated with low rate of serum enzyme elevations and an increase in this risk can therefore be expected with the ribociclib plus NSAI (plus goserelin) or fulvestrant combination. Hepatobiliary toxicity occurred predominantly within the initial 6 months of treatment.

Hepatobiliary toxicity events in Study E2301 were in general uncomplicated, with only a 2% incidence of SAEs in the ribociclib group, and with dose interruptions (6.5% of patients) and reductions (3.2%) reported in limited numbers of patients. Based on the laboratory data, 3 (1 in ribociclib and 2 in placebo group) biochemical Hy's law cases were identified, however, none of them qualified for Hy's law (SCS Study E2301-Section 2.2.8.3.10), (SCS Study E2301-Table 2-18).
Similarly in Study F2301, hepatobiliary toxicity events were uncomplicated, with only a 2.5% incidence of SAEs in the ribociclib group, and with dose interruptions (12.4% of patients) and reductions (2.5%) reported in limited numbers of patients. There were two confirmed Hy's law cases which were not fatal and both the patients recovered after study drug discontinuation (SCS Study F2301-Section 2.1.5.3.4), (SCS Study F2301-Table 2-29).

Subpopulations

No additional safety concerns were raised; subgroup analyses typically demonstrated patterns of events consistent with those reported for the overall population.

The FDA's Assessment:

FDA reviewed the applicant's position above. FDA did not conduct a pooled safety analysis for MONALEESA-3 and MONALEESA-7, as each study is being used to support a different labeling indication and the hormonal therapy and studied patient population differed in each study. FDA's independent analysis of safety has been presented above.

SUMMARY AND CONCLUSIONS

7.5. **Statistical Issues**

The FDA's Assessment:

FDA review showed there are no major statistical issues with this application.

7.6. **Conclusions and Recommendations**

The FDA's Assessment:

Based on the favorable risk-benefit profile, the clinical and statistical reviewers recommend approval of:

KISQALI is a kinase inhibitor indicated in combination with:

- ***an aromatase inhibitor for the treatment of pre/perimenopausal or postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer, as initial endocrine-based therapy; or***
- ***fulvestrant for the treatment of postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer, as initial endocrine based therapy or following disease progression on endocrine therapy.***

The risks identified are addressed in product labeling and are manageable by medical oncologists.

X _____ X _____

Erik Bloomquist, PhD — Primary Statistical Reviewer

Shenghui Tang, PhD — Statistical Team Leader

X	X
Jennifer Gao, MD	Laleh Amiri-Kordestani, MD
Primary Clinical Reviewer	Clinical Team Leader

8 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

FDA did not hold an advisory committee meeting for this sNDA as no outside advice was required.

9 Pediatrics

The Applicant's Position:

Ribociclib was not studies in pediatric patients. Novartis has submitted a PREA waiver.

The FDA's Assessment:

FDA's Pediatric Review Committee agrees with the plan for a full waiver.

10 Labeling Recommendations

10.1. **Prescription Drug Labeling**

Summary of Significant Labeling Changes *(High level changes and not direct quotations)*		
Section	**Applicant's Proposed Labeling**	**FDA's proposed Labeling** *(As of July 10, 2018)*
1. Indications and Usage	(b) (4)	KISQALI is a kinase inhibitor indicated in combination with: • an aromatase inhibitor for the treatment of pre/perimenopausal or postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer, as initial endocrine-based therapy; or • fulvestrant for the treatment of postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer, as initial endocrine based therapy or following

	(b) (4)	disease progression on endocrine therapy. **FDA moved this information was to the 2. Dosage and Administration section to be consistent with FDA labeling guidance.**
2. Dosage and Administration	**Table 4: Dose Modification and Management for QT Prolongation** **Dose Modification for Renal Impairment** No dose adjustment is necessary in patients with mild or moderate renal impairment. The recommended starting dose is 200 mg KISQALI once daily for patients with severe renal impairment *[see Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)].*	**FDA agrees with the applicant's proposed labeling.**
5. Warnings and Precautions	**5.1 QT Interval Prolongation** Across (b) (4) (MONALEESA-2), (b) (4) (MONALEESA-7), and (b) (4) (MONALEESA-3) in patients with advanced or metastatic breast cancer who received the combination of KISQALI plus an aromatase inhibitor or fulvestrant, 14 out of 1054 patients (b) (4) had >500 msec post-baseline QTcF value, and 59 out of 1054 patients (b) (4) had a >60 msec increase from baseline in QTcF intervals. These ECG changes were reversible with dose interruption and the majority …	**Section 5.1: FDA does not agree with including the statements of "There were no reported cases of Torsades de Pointes" and "No cases of sudden death** (b) (4) **" and these statements were removed from the label.** **FDA included the following as a separate Warning and Precaution:** **5.2 Increased QT Prolongation with Concomitant Use of Tamoxifen**

	No cases of sudden death (b) (4) *[see Adverse Reactions (6)]*. (b) (4) (b) (4) **Hepatobiliary Toxicity** In (b) (4) increases in transaminases were observed. Across all studies, Grade 3 or 4 increases in ALT (10% versus 2%) and AST (7% versus 2%) were reported in the KISQALI	KISQALI is not indicated for concomitant use with tamoxifen. (b) (4) the observed mean QTcF increase from baseline was ≥10 msec in the tamoxifen plus placebo subgroup compared with the NSAI plus placebo subgroup. An increase of >60 msec from baseline in the QTcF interval was observed in 14/87 (16 %) of patients in the KISQALI and tamoxifen combination and in 18/245 (7%) of patients receiving KISQALI plus an NSAI. In the placebo arm, an increase of >60 msec from baseline occurred in 6/90 (7%) of patients receiving tamoxifen, and in no patients receiving an NSAI. *[see Clinical Pharmacology (12.2)].* **FDA agrees with the proposed language for hepatobiliary toxicity and neutropenia**

	and placebo arms, respectively. … No cases occurred in (b) (4) (b) (4) **Neutropenia** In (b) (4) neutropenia was the most frequently reported adverse reaction (74%) and a Grade 3/4 decrease in neutrophil count (based on laboratory findings) was reported in 58% of patients receiving KISQALI plus an aromatase inhibitor or fulvestrant. Among the patients who had Grade 2, 3, or 4 neutropenia, the median time to Grade > 2 neutropenia was 16 days. The median time to resolution of Grade ≥ 3 (to normalization or Grade < 3) was 12 days in the KISQALI plus aromatase inhibitor or fulvestrant treatment group. Febrile neutropenia was reported in (b) (4) of patients receiving KISQALI plus an aromatase inhibitor or fulvestrant. Treatment discontinuation due to neutropenia was 0.8%.	
6. Adverse Reactions	(b) (4) **(MONALEESA-7): KISQALI in combination with an Aromatase Inhibitor** (b) (4)	**FDA agrees with the proposed adverse reaction information and tables for the MONALEESA-7 and MONALEESA-3 trials with some formatting revisions and revisions to the reported rates of permanent discontinuation of KISQALI and KISQALI+hormonal therapy for MONALEESA-2,**

	(b) (4)	**MONALEESA-3, MONALEESA-7.**
	The most common ARs (reported at a frequency ≥ 20% on the KISQALI arm and ≥2% higher than placebo) were neutropenia, infections, leukopenia, arthralgia, nausea, and alopecia. The most common Grade 3/4 ARs (reported at a frequency ≥5%) were neutropenia, leukopenia, and abnormal liver function tests. See Table 8 below. **Table 8: Adverse reactions occurring in ≥10% and ≥2% higher than placebo arm in (b) (4) (NSAI) (All grades)** … Additional adverse reactions in (b) (4) for patients receiving KISQALI plus NSAI included asthenia (12%), dry skin (b) (4), thrombocytopenia (9%), oropharyngeal pain (7%), dyspepsia (5%), lacrimation increased (4%), dry eye (4%), vitiligo (3%), hypocalcemia, (2%), blood bilirubin increased (b) (4) and syncope (0.4%). **Table 9: Laboratory Abnormalities Occurring in ≥ 10% of Patients in (b) (4)** **(b) (4) (MONALEESA-3):**	

KISQALI in combination with Fulvestrant

(b) (4)

The most common ARs (reported at a frequency ≥ 20% on the KISQALI arm and ≥2% higher than placebo) were neutropenia, infections, leukopenia, cough, nausea, diarrhea, vomiting, constipation, pruritus, and rash. The most common Grade 3/4 ARs (reported at a frequency ≥ 5%) were neutropenia, leukopenia, infections, and abnormal liver function tests. See Table 10.

Table 10: Adverse Reactions Occurring in ≥ 10% and ≥ 2% higher than Placebo Arm in (b) (4) **(All Grades)**

…

Additional adverse reactions in (b) (4) for patients receiving KISQALI plus fulvestrant included asthenia (14%), dyspepsia (10%), 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%), and syncope (1%). **Table 11: Laboratory Abnormalities Occurring in ≥ 10% of Patients in** (b) (4)	
7. Drug Interactions	N/A	
8. Use in Specific populations	**8.3 Females and Males of Reproductive Potential** **…** (b) (4) **8.5 Geriatric Use** … Of 484 patients who received KISQALI in (b) (4) 226 patients (47%) were ≥65 years of age and 65 patients (14%) were ≥75 years of age. **8.7 Renal Impairment** Based on a population pharmacokinetic analysis, no dose adjustment is necessary in patients with mild or moderate renal impairment. Based on a renal impairment study in healthy subjects and non-cancer subjects with severe renal impairment (eGFR 15 to < 30 mL/min/1.73m2), a starting dose of 200 mg is recommended. KISQALI has not been studied in breast cancer patients with severe renal impairment [see Dosage and Administration	**Section 8.3: FDA removed the proposed** (b) (4) **This information is retained in 13.1 Nonclinical Toxicology.** **Section 8.5: FDA agrees to the updated information proposed in 8.5 Geriatric Use.** **Section 8.7:** Based on a population pharmacokinetic analysis, no dose adjustment is necessary in patients with mild (60 mL/min/1.73m^2 ≤ estimated glomerular filtration rate (eGFR) < 90 mL/min/1.73m^2) or moderate (30 mL/min/1.73m^2 ≤ eGFR < 60 mL/min/1.73m^2) renal impairment.

	(2.2) and Clinical Pharmacology (12.3)].	
12. Clinical Pharmacology	**12.1 Mechanism of Action** **…** (b) (4)	**Section 12.1:** **…** Additionally, the combination of ribociclib and fulvestrant resulted in tumor growth inhibition in an estrogen receptor positive breast cancer xenograft model.
	12.2 Pharmacodynamics **Cardiac Electrophysiology** … The analysis suggested that ribociclib causes concentration-dependent increases in the QTcF interval. The estimated mean change from baseline in QTcF for KISQALI 600 mg in combination with aromatase inhibitors or fulvestrant was 22.0 ms (90% CI: (b) (4), (b) (4)) and 23.7 ms (90% CI: (b) (4), (b) (4)), respectively, and was 34.7 ms (90% CI: (b) (4), (b) (4)) in combination with tamoxifen at the geometric mean Cmax at steady-state.	**Section 12.2: FDA agrees with the proposed labeling with format revisions.**
	12.3 Pharmacokinetics **…** The effect of renal impairment on the pharmacokinetics of ribociclib was (b) (4) assessed in a renal impairment study (b) (4) with	**Section 12.3:** **…** The effect of renal impairment on the pharmacokinetics of ribociclib was assessed in a renal impairment study in non-

	normal renal function (eGFR ≥90 mL/min/1.73 m2), (b) (4) (b) (4) severe renal impairment (eGFR 15 to <30 mL/min/1.73 m2), and (b) (4) (b) (4) End Stage Renal Disease (ESRD; eGFR <15 mL/min/1.73 m2) (b) (4) In subjects with severe renal impairment, AUCinf increased by 1.96 fold, and Cmax increased by 1.51 fold compared to subjects with normal renal function. (b) (4) … 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: (b) (4)	cancer subjects with normal renal function (eGFR ≥90 mL/min/1.73 m2), severe renal impairment (eGFR 15 to <30 mL/min/1.73 m2), and End Stage Renal Disease (ESRD; eGFR <15 mL/min/1.73 m2). In subjects with severe renal impairment, AUCinf increased by 1.96 fold, and Cmax increased by 1.51 fold compared to subjects with normal renal function. … … **FDA agrees with the proposed information for fulvestrant.** **Tamoxifen:** KISQALI is not indicated for concomitant use

	(b) (4)	with tamoxifen. Data from a clinical trial in patients with cancer indicated that tamoxifen Cmax and AUC increased approximately 2-fold following coadministration of 600 mg ribociclib.
13 Nonclinical toxicology	**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility** … (b) (4) …	**Section 13.1:** **…** 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). …
14. Clinical studies	(b) (4) **KISQALI in Combination with an Aromatase inhibitor (MONALEESA-7)** … (b) (4)	**FDA agrees with the proposed study description, demographics and baseline disease characteristics, and treatment regimens for the MONALEESA-7 trial.** **…** **FDA removed the first paragraph to be consistent with the approved indications.** The efficacy results from a pre-specified subgroup analysis of 495 patients who had received KISQALI or

	(b) (4)	placebo with NSAI plus goserelin are summarized in Table 13 and Figure 2. (b) (4)
	Table 13: Efficacy Results – (b) (4) (NSAI, Investigator Assessment) **Figure 2: Kaplan-Meier Progression Free Survival Curves – (b) (4) (NSAI, Investigator Assessment)**	**FDA accepted Table 13 and Figure 2 and revised the footnotes to clarify results were based on confirmed responses (b) (4)**

	(b) (4) **KISQALI in Combination with Fulvestrant (MONALEESA-3)** … … (b) (4) **Table 14: Efficacy Results –** (b) (4) **(Investigator Assessment, Intent-to-Treat Population)** **Figure 3:Kaplan-Meier Progression Free Survival Curves –** (b) (4) **(Investigator assessment)**	**FDA agrees with the proposed study description, demographics and baseline disease characteristics, and treatment regimens for the MONALEESA-3 trial with two exceptions. FDA removed** (b) (4) **FDA asked the Applicant to clarify the stratification factor for "prior endocrine therapy".** **…** The efficacy results from (b) (4) are summarized in Table 14 and Figure 3. Results were consistent across subgroups of prior endocrine treatment status and (b) (4) At the time of the PFS analysis, (b) (4) of patients had died, and overall survival data were immature. **FDA accepted Table 14 and Figure 3.**
17. Patient Counseling Information	**…**	**FDA added the following:** Dosing • Instruct patients to take the doses of KISQALI at approximately the same time every day and to swallow whole (do not chew, crush, or split them prior to swallowing) *[see Dosage and Administration (2.1)].* • If patient vomits or misses a dose, advise the patient to

		take the next prescribed dose at the usual time *[see Dosage and Administration (2.1)].* • Advise the patient that KISQALI may be taken with or without food *[see Dosage and Administration (2.1)].*

10.2. **Patient Labeling**

The Patient Information for Kisqali was revised to be consistent with FDA revisions to the Indications and Usage section of labeling (i.e., What is Kisqali?) and the Adverse Reactions section (i.e., What are the possible side effects of Kisqali?) in the Prescribing Information.

11 Risk Evaluation and Mitigation Strategies (REMS)

The Applicant's Position:

No REMS is recommended.

The FDA's Assessment:
None

12 Postmarketing Requirements and Commitment

The FDA's Assessment:

The following Postmarketing Commitments (PMC) were recommended and agreed upon with the applicant:

- **Submit the interim overall survival (OS) report with data and analysis; the final OS report with data and analysis from clinical trial MONALEESA-7 entitled: "A phase III randomized, double-blind, placebo-controlled study of LEE011 or placebo in combination with tamoxifen and goserelin or a non-steroidal aromatase inhibitor (NSAI) and goserelin for the treatment of premenopausal women with HR+, HER2 negative advanced breast cancer".**
    - **PMC Schedule Milestones**
        - **Final Protocol Submission: 04/2017**
        - **Trial Completion: 12/2020**
        - **Interim OS Data and Analysis Submission: 12/2019**
        - **Final OS Data, Analysis and Report Submission: 06/2021**

- **Submit the interim overall survival (OS) report with data and analysis; the final OS report with data and analysis, from clinical trial MONALEESA-3 entitled: "A randomized, double-blind, placebo-controlled study of ribociclib in combination with fulvestrant for the treatment of men and postmenopausal women with HR+, HER2 negative advanced breast cancer who have received no or only one line of prior endocrine treatment".**
    - **PMC Schedule Milestones**
        - **Final Protocol Submission: 09/2016**
        - **Trial Completion: 09/2022**
        - **Interim OS Data and Analysis Submission: 09/2020**
        - **Final OS Data, Analysis and Report Submission: 03/2023**

13 Division Director (OCP)

X _____

Nam Atiqur Rahman, PhD
Director, DCP V

14 Division Director (OB)

X

Jason Schroeder, PhD
Associate Director

15 Division Director (Clinical)

X

Julia Beaver, MD
Director, Division of Oncology Products 1

16 Office Director (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

Julia Beaver, MD

17 Appendices

17.1. References

The Applicant's References:

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The FDA's References:

1) **NCI SEER Program, Cancer Stat Facts: Female Breast Cancer, Available at https://seer.cancer.gov/statfacts/html/breast.html, Accessed July 3, 2018**
2) **Mariotto, A. B., R. Etzioni, M. Hurlbert, L. Penberthy and M. Mayer (2017). "Estimation of the Number of Women Living with Metastatic Breast Cancer in the United States." Cancer Epidemiology Biomarkers & Prevention.**
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4) **"Breast Cancer Survival Rates." (2017) American Cancer Society, https://www.cancer.org/cancer/breast-cancer/understanding-a-breast-cancer-diagnosis/breast-cancer-survival-rates.html, accessed August 31, 2017.**

17.2. **Financial Disclosure**

The Applicant's Position:

As agreed with FDA at the pre-NDA meeting for study E2301 in January 18, 2018 and in the preliminary comments for the April 24, 2018 pre-NDA meeting for study F2301, studies CLEE011E2301 (MONALEESA-7) and CLEE011F2301 (MONALEESA-3) were considered as covered by the "Financial Disclosure for Clinical Investigators" rule. All investigators were assessed for equity interest, significant payments, proprietary interest, and other compensation. Of the 1963

clinical investigators in the MONALEESA-7 study, certification was provided for 1951 (99.3%) investigators. Two of the 1963 clinical investigators in the MONALEESA-7 study had financial information to disclose (0.1%); these investigators constituted 8 of the total 672 randomized patients in the trial (1.2%). These disclosures are summarized in Table 17-1 below.
Of the 1465 clinical investigators listed in the MONALEESA-3 study, certification was provided for 1459 (99.6%) investigators. No investigators from MONALEESA-3 had financial arrangements or interests to disclose.

Table 17-1: Summary of Financial Disclosures from Study E2301 (MONALEESA-7)

Clinical site numbers	Investigator Name (PI or SI)	Disclosure
(b) (6)		Greater than $25,000 (speaking honoraria)
		Greater than $25,000 (consulting)

PI: Principle Investigators; SI: sub-investigators. Source NDA 209092 Financial Disclosures

The FDA's Assessment:

The applicant's position on financial disclosures was reviewed and no concerns noted.

Covered Clinical Study (Name and/or Number):* Study LEE011E2301

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1963		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: Significant equity interest held by investigator in S Sponsor of covered study: 2		
Is an attachment provided with details	Yes ☒	No ☐ (Request details from

of the disclosable financial interests/arrangements:		Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 2		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number):* Study LEE011F2301

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1465		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Significant payments of other sorts: Proprietary interest in the product tested held by investigator: Significant equity interest held by investigator in S Sponsor of covered study:		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

17.3. OCP Appendices (Technical documents supporting OCP recommendations)

17.3.1. Population PK Analysis

The Applicant submitted an updated population PKPD report entitled "Population pharmacokinetics of ribociclib and exposure response relationship for neutropenia in cancer patients updated with studies MONALEESA-3 and MONALEESA-7 Modeling Report". The Agency has reviewed the previously developed population PK and the ANC E-R analyses and agreed with the conclusions from the Applicant.

Objectives: The objectives of the population PK analysis were as follows:

- To update the evaluation of covariate effects on ribociclib PopPK;
- To generate individual post-hoc longitudinal C_{trough} of ribociclib to enable exposure-efficacy analyses.

Data: The population pharmacokinetic analysis included data from six clinical studies (X1101, X2101, X2107, A2301, E2301, and F2301). A total of 7960 PK observations from 1059 subjects were included in the population PK analysis. The distribution of patient intrinsic characteristics, such as body weight, age, dGFR, and race are presented in **Table 17-2**.

Table 17-2: Distribution of Intrinsic Factors in PopPK Analysis Dataset

Covariate	Category	N
BW#	<50kg	73
	50-60kg	205
	60-70kg	283
	70-80kg	234
	80-90kg	130
	>=90kg	130
Age	<30y	11
	30-40y	91
	40-50y	220
	50-60y	269
	60-70y	280
	>=70y	188
eGFR#	Severe (<30 mL/min/1.73m²)	0
	Moderate (30-60 mL/min/1.73m²)	113
	Mild (60-90 mL/min/1.73m²)	488
	Normal (>=90 mL/min/1.73m²)	438
Race*	Caucasian	776
	Asian	162
	Others/unknown	121

Source: Table 5-3 on page 33 of Applicant's population PK report

Population PK Model Development

Base Model: Ribociclib structure model was the same as previously described in ribociclib population PK analysis that was used to support the original submission. The previous final model was a 2-compartment model with delayed zero-order oral absorption and clearance from the central compartment. Dose was incorporated as a structural covariate and body

weight (BW) was retained as a significant covariate in the final population PK model. Parameter estimates of previously established final model is summarized in **Table 17-3**.

Table 17-3: Parameter Estimates of Previously Established Final PopPK Model

Parameter	Estimate	SE	RSE (%)	95% CI	Shrinkage (%)
ALAG1 (h)	0.405	0.004	0.99	(0.397 - 0.413)	-
D1 (h)	3.4	Fixed	-	-	-
CL (L/h)	26.433	0.969	3.67	(24.534 - 28.332)	-
Q (L/h)	81.5	8.589	10.54	(64.666 - 98.334)	-
V1 (L)	239.492	19.107	7.98	(202.042 - 276.942)	-
V2 (L)	850.144	39.167	4.61	(773.377 - 926.911)	-
Dose~CL (-)	-0.308	0.064	20.78	(-0.433 - -0.183)	-
Dose~Q (-)	-0.519	0.097	18.69	(-0.709 - -0.329)	-
Dose~V2 (-)	-0.344	0.063	18.31	(-0.467 - -0.221)	-
BW~CL (-)	0.652	0.113	17.33	(0.431 - 0.873)	-
BW~Q (-)	1.216	0.233	19.16	(0.759 - 1.673)	-
BW~V2 (-)	0.773	0.211	27.3	(0.359 - 1.187)	-
ω^2_{V1}	0.925	0.15	16.22	(0.631 - 1.219)	4.8
ω^2_{CL}	0.263	0.028	10.65	(0.208 - 0.318)	2.94
$\omega^2_{CL\text{-}Q}$	0.124	0.038	30.65	(0.05 - 0.198)	-
ω^2_{Q}	0.259	0.116	44.79	(0.032 - 0.486)	23.82
$\omega^2_{CL\text{-}V2}$	0.192	0.027	14.06	(0.139 - 0.245)	-
$\omega^2_{Q\text{-}V2}$	0.213	0.046	21.6	(0.123 - 0.303)	-
ω^2_{V2}	0.312	0.043	13.78	(0.228 - 0.396)	12.54
$\sigma^2_{additive}$ in log domain	0.203	0.015	7.39	(0.174 - 0.232)	6.35

RSE: relative standard error, calculated using SE/Estimate×100%;

Source: Table 4-1 on page 18 of Applicant's population PKPD report

Full Model: The full covariate model included all the covariates such as race, age, eGFR, combination partners (anastrozole, letrozole, tamoxifen, fulvestrant). Covariates found to be statistically insignificant were RaceAsian_CL, RaceOthers_CL, letrozole_CL, and anastrozole_CL. Model parameters from the full model are summarized in Table

Table 17-4: PopPK Full Covariate Model Parameter Posteriors

Parameter	Mean‡	SD‡	Naive SE‡	Time-series SE‡	Effective N‡	95% CI‡	Null value*
D1 (h)	3.4	Fixed	NA	NA	NA	NA	NA
V1 (L)	248.914	11.749	0.055	0.277	1820	(226.016 - 272.276)	NA
CL (L/h)	25.365	0.811	0.004	0.039	441	(23.822 - 27.027)	NA
Q (L/h)	73.903	3.979	0.019	0.166	573	(66.304 - 82.122)	NA
V2 (L)	825.793	23.891	0.113	0.796	904	(779.197 - 873.179)	NA
ALAG1 (h)	0.403	0.002	0	0	3220	(0.398 - 0.407)	NA
Dose_CL (-)	-0.411	0.048	0	0.002	574	(-0.505 - -0.316)	0
Dose_Q (-)	-0.586	0.085	0	0.002	1517	(-0.754 - -0.419)	0
Dose_V2 (-)	-0.429	0.058	0	0.002	824	(-0.541 - -0.319)	0
BW_CL (-)	0.514	0.078	0	0.003	689	(0.362 - 0.67)	0
BW_Q (-)	1.132	0.187	0.001	0.005	1598	(0.763 - 1.5)	0
BW_V2 (-)	0.751	0.106	0.001	0.003	975	(0.541 - 0.956)	0
Age_CL (-)	-0.311	0.063	0	0.002	890	(-0.434 - -0.189)	0
eGFR_CL (-)	0.155	0.045	0	0.002	898	(0.069 - 0.246)	0
RaceAsian_CL (-)	0.972	0.037	0	0.001	855	(0.903 - 1.047) #	1
RaceOthers_CL (-)	1.01	0.039	0	0.001	772	(0.937 - 1.088) #	1
Letrozole_CL (-)	1.051	0.041	0	0.002	740	(0.971 - 1.135) #	1
Anastrozole_CL (-)	1.125	0.106	0	0.002	1818	(0.93 - 1.344) #	1
Tamoxifen_CL (-)	1.364	0.087	0	0.003	1100	(1.199 - 1.543)	1
Fulvestrant_CL (-)	1.08	0.032	0	0.002	419	(1.019 - 1.145)	1
ω^2_{V1}	0.743	0.063	0	0.001	3291	(0.627 - 0.873)	NA
ω^2_{CL}	0.221	0.013	0	0	7246	(0.198 - 0.248)	NA
ω^2_{CL-Q}	0.108	0.021	0	0.001	1367	(0.068 - 0.152)	NA
ω^2_{Q}	0.264	0.051	0	0.002	663	(0.177 - 0.375)	NA
ω^2_{CL-V2}	0.19	0.016	0	0	2693	(0.161 - 0.222)	NA
ω^2_{Q-V2}	0.177	0.029	0	0.001	1078	(0.125 - 0.239)	NA
ω^2_{V2}	0.24	0.022	0	0.001	1966	(0.198 - 0.286)	NA
$\sigma^2_{additive}$ in log domain	0.207	0.004	0	0	9871	(0.2 - 0.215)	NA
MCMCOBJ	-7306.53	296.333	1.397	12.807	534	(-7914.416 - -6749.068)	NA

Model run number: poppk.coveval.full.

‡: statistics summarized (using the coda package) from pooled Bayesian posterior samples from 3 chains with 15000 samples per chain. SD, standard deviation; naïve SE, standard error without consideration of autocorrelation within a chain; time-series SE, standard error with consideration of autocorrelation; effective N, posterior sample size void of autocorrelation; 95% CI, 2.5th – 97.5th percentiles of the posterior samples.

*: null values: reference values indicating that there are no covariate effects;

#: parameter estimate statistically insignificant, i.e., 95% CI includes the null value;

Source: Table 5-7 on page 39 of Applicant's population PKPD report

Final Model: Covariates that were both statistically insignificant (95% CI of a parameter estimate includes the null value) and not clinically important (95% CI of covariate effect is within ±20% from the reference value) were dropped from the full model. Covariates that have effects extending slightly outside the reference range were dropped as they were not considered clinically important. Covariates for which the dataset was considered not sufficiently informative for the evaluation due to limited sample size were also dropped. The following covariates were removed per the predefined criteria.

- RaceAsian, RaceOthers, and letrozole, due to statistical insignificance and clinical nonimportance;
- BW on CL, Age, eGFR, and fulvestrant, due to clinical non-importance; and
- Anastrozole, due to its effect estimated to be minor with only 25% probability being >20% from the reference value, and the evaluation limited by the sample size (N=31

with the use of anastrozole, accounting for only 2.9% of the population in the analysis dataset).

The final model retained tamoxifen as a covariate on CL, in addition to BW on Q and V_2 and the structural covariate of dose already in the previous model. The parameter estimates from the final model including covariate effects are summarized in **Table 17-5**.

Table 17-5: Parameter Estimates and Covariate Effects for Ribociclib Population Pharmacokinetic Final Model

Parameter	Mean‡	SD‡	Naive SE‡	Time-series SE‡	Effective N‡	95% CI‡	Null value*
D1 (h)	3.4	Fixed	NA	NA	NA	NA	NA
V1 (L)	249.827	11.443	0.054	0.238	2329	(228.034 - 272.549)	NA
CL (L/h)	26.761	0.484	0.002	0.01	2289	(25.828 - 27.723)	NA
Q (L/h)	73.465	3.893	0.018	0.149	680	(65.961 - 81.351)	NA
V2 (L)	839.908	23.001	0.108	0.668	1199	(794.101 - 885.565)	NA
ALAG1 (h)	0.403	0.002	0	0	3648	(0.398 - 0.407)	NA
Dose_CL (-)	-0.404	0.049	0	0.002	573	(-0.503 - -0.313)	0
Dose_Q (-)	-0.59	0.085	0	0.002	1789	(-0.757 - -0.426)	0
Dose_V2 (-)	-0.438	0.06	0	0.002	920	(-0.557 - -0.323)	0
BW_Q (-)	0.834	0.175	0.001	0.004	2146	(0.482 - 1.171)	0
BW_V2 (-)	0.316	0.079	0	0.002	1431	(0.161 - 0.472)	0
Tamoxifen_CL (-)	1.409	0.082	0	0.002	1354	(1.251 - 1.572)	1
ω^2_{V1}	0.729	0.063	0	0.001	3406	(0.616 - 0.861)	NA
ω^2_{CL}	0.238	0.013	0	0	8032	(0.213 - 0.266)	NA
$\omega^2_{CL\text{-}Q}$	0.109	0.021	0	0.001	1386	(0.068 - 0.152)	NA
ω^2_{Q}	0.263	0.05	0	0.002	585	(0.176 - 0.373)	NA
$\omega^2_{CL\text{-}V2}$	0.199	0.016	0	0	2948	(0.168 - 0.231)	NA
$\omega^2_{Q\text{-}V2}$	0.186	0.029	0	0.001	1079	(0.134 - 0.246)	NA
ω^2_{V2}	0.251	0.024	0	0.001	1954	(0.208 - 0.3)	NA
$\sigma^2_{additive}$ in log domain	0.207	0.004	0	0	12807	(0.2 - 0.215)	NA
MCMCOBJ	-7200.39	300.736	1.418	13.735	479	(-7827.086 - -6650.075)	NA

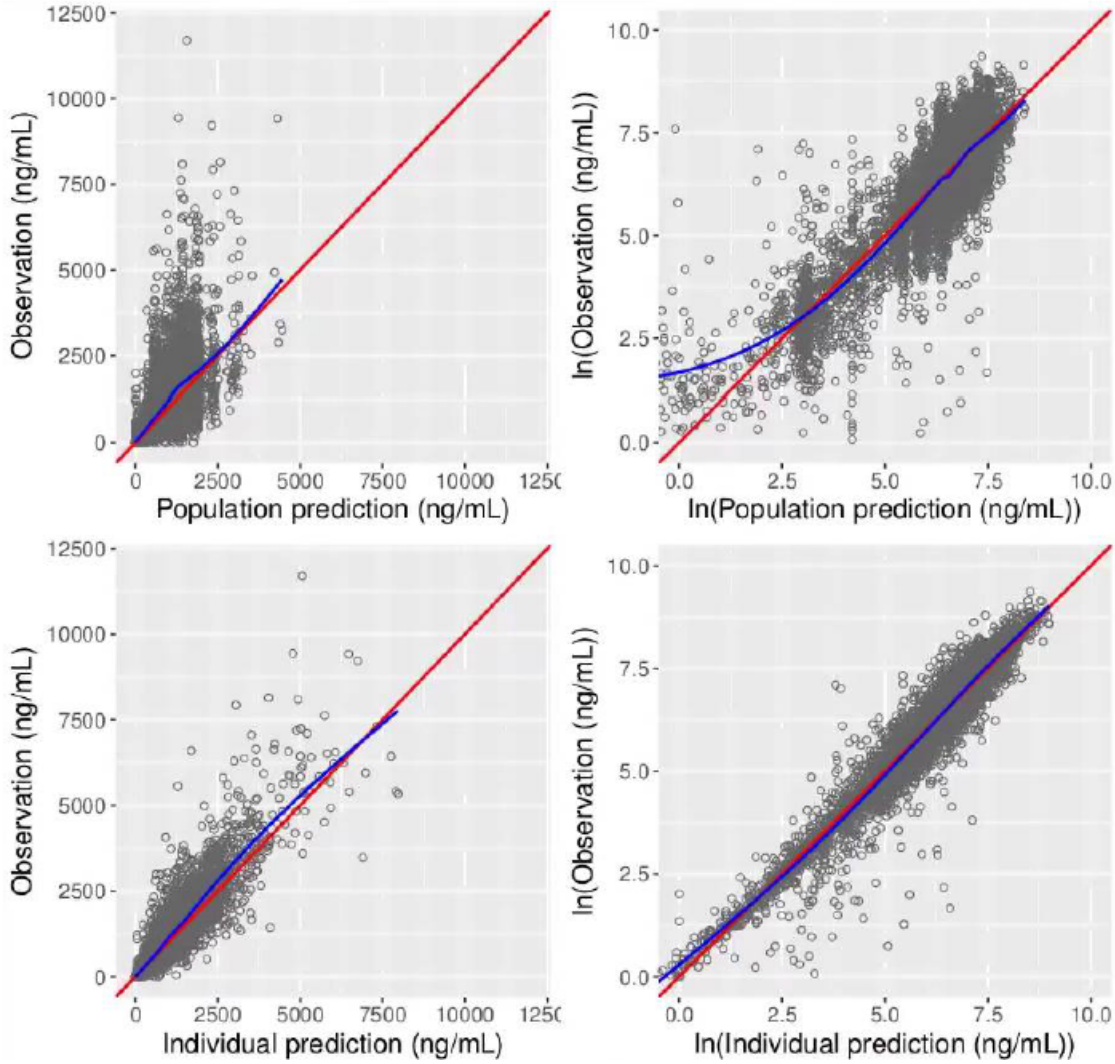
Model run number: poppk.coveval.final.

‡: statistics summarized (using the coda package) from pooled Bayesian posterior samples from 3 chains with 10000 samples per chain. SD, standard deviation; naïve SE, standard error without consideration of autocorrelation within a chain; time-series SE, standard error with consideration of autocorrelation; effective N, posterior sample size void of autocorrelation; 95% CI, 2.5th – 97.5th percentiles of the posterior samples.

Source: Table 5-10 on page 50 of Applicant's population PK report

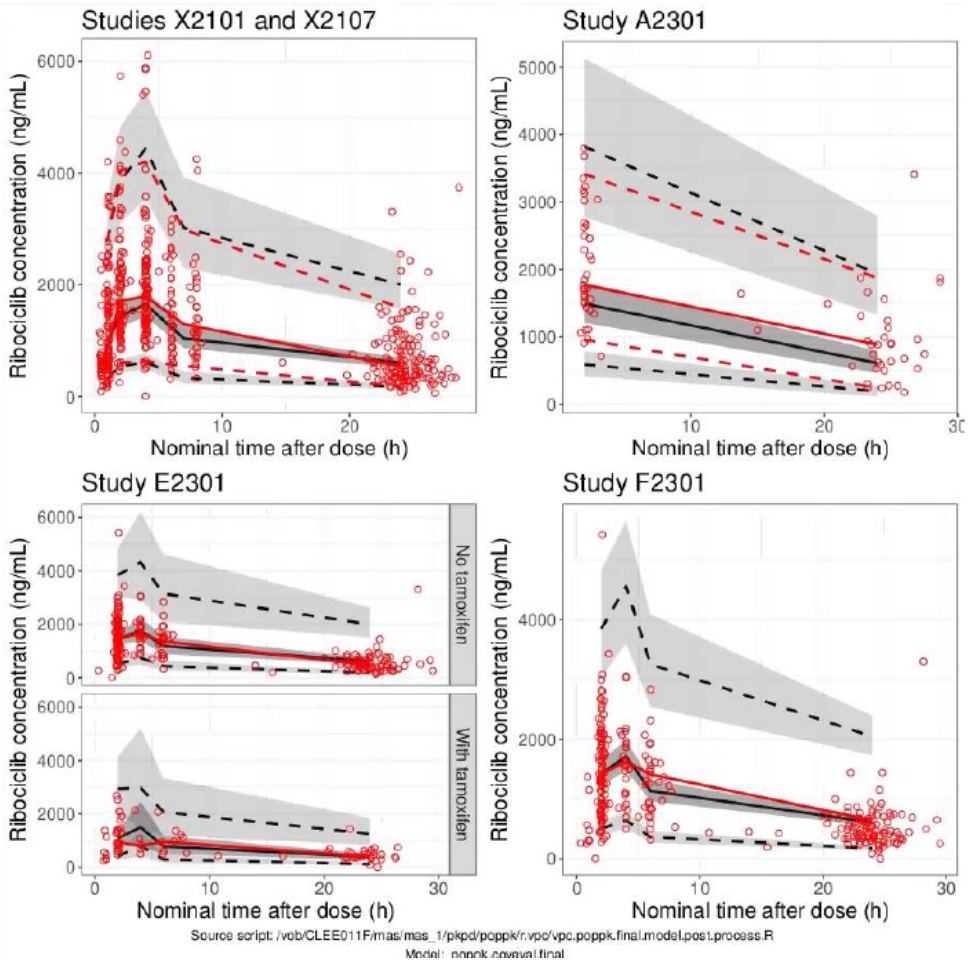
Model Evaluation: The final model was evaluated graphically by goodness-of-fit plots, visual predictive checks (VPCs) as well as bootstrap evaluation. The goodness-of-fit plots for the final model are displayed in Figure 17-1 and the VPCs plots are demonstrated in

Figure 17-1: Goodness-of-Fit Plots for the Final Population Pharmacokinetic Model



Source: Figure 5-6 on page 46 of Applicant's population PK report

Figure 17-2: VPC for Final PopPK Model (at 600 mg steady state)



Note: Red circles: observed data; red solid and broken lines: median and 5th or 95th percentile of observed data; black solid and broken lines: means of the median and 5th or 95th percentile of model simulations; gray areas indicate 90% confidence intervals of the above means. For statistical summarization, data and simulated values were binned by nominal time points 1, 2, 4, 7, and 24 h in studies X2101 and X2107, 2 and 24 h in study A2301, and 2, 4, 6, and 24 h in studies E2301 and F2301 after previous dose.

Source: Figure 5-8 on page 48 of Applicant's population PK report

Posthoc PK Parameter Estimation: Simulated ribociclib exposures (Cmax and AUC24h) using the final model are summarized in **Table 17-6** for 600 mg QD after the first dose and at steady state.

Table 17-6: Simulated Cmax and AUC24h for Ribociclib 600 mg QD after the First Dose and at Steady State

Statistic	After 1st dose	Steady state
	Cmax (ng/mL)	
Geomean (CV%)	1185.4 (53.9)	1865.8 (42.1)
Mean (90% CI)	1335 (1256.1, 1418.2)	2021.1 (1919.3, 2136.2)
Q05 (90% CI)	499.6 (408.2, 580.5)	970.6 (864, 1082.1)
Q95 (90% CI)	2528.1 (2305.5, 2835)	3557.5 (3221.7, 3973.4)
	AUC24h (ng/mL×h)	
Geomean (CV%)	10127.5 (43.2)	22631.2 (51.2)
Mean (90% CI)	11018.7 (10393.9, 11667.1)	25424.6 (23717.7, 27001.2)
Q05 (90% CI)	5175.2 (4580.9, 5664.4)	10291.2 (8868.3, 11693.4)
Q95 (90% CI)	19697.6 (17605.3, 21984.6)	49279.9 (43065.4, 55325)

Source: Table 9-1 on page 90 of Applicant's population PK report

Reviewer's comments: The applicant's population PK analysis is acceptable. The goodness-of-fit plots and the visual predictive check indicate that the updated population PK model is adequate in characterizing the PK profile of ribociclib in patients with breast cancer. The inter-individual variability for CL/F and Vc/F are modest. Shrinkages for CL/F, Vc/F are reasonable. The estimated PK parameters, such as CL/F and Vc/F are not very different from the previous model. The applicant's analyses were verified by the reviewer, with no significant discordance identified (Applicant's table/figures not shown).

17.3.2. Exposure-Response Analyses

17.3.2.1 Exposure-Response for ANC

The Applicant submitted an exposure-response (ER) analysis for ANC in the population PK/PD report. The ANC ER model was updated by addition of data from study E2301 and F2301 based on a previously established ANC E-R model. The focus of the analysis was to evaluate or re-evaluate covariate effects on ANC E-R relationship following ribociclib treatment.

Objective: The objective of the ANC E-R model was to update the evaluation of covariate effects on the ANC E-R relationship associated with ribociclib treatment. The analysis was based on established models to support indication expansion; No further model development was pursued.

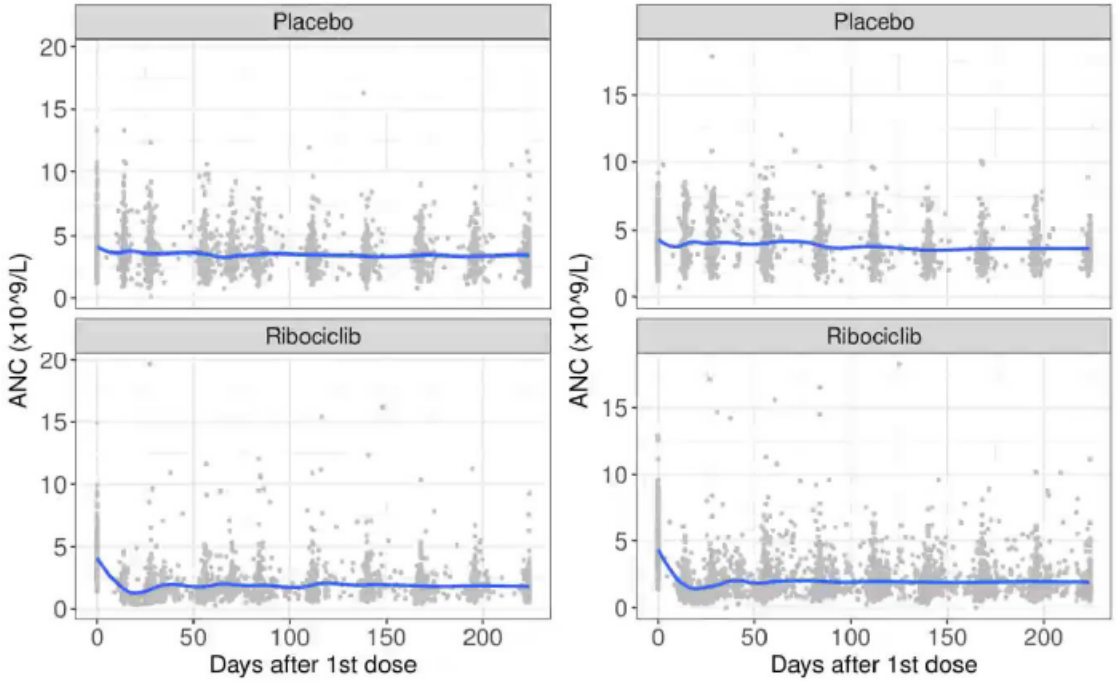
Data: The ANC data included in this analysis were from six clinical studies (X1101, X2101, X2107, A2301, E2301, and F2301). Study E2301 and F2301 designs and hematology sampling schedules are summarized in **Table 17-7**. The analysis dataset included 7786 ANC data points from 1052 subjects. The ANC profiles in the placebo and ribociclib group up to the 8th cycles in studies E2301 and F2301 are shown in Figure 17-3.

Table 17-7: Study E2301 and F2301 Designs and Hematology Sampling Schedules

Study	Sample size[a]	Ribociclib regimen	Combination therapy	Hematology sampling point[c]
E2301	330 (ribociclib) 330 (placebo)	600 mg QD, 3 weeks on /1 week off	Letrozole[b] Anastrozole[b] Tamoxifen[b]	Baseline (or C1D1), C1D15, C2D1, C3D1, C3D15, CnD1, within 15 days after last dose
F2301	440 (ribociclib) 220 (placebo)	600 mg QD, 3 weeks on /1 week off	Fulvestrant	Baseline (or C1D1), C1D15, C2D1, C3D1, C3D15, CnD1, within 15 days after last dose

Source: Table 3-4 on page 16 of Applicant's PKPD report

Figure 17-3: ANC Profiles in the First 8 Cycles in Studies E2301 (left) and F2301 (right)



Note: Gray symbols represent individual observations and blue curves are loess smoothing

Source: Figure 5-9 on page 16 of Applicant's PKPD report

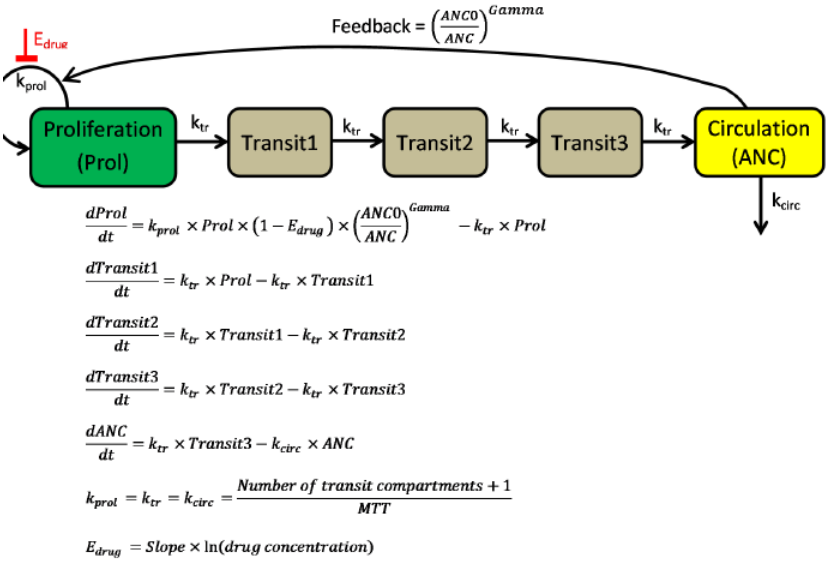
ANC E-R Modeling:

Base Model: The previous ANC E-R mode was used as the base model. The final ANC E-R model established previously was developed with the effect of ribociclib inhibiting proliferation of progenitor cells described using a loglinear function. The model structure and key equations are shown in Figure 17-4. In the final model, cancer type (breast vs. others) and use of letrozole (vs. without letrozole) were retained as covariates on the Slope (a parameter reflecting ribociclib potency for inhibiting progenitor cell proliferation). The analyses were performed using

NONMEM VII version 3 (Icon Development Solutions, Ellicott City, MD, USA), utilizing the MODESIM high performance computing environment.
R version 3.2.3 was used for pre- and post-processing. Modeling was performed using the Markov Chain Monte Carlo (MCMC) Bayesian method on log-transformed PK and ANC data.

The parameter posteriors of the ANC E-R model are listed in **Table 17-8**.

Figure 17-4: Structure and Key Equations of ANC E-R Model



Source: Figure -2 on page 19 of Applicant's PKPD report

Table 17-8: Parameter Posteriors of Previously Established ANC E-R Final Model

Parameter	Mean	SD	Naive SE	Time-series SE	Effective N	95% CI
Base (x10^9/L)	3.5719	0.2953	0.0017	0.0241	157	(3.0365 - 4.1808)
Slope (1/log(ng/mL))	0.0293	0.0019	0.0000	0.0001	251	(0.0256 - 0.0332)
MTT (h)	140.3229	2.4944	0.0144	0.0859	845	(135.3201 - 145.162)
Gamma (-)	0.2235	0.0063	0.0000	0.0002	657	(0.211 - 0.2361)
Cancer~Base (-)	1.2899	0.108	0.0006	0.0081	188	(1.0932 - 1.5143)
ECOG~Base (-)	1.1989	0.0733	0.0004	0.0043	291	(1.0606 - 1.3536)
Letroz~Base (-)	0.8599	0.0866	0.0005	0.0059	224	(0.7015 - 1.0484)
RaceAsian~Base (-)	0.7876	0.0772	0.0004	0.0041	347	(0.6442 - 0.9475)
Cancer~Slope (-)	0.8555	0.0626	0.0004	0.0043	220	(0.7402 - 0.9905)
Letroz~Slope (-)	0.8835	0.078	0.0005	0.0043	329	(0.7433 - 1.0458)
ω^2_{Base}	0.1597	0.0191	0.0001	0.0002	7988	(0.1259 - 0.2009)

Parameter	Mean	SD	Naive SE	Time-series SE	Effective N	95% CI
$\omega^2_{Base\sim Slope}$	0.0018	0.0122	0.0001	0.0002	5356	(-0.0213 - 0.0269)
ω^2_{Slope}	0.098	0.0154	0.0001	0.0002	4187	(0.0717 - 0.1317)
$\sigma^2_{additive}$ in log domain	0.0926	0.0033	0.0000	0.0000	17755	(0.0862 - 0.0992)
MCMCOBJ	-3067.8653	35.4503	0.2047	0.4631	5919	(-3134.4733 - -2996.3035)

Base: baseline ANC prior to treatment; Slope: a parameter representing the potency of ribociclib for inhibiting proliferation/differentiation of progenitor cells.

Source: Table 4-2 on page 19-20 of Applicant's PKPD report

Full Covariate Model: Prespecified E-R covariates and covariate-parameter relationships were evaluated or re-evaluated as listed in **Table 17-9**. Assessed covariates included race, age, and combination partners.

Table 17-9: Prespecified ANC E-R covariates for Evaluation

Covariate	Reference state	Related E-R parameters	Model description	Coding of covariate
			Intrinsic	
Race	Caucasian	Base, Slope	PV = PVref * $\theta_1^{I_1} * \theta_2^{I_2}$	I_1 = 0 & I_2 = 0, Caucasian; I_1 = 1 & I_2 = 0, Asian; I_1 = 0 & I_2 = 1, all others
Age	60 years old*	Base, Slope	PV = Pvref * (Age/60)^θ	-
			Extrinsic	
Combination partners				
Anastrozole, letrozole, tamoxifen, fulvestrant	No combination partner	Base, Slope	PV = PVref * $\theta_1^{I_1}$ * $\theta_2^{I_2}$ * $\theta_3^{I_3}$ * $\theta_4^{I_4}$	All I's = 0, no combination partners; I_1 = 1, with anastrozole; I_2 = 1, with letrozole; I_3 = 1, with tamoxifen; I_4 = 1, with fulvestrant;

Final ANC E-R Model: A final model was achieved by reduction of the full covariate model following the criteria as follows:

- Drop covariates that are both statistically insignificant (95% CI of a parameter estimate includes the null value) and not clinically important (95% CI of covariate effect is within ±10% from the reference value) from a full model.
- Drop covariates that have effects extending slightly outside the reference range as these covariates were also considered clinically not important and negligible;
- Drop covariates for which the dataset was considered not sufficiently informative for the evaluation due to limited sample size; drop covariates that are not relevant to future application of the mode.

The two versions of the full model suggested that the Slope was not impacted by the covariate tested (age, race, and combination partners), and that the race of Asian and use of letrozole and tamoxifen were significant on Base. From the two versions of the full model, two versions (anc. final1 and anc.final2) of the final model were derived. The two final models differed by the covariates on Base; anc.final1 retained the RaceAsian_Base relation, and anc.final2 retained letrozole_Base and tamoxifen_Base relations. No covariates were retained on the Slope in either model. The two models were equivalent in terms of the E-R relationship for ANC reduction associated with ribociclib treatment as the Slope posteriors were almost identical: mean=0.0254 with 95% CI 0.0243 – 0.0264 from anc.final1 (**Table 17-10**) vs. mean=0.0253 with 95% CI 0.0243 – 0.0262 from anc.final2 (posteriors not presented as they were similar to those from anc.final1)

The parameter posteriors from the final model are listed in **Table 17-10**. The posterior of the key parameter, Slope, was slightly lower than the prior (previous posterior): posterior = 0.0254 per log(ng/mL) with 95% CI 0.0243 - 0.0264 per log(ng/mL) vs. prior = 0.0293 per log(ng/mL) with 95% CI 0.0256 - 0.0332 per log(ng/mL).

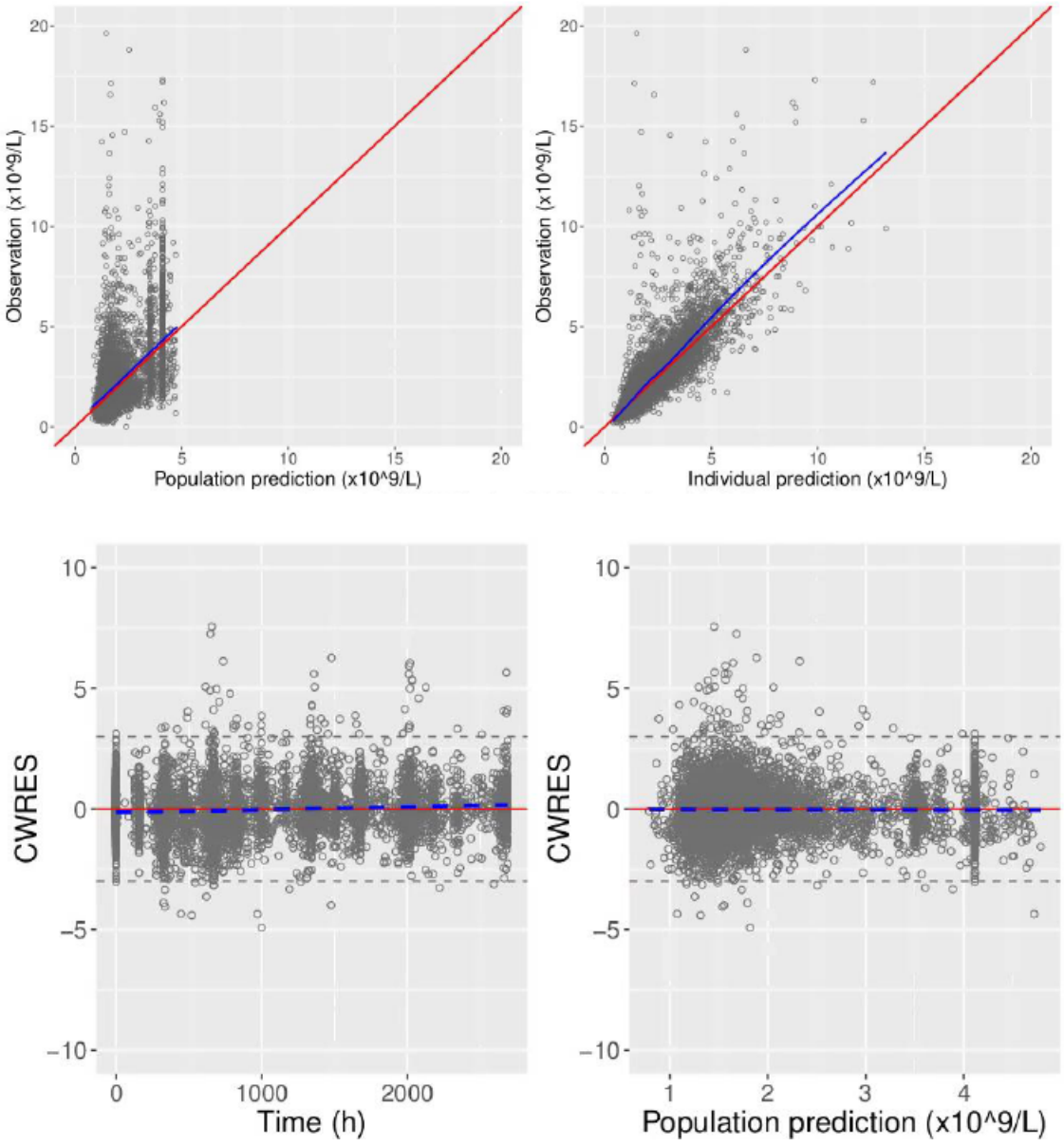
Diagnostic plots of the final ANC E-R model are present in Figure 17-5. No apparent deficiency in the structural or residual model was identified in the residual-based diagnostic plots

Table 17-10: Parameter posteriors from ANC E-R Final Model

Parameter	Mean‡	SD‡	Naive SE‡	Time-series SE‡	Effective N‡	95% CI‡	Null value*
ANCbase (x10^9/L)	4.1166	0.0576	0.0004	0.0019	952	(4.0055 - 4.2311)	NA
Slope (1/log(ng/mL))	0.0254	0.0005	0	0	153	(0.0243 - 0.0264)	NA
MTT (h)	118.7426	1.7826	0.0133	0.1212	222	(115.2961 - 122.105)	NA
Gamma (-)	0.1828	0.0044	0	0.0003	175	(0.1739 - 0.1915)	NA
RaceAsian_Base (-)	0.8541	0.0254	0.0002	0.0012	475	(0.8046 - 0.9027)	1
ω^2_{Base}	0.0974	0.0065	0	0.0002	1464	(0.0852 - 0.1105)	NA
$\omega^2_{Base\sim Slope}$	-0.0069	0.0034	0	0.0001	637	(-0.0135 - 1e-04)	NA
ω^2_{Slope}	0.0179	0.003	0	0.0001	410	(0.0126 - 0.0243)	NA
$\sigma^2_{additive}$ in log domain	0.1161	0.0021	0	0	8750	(0.1121 - 0.1203)	NA
MCMCOBJ	-13607.5	187.9928	1.4011	10.0123	359	(-13995.4576 - -13253.2553)	NA

‡: statistics summarized (using the coda package) from pooled Bayesian posterior samples from 3 chains with 10000 samples per chain. SD, standard deviation; naïve SE, standard error without consideration of autocorrelation within a chain; time-series SE, standard error with consideration of autocorrelation; effective N, posterior sample size void of autocorrelation; 95% CI, 2.5th – 97.5th percentiles of the posterior samples.

Figure 17-5: Goodness-of-fit Plots for ANC E-R Final Model (anc.final1)



Source: Adapted from Figure 5-14 and Figure 5-15 on page 67 of Applicant's PKPD report

None of the covariates were found to have clinically important effect on Slope based on the simulated covariate effect sizes and the relevant predefined criteria. This result suggested that the ANC E-R relationship of ribociclib was not affected by age, race, or the use of letrozole, anastrozole, tamoxifen, or fulvestrant.

Reviewer's Comments: The Applicant's updated ANC E-R model is acceptable. The goodness-of-fit plots indicate that the updated ANC E-R model is adequate in characterizing the ANC profile after ribociclib treatment in patients with breast cancer. The reviewer agrees with the Applicant's conclusion regarding effect of covariate on ANC E-R relationship. Current analyses support ribociclib to be used in (b) (4) *postmenopausal patients with HR+, HER2-negative*

advanced breast cancer, in combination with letrozole, anastrozole, or fulvestrant, irrespective of race, from the standpoints of PK and neutropenia risk.

17.4. Additional Safety Analyses Conducted by FDA

FDA did not conduct additional safety analyses.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SAKAR M WAHBY
07/17/2018

WENTAO FU
07/17/2018

FANG LI
07/17/2018

JINGYU YU
07/17/2018

QI LIU
07/17/2018

ERIK W BLOOMQUIST
07/17/2018

SHENGHUI TANG
07/17/2018

JENNIFER J GAO
07/17/2018

LALEH AMIRI KORDESTANI
07/17/2018

NAM ATIQUR RAHMAN
07/17/2018
I concur with the recommendation.

ROBERT J SCHROEDER
07/17/2018

JULIA A BEAVER
07/17/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209092Orig1s001

CHEMISTRY REVIEW(S)

Office of Lifecycle Drug Products
Division of Post-Marketing Activities I
Review of Chemistry, Manufacturing, and Controls

1. **NDA Efficacy Supplement:** 209092/S001

2. **Submission(s) Being Reviewed**:

Submission	Type	Sub Date	CDER Date	Assigned Date	PDUFA Date	Rev Date
Original Supplement	PA	28-Jun-18	28-Jun-18	02-Jul-18	28-Dec-18	07-Oct-18

3. **(a) Provides For From Acknowledgment Letter:**
   - (b) (4)

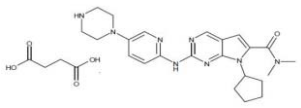
   (b) Additional Change(s) Proposed in the Supplement: none

4. **Review #**: 1
5. **Clinical Review Division**: Division of Oncology Products 1 (DOP1)
6. **Name and Address of Applicant**:
   Novartis Pharmaceuticals Corporation
   One Health Plaza
   East Hanover, NJ 07936-1080

7. **Drug Product**:

Drug Name	Dosage Form	Strength	Route of Administration	Rx or OTC	Special Product
Kisqali®	Tablets, film coated	200mg	oral	Rx	No

8. **Chemical Name and Structure of Drug Substance**:



USAN: ribociclib succinate
Chemical name: Butanedioic acid—7-cyclopentyl-*N*,*N*-dimethyl-2-{[5-(piperazin-1-yl) pyridin-2-yl]amino}-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide (1/1)
Molecular formula: $C_{23}H_{30}N_8O \cdot C_4H_6O_4$
MW: 552.64 g/mol [Free base: 434.55 g/mol].

9. **Indication**: (b) (4)
   (b) (4)

10. **Supporting/Relating Documents**: Environmental assessment categorical exclusion request

11. **Consults**: none

12. **Executive Summary**:
Novartis submits this efficacy supplement for Kisqali (ribociclib) Tablets to support the approval of expanded indication is based on efficacy and safety primarily from two pivotal studies. Study CLEE011E2301 (MONALEESA-7) is a randomized, Phase III, double-blind, global trial evaluating ribociclib or placebo in combination with tamoxifen or a non-steroidal aromatase inhibitor (NSAI; letrozole or anastrozole) and goserelin in pre- and perimenopausal women with HR-positive, HER2-negative, advanced breast cancer who have received no prior hormonal therapy for advanced disease. Study CLEE011F2301 (MONALEESA-3) is a randomized, Phase III, double-blind, global trial evaluating ribociclib or placebo in combination with fulvestrant in postmenopausal women with HR-positive, HER2-negative, advanced breast cancer who have received no or only one line of prior hormonal therapy for advanced disease.

The expanded approved indication is for Kisqali in combination with:

- an aromatase inhibitor for the treatment of pre/perimenopausal or postmenopausal women, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer, as initial endocrine-based therapy; or
- fulvestrant for the treatment of postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer, as initial endocrine based therapy or following disease progression on endocrine therapy.

There are no proposed CMC changes in this efficacy supplement.

The applicant has submitted an Environmental Assessment (EA) exclusion request per 21 CFR 25.31(b). Novartis certifies that this submission for ribociclib (Kisqali) qualifies for a categorical exclusion in accordance with 21 CFR Part 25.31(b) as

the estimated environmental intake concentration of the active moiety, ribociclib, will be significantly less than 1ppb, based on the peak production estimates within the next five years

From CMC perspective, this efficacy supplement is fileable, and recommended for approval.

13. **Conclusions & Recommendations**: This efficacy supplement is recommended for approval from a CMC perspective.

14. **Comments/Deficiencies to be Conveyed to Applicant**: none

15. **Primary Reviewer**: Lorenzo Rocca, CMC Reviewer, Branch 1, DPMA 1, OLDP, OPQ

16. **Secondary Reviewer**: Ramesh Raghavachari, Branch Chief, Branch 1, DPMA 1, OLDP, OPQ

Lorenzo Rocca

Digitally signed by Lorenzo Rocca
Date: 10/07/2018 11:47:16PM
GUID: 508da7210002a0b498ca67191414ff66

Ramesh Raghavachari

Digitally signed by Ramesh Raghavachari
Date: 10/08/2018 10:01:20PM
GUID: 502d0913000029f375128b0de8c50020

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209092Orig1s001

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	209092
Supporting document/s:	403
Applicant's letter date:	June 28, 2018
CDER stamp date:	June 28, 2018
Product:	Kisqali (ribociclib)
Indication:	Hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer
Applicant:	Novartis Pharmaceuticals Canada Inc. 385 boul. Bouchard Dorval, Quebec
Review Division:	Division of Hematology Oncology Toxicology (Division of Oncology Products 1)
Reviewer:	C.J. George Chang, DVM, MS, PhD, DABT
Supervisor/Team Leader:	Tiffany Ricks, PhD (acting)
Division Director:	John K. Leighton, PhD, DABT (Julia Beaver, MD (acting))
Project Manager:	Sakar M. Wahby, RPM

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 209092 are owned by Novartis Pharmaceuticals or are data for which Novartis Pharmaceuticals has obtained a written right of reference. Any information or data necessary for approval of NDA 209092 that Novartis Pharmaceuticals does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 209092.

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1 Executive Summary

1.1 Introduction

On June 28, 2018, Novartis (the applicant) submitted an efficacy supplement and revised label for Kisqali (ribociclib) for the treatment of HR+, HER2- advanced or metastatic cancer. This nonclinical review addresses one nonclinical xenograft study and one female rat fertility and early embryonic development study submitted. The applicant included changes to nonclinical sections of the label based on results from these two studies.

1.2 Brief Discussion of Nonclinical Findings

In a nonclinical anti-tumor activity study following 28 days of treatment, ribociclib and fulvestrant combination treatment inhibited tumor growth in an athymic mouse estrogen receptor positive breast cancer xenograft model when compared with negative control.

In a GLP female fertility and early embryonic development study in rat, no ribociclib-related early mortalities, changes in body weight, food consumption, estrus cycles, fertility, and early embryonic development were noted at doses up to 300 mg/kg/day. The no-observed-adverse-effect level (NOAEL) of ribociclib for maternal toxicity, female fertility, and early embryonic development in rats is 300 mg/kg/day.

1.3 Recommendations

1.3.1 Approvability: Yes

This sNDA for Kisqali is recommended for approval from the perspective of the pharmacology/toxicology discipline.

1.3.3 Labeling

Changes to section 12.1 Mechanism of Action were to include results from an anti-tumor activity study in an estrogen receptor positive breast cancer xenograft model treated with ribociclib and fulvestrant. In addition, data from a fertility and early embryo-fetal development study in female rats were included in section 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility. See prescribing information for the finalized language.

2.7 Regulatory Background

Kisqali (ribociclib) was approved in the United States in 2017, when in combination with an aromatase inhibitor, as initial endocrine-based therapy for the treatment of postmenopausal women with HR+/HER2- advanced or metastatic breast cancer.

3 Studies Submitted

3.1 Studies Reviewed

Study No.	Title	Location
	Pharmacology	
RD-2016-00052	In vivo assessment of NVP-LEE011 in estrogen receptor positive (ER+) human breast cancer cell line xenografts	4.2.1.1
	Development and Reproductive Study	
9000740 (Novartis 1570198)	An oral (gavage) female fertility and early embryonic development study in the rat	4.2.3.5.1

3.3 Previous Reviews Referenced

See NDA-209092 multidisciplinary review.

4 Pharmacology

4.1 Primary Pharmacology

Study title: In vivo assessment of NVP-LEE011 in estrogen receptor positive (ER+) human breast cancer cell line xenografts

Study no:	RD-2016-00052
Study report location:	4.2.1.1
Conducting laboratory and location:	Novartis East Hanover, NJ
Date of study initiation:	Not reported
GLP compliance:	No
QA statement:	Not applicable
Drug, lot #, and % purity:	NVP-LEE011; batch and purity not reported

Note: This review was focused on the results of combination treatment of LEE011 (ribociclib) and fulvestrant in the ZR751 (PTEN-null) ER+ human breast cancer xenograft model.

Key Study Findings

Anti-tumor activity was noted when LEE011 was combined with fulvestrant in the ZR751 mouse xenograft model. At the end of the 28-day of treatment, LEE011 and fulvestrant combination treatment led to inhibition of tumor growth.

Methods

Doses in definitive study:	LEE011: 75 mg/kg Fulvestrant: 5 mg/week
Frequency of dosing:	LEE011: Once daily Fulvestrant: Once weekly
Route of administration:	LEE011: Oral gavage Fulvestrant: Subcutaneously (SC)
Dose volume:	Not reported
Formulation/Vehicle:	OEE011: 0.5% w/v Methylcellulose/water Fulvestrant: Castor oil/ethanol
Species/Strain:	CD-1 athymic nude mice
Number/Sex/Group:	6-8 mice
Satellite groups:	None
Basis of dose selection:	Not specified
Negative control:	Daily 0.5% w/v methylcellulose/water PO and weekly castor oil/ethanol (SC)
Positive control:	None

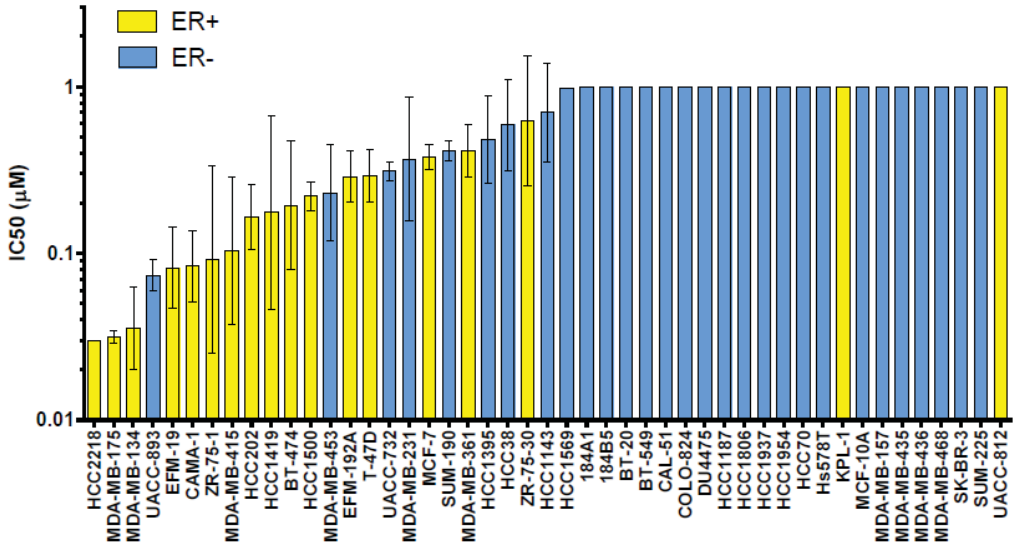
Study Validity

Vehicle control showed a steady tumor growth in xenograft mouse model.

Results

In vitro IC_{50} of LEE011 for ZR-75-30 cancer line was around 0.5 μM. See figure below.

Figure 1 In Vitro IC_{50} Values of LEE011 for Various ER+ (Yellow) and ER- (Blue) Breast Cancer Cell Lines

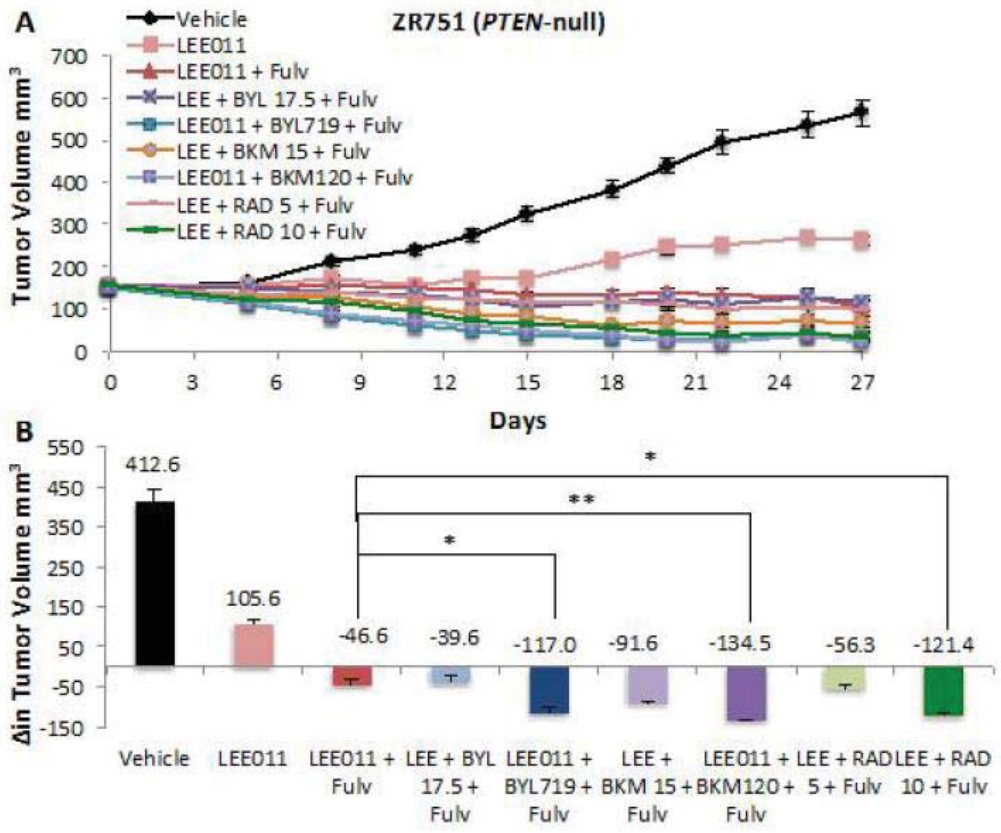


LEE011 was prepared for in vitro studies in DMSO (10 mM). Yellow bars represent ER+ breast cancer cell lines and blue bars represent ER- breast cancer cell lines. Data represent mean IC50 +/- 95% condidence interval where available.

(Excerpted from the applicant's submission)

At the end of the 28-day of treatment (started on Day 0), the average increase in tumor volume for vehicle control group was 412.6 mm^3, and that of LEE011 and fulvestrant combination group was -46.6 mm^3. See figures below.

Figure 2 In Vivo Anticancer Efficacy Results of LEE011 and LEE011 with Fulvestrant in ER+ Breast Cancer ZR751 Xenografts in Athymic Mice



(A) Growth curves and (B) histograms representing the anti-tumor activity of single agent LEE011 (LEE) or combination with fulvestrant (fulv) or fulvestrant + BYL179 (BYL), BKM120 (BKM) or RAD001 (RAD). MCF7 (PIK3CA mutant). Fulvestrant given 5 mg/week by subcutaneous injection. All treatment arms are statiscally different from vehicle control. *Represent triple combination arms that are statistically different from the LEE011 + Fulvestrant combination, $p < 0.05$. P-values calculated using a two-way pair Student t-test. Data represent mean +/- SEM.

(Excerpted from the applicant's submission)

9 Reproductive and Developmental Toxicology

9.1 Fertility and Early Embryonic Development

Study title: LEE011 – An oral (gavage) female fertility and early embryonic development study in the rat

Study no.:	9000740 (Novartis No. 1570198)
Study report location:	4.2.3.5.1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	September 9, 2016
GLP compliance:	Yes
QA statement:	Provided
Drug, lot #, and % purity:	LEE011 (LEE011-BBA.005); Batch #1010003045; 100% purity

Key Study Findings

- No LEE011-related early mortalities, changes in body weight, food consumption, estrous cycles, fertility, and early embryonic development were noted at doses up to 300 mg/kg/day.
- No-observed-adverse-effect level (NOAEL) of LEE001 for maternal toxicity, female fertility, and early embryonic development in rats is 300 mg/kg/day.

Methods

Doses:	0, 10, 30, and 60 mg/mL
Frequency of dosing:	Once daily during 14 days prior to cohabitation, during, cohabitation, and up to Day 6 postcoitum (pc) when terminal euthanasia (see deviation below)
Dose volume:	5 mL/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% (w/v) Methylcellulose 400 cPs, aqueous solution
Species/Strain:	Wistar Hannover Crl:WI (Han) rats
Number/Sex/Group:	24 Females
Satellite groups:	None
Study design:	See table below.
Deviation from study protocol:	Five out of 24 rats in Group 1, 9/24 rats in Group 2, and 5/24 rats in Group 3, and 10/24 rats in Group 4 were dosed on Day 7 pc. Other deviations reported were not significant.

Table 1 Design of Female Fertility and Early Embryonic Development Study in Rats

Group no.	Dose Level (mg/kg/day)	Dose Volume (mL/kg)	Concentration (mg/mL)[a]	Animal Number
				Females
1/ Vehicle Control	0	5	0	1501-1524
2/ LEE011	50	5	10	2501-2524
3/ LEE011	150	5	30	3501-3524
4/ LEE011	300	5	60	4501-4524

a Dose concentrations are expressed as base. Concentrations were adjusted for the salt factor. The salt/base ratio for LEE011 was 1.272.

(Excerpted from the applicant's submission)

Observations and Results

Measurements	Schedule
Mortality	Twice daily
Clinical Observations (Cageside)	Non-dosing days: Once daily Dosing days: Pre-dose and 3 hours postdose
Clinical Observations (Detailed)	On days of body weight assessment
Body Weight	From randomization to Day 1 of dosing: Twice weekly

<table>
<tr><td></td><td>Mated females: on Days 0, 3, 6, 9, and 13 postcoitum (pc)</td></tr>
<tr><td>Food Consumption</td><td>From randomization until initiation of mating period: Twice weekly
Mated females: on Days 0-3, 3-6, 6-9, and 9-13 pc</td></tr>
<tr><td>Estrus Cycle or Pregnancy Confirmation: (vaginal lavage for copulatory plug)</td><td>Cohabitation/Mating period (14 days): Daily</td></tr>
<tr><td>Necropsy</td><td>1. Females without evidence of mating but visibly pregnant: Between 4-8 days after completion of mating period.

2. Females with evidence of mating: 13 days pc (See table below for procedure)
<table>
<tr><th rowspan="2">Group No.</th><th rowspan="2">No. of Female Rats</th><th rowspan="2">Scheduled Euthanasia Day (pc)</th><th colspan="4">Necropsy Procedures</th></tr>
<tr><th>Ovarian/ Uterine Examination</th><th>Necropsy</th><th>Tissue Collection[a]</th><th>Organ Weights</th><th>Histology Histopathology</th></tr>
<tr><td>1</td><td>24</td><td rowspan="3">13</td><td rowspan="3">X</td><td rowspan="4">Full Exam</td><td rowspan="4">X</td><td rowspan="4">-</td><td rowspan="4">-</td></tr>
<tr><td>2</td><td>24</td></tr>
<tr><td>3</td><td>24</td></tr>
<tr><td>4</td><td>24</td><td rowspan="3">-</td></tr>
<tr><td colspan="3">Without Evidence of Mating[b]</td></tr>
<tr><td colspan="3">Without Evidence of Mating (but Visibly Pregnant)[b]</td><td>X[b]</td></tr>
<tr><td colspan="3">Unscheduled Occasions (after dosing start)</td><td>-</td></tr>
</table>
X = procedure to be conducted; - = not applicable
a See Tissue Collection and Preservation table for listing of tissues.
b As described in Section 3.6.2
(Excerpted from the applicant's submission)</td></tr>
<tr><td>Tissue Collection and Preservation (F0 Generation)</td><td>Table 2 F0 Generation Tissue Collection / Preservation
<table>
<tr><th>Tissue</th><th>Collect</th><th>Comment</th></tr>
<tr><td>Animal identification</td><td>X</td><td>-</td></tr>
<tr><td>Gland, mammary</td><td>X</td><td>-</td></tr>
<tr><td>Cervix</td><td>X</td><td>Collect with uterus</td></tr>
<tr><td>Gross lesions/masses</td><td>X</td><td>-</td></tr>
<tr><td>Ovaries</td><td>X</td><td>-</td></tr>
<tr><td>Oviducts</td><td>X</td><td></td></tr>
<tr><td>Uterus</td><td>X</td><td>Collect with cervix</td></tr>
<tr><td>Vagina</td><td>X</td><td>-</td></tr>
</table>
X = procedure conducted; - = not applicable
(Excerpted from the applicant's submission)</td></tr>
<tr><td>Parental/Litter Variables</td><td>Table 3 Parental / Litter Variables - Calculation Formula</td></tr>
</table>

	Mating index (%) = No. of females mating / No. of females placed for mating x 100 Fertility index (%) = No. of pregnant females / No. of females placed for mating x 100 Pregnancy index (Conception rate) (%) = No. of pregnant females / No. of mated females x 100 Gestation index (%) = No. of females with live embryos / No. of pregnant females x 100 (Excerpted from the applicant's submission)
Statistical Matrix	**Table 4 Statistical Matrix**

Variables for Inferential Analysis	Statistical Method		
	ANOVA	Non-Parametric	Incidence
Body Weight	X		
Corpora Lutea Count		X	
Numbers of Implants		X	
Live Embryos		X	
Dead Embryos		X	
Number of Early Resorptions		X	
Sum of Resorptions and Dead Embryos		X	
Body Weight Change[a]	X		
Pre Implantation Losses[b]		X	
Post Implantation Losses[b]		X	
Parental Indices			X
Parental Time to Mate		X	

a At each interval and overall values during the premating treatment period and the gestation period (days 0 to 13 pc).

b Calculated based on litter means/values

(Excerpted from the applicant's submission)

Mortality

No drug-related early mortalities were noted.

Clinical Signs

No drug-related clinical signs of toxicity were noted, except for salivation and wetness of lower jaw noted in 1/24 female at 300 mg/kg/day once on Day 19 during premating period, and 2/24 females at 150 mg/kg/day between Days 3 and 13 pc.

Body Weight

No drug-related changes in body weight or body weight gains were noted.

Feed Consumption

No drug-related changes in food consumption were noted.

Dosing Solution Analysis

The analytical results of formulations prepared in Weeks 1 and 5 showed that the dosing formulations were 99.7%-102% to targets with relative standard deviation (RSD) ≤2.7%. See table below.

Table 5 Dosing Concentration Verification Results

Sampling Time	Group ID	Target Conc. (mg/mL)	Measured Conc. (mg/mL)	Percent to Target (%)	RSD (%)
Week 1	1	0	ND	ND	ND
	2	10	10.1	101	1.6
	3	30	30.0	99.9	2.4
	4	60	59.8	99.7	2.7
Week 5	1	0	ND	ND	-
	2	10	10.2	102	-
	3	30	30.7	102	-
	4	60	60.1	100	-

ND: Not detected; RSD: Relative standard deviation;
-: Not measured for RSD

Fertility

Estrous Cycle

No drug-related changes in female estrous cycles. See table below.

Table 6 Group Means of Estrous Cycles Observed

Group	n	Days in Estrous*	Cycles Seen**	Average Cycle Length (Days)
1	24	4.0	3.4	4.19
2	24	4.3	3.8	3.91
3	24	4.0	3.4	4.15
4	24	4.0	3.3	4.23

*: Includes only days in estrous
**: Includes actual cycles seen in estrous and the “unseen” cycles determined

Necropsy

Parental Performance

No drug-related changes in female reproductive performance.

Table 7 Group Mean Parental Performance

Group	Number Placed for Mating		Number Mating	Mean (SD) Day to Mating % Diff (G1)	Number Females Pregnant	Number Females with Live Embryos	Mating Index (%)	Fertility Index (%)	Gestation Index (%)	Conception Rate (%)
	Males	Females								
1	24	24	23 a	3.6 3.6 (N = 20)	22	22	95.8	91.7	100.0	95.7
2	24	24	24	2.4 1.3 (N = 22) -32	24	24	100.0	100.0	100.0	100.0
3	24	24	24	2.5 1.2 (N = 21) -30	24	24	100.0	100.0	100.0	100.0
4	24	24	24	2.3 1.5 (N = 22) -35	22	21	100.0	91.7	95.5	91.7

Significantly different from control group (group 1) value: D - P ≤ 0.05 E - P ≤ 0.01 F - P ≤ 0.001 (Dunn - day to mating only)

Significantly different from control group (group 1) value: d - P ≤ 0.05 (Fisher's)

a: Animal 1519 was euthanized on Day 6 of gestation and the pregnancy status was not determined

(Excerpted from the applicant's application)

Ovarian and Uterine Findings

No drug-related changes in ovarian and uterine findings. See tables below.

Table 8 Group Mean of Ovarian and Uterine Findings – Including One Dam with Total Resorptions

Group	1	2	3	4
n	19	22	22	20
Corpora Lutea	12.9	12.7	13.4	13.3
Implantation Sites	11.3	11.7	12.6	12.4
Live Embryos	10.8	10.7	11.8	11.6
Dead Embryos	0	0	0	0
Early Resorptions	0.5	1.0	0.9	0.9
Early Resorptions + Dead Embryos	0.5	1.0	0.9	0.9
Preimplantation Loss (%)	12.08	8.14	5.55	7.86
Post Implantation Loss (%)	4.16	8.74	6.57	11.08

Table 9 Group Mean of Ovarian and Uterine Findings – Excluding Dam with Total Resorptions

Group	1	2	3	4
n	19	22	22	19
Corpora Lutea	12.9	12.7	13.4	13.5
Implantation Sites	11.3	11.7	12.6	**13.0***
Live Embryos	10.8	10.7	11.8	12.2
Dead Embryos	0	0	0	0
Early Resorptions	0.5	1.0	0.9	0.8
Early Resorptions + Dead Embryos	0.5	1.0	0.9	0.8
Preimplantation Loss (%)	12.08	8.14	5.55	3.59

Post Implantation Loss (%)	4.16	8.74	6.57	6.40

*: p≤0.05

Microscopic Pathology

No drug-related microscopic findings were noted.

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/s/

CHING-JEY G CHANG
07/11/2018

TIFFANY RICKS
07/11/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209092Orig1s001

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: July 11, 2018

To: Julie Beaver, M.D., Director (Acting)
Division of Oncology Products 1 (DOP1)

Sakar Wahby, PharmD, Regulatory Project Manager, (DOP1)

William Pierce, PharmD, Associate Director for Labeling, (DOP1)

From: Kevin Wright, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Brian Tran, PharmD, M.B.A., Team Leader, OPDP

Subject: OPDP Labeling Comments for Kisqali (ribociclib) tablets, for oral use

NDA: 209092/s-001

In response to DOP1's consult request dated May 8, 2018, OPDP has reviewed the proposed product labeling (PI), and patient package insert (PPI) for Kisqali (ribociclib) tablets, for oral use (Kisqali). This efficacy supplement (s-001) proposes a new indications:

(b) (4)

(b) (4)

OPDP's comments on the proposed labeling are based on the draft PI and PPI received by electronic mail from DOP1 (Sakar Wahby) on June 20, 2018, and are provided below.

Thank you for your consult. If you have any questions, please contact Kevin Wright at (301) 796-3621 or kevin.wright@fda.hhs.gov.

26 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

KEVIN WRIGHT
07/11/2018