CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209935Orig1s000

SUMMARY REVIEW

Division Director Summary Review for Regulatory Action

Date	(electronic stamp)
From	Julia Beaver, MD, (Acting) Division Director
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	209935
Applicant	Novartis
Date of Submission	January 30th, 2017
PDUFA Goal Date	November 20th, 2017
Proprietary Name / **Non-Proprietary Name**	Kisqali Femara Co-Pack ribociclib letrozole
Dosage Form(s) / Strength(s)	200mg Tablet (ribociclib) 2.5mg tablet (letrozole)
Applicant Proposed Indication(s)/Population(s)	*The KISQALI® FEMARA® CO-PACK [ribociclib, a kinase inhibitor, (b) (4) letrozole, an aromatase (b) (4) inhibitor] is indicated 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.*
Action/Recommended Action for NME:	Approval
Approved/Recommended Indication/Population(s) (if applicable)	The KISQALI® FEMARA® CO-PACK is indicated 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.

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Anand Shah
Pharmacology Toxicology Review	Ching-Jey Chang
OPQ Review	Paresma Patel/Xiao Hong Chen Marion Michaelis Gerlie Gieser
OPDP	Kevin Wright/Trung-Hieu Tran
OSE/DMEPA	Tingting Gao/Alice Tu
Patient Labeling	Rowe Medina & Shawna Hutchins / Barbara Fuller

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
DMEPA=Division of Medication Error Prevention and Analysis

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

I concur with the Benefit-Risk Assessment that was made by the clinical team. All members of the review team recommended approval of this application or reported that there were no findings that would preclude approval. NDA 209935 for the ribociclib letrozole copack is based on data previously submitted, NDA 209092 (ribociclib) and NDA 020726 S-031 (letrozole) were cross-referenced, and no new data was submitted with this NDA.

Advanced or metastatic breast cancer is a serious and life-threatening disease. In 2017, it is estimated that approximately 40,000 women will die of breast cancer in the United States. Available endocrine-based therapies for this disease setting include aromatase inhibitors (letrozole, anastrozole, and exemestane) which are commonly used interchangeably, and tamoxifen. These endocrine agents provide a median PFS or median time to progression of approximately 9-12 months. The addition of palbociclib to letrozole provides an additional 10 month improvement in median PFS over letrozole alone. Despite the availability of endocrine-based therapies for the treatment of patients with first-line HR-positive advanced or metastatic breast cancer, patients ultimately develop resistance and progression of disease and go on to receive multiple additional therapies including eventually many lines of toxic chemotherapies.

The trial which forms the primary basis for the safety and efficacy review and the approval recommendation for the ribociclib letrozole co-pack was previously reviewed in NDA 209092. This trial, MONALEESA-2 (CLEE011A2301), an international, multi-center, randomized (1:1), double-blind, placebo controlled trial evaluated the efficacy and safety of treatment with ribociclib plus letrozole (n=334) versus placebo plus letrozole (n=334) in postmenopausal women with HR-positive, HER2-negative advanced breast cancer who received no prior therapy for their advanced or metastatic breast cancer. The major efficacy outcome measure was investigator-assessed PFS, which at the pre-planned interim efficacy analysis, demonstrated a HR of 0.556 (95% CI: 0.429, 0.720; 1-sided p value <0.0001) in favor of ribociclib plus letrozole. Median PFS in the ribociclib plus letrozole arm was not reached (95% CI: 19.3, not reached) and median PFS in the placebo plus letrozole arm was 14.7 month (95% CI: 12, 16.5). Objective response rate (ORR) was supportive with a ORR of 52.7% (95% CI: 46.6, 58.9) in the ribociclib plus letrozole arm and 37.1% (95% CI: 31.1, 43.2) in the placebo plus letrozole arm. Overall survival (OS) data was immature. In addition, Study X2101, a phase I multicenter, open label, dose-escalation study of oral ribociclib in patients with advanced solid tumors or lymphomas showed an ORR of 5.0% (n=4) in seventy six patients (21 with advanced/metastatic breast cancer) who were treated with a monotherapy dose of 600mg of ribociclib on a three week on, one week off schedule. This information further supports the contribution of combination therapy of letrozole to overall therapeutic effect of ribociclib observed in MONALEESA-2.

The most common adverse reactions (AR) experienced in at least 20% of patients on MONALEESA-2 were neutropenia, nausea, fatigue, diarrhea, leukopenia, alopecia, vomiting, constipation, headache and back pain. Dose reductions due to ARs occurred in 45% of patients receiving ribociclib plus letrozole and in 3% of patients receiving placebo plus letrozole. Permanent discontinuations due to ARs were reported in 7% of patients receiving ribociclib plus letrozole most commonly from ALT-increase (4%), AST increase (3%), and vomiting (2%). On treatment deaths were reported in three cases due to cause unknown, sudden death (in the setting of Grade 2 QT prolongation and Grade 3 hypokalemia), and progressive disease. Ribociclib has been shown to prolong the QT interval in a concentration dependent manner. In MONALEESA-2, one patient had >500msec post-baseline QTcF value and nine patients out of 329 had a >60 msec increase from baseline in QTcF intervals all which occurred within the first four weeks of therapy and were reversible with dose interruption. Nine patients on the ribociclib plus letrozole arm experienced syncope and no patients experienced torsades de pointe. Although 75% of patients experienced neutropenia, only 1.5% developed febrile neutropenia and only 0.9% required dose discontinuation demonstrating appropriate management by dose interruptions and reductions. Four (1%) patients showed concurrent elevations in ALT or AST greater than three times the upper limit of normal (ULN) and total bilirubin greater than two times the ULN, with normal alkaline phosphatase, in the absence of cholestasis; all patients recovered after ribociclib discontinuation. Concerns over QT interval prolongation were addressed in labeling and are being investigated in a safety postmarketing requirement (PMR) to NDA 209092 examining an alternative dosing regimen. In addition, QT prolongation, hepatobiliary toxicity, and neutropenia were included in the warnings and precautions section of labeling. The safety profile of ribociclib plus letrozole was acceptable for the intended population and supportive of a favorable benefit-risk profile of ribociclib and letrozole for this indication.

In conclusion, ribociclib in combination with letrozole demonstrated a statistically significant improvement in PFS in a large, randomized, double blind study reviewed in NDA 209092 with minimal single agent activity of ribociclib alone and strong pre-clinical evidence supporting the combination therapy. Despite immature OS data, in patients with a life-threatening and incurable malignancy, this PFS improvement represents a clinically meaningful benefit due to the substantial delay of progression and postponement of subsequent toxic therapies. The safety profile is acceptable in the intended population. A serious risk of QT prolongation will be further evaluated with alternative dosing in a FDAAA PMR to NDA 209092 and is included in the warnings and precautions section of labeling. In addition, appropriate labeling for dose modification and inclusion of neutropenia, and hepatobiliary toxicity in warnings and precautions identifies these concerns to prescribers and assists with appropriate management. Therefore, the benefit-risk profile is favorable to support approval of ribociclib letrozole co-pack 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.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• In 2017, it is estimated 252,710 women will be diagnosed with Breast Cancer in the U.S., and 40,610 women will die of their disease. • HR-positive cancers comprise the majority of breast cancer cases. • Strong pre-clinical evidence for combination of CDK inhibitors with anti-endocrine therapies.	**Advanced and metastatic breast cancer is serious, life-threatening, and incurable. There is an unmet medical need to develop therapies for advanced and metastatic breast cancer.**
Current Treatment Options	• Available therapies include aromatase inhibitors (letrozole, anastrozole, and exemestane) or tamoxifen (a selective estrogen receptor modulator). These endocrine agents provide a median PFS or time to progression of ~ 9-12 months. • Palbociclib in combination with letrozole was approved based on a ~10 month improvement in median PFS compared to letrozole alone. • Despite the availability of endocrine-based therapies, patients ultimately develop resistance and progression of disease and go on to receive multiple additional therapies including toxic chemotherapies.	**Endocrine-based therapies are used in the intended population as initial therapy if possible. Subsequent lines of therapy may result in substantial toxicities (some cumulative) for this patient population.**
Benefit	• MONALEESA-2 is a randomized, double-blind, placebo controlled trial evaluating ribociclib plus letrozole (n=334) versus placebo plus letrozole (n=334) in postmenopausal women with HR-positive, HER2-negative advanced breast cancer who received no prior therapy for their advanced or metastatic breast cancer. • Investigator-assessed PFS (primary endpoint) was improved in the ribociclib plus letrozole arm compared to the placebo plus letrozole arm [HR 0.556 (95% CI 0.429, 0.720); 1-sided p-value < 0.0001], with a median PFS not reached (95% CI 19.3, not reached) for the ribociclib plus letrozole arm and 14.7 months (95% CI 13.0, 16.5) for the placebo plus letrozole arm. • Objective response rate (ORR) was 52.7% (95% CI: 46.6, 58.9) in the ribociclib plus letrozole arm and 37.1% (95% CI: 31.1, 43.2) in the placebo plus letrozole arm. • In another study of 76 patients, 21 with breast cancer, single agent ribociclib demonstrated a 5% ORR.	**Evidence of effectiveness was supported by a statistically significant and clinically meaningful PFS improvement in MONALEESA-2. MONALEESA-2 was large, double-blind, placebo controlled, and randomized which decreases uncertainty. Supportive ORR, BICR, 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 delay of progression and postponement of subsequent toxic therapies. Single agent ribociclib has low ORR, supporting letrozole contribution to the combination regimen.**

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk	• The most common adverse reactions (AR) experienced in at least 20% of patients on MONALEESA-2 were neutropenia, nausea, fatigue, diarrhea, leukopenia, alopecia, vomiting, constipation, headache and back pain. • Three on treatment deaths due to unknown cause, sudden death (in the setting of Grade 2 QT prolongation and Grade 3 hypokalemia), and progressive disease. • QT interval was prolonged in a concentration dependent manner in patients treated with ribociclib. One patient had >500msec post-baseline QTcF value and nine patients out of 329 had a >60 msec increase from baseline in QTcF intervals all which occurred within the first four weeks of therapy and were reversible with dose interruption. There were no torsade de pointes cases, and syncope occurred in 9 patients (2.7%) in the ribociclib plus letrozole arm. • Neutropenia was seen in 75% of patients on the ribociclib plus letrozole arm, and 0.9% of patients required discontinuation due to neutropenia. • Four (1%) patients showed labs consistent with Hy's law but recovered upon discontinuation of ribociclib. • Additional clinical data of anastrozole or exemestane in combination with ribociclib showed no drug drug interactions or novel safety signals.	**The safety profile of ribociclib is acceptable for the intended population. To address the serious risk of QT prolongation a FDAAA PMR was agreed upon with NDA 209092 to conduct a trial to study alternative dosing. Neutropenia appeared to be appropriately managed as evidenced a low frequency of discontinuations. Hepatobiliary toxicity was manageable with appropriate dose modifications which are clearly delineated in labeling. Additional aromatase inhibitor data supports a broadened indication combining ribociclib with the class of aromatase inhibitors.**
Risk Management	• Labeling for QT interval prolongation, hepatobiliary toxicity, and neutropenia are included in warnings and precautions. • Labeling details dose interruption, reduction, or discontinuation • Laboratory monitoring (including electrolytes), and ECG monitoring is recommended before and during treatment. • There may be an alternative dose which mitigates QT interval prolongation but does not impact efficacy. • Oncologists are well versed in the identification and management of the toxicities associated with ribociclib.	**The safe use of ribociclib can be managed through accurate labeling and routine oncology care. No REMS is indicated. a FDAAA PMR was agreed upon with NDA 209092 to conduct a trial to study alternative dosing that may maximize safety while not compromising efficacy.**

2. Background

Excerpted and edited from the clinical review:

Product Information
Ribociclib is an orally bioavailable small-molecule inhibitor of cyclin-dependent kinase (CDK) 4 and 6 that induces G1 arrest. Letrozole is a nonsteroidal competitive inhibitor of the aromatase enzyme system, resulting in a reduction of estrogen biosynthesis in all tissues. In postmenopausal women, estrogens are mainly derived from the action of the aromatase enzyme. The suppression of estrogen biosynthesis in peripheral tissues and in tumor can therefore be achieved by specifically inhibiting the aromatase enzyme.

Antiestrogen drugs may demonstrate activity in hormone receptor (HR)-positive breast cancer cells through decreased cyclin D1 expression/activity and subsequent impairment in Rb phosphorylation (Watts et al., Mol Endocrinol, 1995). In addition, endocrine therapy resistance in HR-positive breast tumors may be associated with cyclin D1 overexpression and Rb phosphorylation (Thangavel et al., Endocr Relat Cancer, 2001). These findings suggest that for patients with HR-positive breast cancer, therapies targeting the CDK4/6-D-type cyclin-Rb pathway and endocrine pathway may be efficacious (Mayer et al. Curr Oncol Rep 2015; Murphy et al. Oncologist 2015; Finn et al. Breast Cancer Res. 2009;

Available therapies
The treatment of patients with advanced (locally advanced not amenable to curative treatment) or metastatic breast cancer is palliative as there are no curative treatment options in this setting. In postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer, hormonal therapies are used prior to chemotherapies provided there is no visceral crisis. These hormonal therapies include the selective estrogen receptor modulator tamoxifen and the aromatase inhibitors, anastrozole, letrozole and exemestane (as shown in Table 1). Palbociclib, a CDK 4/6 inhibitor, is approved in combination with letrozole forthe first-line treatment of advanced or metastatic HR-positive, HER2-negative breast cancer. Ribociclib, also a CDK 4/6 inhibitor, is approved in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor HR-positive, HER2 -negative advanced or metastatic breast cancer.

Table 1: Available Therapy for the Proposed Patient Population

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Basis for approval	Important Safety and Tolerability Issues	Drug Class
FDA Approved Treatments						
Letrozole	First and second-line treatment of postmenopausal women with hormone receptor positive or unknown advanced breast cancer	1997	2.5mg daily by mouth	Vs. tamoxifen **TTP**: 9.4 months vs. 6.0 months HR 0.72 (p<0.0001) **OS**: 35 months vs. 32 months (P=0.5136)	Bone mineral density decrease, hot flashes, and arthralgias	Aromatase inhibitor
Anastrozole	First-line treatment of postmenopausal women with HR-positive or unknown locally advanced or metastatic breast cancer	1995	1mg daily by mouth	Vs. tamoxifen **TTP**: 11.1 vs. 5.6 months (p=0.006) and 8.2 vs. 8.3 months (p=0.92)	Bone mineral density decrease, hot flashes, and arthralgias	Aromatase inhibitor
Tamoxifen	In the treatment of metastatic breast cancer in women and men. Patients whose tumors are estrogen receptor positive are more likely to benefit.	1977	20mg daily by mouth	Response rate in 14 Phase 2 studies and nine literature reports. The overall database included 1164 patients	Uterine malignancies, stroke, pulmonary embolism and hot flashes	Selective estrogen receptor modulator
Palbociclib	First-line treatment of postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer in combination with letrozole.	2015	125mg daily for 21 consecutive days followed by 7 days off treatment with letrozole 2.5mg daily continuously throughout the 28-day cycle	Phase 1/2 vs. letrozole alone **PFS**: 20.2 vs. 10.2 months HR 0.488 (p=0.0004)	Neutropenia, leukopenia, fatigue, anemia, URI, nausea	CDK 4/6 inhibitor

Ribociclib	First-line treatment of postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer in combination with an aromatase inhibitor.	2017	600mg daily for 21 consecutive days followed by 7 days off treatment with an aromatase inhibitor daily continuously throughout the 28-day cycle	Phase 3 vs. letrozole alone **PFS**: NR vs. 14.7 months HR 0.556 (p<0.0001)	Neutropenia, hepatotoxicity, QT interval prolongation	CDK 4/6 inhibitor
Other Treatments						
Exemestane	Treatment of advanced breast cancer in postmenopausal women whose disease has progressed following tamoxifen therapy	1999	25mg daily by mouth	Vs. megestrol acetate **TTP**: 20.3 weeks vs. 16.6 weeks (HR 0.84)	Bone mineral density decrease, hot flashes, and arthralgias	Aromatase inhibitor

TTP: Time to Tumor Progression; OS: Overall Survival; NR: not reached
Source: drugs@fda.com

Regulatory History

July 25, 1997: NDA 20-726 (letrozole) was approved by FDA for advanced breast cancer in postmenopausal women with disease progression after anti-estrogen therapy.
July 27, 2010: IND (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.
July 21, 2016: A Type B Pre-NDA meeting was conducted. At this meeting, FDA agreed that data from Study A2301 was adequate to assesses efficacy and safety of ribociclib for the proposed indication in combination with letrozole.
August 2, 2016: FDA granted the 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 (ribociclib) was submitted to FDA.
January 30, 2017: NDA 209935 (ribociclib copackaged with letrozole) was submitted to FDA.
March 13, 2017: Ribociclib was 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.

3. Product Quality

The following is excerpted and edited from the Product Quality Reviews:

CMC information for Kisqali® Femara Co-Pack tablets is provided by referencing the respective NDA 209092 for Kisqali® (Ribociclib) tables and NDA 020726 for Femara (letrozole) tables. Both NDAs are approved and current, and the referenced drug products are legally manufactured in the US. The facility review recommends "Approval" for all manufacturing facilities involved in both NDAs. Therefore, the NDA is recommended for **Approval** from the CMC standpoint.

The NDA was submitted to seek approval for the co-packaged (200 mg) ribociclib and (2.5 mg) letrozole tablets. Letrozole is US marketed drug since its approval by FDA in 1997. Ribociclib, in combination with letrozole, was recently approved (2017) under NDA 209092 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 ribociclib plus letrozole "co-pack" is to facilitate both patient compliance and convenience, simplifying adherence to the 28-day cycle dosing regimen and allowing an easier distribution option to patients.

There are no changes to the manufacturing of these two individual drugs that will be included in the co-pack. CMC information for ribociclib is cross referenced to NDA 209092. CMC information for letrozole is cross referenced to NDA 020726. The supplement S-031 for NDA 020726 provides for a comparability protocol of the study to compare Moisture Vapor Transition Rate per tablet (MVTR/tablet) (USP <671>) of the proposed 28-tablet count presentation of letrozole to the marketed 30-tablet count presentation, both of which are packaged into the 90-cc HDPE bottles of the same construction and materials. If the MVRT/tablet of the proposed 28-count presentation falls within the MVTR/tablet range for approved packaging counts, Novartis expects the new container count for co-packaging Femara w/Ribociclib Film coated tablet to be stable over the currently approved Femara shelf life. NDA 020726/S031 was reviewed by Dr. Lorenzo Rocca, and found the proposed comparability acceptable (review filed in Panorama on 05-Apr-2017). The S031 supplement was approved on 7-Apr-2017. The data for the comparability study will be submitted as a CBE supplement to NDA 20726.

Since the data for the comparability protocol has not been generated, a PMC was initiated by the FDA and agreed by the applicant as described below:

> *Demonstrate the comparability of the proposed packaging configuration to drug product packaged in the registered packaging configurations.*
> *Submit the MVTR data and updated 3.2.P.7 as described in Section 6 of the comparability protocol (protocol referenced to NDA 20726 / S-031), and if MVTR/tablet data of the proposed packaging falls outside the range for the approved packaging, submit a stability report containing three months of accelerated stability data for one batch of drug product using the proposed 28-count packaging configuration.*

Submit a commitment to place the first commercial batch on long-term stability to support the 28-count bottle of Femara.

Final Report Submission: 10/2017

All facility information for both drug products was submitted in their respective NDAs except one facility submitted in the drug product section of this application for secondary packaging of the co-pack, [redacted] (b) (4). This facility happens to do primary packaging of Femara as well. Based on the evaluation for this additional activity the recommendation is "Approval".

The applicant requests a categorical exclusion from the requirement for preparation of an Environmental Assessment. It is found acceptable since the amount of ribociclib in the co-pack is within the estimated usage for the approved NDA 209092. The amount of letrozole in the co-pack is not expected to increase beyond what has been approved in NDA 209092.

4. Nonclinical Pharmacology/Toxicology

I agree with the nonclinical pharmacology/toxicology reviewer, Ph.D., and the team leader, Todd Palmby, Ph.D., who state: The Pharmacology/Toxicology team recommends approval of NDA for the Kisqali Femara Co-pack. Kisqali Femara Co-pack is a co-package of Kisqali (ribociclib) and Femara (letrozole) tablets.

The Femara package insert was not previously in PLLR format according to the Pregnancy and Lactation Labeling Rule, so the nonclinical information for letrozole was updated in this co-pack label to be consistent with PLLR. The nonclinical sections containing information for ribociclib were mostly copied from the approved package insert for Kisqali. The majority of changes for letrozole nonclinical information were not substantive and included moving information to the appropriate section and including greater detail when necessary.

We typically recommend 5 half-lives or 1 month, whichever is longer, for a drug that causes embryo-fetal toxicity but is not clearly genotoxic, such as ribociclib and letrozole. Since no guidance document is currently publically available to provide this recommendation, we accept the Applicant's proposed duration of **3 weeks**, which accounts for 5 half-lives of letrozole and ribociclib and is consistent with the approved Kisqali label.

5. Clinical Pharmacology

Not applicable as no updates to clinical pharmacology were provided and no review was performed.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

This application is primarily supported by a international, multi-center, randomized (1:1), double-blind, placebo controlled trial evaluated the efficacy and safety of treatment with ribociclib plus letrozole (n=334) versus placebo plus letrozole (n=334) in postmenopausal women with HR-positive, HER2-negative advanced breast cancer who received no prior therapy for their advanced or metastatic breast cancer. The following is excerpted from the clinical studies section (14) of the agreed upon text in the ribociclib letrozole co-pack package insert regarding the design and efficacy results:

Study 1 (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 and letrozole (n= 334) or placebo and 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 Study 1 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.

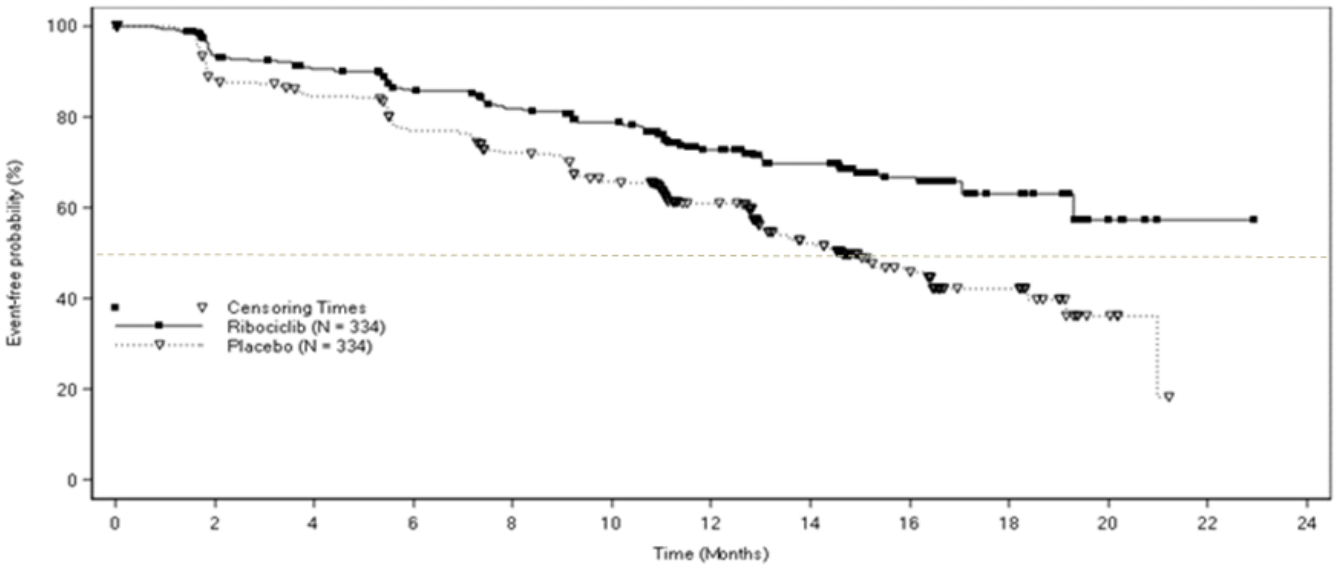
The efficacy results from Study 1 are summarized in Table 8 and Figure 1. The results shown are from a pre-planned interim efficacy analysis of PFS. Results were consistent across patient subgroups of prior adjuvant or neoadjuvant chemotherapy or hormonal therapies, liver and/or lung involvement, and 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 8: Efficacy Results – Study 1 (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 – Study 1 (Intent-to-Treat Population)



8. Safety

The safety results from this trial are summarized below in the following excerpt from section 6.1 of the agreed-upon package insert:

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

The safety data reported below are based on Study 1 (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. Permanent discontinuations due to ARs were reported in 7% of patients receiving KISQALI plus letrozole and 2% in patients receiving placebo plus letrozole. The most common ARs leading to treatment discontinuation of both KISQALI and letrozole in patients receiving KISQALI plus letrozole were ALT increased (4%), AST increased (3%), and 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%) were neutropenia, nausea, fatigue, diarrhea, leukopenia, alopecia, vomiting, constipation, headache and back pain.

The most common Grade 3/4 ARs (reported at a frequency > 2%) were neutropenia, leukopenia, abnormal liver function tests, lymphopenia, and vomiting.

ARs and laboratory abnormalities occurring in patients in Study 1 are listed in Table 6 and Table 7, respectively.

Table 6: Adverse Reactions Occurring in ≥ 10% and ≥ 2% higher than Placebo Arm in Study 1 (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 Study 1

	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

ARs listed are based on the data of KISQALI in combination with letrozole (FEMARA). For the complete list of known ARs with FEMARA, see the Full Prescribing Information of FEMARA.

Bone Effects:

In Study 1, with a median duration of safety follow-up of 20.1 months, 12 patients (4%) in the ribociclib plus letrozole arm and 18 patients (6%) in the placebo plus letrozole arm experienced fractures. Osteoporosis (all grades) was experienced in three patients (0.9%) in the ribociclib plus letrozole arm and 2 patients (0.6%) in the placebo plus letrozole arm.

The following Warnings and Precautions were included in the Package Insert:

5.1 QT Interval Prolongation

KISQALI has been shown to prolong the QT interval in a concentration-dependent manner, with estimated mean increase in QTc interval exceeding 20 ms (22.9 ms (90% CI: 21.6, 24.1)) at the mean steady-state C_{max} following administration at 600 mg once daily dose *[see Clinical Pharmacology (12.2)]*. In Study 1 (MONALEESA-2), one patient (0.3%) had >500 msec post-baseline QTcF value

(average of triplicate), and nine patients out of 329 patients (3%) had a >60 msec increase from baseline in QTcF intervals (average of triplicate). These ECG changes occurred within the first four weeks of treatment and were reversible with dose interruption. There were no reported cases of Torsades de Pointes. Syncope occurred in 9 patients (2.7%) in the Kisqali plus letrozole arm versus 3 (0.9%) in placebo plus letrozole arm. 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 *[see Adverse Reactions (6)]*.

Assess ECG prior to initiation of treatment. Initiate treatment with KISQALI FEMARA CO-PACK only in patients with QTcF values less than 450 msec. 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 FEMARA CO-PACK therapy *[see Dosage and Administration (2.2)]*.

Avoid the use of KISQALI FEMARA CO-PACK in patients who already have or who are at significant risk of developing QTc 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 FEMARA CO-PACK with drugs known to prolong QTc interval and/or strong CYP3A inhibitors as this may lead to prolongation of the QTcF interval *[see Drug Interactions (7.4), Clinical Pharmacology (12.3)]*.

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)]*.

5.2 Hepatobiliary Toxicity

In Study 1, increases in transaminases were observed. Grade 3 or 4 increases in ALT (10% versus. 1%) and AST (7% versus 2%) were reported in the KISQALI FEMARA CO-PACK and placebo arms respectively.

Among the patients who had Grade ≥ 3 ALT/AST elevation, the median time-to-onset was 57 days for the KISQALI FEMARA CO-PACK treatment group. The median time to resolution to Grade ≤ 2 was 24 days in the KISQALI plus letrozole treatment group.

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 4 (1%) patients in Study 1 and all patients recovered after discontinuation of KISQALI.

Perform LFTs before initiating therapy with KISQALI FEMARA CO-PACK. 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.

5.3 Neutropenia

In Study 1, neutropenia was the most frequently reported adverse reaction (75%) and a Grade 3/4 decrease in neutrophil count (based on laboratory findings) was reported in 60% of patients receiving KISQALI FEMARA CO-PACK. 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 15 days in the KISQALI FEMARA CO-PACK treatment group. Febrile neutropenia was reported in 1.5% of patients receiving KISQALI FEMARA CO-PACK. Treatment discontinuation due to neutropenia was 0.9%.

Perform CBC before initiating therapy with KISQALI FEMARA CO-PACK. 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)]*.

5.4 Embryo-Fetal Toxicity

Based on findings from animal studies and the mechanisms of action, KISQALI FEMARA CO-PACK 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).

Letrozole caused embryo-fetal toxicities in rats and rabbits at maternal exposures that were below the maximum recommended human dose (MHRD) on a mg/m^2 basis.

Advise pregnant women of the potential risk to a fetus. Advise women of reproductive potential to use effective contraception during therapy with KISQALI FEMARA CO-PACK and for at least 3 weeks after the last dose *[see Use in Specific Populations (8.1, 8.3) and Clinical Pharmacology (12.1)]*.

9. Advisory Committee Meeting

This NDA was not referred to a meeting of the Oncologic Drugs Advisory Committee as the application did not raise significant safety or efficacy issues that required the advice of the ODAC to make a risk-benefit assessment of ribociclib letrozole co-pack in this patient population.

10. Pediatrics

A pediatric waiver was granted by the PeRC.

11. Other Relevant Regulatory Issues

There were no other relevant regulatory issues. No clinical inspections were performed as the sponsor and study sites had recently been inspected for NDA 209092.

12. Labeling

Agreement has been reached on the labeling.

The proposed indication was as follows:

> The KISQALI® FEMARA® CO-PACK [ribociclib, a kinase inhibitor, (b) (4) letrozole, an aromatase (b) (4) inhibitor] is indicated as initial endocrine-based therapy for the treatment of postmenopausal women with hormone (b) (4) receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer.

The final indication is as follows:

> The KISQALI® FEMARA® CO-PACK is indicated 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.

There were internal labeling discussions with all review disciplines regarding the Prescribing Information (PI) and Patient Package Insert (PPI). Key clinical labeling recommendations included:

- Update of Indications and Usage
- Since this is a co-packaged product, the Warnings and Precautions unique to Femara (i.e., Bone Effects, Hepatic Impairment, Fatigue and Dizziness) were reviewed to determine if these should be included in this PI. For this patient population and indication, FDA determined that hepatic impairment was adequately addressed in the Dosage and Administration section, fatigue was adequately captured in the Adverse Reactions section, and bone effects should be included in Section 6 (Adverse Reactions). Inclusion of bone effects in Section 6 was based primarily on the incidence and severity of these effects and existing standards of care.
- Update of pregnancy (8.1), lactation (8.2), and females and males of reproductive potential (8.3) information to reflect the most current information related to Femara for these sections.

The efficacy (14) and safety (5, 6.1) sections of the package insert are discussed in prior sections of this review.

13. Postmarketing

There was no recommendation for Postmarketing Risk Evaluation and Mitigation Strategies.

The applicant has agreed to the following post marketing commitment:

3200-1 Demonstrate the comparability of the proposed packaging configuration to drug product packaged in the registered packaging configurations. Submit the MVTR data and updated 3.2.P.7 as described in Section 6 of the comparability protocol (protocol referenced to NDA 020726/S-031), and if MVTR/tablet data of the proposed packaging falls outside the range for the approved packaging, submit a stability report containing three months of accelerated stability data for one batch of drug product using the proposed 28-count packaging configuration. Submit a commitment to place the first commercial batch on long-term stability to support the 28-count bottle of Femara.

Final Report Submission: 10/2017

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JULIA A BEAVER
05/02/2017