CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209092Orig1s000

MULTI-DISCIPLINE REVIEW

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

MEMORANDUM

Date: March 15, 2017
From: C.J. George Chang, DVM, PhD, DABT
Pharmacology Reviewer
Division of Hematology Oncology Toxicology for Division of Oncology Products 1
Through: Todd Palmby, PhD
Supervisory Toxicologist
Division of Hematology Oncology Toxicology for Division of Oncology Products 1
To: File for NDA #209092
KISQALI® (ribociclib)
Re: Approvability of Pharmacology and Toxicology

Novartis Pharmaceuticals Corporation submitted NDA 209092 for KISQALI® (ribociclib), in combination with an aromatase inhibitor, for the treatment of patients with postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer. Ribociclib is an inhibitor of cyclin-dependent kinase (CDK) 4 and 6. The nonclinical review is complete and has been added to the Multi-disciplinary Review and Evaluation, which has been uploaded to DARRTS. Refer to the Multi-disciplinary Review and Evaluation for additional details. There are no outstanding issues from a pharmacology/toxicology perspective that would prevent approval of this application.

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/s/

CHING-JEY G CHANG
03/15/2017

TODD R PALMBY
03/15/2017

NDA/BLA Multi-disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	209,092
Priority or Standard	Priority
Submit Date(s)	29 August 2016
Received Date(s)	29 August 2016
PDUFA Goal Date	29 April 2017
Division/Office	DOP1/OHOP/OND
Review Completion Date	10 March 2017
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)	KISQALI® is a cyclin dependent kinase inhibitor (CDKi) indicated in combination with letrozole for the treatment of 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.
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	KISQALI® is 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.

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Reviewers of Multi-Disciplinary Review and Evaluation

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OPDP	Kevin Wright
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OSE/DRISK	Till Olickal
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DPV	Peter Waldron/Pritpal Singh

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

1.1. Product Introduction

Ribociclib (KISQALI®) is a new molecular entity and 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 Applicant's proposed indication at the time of NDA submission was:
KISQALI® is a cyclin dependent kinase inhibitor (CDKi) indicated in combination with letrozole for the treatment of 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.

The recommended indication is:
KISQALI® is 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.

The recommended dose for ribociclib is 600mg taken orally, once daily for 21 consecutive days followed by 7 days off treatment resulting in a complete cycle of 28 days. Treatment should be continued until disease progression or unacceptable toxicity.

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1.2. Conclusions on the Substantial Evidence of Effectiveness

The recommendation for the approval of ribociclib, according to 21 Code of Federal Regulations (CFR) 314.126(a)(b), is primarily based on the efficacy and safety data from a randomized (1:1), double-blind, placebo-controlled, multicenter clinical trial of ribociclib plus letrozole versus placebo plus letrozole conducted in 668 postmenopausal patients with HR positive, HER2 negative, advanced or metastatic breast cancer who received no prior therapy for their advanced or metastatic disease. The improvement in Progression Free Survival (PFS) of the ribociclib treated patients compared to the placebo treated patients [HR 0.556 (95% CI: 0.429, 0.720); 1-sided p value <0.0001] is statistically significant and considered clinically meaningful. In addition, the safety profile of ribociclib is acceptable for the intended population and supportive of a favorable benefit-risk profile of ribociclib for this indication. Concerns over QT interval prolongation are addressed in labeling and will be investigated in a safety postmarketing requirement (PMR) examining an alternative dosing regimen. Additional supportive data from patients treated with ribociclib in combination with other aromatase inhibitors allowed for the inclusion of a class of agent, aromatase inhibitor, as the combination partner for ribociclib in the indication. All disciplines were in agreement with approval of ribociclib, or did not identify any outstanding issues that precluded approval. In summary, ribociclib 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 demonstrates a favorable benefit-risk profile with enough evidence to recommend approval.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Ribociclib (Kisqali) is a kinase inhibitor recommended for approval 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.

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 (a CDK 4/6 inhibitor approved under accelerated approval) 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. There remains a clear medical need to develop new therapies for the treatment of advanced breast cancer in order to extend life, delay disease progression, and/or lessen breast cancer related symptoms.

The effectiveness of ribociclib was demonstrated in MONALEESA-2 (CLEE011A2301), an international, multi-center, randomized (1:1), double-blind, placebo controlled trial evaluating 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. Letrozole is an active control arm and the addition of ribociclib to letrozole demonstrates an improvement in PFS that represents a statistically significant and clinically meaningful result.

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. Due to concerns regarding QT prolongation, deemed a serious risk related to the use of the drug, a safety postmarketing requirement to study an alternative dosing regimen under Section 505(o) of the Federal Food, Drug, and Cosmetic Act [created by Section 901, in Title IX of the Food and Drug Administration Amendments Act of 2007 (FDAAA)] was agreed upon with the applicant. In addition, QT prolongation, hepatobiliary toxicity, and neutropenia were included in the warnings and precautions section of labeling. Additional data submitted during the review demonstrated no alteration in safety signal with ribociclib in combination with exemestane or anastrozole, and also showed no clinically relevant drug interactions between these agents.

In conclusion, ribociclib in combination with letrozole demonstrated a statistically significant improvement in PFS in a large, randomized, double blind study. 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 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. 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. Therefore, the benefit-risk profile is favorable to support approval of ribociclib 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.

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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. • Patients with ER and PR positivity have specific treatment options centered on endocrine-based therapy.	**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. • Aromatase inhibitors are commonly substituted and used interchangeably in clinical practice. • Palbociclib in combination with letrozole was approved under accelerated approval as initial endocrine-based therapy 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. Letrozole is considered an active comparator arm. In this setting, aromatase inhibitors are commonly interchanged. 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.	**Evidence of effectiveness was supported by a statistically significant and clinically meaningful PFS improvement. The study 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**

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• The PFS assessment based on a blinded independent central radiological (BICR) review was consistent with investigator assessment. • 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. • 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. • At the time of the PFS analysis, only 6.5% of patients had died, and overall survival data were immature.	**benefit due to delay of progression and postponement of subsequent toxic therapies. A PMC was agreed upon to submit the third interim and final OS analysis.**
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.	**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 the applicant 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.**

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Additional clinical data of anastrozole or exemestane in combination with ribociclib showed no drug drug interactions or novel safety signals.	
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. • Patients at risk of QTc prolongation should avoid ribociclib use. • 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 rucaparib can be managed through accurate labeling and routine oncology care. No REMS is indicated. A safety PMR was agreed upon to study if an alternative dosing regimen would mitigate the QT interval prolongation risk without compromising efficacy.**

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{See appended electronic signature page}

Julia Beaver, MD
Acting Cross-Disciplinary Team Leader
Associate Director DOP1

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2 Therapeutic Context

2.1. Analysis of Condition

In 2017, it is estimated that 252,710 women will be diagnosed with Breast Cancer in the United States (U.S.) and it is estimated that 40,610 women will die of their disease (1). In the U.S., 60.8% of patients are diagnosed with early stage localized disease, 32% of patients have spread to regional lymph nodes and are still considered early stage, 2% have unknown stage and 5% are diagnosed with de-novo metastatic disease (2). The median age of breast cancer at diagnosis is 61. Breast cancer can be categorized into different histopathologic subtypes based on expression of estrogen receptor (ER), progesterone receptor (PR) and HER2 overexpression. ER and PR positive cancers comprise the majority of breast cancer cases at approximately 60-65% (3). Patients with ER and PR positivity have specific treatment options centered on hormone directed therapy. Postmenopausal patients have multiple options for hormone directed therapy due to the main source of their estrogens resulting from the conversion of androgens to estrogens via aromatase enzyme activity. Postmenopausal patients with advanced or metastatic breast cancer have the option for treatment with three steroidal and non-steroidal aromatase inhibitors (letrozole, anastrozole and exemestane) or tamoxifen a selective estrogen receptor modulator. Exemestane is not approved for first-line treatment of post-menopausal patients with metastatic breast cancer however is used in this setting occasionally. Patients with hormone receptor positive advanced disease should be treated in the first-line setting with hormonal therapy if appropriate (4). In 2015, FDA approved an oral CDK 4/6 inhibitor, palbociclib, in combination with letrozole as initial endocrine-based therapy for postmenopausal women with advanced or metastatic disease (5). Patients in whom visceral crisis is impending should not be treated with hormonal therapy and instead are treated with chemotherapy. Patients whose tumors overexpress HER2 have separate prognoses and distinct treatment options.

2.2. Analysis of Current Treatment Options

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 hormone receptor (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). As of this report, palbociclib, a CDK 4/6 inhibitor, is approved under accelerated approval in combination with letrozole for the first-line treatment of advanced or metastatic HR-positive, HER2-negative 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[a]	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

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
a: approved under accelerated approval
Source: drugs@fda.com

Notably, the mechanism of action of all aromatase inhibitors is similar, by blocking the conversion of androgens to estrogens in peripheral tissues, through inhibition of the aromatase enzyme and suppression of plasma concentrations of estrogens within days following the start of administration. Aromatase inhibitors have biological similarity with respect to efficacy and safety. In clinical practice aromatase inhibitors are considered interchangeable (4).

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Ribociclib is a new molecular entity (NME) and not currently marketed in the United States.

3.2. Summary of Presubmission/Submission Regulatory Activity

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.

June 23, 2014: A preclinical / clinical pharmacology / CMC Type C meeting scheduled for this date was cancelled by the Applicant based on preliminary responses sent by FDA. Agreement was reached on an ECG monitoring plan for QTc prolongation and that a waiver could be requested for the need to conduct a formal thorough QTc study. FDA agreed that clinical pharmacology and nonclinical toxicology package are acceptable.

March 26, 2015: A clinical Type C meeting took place. FDA agreed with the proposal for

removing the futility analysis from Study A2301. FDA agreed to changing the interim analysis for efficacy based on PFS events. FDA advised the Applicant to adjust the efficacy boundary so that the minimum hazard ratio would be 0.56 (with the corresponding p-value derived from the Haybittle-Peto boundary).

June 2, 2015: FDA issued email correspondence agreeing to Applicant waiver request for not conducting a thorough QTc study.

September 25, 2015: This was follow up teleconference to the March 26, 2015 Clinical Type C meeting. FDA agreed in general with an NDA containing 9 months drug substance (DS) / drug product (DP) stability data. The original NDA included 12 months DS stability and 9 months DP stability. Following NDA submission, 12 months DP stability data was submitted to FDA on September 9, 2016. FDA agreed that the interim analysis plan for Study A2301 was adequate.

April 27, 2016: FDA provided written responses to the questions contained in the Type C meeting background package dated February 12, 2016. The purpose of the requested meeting was to obtain agreement from the Agency that the planned data analyses and overall presentation of data are adequate to support a potential NDA submission. Briefly, FDA agreed with the proposed clinical package to be included in the NDA submission. FDA agreed that the statistical methodology and proposed analyses for Study A2301 is as adequate to support the NDA submission. FDA agreed to the format of the ISS and ISE, proposed pooling strategy for the SCS, submission of the patient narratives and CRFs, and the submission of the electronic datasets.

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.

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 demonstrated substantial improvement in PFS compared with existing therapies.

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

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

4.1. Office of Scientific Investigations (OSI)

The Office of Scientific Investigations (OSI) audit was requested for this NDA. See Clinical Inspection Summary written by Lauren Iacono-Connors, Ph.D, Good Clinical Practice Assessment Branch, Division of Good Clinical Practice Compliance, OSI. The OSI inspected 4 of the highest accruing sites as well as the Applicant. A summary of the site inspections is provided in Table 2.

Table 2. Summary of Office of Scientific Investigations Findings

Name of CI, Site #, Address	Protocol # and # of Subjects	Inspection Date	Final Classification
CI #1: Lowell Hart (Site 5044) 4415 Metro Parkway suite 310 Fort Myers, FL 33916	Protocol: CLEE011A2301 Subjects: 9	January 23-26, 2017	NAI
CI #2: Gabriel Hortobagyi (Site 5095) 1515 Holcombe Boulevard - 1354 Houston, TX 77030	Protocol: CLEE011A2301 Subjects: 15	February 13-16, 2017	NAI
CI #3: Cristian Villanueva (Site 3004) 3, bd Alexandre Fleming Besancon Cedex, 25030 France	Protocol: CLEE011A2301 Subjects: 10	January 16-23, 2017	NAI
CI#4: Salomon Stemmer (Site 1302) Belinson Campus 39 Jabotinsky St. Davidoff Center POB 85 Petach Tikva, 49100 Israel	Protocol: CLEE011A2301 Subjects: 14	January 29, 2017 – February 1, 2017	NAI
Applicant: Novartis Pharmaceuticals Corp. One Health Plaza East Hanover, NJ 07936-1080		February 23, 2017	NAI

CI: Clinical Investigator, NAI: No action indicated and no deviation from regulations

Reviewer comment*: No substantial issues were discovered during site inspections.*

4.2. Product Quality

Novel excipients: Yes/No *[provide additional information only if the answer is "yes"]*

Any impurity of concern: Yes/No *[provide additional information only if the answer is "yes"]*

4.3. Clinical Microbiology

See the FDA product quality review for details.

4.4. Devices and Companion Diagnostic Issues

Not applicable.

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5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The mammalian cell cycle involves sequential activation of related heterodimeric protein kinases, including a catalytic subunit, the cyclin-depdentent kinase (CDK), and a regulatory subunit, the cyclin. (6) CDK4 and CDK6 are activated by the D-type cyclins and implicated in regulating the early phases of the cell cycle, especially during exit from quiescence. CDK4/6-cyclin D heterodimeric kinases promote re-entry into the cycle by initiating phosphorylation of the retinoblastoma protein family, Rb, p107, and p130. (7) (8) Rb phosphorylation results in the liberation of transcription factors, e.g., members of the E2F family (9) (10), which are bound to the hypophosphorylated Rb proteins in non-proliferation cells. These transcription factors are responsible for directing the expression of genes essential for advancing cells through the S phase of the cell cycle. (7) The expression of cyclins, such as Cyclin-D1, determines, in part, the extent to which their CDK counterparts are activated. Cyclin expression is regulated by gene transcription downstream of cellular signaling pathways, such as those activated by mitogenic stimuli. (11) In addition, regulation of the cell cycles includes cellular inhibitors of CDKs and cyclin-CDK complexes, such as p27/Kip1 or p16/INK4a, and other signaling molecules. (12) There is some redundancy of the activities among the different types and pairings of cyclin-CDKs, such that loss or inhibition of one or more of these complexes in a certain cell type may be compensated for by another cyclin-CDK or through some other compensatory mechanism and cell division may not be completely blocked. (13) (14) The expression pattern of cyclins, CDKs and cyclin-CDK inhibitors in various cell types may determine whether a CDK has a redundant or non-redundant role in a specific cell type.

Ribociclib (Kisqali) is an orally bioavailable, small-molecule, kinase inhibitor targeting cyclin-dependent kinase 4 and 6 (CDK4/6). The IC_{50} values for biochemical inhibition of CDK4 and CDK6 are 8 and 39 nM, respectively. Ribociclib is 10 times more potent for CDK4 than for CDK6, and 190 and 39 times more potent for CDK4/cyclin D1 and CDK6/cyclin D2 complexes, respectively, than for the next closest cyclin-dependent protein kinase, CDK9/cyclin T1 complex.

In cell-based assays, ribociclib induced G1 phase cell cycle arrest in pRb-positive breast cancer cells by inhibiting Rb phosphorylation. The presence of pRb was necessary for ribociclib to confer growth inhibition in vitro, as breast cancer cell lines without functional pRb were not sensitive to ribociclib. Ribociclib inhibited the growth of the majority of the Rb-positive breast cancer cells tested with IC50 values <1 µM in all assays. Estrogen receptor (ER)-overexpressing cells were sensitive to ribociclib growth inhibition. pRb-positive breast cancer cell lines of either luminal or basal origin were similarly sensitive to ribociclib G1 phase cell cycle arrest.

In a mouse xenograft model with Jeko-1 mantle cell lymphoma cells (MCL; t11:14 translocation of cyclin D1; with pRb), oral ribociclib administration at doses up to 150 mg/kg once daily for 4

consecutive days inhibited Rb phosphorylation. When administered for 21 consecutive days, ribociclib lead to reduction of tumor volume up to 40% compared to control group. Reduction of tumor volume correlated with decreased nuclear staining of ppRB780 in tumors determined by immunohistochemistry. Combination treatment with ribociclib (75 mg/kg/day) and letrozole (2.5 mg/kg/day) in a mouse xenograft model with human ER-positive breast cancer cells (HBCx-34) led to decreased tumor volume that was greater than with either drug alone. The maximal individual body weight loss was 13.1% on Day 75 when co-administered orally once daily for 56 consecutive days. Based on available pharmacology data with ribociclib, the Established Pharmacological Class (EPC) of "kinse inhibitor" appears to be supported as scientifically valid and clinically meaningful.

A secondary pharmacology screen identified off-target binding of ribociclib to 4 phosphodiesterase 4D (PDE4D), rat vesicular monoamine transporter VMAT2, orexin-2 receptor, and apelin receptor that lead to ≥ 50% inhibition of ligand binding in vitro. In a separate screen with the major metabolite, LEQ803, binding to 7 off-target receptors including PDE4D, serotonin 5HT3 channel, neuronal nicotinic alpha 2 channel, cannabinoid CB1 receptor, peripheral rat immidazoline I2 receptor, rabbit monoamine transporter VMAT2, and rat brain sodium channel site II was reported. The potential impact of off-target binding of ribociclib and LEQ803 to these receptors was not further investigated.

The binding of ribociclib to the hERG potassium channel or its inhibition of tail current were evaluated in vitro and resulted in IC_{50} values ranging from 5.5 to 53 µM. The binding of the ribociclib metabolite, LEQ803, to the hERG potassium channel or its inhibition of tail current was evaluated in vitro and resulted in IC_{50} values ranging from 4.5 to 15.8 µM. Neither ribociclib nor LEQ803 inhibited hERG channel trafficking, in vitro. In the patch clamp assay, ribociclib inhibited the $Na_v1.5$ sodium channel with an IC_{50} of 4.5 µM, but did not inhibit the $Ca_v1.2$ calcium channel up to 30 µM. Ribociclib did not cause respiratory or CNS effects in rats, but caused a dose-related prolongation of QTc interval in dogs at an exposure similar to patients receiving the recommended dose of 600 mg, consistent with QTc prolongation observed clinically. Ribociclib also induced premature ventricular contractions (PVCs) in a dog which had approximately 5 times the exposure in patients at the recommended dose of 600 mg, based on C_{max}.

Hematological findings noted in 27-week rat and 39-week dog repeat-dose GLP toxicology studies included anemia at doses ≥75 mg/kg/day and decreases in reticulocytes, lymphocytes, and monocytes at 100 mg/kg/day in rats, and anemia and leucopenia (including all differentials) at 10 mg/kg/day in dogs. Major target organs of toxicity included liver (vacuolation of biliary epithelia), testes (seminiferous tubule degeneration), epididymis (epithelial vacuolation, luminal cellular debris, hypospermia), thymus (involution) and lymph nodes (lymphoid depletion). The effects of ribociclib on the male reproductive organs, the thymus and lymph nodes and on the bone marrow are likely related to the primary pharmacological activity of inhibiting CDK4/6 activity. 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 exposure in patients at the recommended dose of 600 mg/day based on AUC, respectively.

In a 4-week GLP repeat-dose study in rats, ribociclib led to decreases in red blood cell mass, reticulocytes, eosinophils and neutrophils at doses ≥25 mg/kg/day. Target organs identified included bone marrow (hypocellularity), thymus (lymphoid depletion), lymph nodes (reduced germinal centers and lymphoid depletion), lung (alveolar macrophages), and testes (disturbance of spermatogenesis). All changes were reversible or showed a tendency toward reversibility, except for bone marrow hypocelluarity which remained at the end of the 4-week recovery period.

Additional target organs noted in 2-week (non-GLP) and 15-week (GLP) repeat-dose studies in dogs included liver, gall bladder, gut-associated lymphoid tissues (GALT), intestine, and skin. Microscopic lesions included hyperplasia/hypertrophy of the major intrahepatic bile ducts with periductular fibrosis and inflammatory cells, hyperplasia/proliferation of the small bile ducts, cholestasis, inspissated bile with calculi in gallbladder, arteriopathy with focal wall degeneration, hemorrhage and fibrin in medium-sized arteries near the liver hilus, lymphoid depletion in GALT, atrophy and villus thinning with glandular dilatation, hyaline plugs in duodenum and jejunum, and atrophy of skin. All microscopic findings in dogs following repeat-dosing were either reversible or showed a trend toward recovery. Due to the effects on the male reproductive organs, ribociclib may impair fertility in male patients.

In rats, males were exposed up to 7 times higher to ribociclib than females in terms of AUC_{0-24h}/dose. In dogs, the exposure to ribociclib was similar for both genders in terms of AUC_{0-24h}/dose. Ribociclib accumulated at the end of the 27-week rat study up to 2 times compared to the first dose, but there was no accumulation noted in dogs.

LEQ803 is a metabolite of ribociclib in rats, dogs and humans through N-demethylation. In dogs, the AUC_{0-24h} ratio [metabolite (LEQ803) to ribociclib] was 0.84 after a single oral dose and 0.25 after a single intravenous dose. In the 27-week rat repeat-dose toxicology study, males were exposed up to 25 times higher than females to LEQ803 in terms of AUC_{0-24h}/dose [metabolite (LEQ803) to dose of ribociclib]. In the dog 39-week repeat-dose toxicology study, the exposure to LEQ803 was similar for both genders in terms of AUC_{0-24h}/dose. At the end of the 27-week rat study, LEQ803 accumulated up to 2.5 times the level after the initial dose, but no accumulation was noted in dogs.

Reactive metabolites of ribociclib formed by CYP3A4, and to a lesser extent FMO-3, covalently bound to a range of cellular proteins to form adducts in human liver microsomes and human, rat, or dog hepatocytes, in vitro. No further follow-up was conducted to characterize these drug-protein adducts. These findings provide a potential mechanism of the hepatobiliary toxicity observed in animals and patients receiving oral ribociclib, although there is no definitive evidence that they are related. Given that the hepatic toxicities in patients were managed in

the clinical trials and resolved following ribociclib cessation, no further nonclinical studies are warranted at this time.

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.

Based on its mechanism of action and effects in animal developmental and reproductive toxicity studies, ribociclib can cause fetal harm if administered to a pregnant woman. In an embryo-fetal developmental toxicity study in rats, decreased fetal weights with skeletal changes coincided with decreases in maternal body weight at 300 mg/kg/day. In an embryo-fetal developmental toxicity study in rabbits, ribociclib caused fetal malformations and visceral and skeletal variations at doses ≥ 30 mg/kg/day. Fetal malformations noted included small eyes (microphthalmia), reduced/small lung lobes, additional vessel on the descending aorta, additional vessel on the aortic arch, and diaphragmatic hernia. Visceral variants noted included absent accessory lobe or (partly) fused lung lobes and reduced/small accessory lung lobe. Skeletal variants noted included extra/rudimentary 13th ribs, misshapen hyoid bones, and reduced number of phalanges in the pollex. At 300 mg/kg/day in rats and 30 mg/kg/day in rabbits, the maternal systemic exposures were approximately 0.6 and 1.5 times, respectively, the exposure in patients in terms of AUC at the recommended dose of 600 mg/day. Since ribociclib was teratogenic, but not genotoxic, the Applicant's proposed duration of contraception use in females of reproductive potential of 3 weeks following the last dose is acceptable. The half-lives of ribociclib and LEQ803 in patients are approximately 32 and 31 hours, respectively, so 5 half-lives would be approximately 7 days.

In addition, ribociclib administration to lactating rats was transferred to pups through maternal milk. Ribociclib concentration in the milk was 3.65-fold higher compared to maternal plasma, in terms of C_{max}. Due to its mechanism of action and results from animal studies, lactating women are advised not to breastfeed during treatment or for 3 weeks following the last dose. This duration following the last dose is based on 5 half-lives of approximately 7 days.

Reports of studies in CDK4 knockout mouse models describe insulin-deficient diabetes in CDK4 deficient mice due to lack of β-islet cells in the pancreas. (15) Ribociclib did not appear to affect glucose or insulin levels or β-islet proliferation when administered to immature rats for up to 27 weeks. It is not clear why ribociclib did not affect the β-islet cells in these rat studies as another CDK4/6 inhibitor, palbociclib, did as noted in its package insert.

The Applicant provided adequate nonclinical data to support the pharmacology and toxicology characterization of ribociclib. This application is approvable from the pharmacology/toxicology perspective.

5.2. Referenced NDAs, BLAs, DMFs

None

5.3. Pharmacology

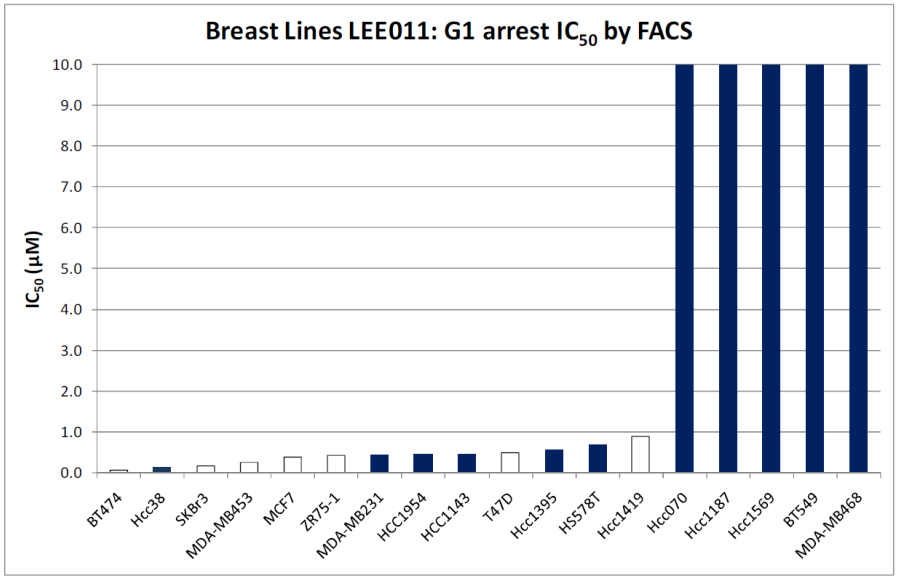
Primary pharmacology

Biochemically, ribociclib inhibited CDK4/cyclin D1 and CDK6/cyclin D3 complexes with 50% inhibition (IC_{50}) values of 8 nM and 39 nM, respectively. In vitro, ribociclib was 190 and 39 times more potent for CDK4/cyclin D1 and CDK6/cyclin D2 complexes than for the next closest cyclin-dependent protein kinase, CDK9/cyclin T1 complex (IC_{50} of 1,520 nM).

Breast cancer cell lines without functional pRb were not sensitive to ribociclib growth inhibition, in vitro. Ribociclib inhibited the growth of the majority of pRb-positive breast cancer cells with IC_{50} values <1 µM in all assays. HER2/neu- and ER-overexpressing cells were sensitive to ribociclib. pRb-positive triple negative tumor cells were sensitive to ribociclib, with IC_{50} values similar to those in cyclin D1-amplified, Her2/neu overexpressing, or ER overexpressing cells. These results indicate that ribociclib had growth inhibitory activity in breast cancer cells as long as functional pRb was present.

pRb-positive breast cancer cell lines of either luminal or basal origin were arrested in G1 of the cell cycle as determined by FACS analysis following exposure to ribociclib (Figure 1).

Figure 1. Ribociclib IC_{50} Values for G1 Arrest in FACS Analysis for Breast Cancer Cell Lines



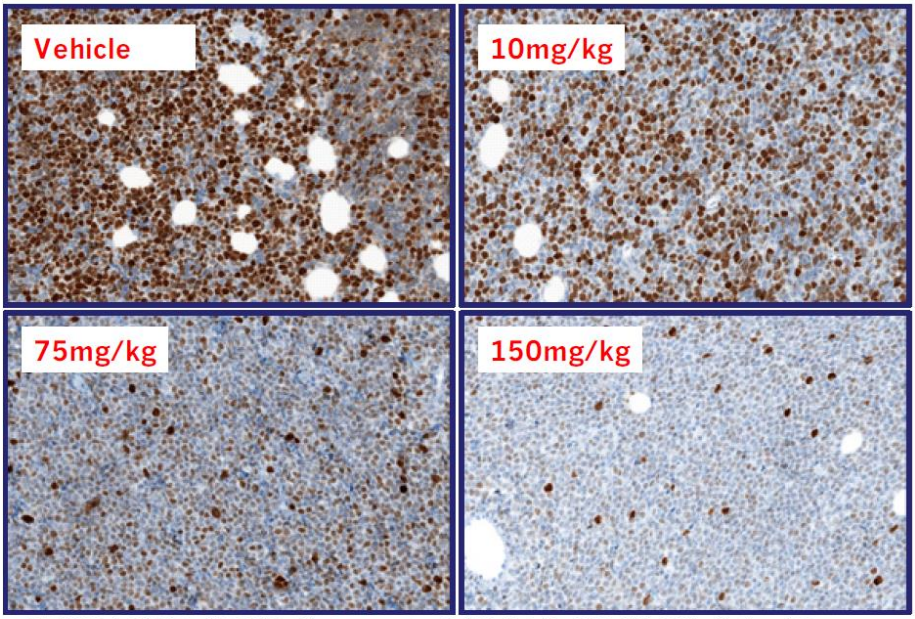
Growth arrest of breast cancer cells measured by flow cytometry. Open bars represent cells of luminal origin and close bars represent those of basal origins. HCC70, HCC1187, HCC1569, BT549 and MDA-MB468 cells do not express functional pRb.

(Excerpted from the Applicant's Submission)

Ribociclib at oral gavage doses up to 150 mg/kg/day once daily for up to 21 consecutive days was well tolerated with a dose-dependent antitumor activity in female SCID beige mice bearing xenograft of pRb-positive, jeko-1 mantle cell lymphoma (MCL; t11:14 translocation, resulting in cyclin D1 overexpression). This dose-dependent antitumor activity, including tumor volume reduction (compared to controls), tumor stasis and regression, correlated well with ribociclib plasma and tumor concentrations and inhibition pRb phosphorylation in tumor by up to 100% also in a dose-related manner.

Ribociclib was administered at 10, 75, and 150 mg/kg once daily by oral gavage to nude rats bearing Jeko-1 MCL tumors, which resulted in a maximal decrease of pRb of 35%, 80%, and 100%, respectively. These decreases in pRb correlated well with tumor and plasma ribociclib concentrations. The decreased pRb levels were consistent with the decreased nuclear staining of ppRB780 determined by immunohistochemistry (IHC) analysis (Figure 2). At the 150 mg/kg dose, inhibition of phosphorylation of pRb was maintained over the 24 hours dose interval, while at 10 and 75 mg/kg doses, pRb levels decreased during the dose interval. The plasma and tumor concentrations of ribociclib at 24 hours were approximately dose-proportional between 75 and 150 mg/kg and less than dose-proportional between 10 and 75 mg/kg.

Figure 2. ppRB780 Staining of Jeko-1 Xenograft Tumors after 5 Days of Ribociclib Treatment



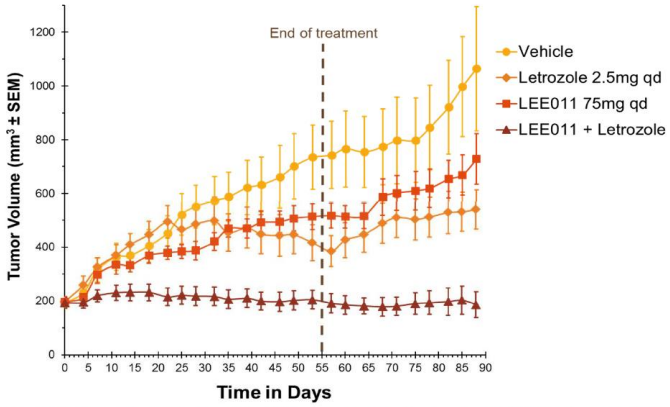
ppRB 780 (abCAM Cat# 32513); Ventana protocol: 436 (CC1S_R60_NH_OM), dilution 1:80
A total 5 doses of NVP-LEE011 at 10, 75 and 150 mg/kg qd, po were evaluated.
Tumors were collected at 4 hours post last dose.

(Excerpted from the Applicant's Submission)

Combination treatment of ribociclib (75 mg/kg/day) and letrozole (2.5 mg/kg/day) in nude mice bearing HBCx-34 breast cancer tumors resulted in a greater inhibition of tumor growth delay

(index (TGDi)>2.55, tumor growth inhibition (TGI)=100.31%, and tumor volume change treated over control (T/C)=25.84% on Day 57) compared to ribociclib or letrozole alone (Figure 3). A maximal individual body weight loss of 13.1% on Day 75 occurred when ribociclib and letrozole were co-administered orally once daily for 56 consecutive days.

Figure 3. Tumor Growth Changes in HBCx-34 Breast Patient-Derived Xenograft (XTS-1118)



Animals (n=10/group at start of treatment) were treated once daily for 55 days, followed by an observation period of 57 days, for total time on study of 89 days (Day 0 to Day 112). Treatment doses were shown in the graph [Table 2.6.3.2-RD-2015-00085].

(Excerpted from the Applicant's Submission)

Secondary Pharmacology

Ribociclib was assessed for its off-target activity on 147 G protein-coupled receptors (GPCRs), transporters, ion channels, nuclear receptors, and enzymes. Ribociclib's activity of >50% inhibition at 10 µM was found on 4 targets (Table 3).

LEQ803, a major metabolite of ribociclib in rat, dog, and human, was assessed for its off-target activity on 144 GPCRs, transporters, ion channels, nuclear receptors, and enzymes. LEQ803's activity of >50% inhibition at 10 µM was found on 7 targets (Table 3).

Table 3. Off-Target Activity of Ribociclib and LEQ803

	Off-Targets	**IC_{50} (µM)**	**Inhibition at 10 µM**
Ribociclib			
	Phosphodiesterase 4D (n=2)	0.64 (average)	97%
	Rat Vesicular monoamine transporter VMAT2 (n=2)	6.35 (average)	71%
	Orexin-2 receptor	N/T	70%
	Apelin receptor	N/T	54%

LEQ803			
	Phosphodiesterase 4D	0.6	95%
	Serotonin 5HT3 channel	2.63	81%
	Neuronal nicotinic alpha 2 channel	5.7	66%
	Cannabinoid CB1 receptor	28	53%
	Peripheral rat immidazoline I2 receptor	N/T	71%
	Rabbit monoamine transporter VMAT2	N/T	84%
	rat brain sodium channel site II	N/T	70%

N/T: Not tested for IC_{50} determination

Safety Pharmacology

Study title/ number: Ribociclib: Electrophysiological safety measurements of hERG currents in stably transfected HEK293 cells (Novartis Study No. 0870394 – GLP)
The effect of ribociclib on hERG current was assessed by path clamp technique in HEK293 whole-cell configuration at 35°C. Ribociclib at 10, 30, 100, and 143.4 µM inhibited dose-dependently hERG channel activity with an IC_{50} value of 53 µM.

Study title/ number: LEQ803: Effects on hERG channel currents in stably transfected HEK293 cells (Novartis Study No. 0814568 – non-GLP)
The effect of LEQ803 on hERG current was assessed by path clamp technique in HEK293 at 35°C. LEQ803 at 1, 3, and 10 µM inhibited dose-dependently hERG channel activity with an IC_{50} value of 4.5 µM.

Study title/ number: Ribociclib: Effects on hERG surface expression in stably transfected HEK293 cells (Novartis Study No. 0915613 – non-GLP)
The potential trafficking-inhibition effect of ribociclib on surface expression of the hERG potassium channel was assessed in the wild-type (WT) channel stably expressed in HEK293 (hERG-WT) at 37°C. hERG surface expression was assessed chemiluminescently with a primary antibody against an extracellular epitope incorporated into the hERG channel and a secondary antibody coupled to a light-generating enzyme. Ribociclib at 1, 10, and 30 µM did not inhibit hERG channel-trafficking.

Study title/ number: LEQ803: Effects on hERG surface expression in stably transfected HEK293 cells (Novartis Study No. 0915612 – non-GLP)
The potential trafficking inhibition effect of LEQ803 on surface expression of the hERG potassium channel was assessed in the WT channel stably expressed in HEK293 at 37°C. hERG surface expression was assessed chemiluminescently with a primary antibody against an extracellular epitope incorporated into the hERG channel and a secondary antibody coupled to a light-generating enzyme. LEQ803 at 1, 10, and 30 µM did not inhibit hERG channel trafficking.

Study title/ number: Ribociclib: Study of the effects of ribociclib on the hERG potassium channel (Novartis Study No. RD-2009-50105 – non-GLP)
The effects of ribociclib on the hERG channel heterologously expressed in a CHO cell line were assessed using [^{3}H]dofetilide membrane binding assay and a functional cell-based assay on the QPatch automated electrophysiology platform. Ribociclib inhibited the [^{3}H]dofetilide binding to crude cell membrane preparation of CHO cell line with an IC_{50} value of 5.5 µM. Ribociclib at 0.24, 1.2, 6, and 30 µM inhibited dose-dependently the hERG tail current with an IC_{50} value of 20.9 µM.

Study title/ number: LEQ803: Study of the effects of NVP-LEQ803 on the hERG potassium channel (Novartis Study No. RD-2009-50786 – non-GLP)
The effects of LEQ803 on the hERG channel heterologously expressed in a CHO cell line were assessed using [^{3}H]dofetilide membrane binding assay and a functional cell-based assay on the QPatch automated electrophysiology platform. LEQ803 (3 nM to 20 µM) inhibited the [^{3}H]dofetilide binding to crude cell membrane prepared from CHO cell line with an IC_{50} value of 6.3 µM. LEQ803 at 0.24, 1.2, 6, and 30 µM inhibited dose-dependently the hERG tail current with an IC_{50} value of 4.8 µM (n=3) and 15.8 µM (n=4).

Study title/ number: Effects of NVP-LEE011-BB-2 on the Nav1.5 and Cav1.2 ion channels measured with the Quattro Ionworks planar patch-clamp system (Novartis Study No. RD-2010-5020 – non-GLP)
The effects of ribociclib on the sodium channel, Nav1.5, and L-type calcium channel Cav1.2 were assessed through an automated patch-clamp recording platform, IonWorks Quattro. Ribociclib inhibited the Nav1.5 channel at 30 µM by 59% (with estimated IC_{50} value of 24 µM), and inhibited the Cav1.2 channel at 30 µM by 2%.

Study title/ number: Single-dose oral (gavage) safety pharmacology study in rats (nervous system and respiratory functions (Novartis Study No. 0870396 - GLP)
Two groups of male Wistar rats (10 each) were administered a single oral dose of ribociclib at 200 mg/kg or vehicle control. A functional observation battery (FOB) was conducted for assessment of potential CNS toxicity, which was measured at pretest and at 7 hours postdose. No ribociclib-related neurological effects were noted.

At least 7 days following the FOB assessment, the vehicle-dosed male rats were divided into two groups and were administered either ribociclib or vehicle control in a Latin square crossover design (with at least 6 days of wash-out period) for respiratory assessment using plethysmography prior to dosing and at 1, 3, 7, and 24 hours postdose. No ribociclib-related respiratory effects were noted.

Study title/ number: Single-dose oral (gavage) telemetry study in dogs (Novartis Study No. 0870395 - GLP)

Four healthy, telemetered, male Beagle dogs were administered one gavage dose of ribociclib at 0, 20, 50, and 100 mg/kg using a Latin square crossover design; each dog served as its own control.
Cardiovascular impacts of ribociclib were monitored beginning about 1 hour before dosing and ending about 21 hours postdose.

Dose-dependent QTc-interval prolongation was noted in dogs at ribociclib doses ≥20 mg/kg when compared to pretest values. The amplitude of the QTc prolongation and the number of time-points noted with QTc prolongation increased with increasing dose levels, whereas the time of onset was similar at all dose levels. Mean increases of QTc at 20, 50, and 100 mg/kg versus vehicle control, for the time period of 1.75 hours postdose until the end of the recording period, were 12.1 ms (+5.3%), 23.4 ms (+10.2%), and 37.9 ms (+16.5%), respectively. Individual changes in QTc-interval postdose versus pretest values correlated well with both C_{max} and AUC_{0-48}. The group mean exposure at 20 mg/kg in terms of AUC_{0-48h} was 21125 ng*hr/mL when QTc prolongation first occurred, and was slightly lower than the steady state exposure (AUC_{ss} of 23800 ng*hr/mL) in patients at the recommended dose of 600 mg/day.

Study title/ number: A single dose toxicity study with non-invasive telemetry in male dogs (Novartis Study No. 1070060 – non-GLP)
Three male beagle dogs received one oral gavage dose of ribociclib at 100 mg/kg, while ECG was recorded for approximately 26 hours at pretest and after treatment using external jacket telemetry. One dog was removed from the study due to severe postdose clinical signs including retching, pale appearance, decreased motor activity and recumbency; minimal ECG data were recorded from this dog. A slight increase in the incidence of premature ventricular contractions (PVCs) was observed in another dog, which had a high exposure of ribociclib in terms of C_{max} (9720 ng /mL) compared to the third dog at the same dose level (about 2-fold higher). This C_{max} is approximately 5 times the steady state geometric mean C_{max} of 1820 ng/mL in patients at the recommended dose of 600 mg/day.

5.4. ADME/PK

Type of Study	Major Findings
Absorption	
Pharmacokinetics of LEE011 and its metabolite LEQ803 after single intravenous (0.5 mg/kg) and oral (2.0 mg/kg) administration of LEE011 to Cynomolgus monkeys ((b) (4) Study No. NVTS-20081119)	Plasma PK after a single oral dose of ribociclib (2 mg/kg) to male Cynomolgus monkeys: • AUC_{inf} of the major metabolite (LEQ803) was 26.2% of ribociclib • Oral bioavailability of ribociclib was 16.6% • T_{max} of LEQ803 was from 2-4 hours postdose • Plasma clearance of ribociclib was 35.3 mL/(min*kg) • $T_{1/2}$ was approximately 4.69 hrs

Type of Study	Major Findings
Assessment of pharmacokinetics of NVP-LEE011 in dogs (Novartis Study No. RD-2009-50081)	• Volume of distribution was 9.78 L/kg In dogs, ribociclib showed high plasma clearance (31 mL/min/kg) and volume of distribution (28 L/kg) with terminal elimination half-life at 18 hours. The oral bioavailability was at 64%. LEQ803, N-demethylated metabolite, was with a mean exposure AUC_{0-24h} ratio of metabolite (LEQ803) to parent drug of 0.84 after oral dose and 0.25 after intravenous dose.
Distribution	
Galactogenic transfer, kinetics and metabolism in milk and plasma after a single oral (50 mg/kg) administration of [^{14}C]LEE011 succinate in rats (Novartis Study No. 1500178)	Ribociclib was the major radiolabeled compound in both plasma and milk, which contributed to 55.7% and 46% of the total ^{14}C-AUC_{0-8h}, respectively. C_{max} and T_{max} for ribociclib: - 3.45 µM and 0.24 hr for plasma, respectively - 12.6 µM and 1 hr for milk, respectively - ribociclib C_{max} was 3.56-fold higher in milk compared to maternal plasma
Metabolism	
Comparison of exposure ratios, between rat, dog and human, of metabolites identified in human plasma from clinical study CLEE011X2101 (Novartis Study No. R1400329) In vitro metabolism of [^{3}H]LEE001: Assessment of reactive intermediate formation (Novartis Study No. R0800264) In vitro metabolism of [^{3}H]LEE011: Mechanistic investigation of formation of covalent drug-protein adducts (Novartis Study No. R0800525)	Human metabolites of ribociclib had sufficient coverage (ratio of animal: human exposure of metabolites >0.5) by exposure in rats and dogs, the species used for toxicology testing. Elevated levels of covalently bound ribociclib-protein adducts above a pre-defined threshold were detected when radio-labeled ribociclib was incubated with human liver microsome (supersomes), which were also observed in treated human, rat and dog hepatocytes. - CYP3A4 and, to a minor extent, FMO-3 were the main drivers leading to formation of reactive intermediates. - Cellular proteins with a range of molecular weights from human hepatocytes formed adducts
Excretion	

Type of Study	Major Findings
Pharmacokinetics, metabolism and excretion of [^{14}C]LEE011 in male Beagle dogs after oral administration of 5 mg base/kg [^{14}C]LEE011 succinate (Novartis Study No. 1300881)	- Apparent terminal half-lives ($T_{1/2}$) of ribociclib and metabolite LEQ803 were 38.8 h and 76.2 hrs, respectively. - Excreted predominantly via feces (68.8 ± 1.83% of dose within 336 hrs) and to a lesser extent in urine (18.5 ± 2.77% of dose within 168 hrs). - In feces, unchanged ribociclib, LEQ803 and other metabolites, and minor peaks each individually represented 10.2%, 1-6%, and ≤0.994% of the dose (AUC_{0-168}), respectively. In urine, unchanged ribociclib, LEQ803, and numerous minor peaks each individually represented 14.3%, 1.13% and ≤0.937% of the dose (AUC_{0-168}), respectively. At 336 hours after dosing, mass balance was not complete, accounting for 89.0±1.27%.
TK data from general toxicology studies 27-week oral study in rats ((b) (4) Study No. 8300010)	<u>27-week Rat</u> Males: 25, 75, and 150 mg/kg Females: 50, 150 and 300 mg/kg $T_{1/2}$: Not determined Sex difference: Males had higher exposure for ribociclib and LEQ803 than females on both C_{max}/dose and AUC_{0-24h}/dose bases. Accumulation: Less than 2 times for ribociclib; up to 2.5 times for LEQ803 Dose proportionality: Approximately dose-proportional <u>Males</u> (ribociclib) *T_{max} (Day 141; mean; hrs):* 25 mg/kg/day: 3.0 75 mg/kg/day: 7.0 150 mg/kg/day: 7.0 *C_{max} (Day 141; mean; n*g/mL*):* 25 mg/kg/day: 1640 75 mg/kg/day: 2070 150 mg/kg/day: 2320 *AUC_{0-24h} (Day 141; mean*; ng·hr/mL*):* 25 mg/kg/day: 13200 15 mg/kg/day: 32800 150 mg/kg/day: 45300

Type of Study	Major Findings
39-week oral study in dogs ((b) (4) Study No. 8300011)	Females (ribociclib) *T_{max} (Day 141; mean; hrs):* 50 mg/kg/day: 3.0 150 mg/kg/day: 3.0 300 mg/kg/day: 1.0 *C_{max} (Day 141; mean; n*g/mL*):* 50 mg/kg/day: 554 150 mg/kg/day: 1290 300 mg/kg/day: 1890 *AUC_{0-24h} (Day 141; mean*; ng·hr/mL*):* 50 mg/kg/day: 4610 150 mg/kg/day: 9130 300 mg/kg/day: 20000 39-week Dog 1, 3, and 10 mg/kg Sex difference: No Accumulation: No Dose proportionality: Approximately dose-proportional *T_{max} (Day 253; M/F mean; hrs):* 1 mg/kg/day: 3.0 / 2.5 3 mg/kg/day: 3.0 /3.0 10 mg/kg/day: 4.0 /4.0 *C_{max} (Day 253; M/F; mean; n*g/mL*):* 1 mg/kg/day: 47.0 / 44.1 3 mg/kg/day: 165 / 183 10 mg/kg/day: 611 / 555 *AUC_{0-24h} (Day 253; M/F; mean*; ng·hr/mL*):* 1 mg/kg/day: 635 / 536 3 mg/kg/day: 2340 / 2290 10 mg/kg/day: 9260 / 8180
TK data from reproductive toxicology studies Oral gavage of embryo-fetal development in rat ((b) (4) No. 9000421)	Rat - Maternal Ribociclib: Approximately dose-proportional between 50 and 300 mg/kg; > dose proportional between 300 and 1000 mg/kg *T_{max} (GD 16; mean; hrs):* 50 mg/kg/day: 2.38 300 mg/kg/day: 2.50 1000 mg/kg/day: 0.67 *C_{max} (GD 16; mean; ng/mL*): 50 mg/kg/day: 262 300 mg/kg/day: 1190 1000 mg/kg/day: 10000 *AUC_{0-24h} (GD 16; mean ± SD; ng·hr/mL):*

Type of Study	Major Findings
An oral gavage study of embryo-fetal development in rabbit ([redacted] (b) (4) No. 9000577)	50 mg/kg/day: 2090 ± 489 300 mg/kg/day: 13800 ± 3600 1000 mg/kg/day: 92300 ± 41100 LEQ803: Less than dose proportional between 50 and 300 mg/kg; dose proportional between 300 and 1000 mg/kg *T_{max} (GD 16; mean; hrs):* 50 mg/kg/day: 2.17 300 mg/kg/day: 2.50 1000 mg/kg/day: 0.67 *C_{max} (GD 16; mean; ng/mL*): 50 mg/kg/day: 5.96 300 mg/kg/day: 15.8 1000 mg/kg/day: 55.8 *$AUC_{0\text{-}24h}$ (GD 16; mean ± SD; ng·hr/mL):* 50 mg/kg/day: 55.3 ± 12.3 300 mg/kg/day: 195 ± 40.5 1000 mg/kg/day: 614 ± 239 $AUC_{0\text{-}24h}$ $Ratio_{(Ribociclib/LEQ803)}$: ≤ 146 <u>Rabbit - Maternal</u> slightly greater than dose proportional Ribociclib: *T_{max} (GD 19; mean; hrs):* *1*0 mg/kg/day: 1 30 mg/kg/day: 1 60 mg/kg/day: 1 *C_{max} (GD 19; mean; ng/mL*): *1*0 mg/kg/day: 1270 30 mg/kg/day: 5720 60 mg/kg/day: 9680 *$AUC_{0\text{-}24h}$ (GD 19; mean ± SD; ng·hr/mL):* 10 mg/kg: 8510 ± 2090 30 mg/kg: 36700 ± 4040 60 mg/kg: 93000 ± 35500 LEQ803: *T_{max} (GD 19; mean; hrs):* *1*0 mg/kg/day: 1 30 mg/kg/day: 1 60 mg/kg/day: 2.2 *C_{max} (GD 19; mean; ng/mL*): *1*0 mg/kg/day: 37.8 30 mg/kg/day: 200 60 mg/kg/day: 341

Type of Study	Major Findings
	$AUC_{0\text{-}24h}$ (GD 19; mean ± SD; ng·hr/mL): 10 mg/kg: 259 ± 61.6 30 mg/kg: 1170 ± 282 60 mg/kg: 3060 ± 1220 $AUC_{0\text{-}24h}$ $Ratio_{(Ribociclib/LEQ803)}$: ≤ 32

5.5. Toxicology

5.5.1. General Toxicology

Study title/ number: "27-week (3 weeks dosing, 1 week off) oral gavage toxicity and toxicokinetic study in rats administered LEE011" ((b) (4) Study 8300010 – GLP)

Key Study Findings

- Two (2/20) mortalities occurred on Days 120 and 149 in males at 150 mg/kg.
- Decreased body weights and food consumption was noted in males at doses ≥75 mg/kg and in females at 300 mg/kg/day.
- Target organ toxicities included liver (vacuolation of bile duct epithelia); kidney (tubular epithelia degeneration/regeneration); thymus, lymph nodes, bone marrow (hypocellularity); and male reproductive tract (testicular degeneration) at doses ≥75 mg/kg/day in males and at 300 mg/kg/day in females. Trend toward reversibility was noted for all findings.
- $AUC_{0\text{-}24h}$ on Day 150 for male rats at 75 mg/kg/day was 32800 ng*hr/mL (1.4 times the human exposure [AUC_{SS} of 23800 ng*hr/mL] at the recommended dose of 600 mg/day).

Conducting laboratory and location: (b) (4)
GLP compliance: Yes

Methods

Dose and frequency of dosing:	Males: 0, 25, 75, and 150 mg/kg/day (3 weeks on and 1 week off) Females: 0, 50, 150, and 300 mg/kg/day (3 weeks on and 1 week off)
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% (w/v) Methylcellulose (400 cPs) in water
Species/Strain:	Crl:WI(Han) rats
Number/Sex/Group:	20 (10 main study; 10 TK)
Age:	8-9 weeks old
Satellite groups/ unique design:	Sentinel group (8 females) for health monitoring only

Deviation from study protocol affecting interpretation of results: No

Table 4. Observations and Results in Rat Toxicology Study (Changes from Control)

Parameters	Major findings
Mortality	Two (2/20) ribociclib-related early mortalities occurred on Days 120 and 149 in male rats at HD.
Clinical Signs	Oral discharge; occurred within the first 6 weeks in the MD and HD males and females.
Body Weights	Decreases in body weight (-13%) were noted primarily in HD male rats. Decreases in body weight gain (-11%, -15%, -24%) were noted LD, MD and HD male rats, respectively. Decreased body weight gain (-11%) was noted in HD female rats.
Ophthalmoscopy	Unremarkable
Hematology **Coagulation**	Anemia in HD males (-29%) and females (-16%) with increases in MCV (+29% for males, +11% for females) and MCH (+29% for males, +12% for females). Anemia in MD males (-16%) and females (-11%) without changes in MCV or MCH. Decreased reticulocytes in HD females (-18%). Decreased lymphocytes (-24%) and monocytes (-59%) primarily in HD males. Increased platelet counts in LD (+15%), MD (+27%) and HD (+47%) males, and in MD (+10%) and HD (+14%) females. Increased fibrinogen in MD (+17%) and HD (+16%) males, and in MD (+33%) and HD (+19%) females.
Clinical Chemistry	Decreased total protein (-4%) and increased AST (+125%) in HD males.
Urinalysis	Decreased urine pH (-14%) in HD males.
Gross Pathology	Lung (discoloration) and small testes in HD males.
Organ Weights	Decreased thymus (-41% and -32% for males and females, respectively), testes (-50%) and epididymides (-35%), and increased kidney (+10% for males) and liver (+14% for females) weights (relative to brain weight) in HD males and females.

Histopathology
Adequate battery: Yes

Sex	Male				Female			
Dose (mg/kg/day)	0	25	75	150	0	50	150	300
Number examined	20	20	19	18	20	19	20	20
Lung – Infiltrate, macrophage, alveolus								
Total number affected	2	1	12	17	5		1	15
Minimal	2	1	11	3	5		1	13
Slight			1	9				2
Moderate				5				
Liver – Vacuolation, bile duct epithelium								
Total number affected			14	17				8
Minimal			14	17				8
Kidney – Degeneration/regeneration, tubule								
Total number affected			2	14				
Minimal			2	14				
Thymus – Depletion, lymphocytes								
Total number affected			17	12				6
Minimal			17					6
Slight				3				
Moderate				8				
Marked				1				
Lymph node, mandibular – Decrease, germinal centers								
Total number affected	7	6	15	17	1	3	4	15
Minimal	7	6	5	5	1	3	3	9
Slight			8	9				4
Moderate			2	3			1	2
Lymph node, mesenteric - Histiocytes, sinus, increased								
Total number affected			10	17				7
Minimal			10	12				7
Slight				5				
Marrow, femur - Hypocellularity								
Total number affected				10				
Minimal				6				
Slight				4				
Marrow, sternum - hypocellularity								
Total number affected				10	1			
Minimal				9				
Slight				1	1			
Marrow, tibia - hypocellularity								
Total number affected				10				
Minimal				6				
Slight				4				

	Testes – Degeneration, seminiferous epithelium								
	Total number affected	2	1	19	18				
	Minimal	1	1	8					
	Slight			11	3				
	Moderate				13				
	Marked				1				
	Severe	1			1				
	Epididymis - Hypospermia								
	Total number affected	1		16	18				
	Minimal			11					
	Slight			5	3				
	Moderate				9				
	Marked				6				
	Severe	1							
	Epididymis – Debris, cellular, lumen								
	Total number affected			18	18				
	Minimal			9					
	Slight			9	14				
	Moderate				4				
	Epididymis – Vacuolation, epithelium, increased								
	Total number affected			19	18				
	Minimal			17	9				
	Slight			2	9				
	(Reviewer generated table based on histopathology data from (b) (4) study 8300010)								
LAMP-2 Immunohistochemistry (IHC)	Increased LAMP-2 immunohistochemistry (IHC) staining in lung in 6/6 of males at 150 mg/kg and 1/1 female at 300 mg/kg; in liver of 5/5 males at 150 mg/kg; and in the mesenteric lymph nodes 2/4 males at 150 mg/kg, indicating increases in lysosomes (marker of phospholipidosis).								
Toxicokinetics	See ADME/PK section 5.4 above								

LD: low dose; MD: mid dose; HD: high dose.

Study title/ number: "39-Week (3 weeks dosing, 1 week off) oral gavage toxicity and toxicokinetic study in dogs administered LEE011 ((b) (4) Study 8300011 - GLP)

Key Study Findings

- Target organs included testes (degeneration of seminiferous tubules), epididymides (luminal cellular debris and hypospermia), and lymphoid tissues (hypocellularity) at doses ≥1 mg/kg/day.
- $AUC_{0\text{-}24h}$ on Day 253 for males at 1 mg/kg/day was 635 ng*hr/mL, which is 0.03 times the exposure in patients (AUC_{SS} of 23800 ng*hr/mL) at the recommended dose of 600 mg/day.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing:	0, 1, 3, and 10 mg/kg/day for 39 weeks (3 weeks of dosing followed by 1 week off)
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% (w/v) Methylcellulose (400 cPs) in water
Species/Strain:	Beagle dogs
Number/Sex/Group:	4
Age:	10 – 11 months old at dosing start
Satellite groups/ unique design:	None
Deviation from study protocol affecting interpretation of results:	No

Table 5. Observations and Results in Dog Toxicology Study (Changes from Control)

Parameters	**Major findings**
Mortality	None
Clinical Signs	Unremarkable
Body Weights	Unremarkable
Ophthalmoscopy	Unremarkable
ECG	Unremarkable
Hematology	Anemia (-17% for males, -12% for females) and leucopenia (-69% for males and -62% for females; all differentials) with increases in MCV +15% for males, +13% for females) and MCH (+14% for males, +9.9% for females) primarily in HD males and females. Decreased reticulocyte counts in MD (-51%) and HD (-59%) males. WBC differentials- HD males: decreased neutrophils (-76%), lymphocytes (-51%), monocytes (-82%), eosinophils (-84%), and basophils (-75%). HD females: decreased neutrophils (-65%), lymphocytes (-52%), monocytes (-74%), eosinophils (-91%), and basophils (-57%).
Clinical Chemistry	Unremarkable, except for a decrease (-26%) in cholesterol in HD males.
Urinalysis	Unremarkable
Gross Pathology	Unremarkable
Organ Weights	Decreased testes/brain weight ratio in MD (-32%) and HD (-46%) males.

Histopathology
Adequate battery: Yes

Sex	Male				Female			
Dose (mg/kg/day)	0	1	3	10	0	1	3	10
Number examined	4	4	4	4	4	4	4	4
Thymus - Decreased Lymphocytes								
Total number affected	4	4	4	4	1	4	4	4
Minimal	1	2	1			3	3	
Slight	3	2	2	1	1	1	1	1
Moderate				3				2
Marked								1
Severe			1					
Spleen - Decreased Lymphocytes, germinal center								
Total number affected	1	3	4	4	2	2	3	4
Minimal	1		1		1	1	1	
Slight		2	3	4	1	1	2	4
Moderate		1						
Lymph Node, Mesenteric - Decreased Lymphocytes, germinal center								
Total number affected	1		3	4	2	1	2	4
Minimal	1		2	3	2	1		3
Slight			1	1			2	1
Lymph Node, Retropharyngeal - Decreased Lymphocytes, germinal center								
Total number affected		1	3	4	1	3	4	4
Minimal		1	2			2	1	
Slight			1	1	1	1	3	2
Moderate				3				2
Marrow, Sternum – Hypocellularity		3	4	4		2	1	4
Total number affected		3	4	1		2	1	2
Minimal				3				2
Slight								
Testis – Degeneration, seminiferous tubules		4	4	4				
Total number affected		4	2					
Slight			2	3				
Marked				1				
Severe								
Epididymis – Debris cellular, lumen								
Total number affected		2	4	3				
Minimal		2	4	3				
Hypospermia								
Total number affected				4				
Marked				2				
Severe				2				

(Reviewer generated table based on histopathology data from (b) (4) study 8300011)

Toxicokinetics — See ADME/PK section 5.4 above

LD: low dose (1 mg/kg/day); MD: mid dose (3 mg/kg/day); HD: high dose (10 mg/kg/day).
-: indicates decrease in parameters compared to control.

+: indicates increase in parameters compared to control.

General toxicology; additional studies

Study title/ number: "4-Week oral (gavage) toxicity study in rats with a 4-week recovery period (Novartis Study No. 0870393 - GLP)
Ribociclib was administered by oral gavage once daily for a consecutive 4 weeks at 0 (0.5% (w/v) methylcellulose (400 cPs)), 25, 75 or 150 mg/kg/day to rats (10 rats/sex/group), followed by a 4-week recovery phase. No mortalities were noted. Clinical signs of toxicity included increase of salivation and rales at ≥75 mg/kg/day. Slight decreases in body weights and food intake were noted in males at 150 mg/kg/day. Hematological changes included decreases in red blood cell mass, reticulocytes, eosinophils and neutrophils at doses ≥25 mg/kg/day. Target organs include bone marrow (hypocellularity), thymus (lymphoid depletion), lymph nodes (reduced germinal centers and lymphoid depletion), lung (alveolar macrophages), and testes (disturbance of spermatogenesis). All changes were reversible or showed a tendency toward reversibility, except bone marrow hypocellularity, which remained at the end of the recovery period.

Study title/ number: "2-Week oral (gavage) dose range finding study in dogs (Novartis Study No. 0870165 - non-GLP)
Ribociclib was administered by oral gavage once daily at 0 (0.5% (w/v) methylcellulose (400 cPs) aqueous suspension), 5, 15 and 25 mg/kg/day for 14 days to Beagle dogs. There were 2 dogs/sex in the 25 mg/kg/day group and 1 dog/sex/group for the rest of the dosing groups.
Clinical signs of toxicity included vomiting and salivation noted between 0.5 to 1 hour postdose at 25 mg/kg/day. Drug-related marked decrease in body weight was noted in 50% of dogs at 25 mg/kg/day, coinciding with severe decrease in food consumption.

Hematological findings included slight to moderate decreases in neutrophils, lymphocytes, monocytes, eosinophils, and basophils at doses ≥5 mg/kg/day. Coagulation parameters included minimal to slight increases in fibrinogen at doses ≥15 mg/kg/day. Clinical chemistry findings included marked increases in ALP, ALT, AST and total bilirubin; moderate decrease in triglyceride; slight to moderate decreases in sodium, chloride, potassium, calcium, magnesium, and/or phosphorus; and slight decreases in albumin and globulin at 25 mg/kg/day.

Microscopic findings included epithelial hyperplasia/hypertrophy and single cell degeneration in intrahepatic and extra-hepatic bile ducts, periductal fibrosis, inflammatory cells, small bile duct proliferation, and foamy macrophages in the wall of the common bile duct; gallbladder hyperplasia/hypertrophy with wall and arterial necrosis, inspissated bile, iron- and lipofuscin-positive pigment in Kupffer cells, lysis of periportal hepatocytes, portal arterial necrosis, and arteriopathy in the hilar region;

decreased germinal centers and/or lymphoid depletion in spleen, lymph nodes, and intestinal lymphoid tissue (GALT), with foamy macrophages and brown pigment deposits in lymph nodes and GALT; minimal decrease in chondrocytes and cartilage column at the costochondral junction of ribs; and dose-related, minimal skin epidermal atrophy at ≥10 mg/kg/day.

Study title/ number: "15-Week (3 weeks dosing, 1 week off) oral gavage toxicity and toxicokinetic study in dogs administered LEE011 with 4 weeks of recovery ((b) (4) Study No. 8286778 - GLP)

Ribociclib was administered by oral gavage once daily at 0 (0.5% (w/v) Methylcellulose (400 cPs) aqueous suspension), 1, 3, and 10 mg/kg/day for 15 weeks (3 weeks on and 1 week off) to Beagle dogs.

There were no apparent effects at any dose level, except for clinical pathology and pathology parameters. Clinical Pathology: Pancytopenia with partial recovery was noted (at doses ≥3 mg/kg/day for RBC and WBC; at 10 mg/kg/day for platelet). Target organs of ribociclib noted included testes (seminiferous tubule degeneration), epididymis (epithelial vacuolation, luminal cellular debris, hypospermia), thymus (involution) and lymph nodes (lymphoid depletion) at doses ≥1 mg/kg/day. Other than the atrophic changes seen in the testes, which showed a trend toward reversibility, all other changes were not observed after a 4-week treatment-free period.

Ribociclib-related microscopic findings were limited to mainly the HD groups and included the liver, gallbladder, lymphoid organs, intestine, and skin. They were hyperplasia/hypertrophy of the major intrahepatic bile ducts with periductular fibrosis and inflammatory cells, hyperplasia/proliferation of the small bile ducts, cholestasis, inspissated bile with calculi in gallbladder, arteriopathy with focal wall degeneration, and hemorrhage and fibrin in medium-sized arteries near the liver hilus; lymphoid depletion in thymus, bone marrow, spleen, and GALT; atrophy, villus thinning with glandular dilatation and hyaline plugs in duodenum and jejunum, and atrophy of skin.

5.5.2. Genetic Toxicology

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study title/ number: "Mutagenicity test using *Salmonella typhimurium*" (Novartis Study No. 0870397 - GLP)

Key Study Findings:

- Ribociclib was not mutagenic under the experimental condition used.

GLP compliance: Yes

Test system: *Salmonella typhimurium* strains TA1535, TA97, TA100 and TA102; up to 5000 µg/plate +/- S9

Study is valid: Yes

Study title/ number: "Evaluation of the mutagenic activity of LEE011-A4 in the *Salmonella typhimurium* reverse mutation assay (with independent repeat)" ((b) (4) Study No. 504752 - GLP)
Key Study Findings:

- Ribociclib was not mutagenic under the experimental condition used.

GLP compliance: Yes
Test system: *Salmonella typhimurium* strains TA1535, TA97, TA100 and TA102; up to 5000 µg/plate +/- S9
Study is valid: Yes

In Vitro Assays in Mammalian Cells

Study title/ number: "Induction of chromosome aberrations in cultured human peripheral blood lymphocytes" ((b) (4) Study No. 1463/236 – GLP)
Key Study Findings:

- Ribociclib did not induce chromosome aberrations in cultured human peripheral blood lymphocytes, when tested to its limit of cytotoxicity in both the absence and presence of a rat liver metabolic activation system (S9).

GLP compliance: Yes
Test system: Cultured human lymphocyte
Study is valid: Yes

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

Study title/ number: "Induction if micronuclei in the bone marrow of treated rats" ((b) (4) Study 8295463 – GLP; Novartis Ref. No. 1370729)
Key Study Findings:

- Ribociclib was negative for inducing micronuclei in the bone marrow from treated male and female rats under the conditions of this study

GLP compliance: Yes
Test system: Han Wistar rats, bone marrow micronuclei; two doses (one dose on Days 1 and 2 each) 35, 175 and 350 mg/kg/day in males; 70, 350 and 700 mg/kg/day in females
Study is valid: *Yes*

Results:
Males

- Ribociclib did not induce micronuclei (MN) in the polychromatic erythrocytes (PCE) of the bone marrow of male rats at doses up to 350 mg/kg/day.

Females

- Statically significant increases in %MN PCE were observed in bone marrow of female rats at doses of 350 (0.34%, p≤ 0.01) and 700 mg/kg/day (0.21%, p≤ 0.05).
- These changes were determined not to be of biological significance due the following:
  - Ribociclib caused toxicity to males and females as seen in clinical signs and mortality.
  - Dose levels were justified by an MTD in a range-finding study.
  - %PCE in treated males and females were comparable to vehicle control.
  - Statistically significant increase in %MN PCE was only seen in females with no dose response. The %MN PCE values in females were all within the historical control distribution range (0 to 0.45) for female Han Wistar rats except for 1/6 animals (0.68) at the MD. There was a similar reduction in %PCE at the MD in females (see Table 6).
- Conclusion is that ribociclib did not induce MN in the PCE of the bone marrow of female rats at doses up to 700 mg/kg/day.

Table 6. Summary of Micronucleus Data for Females

Group / Treatment (mg/kg/day)	PCE scored	Number of MN PCE	% PCE	MN / 2000 PCE	% MN PCE	SD	Heterogeneity		Wilcoxon test vs vehicle control	
							X^2	S	P value	S
1F / Vehicle (0)	24000	35	51.13	2.92	0.15	0.02	0.49	NS	-	-
3F / LEE011 (70)	24000	35	47.07	2.92	0.15	0.09	10.10	NS	0.6991	NS
5F / LEE011 (350)	24000	81	39.82	6.75	0.34	0.18	19.73	p≤0.01	0.0022	p≤0.01
6F / LEE011 (700)	20000	41	41.04	4.10	0.21	0.05	2.30	NS	0.0281	p≤0.05
7F / CPA (20)	12000	118	44.17	19.67	0.98	0.05			0.0119	p≤0.05

Terpstra-Jonckeere trend test (Groups 1,3,5,6; upper tail) P-value: 0.0189, p≤0.05

F	Female	MN	Micronucleated
PCE	Polychromatic erythrocyte	NCE	Normochromatic erythrocyte
NS	Not significant	S	Significance
SD	Standard deviation		

(Excerpted from the Applicant's Submission)

Other Genetic Toxicity Studies

None

5.5.3. Carcinogenicity

Carcinogenicity studies were not conducted to support the proposed indication as per ICH S9 recommendations.

5.5.4. Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development
Fertility studies were not conducted to support the proposed indications per ICH S9 recommendations.

Embryo-Fetal Development

Study title/ number: "An oral gavage study of embryo-fetal development in the rat" ((b) (4) Study No. 9000421 – GLP)

Key Study Findings

- Early mortalities (6) of pregnant rats occurred at 1000 mg/kg/day; dosing for rats at 1000 mg/kg/day was stopped early.
- Decreases of fetal weights with skeletal changes coincided with decreases in maternal body weight gain at 300 mg/kg.
- At 300 mg/kg/day, the maternal systemic exposure in terms of $AUC_{0\text{-}24h}$ was 13800 ng*hr/mL, which was approximately 0.6 times the exposure in humans (AUC_{ss} 23800 ng*hr/mL) at the highest recommended dose of 600 mg/day.

Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	0, 50, 300, and 1000 mg/kg/day; once daily
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% (w/v) methylcellulose 400 cP aqueous solution
Species/Strain:	Wistar Hannover Crl:WI (Han) rats
Number/Sex/Group:	24 females/group
Satellite groups:	For Toxicokinetics: 3 Females in control group and 5 females in treated groups
Study design:	Gestating female rats of approximately 77 to 85 days old were administered 0, 50, 300, and 1000 mg/kg/day ribociclib by oral gavage, once daily on GD6 through GD17.
Deviation from study protocol affecting interpretation of results:	No

Table 7. Observations and Results of Rat Embryo-Fetal Toxicology Study

Parameters	Major findings
Mortality	1000 mg/kg/day: 5 females were found dead and 1 moribund sacrificed occurred between GD13 and GD16.
Clinical Signs	Early deaths: Decreased activity, skin pallor, coldness to touch, lying on side, abnormal respiratory sounds, decreased muscle tone, weakness, and vaginal discharge. Scheduled sacrifice: ≥300 mg/kg/day: Salivation prior to and following dosing.
Body Weights	Marked decreases in body weight gain and/or body weight losses were noted in HD pregnant females (up to -70% between Days 8 and 12 pc).
Necropsy findings Cesarean Section Data	LD and MD: Unremarkable HD: 7 Dams with total resorptions.
Necropsy findings Offspring	LD: Unremarkable MD: No drug-related malformations or external or visceral variants were noted. Multiple variations in ribs related to lower fetal weights were noted. Increased incidence (number of fetuses and litters affected) of ossification centers on the 7th cervical vertebra, ribs on the 7th cervical vertebra, and unossified/incomplete/irregular/semi-bipartite/bipartite sternebrae 5 and xiphisternum were noted. HD: Not examined
Toxicokinetics	See ADME/PK section 5.4 above

LD: low dose; MD: mid dose; HD: high dose

Study title/ number: "An oral gavage study of embryo-fetal development in the rabbit" ((b) (4) Study No. 9000577 – GLP)

Key Study Findings

- Ribociclib was teratogenic in rabbits in the absence of maternal toxicity, with lower fetal weights and increased incidence of fetal malformations and visceral and skeletal variants at ≥30 mg/kg/day.
- Fetal malformations noted included small eyes (microphthalmia), reduced/small lung lobes, additional vessel on the descending aorta, additional vessel on the aortic arch, and diaphragmatic hernia. Visceral variants noted included absent accessory lobe or (partly) fused lung lobes and reduced/small accessory lung lobe. Skeletal variants noted included extra/rudimentary 13th ribs, misshapen hyoid bones, and reduced number of phalanges in the pollex.

- At 30 mg/kg/day in rabbits, the maternal systemic exposure in terms of $AUC_{0\text{-}24h}$ was 36700 ng*hr/mL, which is approximately 1.5 times the exposure in patients (AUC_{ss} of 23800 ng*hr/mL) at the recommended dose of 600 mg/day.

Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes
Methods	
Dose and frequency of dosing:	0, 10, 30, and 60 mg/kg/day; once daily
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% (w/v) methylcellulose 400 cPs aqueous suspension
Species/Strain:	New Zealand White (Hra[NZW[SPF] rabbits
Number/Sex/Group:	20 females/group
Satellite groups:	TK study: 3 females in control group and 5 females in treated groups
Study design:	Gestating female rabbits of approximately 5 to 6 months old were administered 0, 10, 30 and 60 mg/kg/day ribociclib by oral gavage, once daily on GD7 through GD20.
Deviation from study protocol affecting interpretation of results:	No

Table 8. Observations and Results of Rabbit Embryo-Fetal Toxicology Study

Parameters	Major findings
Mortality	60 mg/kg/day: 1 female was found dead on GD11 that may be related to ribociclib.
Clinical Signs	Unremarkable
Body Weights	Unremarkable in pregnant females
Necropsy findings Cesarean Section Data	LD and MD: Unremarkable HD: lower mean fetal weight (-11%; $p \leq 0.01$ compared to control)

<table>
<tr><td>Necropsy findings
Offspring</td><td>
<table>
<tr><th>Dose (mg/kg/day)</th><th>0</th><th>10</th><th>30</th><th>60</th></tr>
<tr><td># Fetuses Examined (Litters)</td><td>181 (20)</td><td>135 (18)</td><td>159 (19)</td><td>161 (18)</td></tr>
<tr><td colspan="5">Malformations: # of fetuses affected (litters) – presented as %</td></tr>
<tr><td>Small eyes (microphthalmia)</td><td>0 (0)</td><td>0 (0)</td><td>0.6 (5.3)</td><td>1.2 (11.1)</td></tr>
<tr><td>Reduced/small lung lobes</td><td>0 (0)</td><td>0 (0)</td><td>1.9 (10.5)</td><td>7.5*** (44.4***)</td></tr>
<tr><td>Additional vessel on the descending aorta</td><td>0 (0)</td><td>0 (0)</td><td>0.6 (5.3)</td><td>0.6 (5.6)</td></tr>
<tr><td>Additional vessel on the aortic arch</td><td>0 (0)</td><td>0 (0)</td><td>1.3 (10.5)</td><td>2.5* (11.1)</td></tr>
<tr><td>Diaphragmatic hernia</td><td>0 (0)</td><td>0 (0)</td><td>1.3 (10.5)</td><td>6.8*** (38.9**)</td></tr>
<tr><td colspan="5">Visceral Variations: # of fetuses affected (litters) – presented as %</td></tr>
<tr><td>Absent accessory lobe or (partly) fused lung lobes</td><td>2.2 (20.0)</td><td>3.0 (22.2)</td><td>10.7** (31.6)</td><td>14.3*** (72.2**)</td></tr>
<tr><td>Reduced/small accessory lung lobe</td><td>0 (0)</td><td>0 (0)</td><td>0 (O)</td><td>4.3** (33.3**)</td></tr>
<tr><td colspan="5">Skeletal Variations: # of fetuses affected (litters) – presented as %</td></tr>
<tr><td>Extra/rudimentary 13th ribs</td><td>40.9 (80.0)</td><td>50.4 (94.4)</td><td>76.7*** (100.0)</td><td>85.7*** (100.0)</td></tr>
<tr><td>Misshapen hyoid bone</td><td>0.6 (5.0)</td><td>1.5 (11.1)</td><td>3.8 (21.1)</td><td>5.0* (33.3)</td></tr>
<tr><td>Bent hyoid bone alae</td><td>1.1 (10.0)</td><td>4.4 (16.7)</td><td>1.9 (15.8)</td><td>2.5 (16.7)</td></tr>
<tr><td>Reduced number of phalanges in pollex</td><td>0 (0)</td><td>0 (0)</td><td>1.3 (5.3)</td><td>11.2*** (50)***</td></tr>
</table>
(Reviewer generated table based on fetal examination data from (b) (4) Study 9000577)
*, p≤ 0.05 versus controls; **, p≤ 0.01 versus controls, ***, p≤ 0.001 (Fisher's)
</td></tr>
<tr><td>Toxicokinetics</td><td>See ADME/PK section 5.4 above</td></tr>
</table>

LD: low dose; MD: mid dose; HD: high dose

Prenatal and Postnatal Development

Prenatal and postnatal developmental studies were not conducted to support the proposed indication as per ICH S9 recomendations.

{See appended electronic signature page}

George Ching-Jey Chang, PhD
Primary Reviewer

Todd Palmby, PhD
Team Leader

6 Clinical Pharmacology

6.1. Executive Summary

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 in a complete treatment cycle of 28 days. The evidence of efficacy was supported by a Phase 3 randomized, double-blind, placebo-controlled study (Study A2301) of ribociclib in combination with letrozole.

The key review questions focus on appropriateness of ribociclib dose, recommendations for ribociclib dose in patients with hepatic or renal impairment, dose adjustments for ribociclib due to drug-drug interaction (DDI), and DDI potentials between ribociclib and coadministrated aromatase inhibitors.

Recommendations

The Office of Clinical Pharmacology has reviewed the information contained in NDA 209092. This NDA is approvable from a clinical pharmacology perspective. The key review issues with 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 A2301.
General dosing instructions	The proposed ribociclib dosing regimen of 600 mg orally once daily is effective and appears to have a manageable safety profile. Ribociclib can prolong the QT interval in a concentration-dependent manner, with mean increase in QTc interval exceeding 20 ms at 600 mg once daily dosing. Syncope and sudden death occurred in patients taking ribociclib. Based on exposure-response relationship for QT prolongation and simulation of exposure data, an alternative dosing regimen, such as 300 mg BID or 400 mg QD, would potentially reduce the QT prolongation risk. Only 600 mg dose was studied in the Phase 3 Study A2301, exposure-response relationships for efficacy could not be established due to the lack of data (i.e., only 44/334 (13%) had valid pre-dose PK samples). A PMR to study effect of an alternative dosing regimen on safety and efficacy is proposed. See Post-Marketing Requirements and Commitments for PMR regarding an alternative dosing regimen for more

	information.
Dosing in patient subgroups (intrinsic and extrinsic factors)	• A dose reduction to 400 mg is recommended for patients with moderate to severe hepatic impairment. • The pharmacokinetics (PK) of ribociclib in patients with severe renal impairment is unknown. See Post-Marketing Requirements and Commitments for PMR regarding severe renal impairment. • A dose reduction to 400 mg is recommended for patients concomitantly taking a strong CYP3A inhibitor.
Coadministrated aromatase inhibitors	Ribociclib is proposed to be administrated in combination with an aromatase inhibitor (letrozole, anastrozole or exemestane). However, the Phase 3 Study A2301 only evaluated letrozole in combination with ribociclib. Based on results from clinical trials, there is no clinically relevant drug interaction between letrozole, anastrozole or exemestane and ribociclib. No dose adjustment is recommended for a coadministrated aromatase inhibitor.
Labeling	Generally acceptable. The review team has specific content and formatting change recommendations.
Bridge between the to-be-marketed and clinical trial formulations	A formal bioequivalence Study A2103 was performed to evaluate differences between a drug-in-capsule (DiC) formulation (used in the Phase 3 study A2301) and a tablet formulation (the to-be-marketed formulation). The two formulations were identified as bioequivalent. A consult was sent for analytical site and clinical site inspection for bioequivalence Study A2103. Analytical site inspection: Office of Study Integrity and Surveillance (OSIS) concluded that data from the study are reliable and can be accepted for FDA review. Clinical site inspection: The site was recently inspected by OSIS and they recommended accepting data without an on-site inspection.

Post-Marketing Requirements and Commitments

PMC or PMR	Key Issue(s) to	Rationale	Key Considerations for Design Features
PMR	Effect of an alternative dosing regimen on safety and efficacy.	Torsades de pointes (TdP) is a specific type of abnormal heart rhythm that can lead to ventricular fibrillation and sudden death. QT prolongation, a surrogate marker for risk of developing TdP, is an established serious side effect of many approved therapeutic products. Ribociclib 600mg QD in combination with letrozole provides clinically meaningful and statistically significant improvement in the progression-free survival of post-menopausal women with HR+, HER2- advanced or metastatic breast cancer as initial endocrine-based therapy. However, QT prolongation is an important identified safety risk for ribociclib. Ribociclib can prolong QT interval in a concentration-dependent manner, with mean increase in QTc interval exceeding 20ms at 600 mg once daily dosing. The Agency believes appropriate measures should be taken to mitigate the risk for QT prolongation, which includes studying an alternative dosing regimen which could prove to have a lower risk of QT prolongation with comparable efficacy.	Conduct a clinical trial to assess the efficacy and safety of an alternative dosing regimen after evaluation of ECG, PK and efficacy data from on-going 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 afety assessments should include QT prolongation, hepatobiliary toxicities and neutropenia. The primary efficacy endpoint should be objective response rate (ORR).

PMR	Ribociclib dose in patients with severe renal impairment.	Ribociclib is indicated for the treatment of postmenopausal women with hormone receptor-positive, human epidermal growth factor receptor-negative advanced or metastatic breast cancer. Small subpopulation of patients is expected to have severe renal impairment (eGFR < 30 mL/min/1.73m^2). There is no pharmacokinetic data to determine ribociclib dose for patients with severe renal impairment. The clinical trial can provide understanding for ribociclib dose adjustment for this patients subpopulation.	Complete on-going clinical pharmacokinetic trial CLEE011A2116 (part 1) to determine an appropriate dose of ribociclib in patients with severe renal impairment.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Ribociclib exhibited over-proportional increases in exposure across the dose range of 50 mg to 1200 mg following both single dose and repeated doses (See Section 13.3.2 for detail). 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).

ADME Properties

Absorption: The time to reach Cmax (Tmax) following ribociclib administration was between 1 and 4 hours. Absolute bioavailability has not been determined. Ribociclib showed no clinically significant food effect.

Distribution: The apparent volume of distribution at steady-state estimated from population PK analysis was 1,090 L. Plasma protein binding was 70%. Blood-to-plasma ratio was 1.0.

Metabolism: Ribociclib is metabolized primarily by CYP3A. Following oral administration of a single 600 mg dose of radio-labeled ribociclib to humans, ribociclib was the major circulating drug-derived entity in plasma. No major metabolite was considered to have clinically relevant contribution to efficacy and safety. Ribociclib was extensively metabolized with unchanged drug accounting for 17% and 12% in feces and urine, respectively. Metabolite LEQ803 represented approximately 14% and 4% of the administered dose in feces and urine, respectively. All other

metabolites were detected in both feces and urine in minor amounts (≤ 3% of the administered dose).

Elimination: The geometric mean apparent plasma clearance was 25.5 L/h and the geometric mean plasma elimination half-life was 32 hours (range 8 to 98 hours) at steady-state at 600 mg once daily dosing.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The applicant proposes an oral dosing regimen of 600 mg once daily with or without food for 21 consecutive days followed by 7 days off treatment in a complete cycle of 28 days. The Phase 3 Study A2301 evaluated ribociclib at the proposed dose in postmenopausal women with HR+, HER2- advanced or metastatic breast cancer (N=334). The proposed dose is effective and has a manageable safety profile. However, the positive concentration-QT relationship and estimated mean ΔQTcF of 22.9 ms at the steady-state Cmax of 600 mg QD suggested that an alternative dosing regimen approach, which targets to reach lower steady-state Cmax, would likely be safer. The efficacy of ribociclib was only studied at the 600 mg QD dosing regimen. A PMR is proposed to the applicant to evaluate an alternative dosing regimen (such as 300 mg BID or 400 mg QD) in a future trial.

Therapeutic Individualization

Specific Populations

Patients with Hepatic Impairment: In a dedicated hepatic impairment trial, mild hepatic impairment (Child-Pugh A; N=6) 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]: 1.5 for Cmax; 1.3 for AUC_{INF}) and severe (GMR: 1.3 for Cmax and AUC_{INF}) hepatic impairment. A starting dose of 400 mg is recommended for patients with moderate or severe hepatic impairment.

Patients with Renal Impairment: The PK of ribociclib in patients with severe renal impairment (eGFR < 30 mL/min/1.73m^2) is unknown (See Post-Marketing Requirements and Commitments for PMR regarding severe 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.

Drug-Drug Interactions

CYP3A Inhibitors: In a dedicated drug-interaction trial, concomitant ritonavir (a strong CYP3A4 inhibitor) increased a single dose ribociclib's Cmax by 1.7-fold and the AUC by 3.2-fold. Ribocicilb is a reversible and time-dependent CYP3A inhibitor. CYP3A contribution to ribociclib

clearance is predicted to decrease at steady state due to auto-inhibition. PBPK simulation (See Section 13.3.5.4 for details) predicted a dose reduction to 400 mg QD in combination with ritonavir provided a comparable ribociclib exposure with these from 600 mg QD administration without a CPY3A inhibitor. A dose reduction to 400 mg is recommended for concomitant use of a strong CYP3A4 inhibitor if concomitant with a strong CYP3A inhibitor cannot be avoided.

CYP3A Inducers: Coadministration of a strong CYP3A4 inducer (rifampin) decreased the plasma AUC of ribociclib by 89%. The concomitant use of strong CYP3A4 inducers with ribociclib should be avoided.

CYP3A Substrates: Coadministration of midazolam (CYP3A4 substrate) with multiple doses of 400 mg ribociclib increased the midazolam exposure by 3.8-fold. Simulations using PBPK models suggested that ribociclib given at dose of 600 mg once daily is expected to increase the midazolam AUC by 5.2-fold. Caution is recommended when ribociclib is administered with CYP3A substrates with a narrow therapeutic index.

Letrozole: Data from a clinical trial in patients with breast cancer and population PK analysis indicated no DDI between ribociclib and letrozole.

Anastrozole: Data from a clinical trial in patients with breast cancer indicated no clinically relevant DDI between ribociclib and anastrozole.

Exemestane: Data from a clinical trial in patients with breast cancer indicated no clinically relevant DDI between ribociclib and exemestane.

6.2.3. Outstanding Issues

We have issued two PMRs: (1) a trial to study effect of an alternative dosing regimen on safety and efficacy; (2) a renal impairment trial with severe renal impairment patients. Refer to Post-Marketing Requirements and Commitments for detail.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of Action	Ribociclib is an inhibitor of CDK 4 (IC_{50} = 0.01 μM) and 6 (IC_{50} = 0.04 μM).
Active Moieties	Ribociclib. No metabolite was identified with clinically relevant contribution to efficacy and safety.
QT Prolongation	Estimated ΔQTcF was 22.9 ms (90% CI: 21.6, 24.1) at 600 mg once daily dose mean Cmax,ss.
General Information	

Bioanalysis	Ribociclib and its major metabolite (LEQ803) were measured using validated LC/MS/MS methods. A summary of the method validation reports is included as an appendix (Section 13.4.1).		
Healthy Volunteers vs. Patients	Slightly lower exposure was observed for ribociclib in healthy subjects compared to patients with cancer. Following a single 600 mg dose, the geometric mean Cmax and AUC_{0-24h} in healthy subjects in studies ranged from 507 to 792 ng/mL and 5910 to 9350 h·ng/mL, respectively. The geometric mean Cmax and AUC_{0-24h} in patients with cancer ranged from 992 to 1260 ng/mL and 9700 to 14200 h·ng/mL, respectively.		
Drug exposure at steady state following the therapeutic dosing regimen	The AUC_{0-24} and Cmax (geometry mean (CV%)) based on intensive PK sampling in Study X2101 in patients at the 600 mg daily dose DiC formulation (N=74) on Cycle 1 day 18 or Cycle 1 day 21 were 23800 (66.0%) ng·h/mL and 1820 (62.4%) ng/mL, respectively.		
Minimal effective dose or exposure	Not available. Ribociclib 600 mg once daily in combination with letrozole were the only combination dosing regimen studied in the Phase 3 and Phase 2 clinical trials.		
Maximal tolerated dose or exposure	Ribociclib 900 mg once daily for 21 consecutive days followed by 7 days off as monotherapy		
Dose Proportionality	Ribociclib showed over-proportional increase in exposure with increasing doses across the dose range from 50 to 1200 mg. See section 13.4 for detail.		
Accumulation	The mean accumulation ratio of 2.5 (range 0.97 to 6.4) was observed at 600 mg once daily dosing steady-state.		
Variability	In patients with cancer after 600 mg multiple doses, CV% for Cmax: 66.0 % and AUC_{0-24}: 62.4%		
Absorption			
Oral Bioavailability	Absolute oral bioavailability has not been determined.		
Bioequivalent (BE) tablets/DiC GMR (90% CI)	BE between tablets and DiC formulation		
	Cmax	AUC_{last}	AUC_{INF}
	1.01 (0.869, 1.17)	1.00 (0.881, 1.14)	0.937 (0.885, 0.991)
Oral Tmax	The Tmax was between 1 and 4 hours.		
Food effect* for Tablets formulation fed/fasted GMR (90% CI)	No food effect		
	Cmax	AUC_{last}	AUC_{INF}
	1.00 (0.898, 1.11)	1.06 (1.01, 1.12)	1.06 (1.01, 1.12)
Food effect* for DiC formulation fed/fasted GMR (90% CI)	No clinically relevant food effect		
	Cmax	AUC_{last}	AUC_{INF}
	0.775 (0.700, 0.858)	0.993 (0.924, 1.07)	0.994 (0.925, 1.07)
Substrate transporter systems [in vitro]	A weak substrate of P-gp. Ribociclib showed moderate to high in vitro passive permeability. P-gp mediated transport is not likely to affect the ribociclib absorption at dose of 600 mg once daily.		
Distribution			
Volume of Distribution	Apparent volume of distribution at steady-state (Vss/F) is 1090 L based on population PK analysis.		
Plasma Protein	70%		
Blood to Plasma Ratio	1.0		

Elimination	
Half-life	The geometric mean plasma effective half-live: 32 hours
Clearance	The geometric mean apparent clearance (CL/F) at steady-state: 25.5 L/hr
Metabolism	
Primary metabolic pathway(s)	In vitro, primarily by CYP 3A4/5 (~ 78%) and to a lesser extent flavin-containing monooxygenase 3 (~20%). In vivo, ribociclib is a victim of CYP3A modulators.
Inhibitor/Inducer	In vitro, ribociclib was a reversible inhibitor of CYP1A2 (Ki,u: 13.0 µM), CYP2E1 (Ki,u: 24.5 µM), and CYP3A4/5 (Ki,u: 30.0 µM) and a time-dependent inhibitor (TDI) of CYP3A4/5 (Ki,u: 4.44 µM; k_{inact}: 0.02 min^{-1}). In vivo, ribociclib is a CYP3A perpetrator . Ribociclib dosed at 400 mg QD increased the coadministrated midazolam (a sensitive CYP3A4 substrate) AUC by 3.8-fold. Ribociclib given at the recommended dose of 600 mg QD is predicted to increase the midazolam AUC by 5.2-fold. Ribociclib is not predicted to have clinically relevant inhibition of CYP1A2. In vitro, ribociclib inhibited breast cancer resistance protein (BCRP, Ki: 24.0 µM), organic cation transporter 2 (OCT2, Ki: 1.90 µM), multidrug and toxin extrusion protein 1 (MATE1, Ki: 1.70 µM), and bile salt export pump (BSEP, Ki: 4.7 µM)
Excretion	
Primary excretion pathways (% dose) ±SD	In an oral mass balance trial, radioactivity recoveries in feces and urine were 69.1% (17.3% unchanged ribociclib) and 22.6% (12.1% unchanged ribociclib), respectively.

**High-fat , high-calorie meal (approximately 800 to 1000 calories) with ~50% calories from fat, ~35 calories form carbohydrates, and ~15% calories from protein*

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes. The primary evidence of effectiveness was obtained from Phase 3 Study A2301.

Study A2301 was a randomized, double-blind, placebo-controlled, multicenter clinical phase 3 study of ribociclib plus letrozole versus plaebo plus letrozole conducted in postmenopausal women with HR-positive, HER2-negative, advanced breast cancer who received no prior therapy for advanced disease. As shown in Table 9, the hazard ratio was 0.556 (95% CI: 0.429, 0.720) based on the median PFS per investigator review. However, no definitive conclusion can be drawn on the E-R relationship for PFS due to limited data of ribociclib exposure in the Phase 3 Study A2301 (i.e., only 44/334 (13%) had valid pre-dose PK samples).

Table 9. Analysis of PFS per Investigator and central blinded independent review committee (BIRC) using Kaplan-Meier methodology for Study A2301

	Investigator review		BIRC review	
	Ribociclib plus letrozole	Placebo plus letrozole	Ribociclib plus letrozole	Placebo plus letrozole
Category	**N=334**	**N=334**	**N=334**	**N=334**
Number of events - n (%)	93 (27.8)	150 (44.9)	50 (15.0)	72 (21.6)
Progression	89 (26.6)	150 (44.9)	46 (13.8)	72 (21.6)
Death[1]	4 (1.2)	0	4 (1.2)	0
Number censored - n (%)	241 (72.2)	184 (55.1)	284 (85.0)	262 (78.4)
Percentiles (95% CI)				
25th	11.1 (9.2, 13.1)	7.2 (5.6, 9.1)	22.9 (15.0,22.9)	14.5 (10.8, NE)
50th	NE (19.3, NE)	14.7 (13.0, 16.5)	22.9 (NE, NE)	NE (NE, NE)
75th	NE (NE, NE)	21.0 (21.0, NE)	22.9 (NE, NE)	NE (NE, NE)
Kaplan-Meier estimate (95% CI)				
Month 6	85.8 (81.4, 89.2)	77.1 (72.1, 81.4)	91.8 (88.1, 94.4)	83.8 (79.1, 87.5)
Month 12	72.8 (67.3, 77.6)	60.9 (55.1, 66.2)	84.5 (79.7, 88.3)	77.3 (71.9, 81.9)
Month 18	63.0 (54.6, 70.3)	42.2 (34.8, 49.5)	80.7 (74.8, 85.4)	68.1 (59.6, 75.2)
P-value ribociclib vs. Placebo[2]	**3.29×10^{-6}**		**0.002**	
Hazard ratio (95% CI) ribociclib vs. Placebo[3]	**0.556 (0.429, 0.720)**		**0.592 (0.412, 0.852)**	

NE=not estimable
[1]Death before progression
[2]One-sided p-value obtained from log-rank test stratified by liver and/or lung metastasis as per IRT
[3]Hazard ratio obtained from Cox PH model stratified by liver and/or lung metastasis as per IRT
Source: [Study A2301-Table 14.2-1.1], [Study A2301-Table 14.2-1.11], [Study A2301-Table 14.2-1.3], [Study A2301-Table 14.2-1.17], [Study A2301-Table 14.2-1.18] and [Study A2301-Table 14.2-1.12]

Source: Table 3-10 of 2.7.3 Summary of Clinical Efficacy of Ribociclib in Combination with Letrozole in HR-positive, HER2-negative, Advanced Breast Cancer (Section 2.7.3)

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

The proposed dose 600mg QD is effective and appears to have a manageable safety profile. However, ribociclib can prolong QT interval in a concentration-dependent manner, with mean increase in QTc interval exceeding 20 ms at 600 mg once daily dosing. Based on the E-R analysis, an alternative dosing regimen, which targets to reach a lower steady-state Cmax, is likely to reduce the risks for QT prolongation.

No definitive conclusion can be drawn on the E-R relationship for PFS due to limited data of ribociclib exposure in the Study A2301. Thus there is no data to support efficacy at an alternative dosing regimen. Therefore, a PMR is requested to evaluate potential alternative dosing regimens.

QT prolongation, hepatobiliary toxicity and neutropenia are important identified risks for ribociclib treatment. Exposure-response analyses showed lower ribociclib exposure was

associated with lower risks of QT prolongation and neutropenia. Safety profiles for alternative dosing regimen of interest, 300mg BID, 400mg BID and 400mg QD, were predicted.

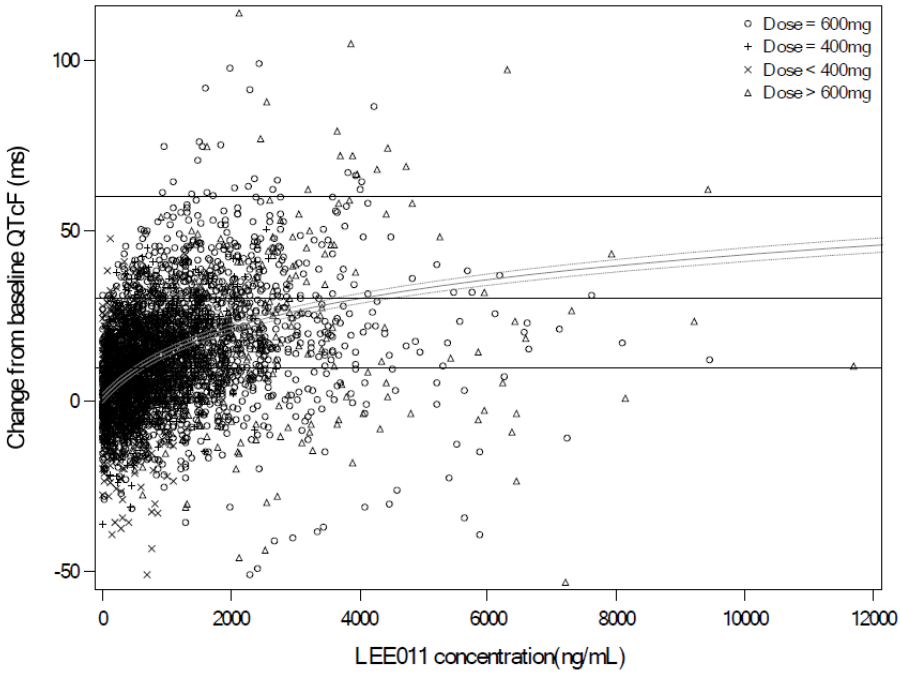
QT prolongation: A log-linear mixed effect model identified concentration-dependent increases in change from baseline QTcF (ΔQTcF). The estimated mean ΔQTcF was 22.9 ms (90% CI: 21.6, 24.1) in patients at the mean steady-state Cmax (2237 ng/mL) following a therapeutic dose of 600 mg QD (Figure 4). The final PopPK model was used to simulate SS Cmax for alternative dosing regimen of ribociclib treatment (300mg BID, 400mg BID, 400mg QD). Mean estimated SS **Cmax** was 1150 and 1140 ng/mL for 300mg BID and 400mg QD respectively, about 40% lower than the predicted SS **Cmax** of 600mg QD. The predicted mean ΔQTCFs at **SS Cmax** of 300mg BID and 400mg QD (1150 and 1140 ng/nL) based on the established log-linear mixed effect model were 15.71 and 15.63 ms, respectively. A 26% relative reduction in QT prolongation is predicted in 300mg BID and 400mg QD compared to the proposed 600mg QD dose.

Hepatobiliary toxicity: 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.

Neutropenia: ANC reduction with treatment of ribociclib was satisfactorily described using a physiological model coupled with a log-linear drug effect model. External model qualification showed the final PK/PD model can adequately predict the time course profile of ANC with ribociclib treatment of 600mg QD in the Study A2301. Simulations using the PK/PD model were conducted to evaluate the dose dependency of neutropenia with ribociclib treatment in a simulated patient population. Based on simulation, the predicted probability of patients experiencing grade 3/4 neutropenia was similar between 300mg BID and 600mg QD (Table 10).

Overall, the proposed 600mg QD was appropriate based on the efficacy shown in pivotal phase 3 Study A2301. The safety appears to be manageable with appropriate dose interruptions and/or dose reductions. Based on the E-R analysis, an alternative dosing regimen, which targets to reach a lower steady-state Cmax, is likely to reduce the risks for QT prolongation.

Figure 4. Scatter plot and final statistical model of ribociclib concentration vs change from baseline QTcF



Median concentration = 734.5 ng/mL, median baseline QTcF = 412.67 ms
Baseline ECG is defined as the last ECG measurements taken prior to the first dose of study drug.
Mean of any replicates (scheduled or unscheduled) is taken prior to calculation baseline.
The solid line is the **estimated value from the** linear mixed effects model with subject as a random effect, and mean function in the form of Delta QTcF = log (concentration/median concentration + 1) + (baseline QTcF – median baseline QTcF).
The broken line is the 90% CI from the linear mixed model.
The dotted lines are the reference lines at 10 ms, 30 ms and 60 ms.

Source: Figure 3-7 of 2.7.2 Addendum 2 for Summary of Clinical Pharmacology of Ribociclib in Combination with Letrozole in HR-positive, HER2-negative, Advanced Breast Cancer (Section 2.7.2)

Table 10. Simulated probability (%) of Grade 3/4 neutropenia with various ribociclib dosing regimens (3 weeks on/1 week off) in a simulated patient population

Table	Grade 3	Grade 4	Grade 3/4
300 mg BID	32.2	6.6	38.8
400 mg BID	37.6	7.5	45.1
400 mg QD	30.7	5.0	35.7
600 mg QD	34.1	7.3	41.4

Source: Table 2-1 of Response to FDA Information Request (IR-10)

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

Yes. Ribociclib is primarily metabolized and hepatic impairment increases ribociclib exposure. Population PK analysis showed that there are no clinically relevant effects of age, body weight, gender, or race on the systemic exposure of ribociclib.

Hepatic Impairment: Based on a dedicated hepatic impairment Study A2109 in healthy subjects with normal hepatic function (N=11) and volunteers with hepatic impairment (N=17), mild (Child-Pugh class A; N=6) 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; N=6; geometric mean ratio [GMR]: 1.50 for Cmax; 1.32 for AUC_{INF}) and severe (Child-Pugh class C; N=5; GMR: 1.34 for Cmax; 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.

- No dose adjustment is necessary in patients with mild hepatic impairment.
- A reduced starting dose of 400 mg is recommended in patients with moderate and severe hepatic impairment.

Renal Impairment: The pharmacokinetics of ribociclib in patients with severe renal impairment (eGFR < 30 mL/min/1.73m^2) is unknown (See Post-Marketing Requirements and Commitments for a PMR trial for patients with severe renal impairment). Based on a population PK analysis, 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. No dose adjustment is necessary in patients with mild hepatic impairment.

Other intrinsic factors: There are no clinically relevant effects of age, body weight, gender, or race on the systemic exposure of ribociclib that would require a dose adjustment. Gender (134 female and 74 male patients) and race (153 Caucasians, 23 Asians and 32 patients with other race) were removed from the final model due to their statistically insignificance. Age (median: 60, range: 23-84) was a statistically significant covariate on clearance but its simulated covariate effect on clearance was mild. Weight (median: 72, range: 34-159) was found to be a statistically significant and clinically important covariate on CL, Q and V2. Simulation suggested a change of BW from 70 kg to 50 or 100 kg would cause up to 22% change in SS Cmax ,Ctrough and AUC_{24h} at 600 mg QD. This covariate effect, however, was small relative to the inherent pharmacokinetic variability (IIV of CL: 51.3%).

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

Ribociclib is a CYP3A substrate. CYP3A inhibitors and inducers have an effect on ribociclib exposures. Avoid concomitant use of strong CYP3A inhibitors or inducers and consider alternative concomitant medications with less potential for CYP3A inhibition or induction. If coadministration of ribociclib with a strong CYP3A inhibitor cannot be avoided, reduce the dose of ribociclib to 400 mg once daily.

Ribociclib is a CYP3A inhibitor, caution is recommended when ribociclib is administered with CYP3A substrates with a narrow therapeutic index.

No clinically relevant food effect was observed with ribociclib DiC and tablet formulation. In a population PK analysis, altered ribociclib absorption was not identified when ribociclib was coadministrated with proton pump inhibitors (PPIs).

Effect of CYP3A Inhibitors and Inducers on Ribociclib

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 Cmax and AUC by 1.7-fold and 3.2-fold, respectively, following a single 400 mg ribociclib dose. Cmax and AUC for LEQ803 (a prominent metabolite of ribociclib, accounting for less than 10% of parent exposure) decreased by 96% and 98%, respectively. The effect of strong inhibitor on the PK of ribociclib after oral QD dosing was predicted using physiologically-based pharmacokinetic (PBPK) models (See section 13.4.5). Simulations show that mean ribociclib exposure after co-administration of ribociclib at 400 mg QD with a strong CYP3A inhibitor is comparable to that after administration of ribociclib at 600 mg QD alone. Avoid concomitant use of strong CYP3A inhibitors and consider alternative concomitant medications with less potential for CYP3A inhibition. If coadministration of ribociclib with a strong CYP3A inhibitor cannot be avoided, reduce the dose of ribociclib to 400 mg once daily.

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 Cmax and AUC by 81% and 89%, respectively, following a single 600 mg ribociclib dose. LEQ803 Cmax increased 1.7-fold and AUC decreased by 27%, respectively. Coadministration of a strong CYP3A4 inducer (rifampin) decreased the plasma exposure of ribociclib in healthy subjects by 89%. Avoid concomitant use of strong CYP3A inducers and consider an alternate concomitant medication with no or minimal potential to induce CYP3A.

Effect of ribociclib on CYP3A4 and CYP1A2 substrates

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 by 2.1-fold and 3.8-fold, respectively. Effect of co-administration of ribociclib at 600 mg QD on the PK of midazolam is predicted using

PBPK modeling. The simulated increase in midazolam C_{max} and AUC were 2.4-fold and 5.2-fold, respectively. Therefore, caution is recommended when ribociclib is administered with CYP3A substrates with a narrow therapeutic index. The effect of multiple doses of 400 mg ribociclib on caffeine was minimal, with C_{max} decreased by 10% and AUC increased slightly by 20%. Only weak inhibitory effects on CYP1A2 substrates are predicted using PBPK modeling at 600 mg ribociclib once daily dose and there is no need for dose adjustment.

DDI between ribociclib and aromatase inhibitors

Letrozole: Clinical data suggested no DDI potential between ribociclib and letrozole. Ribociclib has no clinically relevant effect on letrozole PK based on a comparison of letrozole PK data between letrozole in combination with ribociclib and letrozole in combination placebo in Study A2301. letrozole Ctroughs were similar between these treatment arms (GMR: 0.932; 90% CI: 0.815, 1.07). Plasma concentrations at 2 h post-dose were also similar between these treatment arms (GMR: 0.899; 90% CI: 0.815, 0.992). In a population analysis including 208 patients with cancer, 47 patients had concomitant use of letrozole. Concomitant use of letrozole had no significant effect on ribociclib PK (See section 13.4.3 for detail).

Anastrozole: Clinical data suggested no clinically relevant DDI between ribociclib and anastrozole. Concentrations of ribociclib and anastrozole administered as coadministrated drugs (Study E2301) overlapped with concentrations of ribociclib from Study X2101 (Table 11) and anastrozole administered as a single agent (Table 12).

Table 11. Cross study comparison of steady state ribociclib PK parameters at 600 mg QD dose

PK parameter	Statistics	E2301 [Ribociclib + letrozole] C1D15	E2301 [Ribociclib + letrozole] C3D15	X2101 [Ribociclib single agent][1]
Predose (ng/mL)	n	5	15	64
	Mean (± SD)	742 (± 578)	485 (± 347)	732 (± 586)
	Geo-mean	600	372	558
	CV% geo-mean	80	110	91
Cmax (ng/mL)	n	-	6	57
	Mean (± SD)	-	2470 (± 1022)	2130 (± 1260)
	Geo-mean	-	2334	1820
	CV% geo-mean	-	36	62.4

1. Data derived from Study CLEE011X2101 interim CSR [Sources: Table 14.2-2.5 for predose; Table 14.2-2.1 for Cmax and Tmax]

Source: Table 5-2 PK Summary Report CLEE011E2301 (1-Feb-2017)

Table 12. Cross study comparison of steady state anastrozole PK parameters at 1 mg QD dose

PK parameter	Statistics	E2301 [Ribociclib + anastrozole] C1D15	E2301 [Ribociclib + anastrozole] C3D15	Anastrozole in postmenopausal women with breast cancer [1]	Anastrozole in postmenopausal healthy women (calculated steady-state)[2]
Predose (ng/mL)	N	5	18	130	-
	Mean (± SD)	39 (± 26)	42 (± 18)	37.4 (± 15.2)	-
	Geo-mean	47	38	34.7	-
	CV% geo-mean	34	54	-	-
				-	-
Cmax,ss (ng/mL)	n	-	7	-	-
	Mean (± SD)	-	64 (± 11)	-	61.25
	Geo-mean	-	63	-	-
	CV% geo-mean	-	17	-	-

1. Anastrozole predose after multiple dose administration in postmenopausal subjects [Data derived from The ATAC Trialists' Group, 2001]
2. FDA Biopharmaceutics / Pharmacokinetics Review Document NDA 20-541, 1995

Source: Table 5-1 PK Summary Report CLEE011E2301 (1-Feb-2017)

Exemestane: Clinical data suggested no clinically relevant DDI between ribociclib and exemestane. Concentrations of ribociclib and exemestane administered as coadministrated drugs (Study X2106) overlapped with concentrations of ribociclib (Study X2101) and exemestane administered as a single agent (Table 13).

Table 13. Cross study comparison of concentration (ng/mL) of ribociclib (600 mg QD dose), LEQ803 and exemestane (25 mg QD dose) at 2 hours C1D15 [Mean±SD]

	X2106	X2101	Exemestane postmenopausal advanced breast cancer patients[1]	Exemestane postmenopausal healthy volunteers[1]
Ribociclib	1310 (± 520) n=11	1880 (± 1090) n=58	NA	NA
LEQ803	138 (± 75.8) n=11	121 (± 60.4) n=58	NA	NA
Exemestane	12.7 (± 6.31) n=11	NA	29.6 (± 24.9) [1] n=9	11.4 (± 6.6)[1] n=8

1. Exemestane Cmax [Mean± SD] after multiple dose administration in postmenopausal subjects [Data derived from exemestane Clinical Pharmacology Biopharmaceutics Review(s) Part 1 Table 5]

Source: Table 6-5 Interim Summary Report (cut off 03-Nov-2016) CLEE011X2106

Transporters related DDI

In vitro, ribociclib inhibited breast cancer resistance protein (BCRP, Ki: 24.0 µM), organic cation transporter 2 (OCT2, Ki: 1.90 µM), multidrug and toxin extrusion protein 1 (MATE1, Ki: 1.70 µM), and bile salt export pump (BSEP, Ki: 4.7 µM), which may translate into clinically relevant inhibition at therapeutic doses (BCRP [I]2/Ki = 29.7; BSEP R,total =1.87; OCT2 R,unbound = 1.66; MAT1 R,unbound = 1.74) based on the FDA guidance for drug interaction studies (2012). 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.

Food Effect

DiC Formulation: In a Phase I, randomized, open-label, crossover study to evaluate effect of food following a single oral dose of 600 mg ribociclib DiC formulation in healthy subjects, ribociclib DiC was dosed fasted under treatment A and was dosed with high-fat, high-calorie meal (approximately 800 to 1000 calories with ~50% calories from fat, ~35% calories from carbohydrates, and ~15% calories from protein) under treatment B (Table 14). There was no clinically relevant exposure difference in fed and fasted conditions (Fed/Fasted Cmax GMR: 0.775; 90% CI: 0.700, 0.858; Fed/Fasted AUC_{INF} GMR: 0.994; 90% CI: 0.925, 1.07).

Table 14. Summary of statistical analysis of primary PK parameters for plasma ribociclib under fasted and fed conditions for DiC formulation

					Treatment Comparison	
					90% CI	
PK Parameter (unit)	Treatment	n *	Adjusted Geo-mean	Comparison	Geo-mean Ratio	Lower	Upper
Cmax (ng/mL)	A	24	729				
	B	23	564	B:A	0.775	0.700	0.858
AUClast (ng*hr/mL)	A	24	11900				
	B	23	11800	B:A	0.993	0.924	1.070
AUCinf (ng*hr/mL)	A	24	12100				
	B	23	12000	B:A	0.994	0.925	1.070
Tmax (hr) #	A	24	3.000				
	B	23	6.000	B-A	2.000	-2.000	7.000

- Treatment A = LEE011 600 mg under fasting conditions; Treatment B = LEE011 600 mg with a high-fat, high calorie meal.
- A linear mixed effects model, with treatment, period, and sequence as fixed factors and subjects nested within sequence as a random factor, is fitted to each log-transformed primary PK parameter. Results were back transformed to obtain 'Adjusted Geo-mean, Geo-mean Ratio' and '90% CI'.
- * n = number of subjects with evaluable PK data.
- # Secondary PK parameter Tmax is presented in addition to primary PK parameters with median under 'Adjusted Geo-mean', median difference under 'Geo-mean Ratio', and minimum/maximum under 'Lower' and 'Upper'.

Source: Table 14.2-1.1 of Full Clinical Study Report Study No. LEE011A2111

Tablet formulation: In a Phase I, randomized, open-label, crossover study to evaluate effect of food following a single oral dose of 600 mg ribociclib tablet in healthy subjects, ribociclib tablet was dosed fasted under treatment C and was dosed with high-fat, high-calorie meal (approximately 800 to 1000 calories with ~50% calories from fat, ~35% calories from carbohydrates, and ~15% calories from protein) under treatment D (Table 15). Ribociclib

exposure was similar in fed and fasted conditions (Fed/Fasted Cmax GMR: 1.00; 90% CI: 0.898, 1.11; Fed/Fasted AUC_{INF} GMR: 1.06; 90% CI: 1.01, 1.12).

Table 15. Summary of statistical analysis of primary PK parameters for plasma ribociclib under fasted and fed conditions for tablet formulation

					Treatment Comparison		
						90% CI	
PK Parameter (unit)	Treatment	n *	Adjusted Geo-mean	Comparison	Geo-mean Ratio	Lower	Upper
Cmax (ng/mL)	C	23	790				
	D	24	790	D:C	1	0.898	1.11
AUClast (hr*ng/mL)	C	23	13900				
	D	24	14800	D:C	1.06	1.01	1.12
AUCinf (hr*ng/mL)	C	23	14100				
	D	24	15000	D:C	1.06	1.01	1.12
Tmax (hr)	C	23	3				
	D	24	4	D-C	1	-2	8

- Treatment C: 600mg LEE011 tablet under fasted conditions(reference), Treatment D 600mg LEE011 tablet with high-fat high-calorie meal (test).
- Model is a linear effects model of the log-transformed PK parameters. Included in the model were treatment, period and sequence as fixed effects and subject nested within sequence as a random effect.
- n* = number of subjects with non-missing values.
- The analysis is conducted on log transformed PK parameters. Then the results are back transformed to get adjusted geo-mean, Geo-mean ratio, and 90% CI.
- For Tmax, median is presented under 'Adjusted geo-mean', median difference under 'Geo-mean ratio', and minimum and maximum differences under 90% CI.

Source: Table 14.2-1.1b of Full Clinical Report Study No. LEE011A2103

Effect of Drugs That Elevate the Gastric pH on Ribociclib

In a Population PK analysis including 208 patients with cancer, 52 patients had concomitant use of PPIs. The ratio of the relative bioavailability in patients on PPIs to that in patients not on PPIs was estimated to be 0.95 (95% CI: 0.818, 1.087).

Is the to-be-marketed formulation the same as the clinical trial formulation, and if not, are there bioequivalence data to support the to-be-marketed formulation?

No, the to-be-market formulation is a tablet and the formulation used in the Phase 3 Study A2301 is a DiC formulation. In a Phase I, randomized, open-label, crossover study to evaluate BE of these two formulations, a single 600 mg ribociclib at the tablet formulation was dosed fasted under treatment B and a single 600 mg ribociclib at the DiC formulation was dosed fasted under treatment A (Table 16). The ribociclib tablet formulation and the DiC formulation were identified as BE.

Table 16. Summary of statistical analysis of primary PK parameters for plasma ribociclib for DiC and tablet formulation

					Treatment Comparison		
						90% CI	
PK Parameter (unit)	Treatment	n *	Adjusted Geo-mean	Comparison	Geo-mean Ratio	Lower	Upper
Cmax (ng/mL)	A	31	596				
	B	31	601	B:A	1.01	0.869	1.17
AUClast (hr·ng/mL)	A	31	10600				
	B	31	10600	B:A	1.00	0.881	1.14
AUCinf (hr·ng/mL)	A	30	11500				
	B	31	10800	B:A	0.937	0.885	0.991
Tmax (hr)	A	31	3				
	B	31	3	B-A	0	-4	3

Treatment A: 600 mg ribociclib DiC (reference), Treatment B: 600 mg ribociclib tablet (test).
Source: Table 14.2-1.1a

Source: Table 11-6 of Full Clinical Report Study No. CLEE011A2103

{See appended electronic signature page}

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7 Statistical and Clinical and Evaluation

7.1. Sources of Clinical Data and Review Strategy

7.1.1. Table of Clinical Studies

The single trial supporting the efficacy review of this NDA is the Phase 3 randomized double-blind, placebo-controlled multi-center MONALEESA-2 study (CLEE011A2301) of ribociclib plus letrozole for the treatment of postmenopausal women with hormone receptor positive, HER2-negative, advanced breast cancer who received no prior therapy for advanced disease. As discussed later in the section detailing safety analyses, additional data were reviewed as part of this application. The supportive trials are listed in Table 17.

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Table 17. Listing of Clinical Trials Relevant to this NDA

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety							
A2301 (MONALEESA-2)	Phase III Randomized (1:1)	ribociclib (600 mg once daily, days 1-21 in a 28-day cycle) + letrozole (2.5 mg once daily continuous)	Primary: PFS Secondary: OS, ORR	Until progression or toxicity	668 Ribociclib: 334 Letrozole: 334	First-Line Metastatic Breast Cancer	221 centers in 29 countries
Studies to Support Safety							
X2106 [A]	Phase Ib	ribociclib (600 mg/day three weeks on, one week off) and exemestane (25 mg daily)	Primary PK variable: Cmax, AUClast, AUCinf, and Tmax	Total planned duration of the study treatment was 10 days	14	Advanced Breast Cancer with Resistance to Prior Letrozole or Anastrozole	1 center
E2301 [B]	Phase 3 Randomized	ribociclib (600 mg once daily, days 1-21 in a 28-day cycle) + anastrozole (1 mg once daily continuous)	Primary: PFS Secondary: OS	Until progression or toxicity	70	Advanced Metastatic or Recurrent Breast Cancer (pre-menopausal)	206 centers

A: Supportive safety, efficacy, and PK data for ribociclib plus exemestane
B: Supportive PK data for ribociclib plus anastrozole

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7.1.2. Review Strategy

Data Sources

For this review, we evaluated the Applicant's case report forms in electronic format, the datasets provided in AdAM and SDTM format, and the final clinical study report. Also as part of the review, we evaluated the efficacy and safety data provided in the 90-day safety update. The EDR link to data sources is \\CDSESUB1\evsprod\NDA209092\209092.enx.
Specifically, the clinical review included the following:

- Review of the current literature on breast cancer epidemiology, and treatment
- Review of Applicant submitted Trial MONALEESA-2 including CSR, protocols, protocol amendments and datasets.
- Review and assessment of Applicant analysis of ribociclib efficacy and safety, for evaluation of Applicant's claims
- Review of datasets submitted as .xpt files
- Review of patient narratives of serious adverse events and deaths
- Review of meeting minutes conducted during drug development
- Assessment of the Module 2 summaries including the Summary of Clinical Safety
- Review of reviews conducted by other FDA disciplines including Clinical Pharmacology
- Review of consultation reports of Office of Scientific Investigations
- Requests for additional information from the Applicant and review of Applicant responses
- Formulation of the benefit-risk analysis and recommendations
- Review and evaluation of proposed labeling

Data and Analysis Quality

The data submitted with this application were in AdAM and SDTM formats. The data were of good quality and the Applicant's analyses were reproducible.

7.2. Review of Relevant Individual Trials Used to Support Efficacy

7.2.1 MONALEESA-2

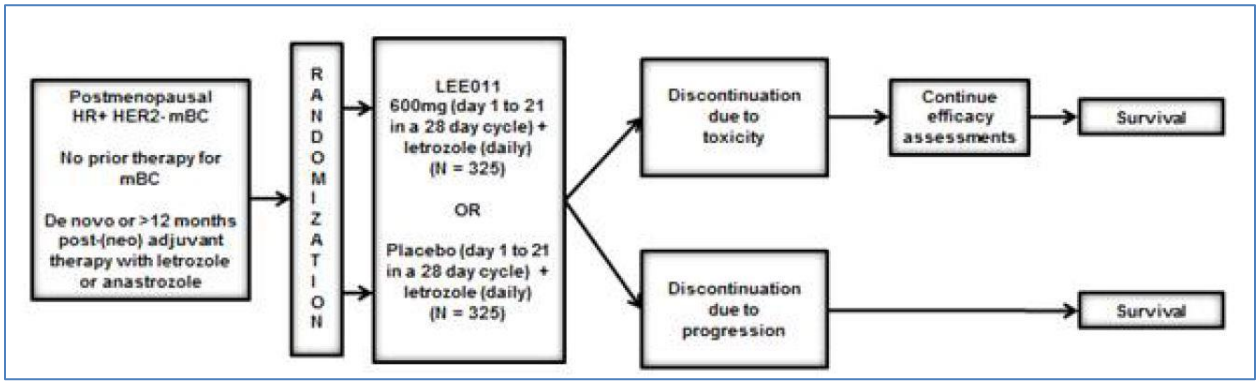
Trial Design and Endpoints

MONALEESA-2 (Study CLEE011A2301) is an international, multi-center, randomized, double-blind, placebo controlled Phase III study evaluating the efficacy and safety of treatment with ribociclib plus letrozole versus placebo plus letrozole in postmenopausal women with HR-positive, HER2-negative advanced breast cancer who received no prior therapy for advanced breast cancer. Eligible patients were randomized using IRT system in a 1:1 ratio to either ribociclib (600 mg once daily, days 1-21 in a 28-day cycle) plus letrozole (2.5 mg once daily

continuous) or placebo (once daily, days 1-21 in a 28-day cycle) plus letrozole (2.5 mg once daily continuous). Randomization was stratified by the presence of liver and/or lung metastases (yes versus no). Study treatment continued until disease progression, unacceptable toxicity, death, or discontinuation from the study treatment for any other reason. Patients in the placebo plus letrozole arm were not allowed to cross over to the ribociclib plus letrozole arm at the time of progression. Figure 5 depicts the MONALEESA-2 study schema.

After randomization, follow-up visits to determine disease progression status occurred every 8 weeks for the first 18 months and 12 weeks thereafter. The study primarily used CT and MRI scans of the chest, abdomen, and pelvis to assess progression. All patients received a whole body bone scan at baseline, with additional whole body bone scans done if clinically indicated. X-rays, skin color photography, and CT/ MRI of other regions, were also used if clinically indicated or if lesions were seen in other areas at screening. Patient reported outcome (PRO) data was provided by subjects using the EORTC QLQ-C30, EORTC QLQ-BR23, EQ-5D-5L instruments. PRO data was collected on the same schedule as the efficacy visits.

Figure 5. MONALEESA-2 (A2301) Study Design (Applicant Figure)



Source: Clinical Study Report Figure 9-1

MONALEESA-2 used progression free survival (PFS) as assessed by the local investigator (RECIST v1.1 criteria) for its primary endpoint. MONALEESA-2 had overall survival as a key secondary endpoint. The study included a blinded independent central review of PFS as a supportive secondary endpoint. Additional secondary endpoints included overall response rate (ORR), clinical benefit rate (CBR), and deterioration of ECOG performance status.

MONALEESA-2 met a pre-specified criteria to conclude superior efficacy at an interim analysis of PFS. The interim analysis occurred when 243 total progression events had occurred; this corresponded to 80% of the planned events for the final analysis (302). More details on the interim analysis are provided in the Statistical Analysis Plan section below. The data cutoff date for the interim analysis was January 29, 2016. In a 90-day safety update provided to FDA, the Applicant provided updated efficacy data on PFS and OS with a data cutoff date of June 22, 2016. An additional PFS analysis was conducted at the second interim analysis of OS, with a data cutoff date of January 2, 2017.

MONALEESA-2 outlined two levels of dose reduction, the first to 400 mg of ribociclib and the second to 200 mg of ribociclib. Dose reduction and dose interruption guidelines were specified for thrombocytopenia (grades 2-4), absolute neutrophil count (grades 3-4), febrile neutropenia (grades 3-4), anemia (grades 3-4), hepatotoxicities (grades 2-4), and QTc prolongation (grades 2-4).

MONALEESA-2 Eligibility Criteria

Inclusion Criteria:

- Adult postmenopausal women (≥ 18 years) at the time of informed consent and had signed
  informed consent before any study related activities and according to local guidelines.
- Women with advanced (loco regionally recurrent or metastatic) breast cancer not amenable to curative therapy.
- 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, toremifen, or ovarian suppression) and follicle stimulating hormone (FSH)
    and estradiol in the postmenopausal range per local normal range.

Note**:** For women with therapy-induced amenorrhea, serial measurements of FSH and/or estradiol were needed to ensure postmenopausal status (National Cancer Center Network (NCCN) Guidelines Version 2 2014). Ovarian radiation or treatment with a luteinizing hormone-releasing hormone agonist (LH-RHa) (goserelin acetate or leuprolide acetate) was not permitted for induction of ovarian suppression in this study.

- Histological and/or cytological confirmation of estrogen receptor (ER)-positive - and/or progesterone receptor positive breast cancer by local laboratory.
- 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.

Patient had either:

- **Measurable disease**, i.e., at least one measurable lesion as per RECIST 1.1 criteria (Tumor lesions previously irradiated or subjected to other loco regional therapy were only to be considered measurable if disease progression at the treated site after completion of therapy was clearly documented)
  OR

- **At least one predominantly lytic bone lesion** (Patients with 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).
- ECOG performance status 0 or 1
- Patient had adequate bone marrow and organ function as defined by the following laboratory values (as assessed by central laboratory):
  - Absolute neutrophil count ≥ 1.5×109/L
  - Platelets ≥ 100×109/L
  - Hemoglobin ≥ 9.0 g/dL
  - Potassium, sodium, calcium (corrected for serum albumin), magnesium, and phosphorus within normal limits of the central laboratory
  - International Normalized Ratio (INR) ≤ 1.5
  - Serum creatinine within normal limits of the central laboratory
  - In absence of liver metastases, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) had to be <2.5×Upper Limit of Normal (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 within normal range of the central laboratory in patients with well documented Gilbert's Syndrome.

Exclusion Criteria:

- Patients who received any CDK4/6 inhibitor previously.
- Patients with known hypersensitivity to any of the excipients of ribociclib or letrozole
- Patients with inflammatory breast cancer.
- Patients who received any prior systemic anti-cancer therapy (including hormonal therapy and chemotherapy) for advanced breast cancer

Note**:**

- Patients who received (neo) adjuvant therapy for breast cancer were eligible. If the prior neo (adjuvant) therapy included letrozole or anastrozole the disease free interval had to be greater than 12 months from the completion of treatment until randomization. Patients who received ≤ 14 days of letrozole or anastrozole for advanced disease prior to randomization were allowed.
- Any prior (neo) adjuvant anti-cancer therapy had to be stopped at least 5 half-lives or 7 days, whichever was longer, before randomization

- Patients currently receiving other anti-cancer therapy.
- Patients who had major surgery within 14 days prior to starting study drug or had not
- recovered from major side effects.
- Patients who have not had resolution of all acute toxic effects of prior anti-cancer therapy

- to NCI-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).
- 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.
- Patients with concurrent malignancy or malignancy within three years of randomization, with the exception of adequately treated, basal or squamous cell carcinoma, nonmelanomatous skin cancer or curatively resected cervical cancer.
- Patients with central nervous system (CNS) metastases.
- Patients with impairment of gastrointestinal (GI) function or GI disease that would significantly alter the absorption of the study drugs (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection).
- Patients with a known history of Human Immunodeficiency Virus (HIV) infection (testing not mandatory).
- 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.).
- Patients who had active cardiac disease or a history of cardiac dysfunction including any of the following:
    - History of angina pectoris, symptomatic pericarditis, or myocardial infarction within 12 months prior to study entry
    - History of documented congestive heart failure (New York Heart Association functional classification III-IV)
    - Documented cardiomyopathy
    - Left Ventricular Ejection Fraction (LVEF) <50% as determined by Multiple Gated acquisition (MUGA) scan or echocardiogram (ECHO)
    - History of any cardiac arrhythmias, e.g., ventricular, supraventricular, nodal arrhythmias, or conduction abnormality in the previous 12 months.
    - On Screening, any of the following cardiac parameters: bradycardia (heart rate <50 at rest), tachycardia (heart rate >90 at rest), pulse rate interval >220 msec, QRS interval >109 msec, or QTcF >450 msec.
    - Systolic blood pressure >160 or <90 mmHg.
- Patients that were currently receiving any of the following medications and could not be discontinued seven days prior to the start of the treatment:
    - Known strong inducers or inhibitors of CYP3A4/5.
    - Those with a known risk to prolong the QT interval or induce Torsades de Pointes.
    - Those with a narrow therapeutic window and are predominantly metabolized through CYP3A4/5.
    - Herbal preparations/medications.

    - Dietary supplements (except vitamins).
- Patients that were currently receiving or those who had received systemic corticosteroids ≤ 2 weeks prior to starting study drug, or who have not fully recovered from side effects of such treatment

Note**:** The use of following corticosteroids was permitted: single doses of topical applications (e.g., for rash), inhaled sprays (e.g., for obstructive airways diseases), and eye drops or local injections (e.g., intra-articular).

MONALEESA-2 Objectives

Primary Objective

- The primary objective of the study was to compare PFS between ribociclib in combination with letrozole and placebo plus letrozole among postmenopausal women with HR-positive, HER2-negative, advanced breast cancer who received no prior therapy for their advanced breast cancer.

Secondary Objectives

- The key secondary objective of the study was to compare the two treatment arms with respect to overall survival (OS).
- Other secondary objectives were:
    - To evaluate the two treatment arms with respect to overall response rate (ORR) and clinical benefit rate (CBR).
    - To evaluate the two treatment arms with respect to time to deterioration of Eastern Cooperative Oncology Group (ECOG) performance status.
    - To evaluate the safety and tolerability of ribociclib in combination with letrozole.
    - To evaluate patient reported outcomes (PROs) for health-related quality of life (QoL) in thetwo treatment arms.
- Exploratory objectives were:
    - To describe time to response and duration of response in each treatment arm.
    - To characterize the exposure of ribociclib (and relevant metabolites such as LEQ803) when administered in combination with letrozole in a subset of patients.
    - To characterize the exposure of letrozole with or without co-administration with ribociclib in a subset of patients.
    - To assess any effect on estradiol (E2) suppression relative to baseline with or without co-administration with ribociclib.
    - To explore exposure/response relationship.

- To explore potential differences in hospital resource utilization.
- To assess differences in molecular alterations (main pathways of interest in breast cancer) in patients deriving benefit from treatment.
- To explore molecular alterations in circulating deoxyribonucleic acid (DNA).
- To explore potential mechanisms of resistance to treatment with ribociclib plus letrozole.

Statistical Analysis Plan

The study was originally designed to enroll 500 patients in order to detect a 4 month difference in median PFS (9.0 months vs. 13.4 months, HR = 0.67, 88.5% power). After a protocol amendment (see below), however, the sample size was changed to 650 patients to increase the power for the secondary endpoint of overall survival. The sample size increase raised the power for the primary endpoint to 93.5%. The Applicant planned to test the primary analysis PFS when 302 events had occurred.

The Applicant originally planned for two interim PFS efficacy analyses at 152 events and 243 events. An O'Brien-Fleming boundary was originally used to determine the efficacy boundary. In protocol amendment #3, the Applicant changed the analysis plan to include only a single interim analysis efficacy boundary when 211 events had occurred (corresponding to 70% information). The Applicant also modified the efficacy boundary to a Haybittle-Peto boundary that set a minimum hazard ratio stopping boundary of 0.56. The efficacy boundary was suggested by the agency in order to provide consistent advice across the CDK 4/6 drug class.

For the key secondary endpoint of overall survival, the Applicant planned an interim OS analysis when the primary endpoint of PFS was successful. An additional interim analysis of OS occurred when 100 events occurred (see amendment 5 below). The Applicant plans for a third interim analysis of OS when 300 events have occurred. The final analysis for OS is planned when 400 total deaths have occurred. The Applicant proposed December 2019 for the third interim OS analysis and June 2022 for the final study report.

To test the primary and secondary endpoints, the Applicant used a stratified log-rank test with a one-sided alpha level of 2.5%.

Protocol Amendments

The protocol was amended a total of five times. Amendments 2,3, and 5 made modifications to the statistical analysis plan and are detailed below. Amendments 1 and 4 were minor and made changes to the inclusion/exclusion criteria, safety monitoring, and the independent review committee.

Amendment 2 (November 24, 2014) increased the sample size from 500 patients to 650 to provide more power demonstrate a statistically significant improvement in overall survival. Amendment 2 also pushed back the OS final analysis (b) (4) to 400 events.

Amendment 3 (April 9, 2015) changed the interim analysis boundary for the primary analysis of PFS from an O'Brien-Fleming type stopping boundary to a Haybittle-Peto boundary. The updated hazard ratio boundary for stopping the trial became 0.56.

Amendment 5 (December 21, 2016) occurred during the review of the ribociclib application. This amendment changed the timing of the second interim analysis of OS (b) (4) to 100 events. The analysis was changed to provide updated PFS and OS data to health regulatory authorities, such as FDA and EMA.

7.2.1. Study Results

Compliance with Good Clinical Practices

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).

The pivotal randomized Phase 3 MONALEESA-2 trial was conducted at 223 sites in 29 countries as follows: Argentina (3 sites), Australia (3), Austria (3), Belgium (5), Brazil (3), Canada (8), Czech Republic (4), Denmark (4), Finland (2), France (12), Germany (20), Hungary (4), Ireland (2), Israel (3), Italy (16), Lebanon (4), Netherlands (10), Norway (2), Province of China Taiwan (5), Republic of Korea (5), Russian Federation (3), Singapore (1), South Africa (1), Spain (12), Sweden (6), Thailand (1), Turkey (5), United Kingdom (2), United States (74).

Please see below for a discussion of the protocol deviations.

Patient Disposition

From December 17, 2013 to January 29, 2016, a total of 668 women were randomized in MONALEESA-2. The total number of patients screened was 958.

In MONALEESA-2, 334 patients were randomized to the ribociclib plus letrozole arm and 334 patients were randomized to the placebo plus letrozole and thus make up the ITT analysis population. Four patients were randomized but not treated, all of whom were in the placebo plus letrozole arm.

At the time of the data cut off on January 29th, 2016, 349 patients were still receiving treatment in the study with 195 (58.4%) on the ribociclib plus letrozole arm and 154 (46.1%) on the placebo plus letrozole arm. At the end of study, 2 (0.6%) patients on the ribociclib plus letrozole arm had died. The patient disposition in MONALEESA-2 is summarized in detail in Table 18.

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Table 18. Patient Disposition in MONALEESA-2

	Ribociclib plus Letrozole N=334 n (%)	**Placebo plus Letrozole N=334 n (%)**
Patients randomized		
Untreated	0	4 (1.2)
Treated	334 (100)	330 (98.8)
Patients treated		
Treatment ongoing[1]	195 (58.4)	154 (46.1)
End of treatment	139 (41.6)	176 (52.7)
Primary reason for end of treatment for all randomized patients[2]	139 (41.6)	180 (53.9)
Progressive disease	87 (26.0)	146 (43.7)
Adverse event[6]	25 (7.5)	7 (2.1)
Subject/guardian decision	12 (3.6)	13 (3.9)
Physician decision	10 (3.0)	13 (3.9)
Protocol deviation	3 (0.9)	1 (0.3)
Death	2 (0.6)	0
Entered post-treatment follow-up[3]	13 (9.4)	6 (3.3)
No longer being followed for study evaluation	3 (2.2)	3 (1.7)
Continued to be followed for study evaluation	10 (7.2)	3 (1.7)
Reason for end of post-treatment follow-up[4]	3 (23.1)	3 (50.0)
Death	0	1 (16.7)[5]
Progressive disease	3 (23.1)	2 (33.3)
Entered survival follow-up[3]	113 (81.3)	161 (89.4)

Source: CSR Table 10-1

(1) Patients continue study treatment at the time of the cut-off January 29, 2016
(2) All percentages in this section use the number randomized as the denominator.
(3) Denominator is the number discontinued from treatment as the denominator.
(4) Patients who enter and then discontinue from the post-treatment follow-up phase at the end of posttreatment follow-up. In this section the denominator is the number of patients who entered posttreatment follow-up.
(5) Death occurred due to study indication during the 30 day follow-up
(6) End of treatment due to adverse event refers to discontinuation of both ribociclib (or placebo) and letrozole

Protocol Violations/Deviations

Overall, 42.4% of subjects were identified as having at least one protocol deviation. Major protocol deviations were reported in 44 subjects (6.6%); these major deviations are

summarized in Table 19 and are well balanced between both treatment arms. Notably, all major protocol deviations are associated with study eligibility criteria. The most common major protocol deviation was criteria for no prior therapy for advanced breast cancer not being met.

Table 19. Major Protocol Deviations in MONALEESA-2

	Ribociclib plus Letrozole N=334 n (%)	**Placebo plus Letrozole N=334 n (%)**
Patients with at least one major protocol deviation	24 (7.2)	20 (6.0)
Selection criteria not met	24 (7.2)	20 (6.0)
Criteria for prior therapy for advanced breast cancer not met	15 (4.5)	9 (2.7)
Postmenopausal status not met*	2 (0.6)	6 (1.8)
Criteria for measurable disease or lytic bone lesion not met	6 (1.8)	3 (0.9)
Breast cancer type (HER2 status) not met	1 (0.3)	1 (0.3)
Concurrent malignancy or malignancy in last 3 years of randomization	0	1 (0.3)
Criteria for advanced disease not met	1 (0.3)	0

Source: CSR Table 10-2
*These patients included those who took letrozole or anastrozole for >14 days or patients who were on any prior neoadjuvant anti-cancer therapy which were not stopped at least 5 half-lives or 7 days before randomization

Table of Demographic Characteristics

Demographic characteristics were well-balanced between both treatment arms of MONALEESA-2. These are summarized in Table 20. Notably, all enrolled patients in this study were female. The median age of patients in the study was 62 years (range 23-91). Overall, 44.2% patients were ≥65 years, 82.2% Caucasian, 7.6% Asian, and 2.5% Black. Most patients were enrolled in Europe (44.3%) followed by 34.3% in North America and 10.2% in Asia.

Table 20. Demographic characteristics of the primary efficacy analysis

	Ribociclib plus Letrozole N=334	**Placebo plus Letrozole N=334**
Age in years		
Mean (SD)	61.4 (11.0)	61.9 (10.5)
Median (min-max)	62 (23-91)	63 (29-88)
Age category (n, %)		
<65 years	184 (55.1)	189 (56.6)
≥65 years	150 (44.9)	145 (43.4)
Race (n, %)		
Caucasian	269 (80.5)	280 (83.8)
Asian	28 (8.4)	23 (6.9)
Black	10 (3.0)	7 (2.1)
Native American	1 (0.3)	0
Pacific Islander	1 (0.3)	0
Other	12 (3.6)	8 (2.4)
Unknown	13 (3.9)	16 (4.8)
ECOG performance status (n, %)		
0	205 (61.4)	202 (60.5)
1	129 (38.6)	132 (39.5)
Region (n, %)		
Europe	150 (44.9)	146 (43.7)
North America	108 (32.3)	121 (36.2)
Asia	35 (10.5)	33 (9.9)
Latin America	7 (2.1)	7 (2.1)
Other	34 (10.2)	27 (8.1)

Source: ADSL.xpt, CSR Table 11-3

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

Baseline breast cancer characteristics were well balanced between the two treatment arms. These are summarized in Table 21. Approximately one-third (34.0%) patients had a de novo breast cancer diagnosis and a similar proportion (33.4%) had an initial diagnosis of stage IV disease. All patients had positive estrogen and/or progesterone receptor status. Except for one patient (0.3%) in each arm, all patients were HER2-negative by protocol definition. Except for 4 patients, all patients had stage IV disease at the time of study entry. Overall, a majority of patients (58.8%) had visceral disease (19.8% with liver and 45.4% with lung involvement). About one-fifth (22.0%) had bone-only metastases at study entry. One-third (34.0%) of the patients had ≥ 3 metastatic sites.

With respect to prior-antineoplastic therapy, the two treatment arms were well balanced. Overall, 46.6% had received chemotherapy and 51.3% had received hormonal therapy in the neoadjuvant or adjuvant setting. Prior anti-neoplastic therapies are summarized in detail in Table 22.

Table 21. Baseline and Patient Disease Characteristics

	Ribociclib plus Letrozole N=334	**Placebo plus Letrozole N=334**
Primary site of cancer (n, %)		
Breast	334 (100)	334 (100)
Histological grade (n, %)		
Well differentiated	30 (9.0)	35 (10.5)
Moderately differentiated	143 (42.8)	128 (38.3)
Poorly differentiated	59 (17.7)	75 (22.5)
Undifferentiated	3 (0.9)	5 (1.5)
Unknown	99 (29.6)	89 (26.6)
Missing	0	2 (0.6)
Stage at initial diagnosis (n, %)		
0	7 (2.1)	6 (1.8)
I	55 (16.5)	48 (14.4)
II	99 (29.3)	107 (32.0)
III	58 (17.4)	62 (18.6)
IV	115 (34.4)	108 (32.3)
Unknown	0	3 (0.9)
Missing	1 (0.3)	0
Stage at time of study entry (n, %)		
III	1 (0.3)	3 (0.9)
IV	333 (99.7)	331 (99.1)
Time since initial diagnosis of primary site (months)		
n	334	333
Mean (SD)	74.7 (75.4)	75.2 (82.8)
25^{th} Percentile	2.0	2.0
Median	58.1	52.1
75^{th} Percentile	126.1	115.9
Disease free interval (n, %)		
De novo	114 (34.1)	113 (33.8)
Non de novo	220 (65.9)	221 (66.2)
≤12 months	4 (1.2)	10 (3.0)
>12 to ≤ 24 months	14 (4.2)	15 (4.5)
>24 months	202 (60.5)	195 (58.4)
Unknown	0	1 (0.3)
Types of lesions at baseline (n, %)		
Target only	32 (9.6)	28 (8.4)
Non-target only	77 (23.1)	88 (26.3)
Both target and non-target	224 (67.1)	217 (65.0)

Unknown	1 (0.3)	1 (0.3)
HER2 receptor status (n, %)		
Positive	1 (0.3)	1 (0.3)
Negative	333 (99.7)	333 (99.7)
Estrogen receptor status (n, %)		
Positive	332 (99.4)	333 (99.7)
Negative	2 (0.6)	1 (0.3)
Progesterone receptor status (n, %)		
Positive	271 (81.1)	278 (83.2)
Negative	55 (16.5)	49 (14.7)
Unknown	8 (2.4)	7 (2.1)
Estrogen and/or progesterone receptor status (n, %)		
At least one positive	334 (100)	334 (100)
Current extent of disease (metastatic sites) – (n, %)		
Breast	8 (2.4)	11 (3.3)
Bone marrow	0	2 (0.6)
Bone	246 (73.7)	244 (73.1)
Bone only	69 (20.7)	78 (23.4)
Visceral	197 (59.0)	196 (58.7)
Liver	59 (17.7)	73 (21.9)
Lung	153 (45.8)	150 (44.9)
Other	22 (6.6)	18 (5.4)
Skin	15 (4.5)	10 (3.0)
Lymph nodes	133 (39.8)	123 (36.8)
Others	20 (6.0)	10 (3.0)
None	2 (0.6)	1 (0.3)
Number of involved metastatic sites (n, %)		
0	2 (0.6)	1 (0.3)
1	100 (29.9)	117 (35.0)
2	118 (35.3)	103 (30.8)
3	64 (19.2)	72 (21.6)
4	36 (10.8)	22 (6.6)
≥5	14 (4.2)	19 (5.7)

Source: ADSL.xpt, CSR Table 11-4

Table 22. Prior Anti-Neoplastic Therapy

	Ribociclib plus Letrozole N=334 n (%)	Placebo plus Letrozole N=334 n (%)
Any therapy		
Yes	334 (100)	334 (100)
Surgery (including biopsy)		
Yes	334 (100)	334 (100)
Radiotherapy		
Yes	178 (53.3)	167 (50.0)
No	156 (46.7)	167 (50.0)
Medication Setting[1]		
Adjuvant	195 (58.4)	189 (56.6)
Neoadjuvant	41 (12.3)	28 (8.4)
Palliative	20 (6.0)	21 (6.3)
Prevention	3 (0.9)	2 (0.6)
Other	24 (7.2)	18 (5.4)
Medication: Chemotherapy Setting[1]		
Adjuvant	118 (35.3)	127 (38.0)
Neoadjuvant	41 (12.3)	25 (7.5)
Palliative	1 (0.3)	1 (0.3)
Other	1 (0.3)	0
Medication: Hormonal Therapy Setting[1]		
Adjuvant	175 (51.8)	166 (49.7)
Neoadjuvant	0	4 (1.2)
Palliative	19 (5.7)	20 (6.0)
Prevention	3 (0.9)	2 (0.6)
Other	23 (6.9)	18 (5.4)
Medication: Other Therapy Setting[1]		
Adjuvant	5 (1.5)	2 (0.6)
Neoadjuvant	1 (0.3)	0
Type of last therapy[3]		
Chemotherapy	7 (2.1)	10 (3.0)
Hormonal Therapy	129 (38.6)	134 (40.1)
Radiotherapy	75 (22.5)	64 (19.2)
Surgery (non-biopsy)	57 (17.1)	62 (18.6)
Setting at last therapy[4]		
Adjuvant	136 (40.7)	135 (40.4)
Neoadjuvant	1 (0.3)	2 (0.6)
Palliative[2]	45 (13.5)	45 (13.5)

Prevention	2 (0.6)	5 (1.5)
Other	21 (6.3)	18 (5.4)

Source: ADSL.xpt, CSR Table 11-5

(1) A patient may have received treatment in more than one setting
(2) These were the patients who received palliative therapy (including medication and radiotherapy) as last therapy prior to randomization.
(3) Last therapy was defined as the last therapy prior to the first dose.
(4) Setting at last therapy was not applicable if the type of last therapy was surgery.

Patients who took letrozole or anastrozole for >14 days or patients who were on any prior neoadjuvant anti-cancer therapy which were not stopped at least 5 half-lives or 7 days before randomization were excluded.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant endorses that no formal treatment compliance measurements were performed for either the ribociclib plus letrozole or placebo plus letrozole arms. Instead, compliance was assessed by the Investigator examining drug administration records and the number of boxes, tablets, capsules dispensed, received, and returned.

A similar number of patients in the ribociclib plus letrozole (98.2%) and placebo plus letrozole (98.5%) received concomitant medications during the study. Notably, use of bisphosphonates (26.3% vs. 23.9%), denosumab (30.8% vs. 25.2%), and corticosteroids (21.9% vs. 15.8%) was comparable in both treatment arms. A higher proportion of patients used prohibited concomitant medications in the ribociclib plus placebo group (31.1% vs. 18.8%); the most commonly used medications were levofloxacin (8.1% vs. 3.3%) and ciprofloxacin (7.2% vs. 6.1%).

Rescue medications were not applicable in this study.

Reviewer comment*: The use of bisphosphonate/denosumab therapy for (1) the treatment of osteoporosis and (2) prevention of skeletal related events for patients with bone metastases was permitted in MONALEESA-2. Given that that the use of this medications was fairly balanced, there was likely minimal impact on treatment efficacy.*

In addition, when an analysis was done adjusting for the use of concomitant bisphosphonate/denosumab therapy, there was no interaction with the treatment arm. When including denosumab and bisphosphonate therapy in a multivariate cox proportional hazard model for PFS, the two bone concomitant medications had a similar HR of approximately 0.87.

Efficacy Results – Primary Endpoint

Investigator-assessed Progression Free Survival

MONALEESA-2 was deemed to show superior efficacy based upon an interim analysis of PFS when 243 total progressions occurred (80.5% of the planned events for the final PFS analysis). The results from the interim analysis are displayed in Table 23 below. Since the estimated hazard ratio crossed the pre-defined hazard ratio threshold of 0.56, the trial was deemed to have superior efficacy. Based upon the interim analysis results, the trial demonstrated a statistically significant improvement in PFS in favor of the ribociclib plus letrozole arm. A Kaplan-Meier plot of the PFS results based upon the interim analysis is shown in Figure 6.

At the 90-day safety update, the Applicant provided approximately 5 months of additional follow-up for progression. This additional follow-up included an additional 54 progression events across both arms. Results based upon the update are shown in Table 24, and a Kaplan-Meier plot of the data is shown in Figure 7. Note that these results are from an unplanned analysis of PFS.

The Applicant provided an additional analysis of PFS at the second interim analysis of OS which was not a planned PFS analysis. Table 25 shows the results of this analysis. The results remained consistent with those seen in the previous two analyses. The median PFS in the ribociclib + letrozole arm is now 25.3 months.

Reviewer comment*: The updated results showed good concordance with the interim analysis of PFS and further support the efficacy of the ribociclib plus letrozole arm over letrozole alone. At the updated analysis, the median was reached in the ribociclb + letrozole arm, but the results were not used in the label because this was an unplanned analysis of PFS.*

Table 23. Primary Analysis Results (PFS by investigator) at Interim Analysis

	Ribociclib plus Letrozole N=334	**Placebo plus Letrozole N=334**
Events, n (%)	93 (27.8)	150 (44.9)
Censored	241 (72.2)	184 (55.1)
Median, months (95% CI)	NE (19.3, NE)	14.7 (13.0, 16.5)
Hazard Ratio, estimate (95% CI)	0.556 (0.429, 0.720)	
p-value	< 0.0001	

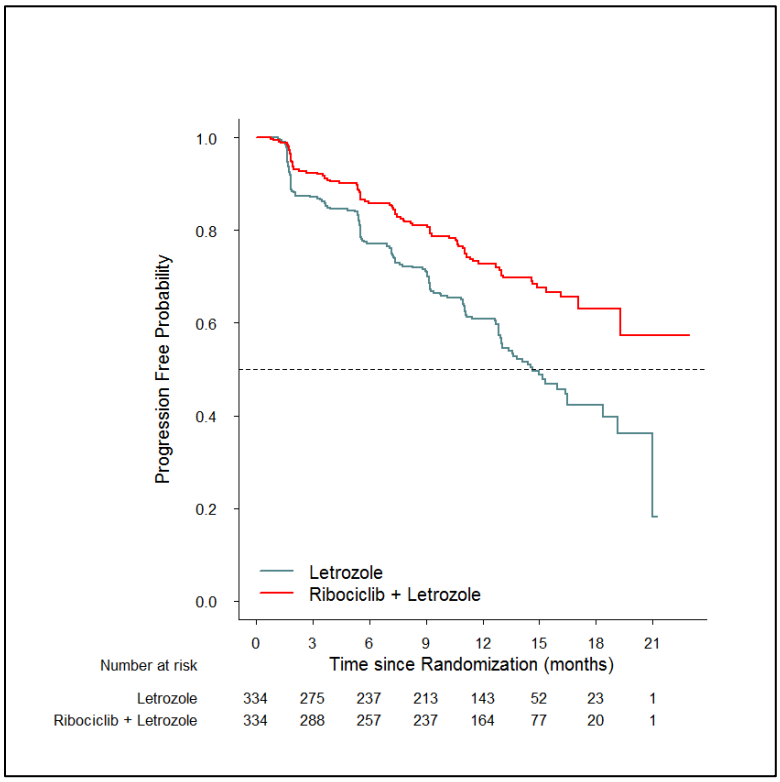
Source: Reviewer's analysis (adrecsl.xpt)

(1) NE=not estimable

(2) These results are based upon a pre-defined interim analysis of PFS.

(3) The data cutoff was January 29, 2016.

Figure 6. Kaplan-Meier Plot of Primary Analysis Results (PFS by investigator) at Interim Analysis



Source: Reviewer's analysis, adrecsl.xpt

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Table 24. Primary Analysis Results (PFS by investigator) at June 22, 2016 cutoff

	Ribociclib plus Letrozole N=334	**Placebo plus Letrozole N=334**
Events, n (%)	118 (35.3)	179 (53.6)
Censored	216 (64.7)	155 (46.4)
Median, months (95% CI)	22.4 (20.8, NE)	15.3 (13.4, 16.7)
Hazard Ratio, estimate (95% CI)	0.559 (0.443, 0.706)	

Source: Reviewer's Analysis (adrecsl.xpt)

(1) NE=not estimable

(2) These results are from a unplanned analysis of PFS

Table 25. Primary Analysis Results (PFS by investigator) at 2nd Interim Analysis for OS

	Ribociclib plus Letrozole N=334	**Placebo plus Letrozole N=334**
Events, n (%)	140 (41.9)	205 (61.4)
Censored	194 (58.1)	129 (38.6)
Median, months (95% CI)	25.3 (23.0, 30.3)	16.0 (13.4, 18.2)
Hazard Ratio, estimate (95% CI)	0.568 (0.457, 0.704)	

Source: Applicant efficacy update Table 3-2

(1) These results are from a unplanned analysis of PFS

(2) The cutoff date for this analysis was January 2, 2017

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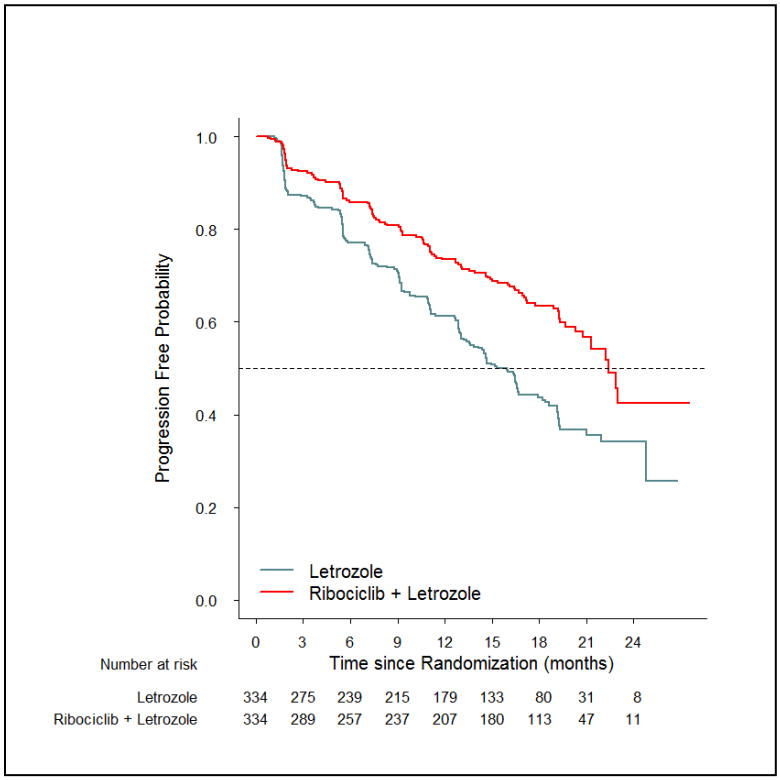
Figure 7. Kaplan-Meier Plot of Primary Analysis Results (PFS by investigator) at Update



Source: Reviewer's analysis, based upon dataset adrecsc.xpt

(1) Results based upon cutoff date of June 22, 2016

(2) These results are based upon an unplanned analysis of PFS.

Efficacy Results – Secondary and other relevant endpoints

BICR-Assessed Progression Free Survival

The Applicant conducted a blinded independent central review (BICR) of the primary PFS results. Table 26 displays the results of the BICR review at the time of the interim analysis of PFS. Although the overall rate of progression events decreased compared with the primary analysis of PFS, the hazard ratio estimate provides support for the efficacy of ribociclib plus letrozole over letrozole alone.

To examine the discordance between the BICR results and the INV results, we estimated the early discrepancy rate (EDR) and late discrepancy rate (LDR) for each arm. The EDR and LDR are two ways to measure the differences between the primary investigator results and the secondary BICR results. By estimating the rates on each arm and then computing the difference, we can get a sense whether investigator bias exists in the primary results.

The EDR rate for the ribociclib + letrozole arm was 58% and the EDR rate on the letrozole arm was 60%. The LDR rate on the ribociclib + letrozole arm was 30.8% and the LDR rate on the

letrozole arm was 27%. Since the differences between arms was less than 5%, there appears to be minimal bias in the primary PFS results.

Table 26. PFS Results assessed by BICR at interim analysis

	Ribociclib plus Letrozole N=334	**Placebo plus Letrozole N=334**
Events, n (%)	50 (15.0)	72 (21.6)
Censored	284 (85.0)	262 (78.4)
Median, months (95% CI)	22.9 (NE, NE)	NE (NE, NE)
Hazard Ratio, estimate (95% CI)	0.592 (0.412, 0.852)	
p-value	< 0.0001	

Source: CSR Table 11-7

(1) BICR = blinded independent review committee
(2) NE = not estimable
(3) The data cutoff was January 29, 2016.

Reviewer Comment: *Since the EDR and LDR are nearly identical between the arms, it suggests minimal bias exists in the primary PFS results.*

Overall Survival

Overall survival results were tested at the time of the interim analysis for PFS, but the results were not significant. OS was also tested at a 2nd interim analysis; the results were also not significant. Table 27 displays the OS results at the time of the first interim OS analysis, and Table 28 presents the results of the 2nd interim analysis. Figure 8 shows a Kaplan-Meier plot of the OS results from the 2nd interim analysis.

Reviewer Comment*: OS was immature at the time of the interim PFS analysis. However despite this, the statistically significant improvement in PFS associated with ribociclib plus letrozole is considered clinically meaningful and of value to patients given the delay of subsequent potentially toxic chemotherapy.*

Table 27. Interim OS Results (Jan 29, 2016 cutoff)

	Ribociclib plus Letrozole N=334	**Placebo plus Letrozole N=334**
Death Events, n (%)	23 (6.9)	20 (6.0)
Censored	311 (93.1)	314 (94.0)
Median, months (95% CI)	NE (NE, NE)	NE (NE, NE)
Hazard Ratio, estimate (95% CI)	1.128 (0.619, 2.055)	
p-value	0.653	

Source: CSR Table 11-12

(1) NE = not estimable

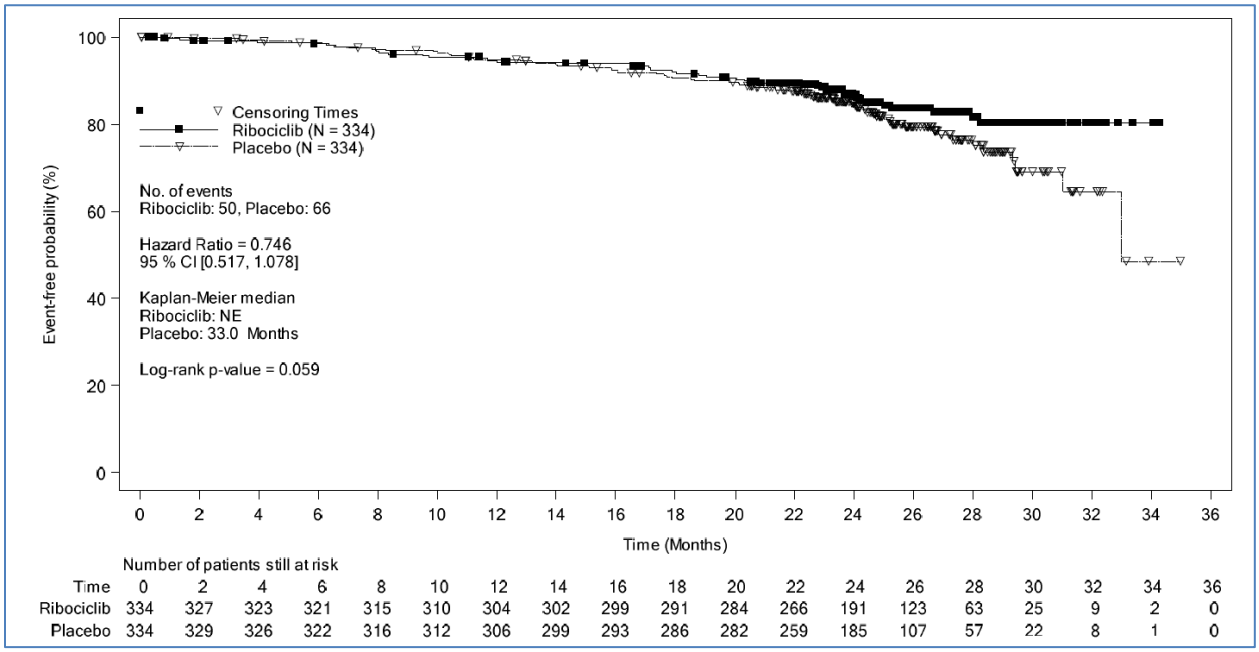
Table 28. 2nd Interim OS Results (Jan 2, 2017 cutoff)

	Ribociclib plus Letrozole N=334	**Placebo plus Letrozole N=334**
Death Events, n (%)	50 (15.0)	68 (19.8)
Censored	284 (85.0)	268 (80.2)
Median, months (95% CI)	NE (NE, NE)	33.0 (33.0, NE)
Hazard Ratio, estimate (95% CI)	0.746 (0.51, 1.08)	
p-value	0.09	

Source: Applicant updated efficacy analysis (Table

(1) NE = not estimable

Figure 8: Kaplan-Meier plot of OS from 2nd interim analysis



Source: Applicant's updated efficacy analysis (Figure 2-1)

Objective Response Rate

The objective response rate at the time of the interim analysis in the ribociclib + letrozole arm was 40.7% with a 95% CI = (35.4, 46.0). The objective response rate in the letrozole arm was 27.5% with a 95% CI = (22.8, 32.3).

Reviewer Comment: *The ORR results help support the activity of ribociclicb in combination with letrozole.*

Additional Analyses Conducted on the Individual Trial

Table 29 shows the primary PFS results by relevant demographic and geographic subgroups. There does not appear to be major differences in efficacy in the subgroups shown.

Table 29. Primary PFS Results by Subgroup

	N	HR	95% CI
AGE			
< 65 Years Old	373	0.52	0.38, 0.72
>= 65 Years Old	295	0.61	0.40, 0.94
RACE			
White	549	0.61	0.46, 0.82
Black	17	0.32	0.02, 3.5
Asian	51	0.44	0.19, 1.00
REGION			
United States	213	0.46	0.29, 0.74
Elsewhere	455	0.60	0.44, 0.82

Source: Reviewer's Analysis, (adrecsl.xpt)

Exploratory subgroup analyses of the primary PFS endpoint were performed on four biomarkers subgroups: Ki67, Cyclin D1, Rb (H-score), and P16 (H-score). Cutpoints used for these exploratory analyses were taken from the clinical study report as determined by the applicant. For Ki67 levels less than 14% (N=107), the HR was 0.636 (0.389, 1.039), and above 14% (127)the HR was 0.44 (0.293, 0.661). For Cyclin D1 levels less than 2001.6 (N=102), the HR was 0.497 (0.309, 0.798), above 2001.6 (N=105), the HR was 0.597 (0.375, 0.950). For high levels of Rb, the HR was 0.502 (0.360, 0.701), and for low levels of Rb, the HR was 0.588 (0.266, 1.303). And finally for low P16 levels (N=89), the HR was 0.581 (0.341, 0.989); for moderate P16 levels (N=88), the HR was 0.576 (0.350, 0.947); for high P16 levels (N=31), the HR was 0.404 (0.157, 1.042).

Sensitivity Analyses

Additional sensitivity analyses were done to assess the robustness of the PFS primary endpoint. An unstratfied analysis of the primary endpoint gave a HR equal to 0.56 (95% CI: 0.430, 0.721). When patients were not censored for receiving chemotherapy, the HR equaled to 0.56 (95% CI: 0.431, 0.720). Finally, when analyzing the per protocol set, the HR equaled 0.536 (95% CI: 0.409, 0.702).

Reviewer Comment: *These sensitivity analyses support the overall conclusion of ribociclib efficacy.*

Patient Reported Outcomes

Patient reported outcome (PRO) data was collected on the same interval as the primary endpoint radiological data: every 8 weeks for the first 18 months and 12 weeks thereafter. Subjects completed PRO data using the EORTC QLQ-C30, the EORTC QLQ-BR23, and the EQ-5D-5L instruments. Compliance for all three instruments at nearly every follow-up visit was good, with compliance levels almost always being above 90% for the first 60 weeks of study follow-up. There also did not appear to be a difference in compliance between the two study arms.

The primary PRO endpoint of interest was global QoL. For time to deterioration of global QoL (10% drop), the HR for the ribociclib + letrozole arm vs. the letrozole only arm was 0.890 (95% CI: 0.670, 1.182). For the mean change from baseline in the global QoL scale, the two arms showed a similar trend and both arms showed improvement in QoL, except for the end of treatment score (EOT) score. Figure 9 below displays the longitudinal trend of the mean change from baseline for the global QoL scale.

For mean changes from baseline to the end of treatment, analyses on the symptom and functional scales of the EORTC QLQ-C30 yielding no differences between the arms. Similar results were seen on scales for the EORTC QLQ-BR23 and the EQ-5D-5L.

Reviewer's Comment: Patient reported outcomes were not allocated alpha so any results should be considered exploratory.

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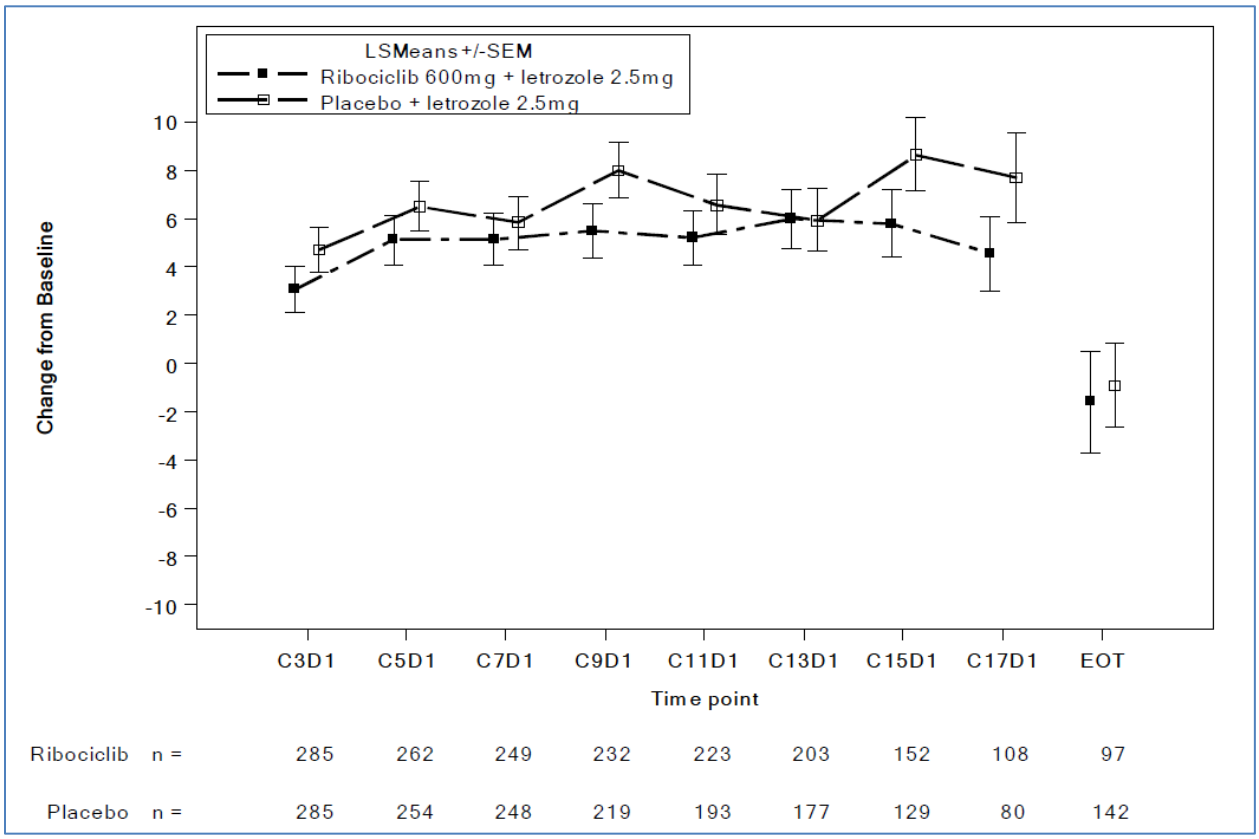
Figure 9. Change from Baseline for Global health status/QoL scale (QoL) score of the EORTC QLQ-C30



CXD1 = Cycle X, Day 1; EOT = End of Treatment

7.3 Intergrated Review of Effectiveness

7.3.1 Assessment of Efficacy Across Trials

Not applicable as the primary efficacy evaluation for ribociclib was based on one trial, MONELESSA-2 as described in sections 7.1 and 7.2.

7.3.2 Integrated Assessment of Effectiveness

Not applicable as the primary efficacy evaluation for ribociclib was based on one trial, MONELESSA-2 as described in sections 7.1 and 7.2.

7.4 Review of Safety

Safety Summary

In this NDA, the Applicant submitted safety data for 964 patients/subjects (industry-sponsored clinical studies) (original submission, 29 August 2016). However, the clinical safety data

supporting this NDA is primarily derived from the Phase 3 registration Study A2301 (also referred to as MONALEESA-2) which enrolled 664 subjects (334 patients in the ribociclib plus letrozole arm, and 330 in the placebo plus letrozole arm), as only this trial and Study X2107 had the dose, schedule, and combination of the proposed indication. The Applicant also submitted supportive safety, efficacy, and PK data for ribociclib plus exemestane from Study X2106 and PK data for ribociclib plus anastrozole from Study E2301 (MONALEESA-7), as described below.

Key safety findings from MONALEESA-2, and from the supportive safety database:

- **Deaths**: There were 4 deaths (3 in the ribociclib plus letrozole group and 1 in the placebo plus letrozole group) within 30 days of study treatment. One subject in each group died from progression of breast cancer. The remaining 2 deaths in the ribociclib group were attributed to sudden death and death from unknown cause.

- **Serious Adverse Events (SAEs), Discontinuations and Dose Modifications**: SAEs were more common in the ribociclib plus letrozole arm compared with the placebo plus letrozole arm (21.3 vs. 11.8%). Treatment-emergent adverse events (TEAEs) leading to drug discontinuation were more frequent in the ribociclib plus letrozole arm compared with the placebo plus letrozole arm (15.0% vs. 3.0%, any grade). The most common TEAEs (any grade, >1% incidence) in the ribociclib plus letrozole arm requiring dose discontinuation were increased ALT, increased AST, and vomiting. TEAEs leading to drug interruption were more frequent in the ribociclib plus letrozole arm compared with the placebo plus letrozole arm (71.3% vs. 14.8%, any grade). The most common TEAEs (any grade, >5% incidence) in the ribociclib plus letrozole arm requiring dose interruption were neutropenia, decreased neutrophil count, vomiting, nausea, increased ALT, and decreased WBC.

- **Grade 3 and 4 Adverse Reactions:** At the preferred term level, the most common grade 3-4 adverse events in the ribociclib plus letrozole arm were Neutropenia (48.2%), Neutrophil Count Decreased (14.1%), and White Blood Cell Count Decreased (12.9%). No grade 5 adverse events were noted.

- **Common Adverse Reactions:** In MONALEESA-2, the common preferred-term level TEAEs (i.e., ≥10% of patients) in the ribociclib plus letrozole arm were Neutropenia (60.8%), Nausea (51.2%), Fatigue (35.9%), Diarrhea (35.0%), Alopecia (33.2), Vomiting (29.3), and Arthralgia (27.2%). The most frequently reported TEAEs in the placebo plus letrozole arm were Fatigue (30.3%), Arthralgia (28.8%), and Nausea (28.5%).

- **Neutropenia:** In Study A2301, neutropenia AEs occurred in a higher proportion of patients in the ribociclib plus letrozole group (n=249, 74.6%) compared with the placebo plus letrozole group (n=17, 5.2%). Grade 3 or 4 grouped neutropenia events occurred in 199 patients (59.6%). There were 6 reported febrile neutropenia events in 5 patients

(1.5%) who received ribociclib plus letrozole; all events were noted by the Investigators to be related to study treatment.

- **Hepatotoxicity:** Hepatic AEs occurred in 78 patients (23.4%) in the ribociclib plus letrozole compared with 40 (12.1%) patients in the placebo plus letrozole group. The most frequent AEs (≥ 2% of patients), regardless of causality, were ALT increased, AST increased, blood ALP increased, GGT increased, and blood LDH increased. Four patients (1.2%) in the ribociclib plus letrozole group met the biochemical definition of Hy's law; three cases were related to study treatment and none resulted in death.

- **QT Interval Prolongation:** QT interval prolongation AEs were more frequently reported in the ribociclib plus letrozole group compared with the placebo plus letrozole group (7.8% vs. 2.4%), with more grade 3/4 events reported in the patients treated with ribociclib plus letrozole (2.4% vs. 0.6%, respectively). The most frequent AEs reported in ribociclib plus letrozole group compared with placebo plus letrozole group were electrocardiogram QT prolonged (4.5% vs 1.2%) and syncope (2.7% vs 0.9%).

7.4.1 Safety Review Approach

The clinical safety data supporting this NDA is primarily derived from the Phase 3 study MONALEESA-2 (A2301) which is a randomized double-blind, placebo-controlled multi-center study of ribociclib plus letrozole for the treatment of post-menopausal women with hormone receptor positive, HER2-negative, advanced or metastatic breast cancer who received no prior therapy for advanced disease. MONALESSA-2 is described above in Section X.X.

In addition, in mid-cycle communication dated January 9, 2017, FDA agreed with the Applicant to consider additional data in support of an indication expansion for ribociclib in combination with an aromatase inhibitor. To this end, the Applicant submitted supportive safety, efficacy, and PK data for ribociclib plus exemestane from Study X2106 and PK data for ribociclib plus anastrozole from Study E2301 (MONALEESA-7).

Study X2106 is an ongoing open label, phase Ib, dose finding study, evaluating ribociclib plus exemestane (doublet) and ribociclib plus everolimus plus exemestane (triplet) combination treatments in patients with ER+/HER2- advanced breast cancer who were resistant to prior letrozole or anastrozole therapy. For all patients, the starting dose was ribociclib 600 mg 3 weeks on 1 week off with a standard dose of exemestane 25 mg daily, which was subsequently confirmed to be the RP2D. The Applicant submitted interim analysis results for key safety, efficacy and PK parameters from the doublet combination (ribociclib plus exemestane, n=14). The cut-off date for this analysis was November 3, 2016.

Study E2301 (MONALEESA-7) is an on-going, double blind, Phase III trial comparing the combination of tamoxifen or non-steroidal aromatase inhibitor (letrozole or anastrozole) (plus goserelin) and ribociclib or placebo in premenopausal women with HR+, HER2-negative,

advanced breast cancer who received no prior hormonal therapy for advanced disease. The Applicant submitted supportive PK data for 70 patients who are receiving/have received treatment with ribociclib/placebo and anastrozole (plus goserelin). To preserve data integrity of this ongoing blinded trial, an independent data monitoring committee, external to the Applicant, will review the PK data only.

The Integrated Assessment of Safety (**Section 7.4.10**) succinctly summarizes the review of safety and incorporates these additional studies into the overall safety assessment. In addition, the overall interpretation of these studies and recommendation for ribociclib approval and indication are described overall in the benefit/risk assessment in Section 1.

Table 30 outlines the safety studies submitted to the NDA, as well as the data cut-offs for initial submission.

Table 30. Summary of Safety Populations submitted to NDA 209092

Study [A]	Design	Population	N	Status	Cut-off (NDA)
Study X1101	Phase 1	Advanced solid tumors	13	Completed	-
Study XUS03	Phase 2	Solid tumors and/or hematologic malignancies	106	Ongoing	18 August 2015
Study X2101	Phase 1	Advanced solid tumors or lymphomas	134	Ongoing	18 September 2015
Study X2107	Phase 1b	Breast cancer	47	Ongoing	30 October 2015
Study X2106	Phase Ib	Advanced Breast Cancer with Resistance to Prior Letrozole or Anastrozole	14[C]	Ongoing	3 November 2016
Study E2301	Phase 3 R	Advanced Metastatic or Recurrent Breast Cancer (pre-menopausal)	70[D]	Ongoing	02 November 2016
Study A2301[B]	Phase 3 R	Advanced Metastatic or Recurrent Breast Cancer (post-menopausal)	664	Ongoing	29 January 2016

A: Healthy Volunteer Studies and Investigator-Initiated Research Studies are not included in this Table.
B: Blinded therapy
C: Supportive safety, efficacy, and PK data for ribociclib plus exemestane
D: Supportive PK data for ribociclib plus anastrozole
Source: modified Table 1-1 (Summary of Clinical Safety, page 18)

Safety Update
A 90-day safety update of MONALEESA-2 was submitted to FDA on November 18, 2016 which provided longer-term follow-up (approximately five additional months) with data cutoff of June

22, 2016. Median follow-up now extends to 20.1 months (compared with 15.3 months at the time of the original submission). Due to the review timeline associated with the original NDA submission, this review is based primarily on the original data cutoff however data was consistent with what was previously demonstrated.

Reviewer Comment*: The 90-day safety update demonstrated no new safety findings and did not change the overall assessment of safety. From January 29, 2016 (original cutoff date) to June 22, 2016 (90-day safety update cutoff date), there were 3 additional deaths in the ribociclib plus letrozole arm within 30 days of the last dose of ribociclib plus letrozole. Review of the death narratives suggests that two of these deaths were attributable to acute respiratory failure and 1 death was attributed to pneumonia. There were no additional cases of death due to cardiac etiology or sudden death.*

7.4.2 Review of the Safety Database

Overall Exposure

Exposure to ribociclib plus letrozole and letrozole in MONALEESA-2 is summarized in Table 31 below. Median relative dose intensity was 87.5% for ribociclib and 100% for placebo. The median daily dose of ribociclib was 525.2 mg (range: 190.9 mg to 671.4 mg). The median daily dose of letrozole was 2.5 mg in both the ribociclib plus letrozole arm (range: 1.8-2.5 mg) and the placebo plus letrozole arm (range: 2.2-2.5 mg).

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Table 31. Drug Exposure and Dose Intensity (Safety Population)

	Ribociclib / Placebo		Letrozole	
	Ribociclib plus Letrozole (N=334)	**Placebo plus Letrozole (N=330)**	**Ribociclib plus Letrozole (N=334)**	**Placebo plus Letrozole (N=330)**
Median exposure (months)	12.2	12.4	13.0	12.4
Dose reduction (%)	180 (53.9)	22 (6.7)	-	-
Dose interruption (%)	257 (77.0)	134 (40.6)	132 (39.6)	107 (32.4)
Mean Cumulative dose	120151.5	149605.5	891.2	836.3
Median Cumulative dose	113800	168000	981.3	942.5
Mean Relative dose intensity (%)	80.9	98.8	98.9	99.4
Median Relative dose intensity (%)	87.5	100	100	100

Source: Tables 12-1, 12-2, 12-3 MONALEESA-2 CSR

Relevant characteristics of the safety population:

Both the safety and efficacy populations used in the following analyses derive primarily from the pivotal Phase 3 MONALEESA-2 trial. As discussed earlier in the discussion of efficacy, the demographic and other baseline disease characteristics were largely balanced between both treatment arms and have been summarized earlier.

Adequacy of the safety database:

The clinical safety data supporting this NDA is primarily derived from the Phase 3 registration Study A2301 (also referred to as MONALEESA-2) which enrolled 664 subjects (334 patients in the ribociclib plus letrozole arm, and 330 in the placebo plus letrozole arm).

Reviewer Comment: *The randomized, placebo-controlled, double-blinded MONALEESA-2 trial is of adequate size to serve as the safety database considering exposure to the appropriate doses, duration of treatment, patient demographics, and disease characteristics with reference to the U.S. target population.*

7.4.3 Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The submission contains all required components of the eCTD. The overall quality and integrity of the application appear to be acceptable. Requests for additional information from the applicant throughout the review process were addressed in a timely fashion.

Categorization of Adverse Events

The Applicant provided detail regarding how adverse events (AEs) were defined. The occurrence of an AE was sought by non-directive questioning of the subject at each visit during the study and 30 days after the last dose of study drug. AEs could also be detected when volunteered by the patient during, between visits or through physical examination, laboratory test results, or other assessments. The Applicant endorses that a consistent approach to the collection of AEs was adopted across studies. Subjects were queried about the occurrence of AEs at each clinic visit. AEs were reported on case report forms (CRFs) using investigator verbatim terms and subsequently coded using the Medical Dictionary for Regulatory Activities.

All AEs and SAEs were coded according to Medical Dictionary for Regulatory Activities (MedDRA). Individual CSRs used the version of MedDRA that was current at the time of the study; Study A2301, Study X2107, and Study X2101 all used MedDRA version 18.1; Study XUS03, version 18.0; and Study X1101, version 17.1. For the Summary of Clinical Safety datasets for both combination therapy and monotherapy safety data, the AEs were mapped to MedDRA version 18.1.

AEs were summarized by MedDRA primary system organ class (SOC), and by Preferred term (PT). The NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 was used for Study X2101 while Version 4.03 was used for Studies A2301, X2107, XUS03, and X1101.

In the Summary of Clinical Safety (page 11), the Applicant noted that preferred terms were combined as follows: neutropenia (inclusive of granulocytopenia, neutropenia, and neutrophil count decreased); leukopenia (inclusive of leukopenia and white blood cell count decreased).

Reviewer Comment: *In the Analysis of Submission-Specific Safety issues (e.g. neutropenia, hepatotoxicity and drug induced liver injury, QT interval prolongation), the reviewer describes additional preferred term combinations that may have been used in FDA analyses.*

Routine Clinical Tests

In MONALEESA-2, routine laboratory analyses (including hemoglobin, WBC, neutrophils, lymphocytes, platelet count. BUN (or urea), creatinine, albumin, AST/ALT, total bilirubin, alkaline phosphatase, LDH, sodium, potassium, calcium, magnesium, phosphorous, fasting glucose, coagulation panel) were obtained at screening (≤7 days prior to dosing), Day 15 of cycle 1, and Day 1 of cycles ≥2 and at the end of treatment visit. Urinalysis was performed at screening and Day 1 of cycles ≥2.

Vital signs and physical exams were obtained at screening (Days -7 to -1), during each cycle, and at the study drug completion visit (within 15 days after last dose of study drug).

Scheduled three consecutive (i.e. triplicate) 12-lead ECGs were performed approximately 2 minutes apart to determine the mean QTc interval.

Screening: 7 days prior to randomization (baseline)
Cycle 1: Day 15 (pre-dose and 2 hours post dose)
Cycles 2-3: Day 1 (pre-dose and 2 hours post dose)
Cycles 4-5: Day 1 (pre-dose)
Cycle 6: Day 1 (pre-dose and 2 hours post dose)
Cycles 7-8: Day 1 (pre-dose)
Cycle 9: Day 1 (pre-dose and 2 hours post dose)
All other cycles (for patients with mean QTcF ≥ 481 ms at any time prior to cycle 10): Day 1 (pre-dose and 2 hours post dose)

Reviewer Comment: *Pregnancy test was not conducted in the study as inclusion specified only post-menopausal patients were eligible.*

7.4.4 Safety Results

Deaths

Deaths listed here include deaths during treatment, deaths occurring up to 30-days of last dose of study drug, and deaths more than 30 days after the last dose of study treatment, as of the clinical cut-off data for the report on January 29, 2016.

Table 32 summarizes the primary causes of death for patients in the all treated safety population in Trial A2301.

Table 32. A2301 Summary of Deaths (All Treated Population)

Primary Cause of Death	**Ribociclib plus letrozole N=334 n (%)**	**Placebo plus letrozole N=330 n (%)**
Patients who Died	23 (6.9%)	19 (5.8%)
Disease Progression	18 (5.4%)	17 (5.1%)
Other	5 (1.5%)	2 (0.6%)
30 Days of Last Dose		
Disease Progression	1 (0.3%)	1 (0.3%)
Other	2 (0.6%)	0 (0%)
After 30 days of Last Dose		
Disease Progression	17 (5.1%)	16 (4.8%)
Other	3 (0.9%)	2 (0.6%)

Source: Clinical Study Report Listing 14.3.2-1.1, ADZD.xpt

Summary of Deaths (Disease Progression) within 30 Days of Last Dose (Ribociclib plus letrozole group)

There was one death attributable to disease progression in the ribociclib plus letrozole arm. The CRF for this patient was reviewed. Subject A2301-3118-002 was discontinued from the study on 26 April 2015 due to progressive disease. The patient expired on (b) (6) due to breast cancer tumor progression.

Reviewer Comment: This reviewer agreed with the cause of death as progressive disease.

Summary of Deaths (Other Causes) within 30 Days of Last Dose (Ribociclib plus letrozole group)

Table 33 below summarizes the narratives for the patients in the ribociclib plus letrozole group with reasons for death other than disease progression within 30 days of the last ribociclib dose.

Table 33. A2301 Deaths for Other than Disease Progression Up to 30 Days of Last Dose (All Treated Population)

Patient ID Group	**Summary of Case**	**Reviewer Comment**
A2301-3113-001 Ribociclib plus letrozole	77 year old female with breast cancer metastatic to sites including bone and skin. Her last dose of ribociclib was on Study Day 5 (16 June 2014). The study treatment was temporarily interrupted on Day 6 and then permanently discontinued	The death is unexplained. She received ribociclib for 4 days before discontinuing study treatment. An information request was sent on 8

Patient ID Group	Summary of Case	Reviewer Comment
	secondary to bone pain. The patient died on Study Day (b) (6) due to unknown reason. An autopsy was not performed. The investigator-attributed relationship to study treatment was "not suspected."	December 2016 to the Applicant for additional information. Following review of this clinical information including the narrative, case report form, and response to FDA information request containing an Investigator letter, laboratory data, and radiology reports, it is difficult to assess the cause of death and this reviewer agrees with attributing death to unknown cause which should be related to ribociclib.
A2301-4102-002 Ribociclib plus letrozole	52 year old woman with breast cancer metastatic to sites including lung, bone and supraclavicular lymph nodes. Notably, the patient continued treatment with methadone (a prohibited concomitant study medication due to QT prolongation risk) after beginning study treatment. Screening ECGs were abnormal with depressed ST segments and premature ventricular complexes. QTcF values were 413 ms, 435 ms, 444 ms and 447 ms. On Study Day 14, ECGs were abnormal with flat T waves and ventricular premature complexes (one ECG with frequent ventricular premature complexes >2): Pre-dose QTcF values were 385 ms, 385 ms, and 443 ms; Post-dose QTcF values: 461 ms, 472 ms, and 487 ms; reported as prolonged electrocardiogram QTcF interval, grade 1. Day 29, ECG QT prolonged worsened to grade 2 with pre-dose QTcF values at 472	The death was most likely due to sudden cardiac death related to ribociclib, based on the information provided. No autopsy was performed. She demonstrated QT prolongation during treatment as seen on ECGs at Study Days 14 and 29.However, no ECG or laboratory follow up occurred between Day 29 and death. The patient was known to be on concomitant methadone during treatment with ribociclib, though methadone was discontinued three weeks before death. The Applicant conducted retrospective review of

Patient ID Group	Summary of Case	Reviewer Comment
	ms, 487 ms, and 492 ms with persistent flat T waves and ventricular premature complexes; contemporaneous neutropenia (grade 3), hypokalemia (grade 3) with a potassium level of 2.70 mmol/L (central lab) and 3.1 mmol/L (grade 2 at local laboratory); oral potassium supplements were initiated. Ribociclib was continued on Day 29 at the same planned dose of 600 mg. Post-dose ECGs performed approximately 7 hours after the pre-dose ECGs showed QT prolongation improved to grade 1 with post-dose QTcF values of 479 ms, 488 ms, and 458 ms. Flat T waves and ventricular premature complexes, present since baseline, were still reported on the post-dose ECGs. On Study Day (b) (6) the patient had sudden death (grade 4) while sleeping per Investigator. The last dose of the study treatment was on Day 39. No autopsy was performed. The investigator-attributed relationship to study treatment was "suspected."	the ECGs and concluded that it was difficult to accurately measure the QT intervals on the screening and C1D15 visits. She also had grade 3 hypokalemia during study treatment requiring oral potassium supplements.

Source: Narratives, CRFs, ADAE.xpt, ADSL.xpt.

Summary of Deaths (Other Causes) after 30 Days of Last Dose (Ribociclib plus letrozole group)

Three patients in the ribociclib plus letrozole group died due to causes other than disease progression. The CRFs and narratives for these patients were reviewed in detail.

Subject A2301-1700-001 received her last ribociclib dose on 6 April 2015. She expired on (b) (6) days after the last dose of ribociclib). The cause of death was attributed to liver failure with contributory reason as breast cancer.

Subject A2301-3323-003 received her last study dose on 8 March 2015. She expired on (b) (6) days after the last dose of ribociclib). The Applicant noted the primary reason for death as cardiac arrest which was, per the Investigator, unrelated to the study treatment. Breast cancer was listed as a contributing reason for death. It is unknown whether an autopsy was performed.

Subject A2301-5010-003 received her last ribociclib dose on 24September 2014. She expired on (b) (6) days after the last dose of study treatment). The primary reason for death was noted as acute respiratory failure. It is unknown whether an autopsy was performed.

Reviewer Comment: Following review of the CRF and narratives provided for these patients, it is unlikely that death was associated with ribociclib treatment.

Summary of Deaths in Patients with an Ongoing Grade 3 or 4 AE at the Time of Death

There were nine patients who died with an ongoing Grade 3 or 4 AE at the time of death. Three of these patients are summarized above (A2301-3113-001, A2301-4102-002, A2301-5010-003). Six patients had an ongoing Grade 3 or 4 AE at the time of death (where death was attributable to disease progression). These patients are summarized in Table 34 below.

Table 34. Summary of Deaths in Patients with an Ongoing Grade 3 or 4 AE at the Time of Death

Patient ID	Group	Adverse Event (PT)	Grade
A2301-3105-001	Ribociclib plus letrozole	Hepatotoxicity	3
		Ascites	3
		Hepatic Failure	3
		Waist Circumference Increased	3
		Hepatotoxicity	3
		Constipation	3
A2301-3117-003	Ribociclib plus letrozole	Ascites	3
A2301-3118-002	Ribociclib plus letrozole	Lymphocyte Count Decreased	3
		General Physical Health Deterioration	3
A2301-3121-001	Ribociclib plus letrozole	Anxiety	3
		Hypoaesthesia Oral	3
A2301-3123-001	Ribociclib plus letrozole	Tumour Marker Increased	3
A2301-3501-002	Ribociclib plus letrozole	Neutropenia	3

Reviewer Comment: Review of the narrative for patient A2301-3105-001 suggests that breast cancer progression involving the liver likely contributed to these LFT increases. The patient's cause of death was reported as breast cancer with hepatic failure due to liver metastases.

Serious Adverse Events

Serious adverse events (SAEs) are summarized in Table 35 below. Overall, SAEs were reported in 21.3% patients in the ribociclib plus letrozole arm compared with 11.8% patients in the placebo plus letrozole arm. The most common SAEs (all grades) in the ribociclib plus letrozole group were vomiting and abdominal pain (both 1.5%). Grade 3 and 4 SAEs were reported in 17.4% patients in the ribociclib plus letrozole arm compared with 8.8% patients in the placebo plus letrozole arm.

Table 35. Serious adverse events (those reported for all grades with incidence ≥1.0% in the ribociclib arm)

System Organ Class Adverse Event (preferred term)	**Ribociclib plus letrozole N=334**		**Placebo plus letrozole N=330**	
	All Grades	**Grades 3/4**	**All Grades**	**Grades 3/4**
	n (%)	**n (%)**	**n (%)**	**n (%)**
Total Patients with SAE	**71 (21.3)**	**58 (17.4)**	**39 (11.8)**	**29 (8.8)**
Blood and Lymphatic System Disorders				
Febrile Neutropenia	4 (1.2)	3 (0.9)	0	0
Anaemia	4 (1.2)	2 (0.6)	1 (0.3)	0
Gastrointestinal Disorders				
Vomiting	5 (1.5)	3 (0.9)	2 (0.6)	2 (0.6)
Nausea	4 (1.2)	2 (0.6)	2 (0.6)	2 (0.6)
Constipation	4 (1.2)	2 (0.6)	0	0
Abdominal Pain	5 (1.5)	3 (0.9)	0	0
Investigations				
Alanine Aminotransferase Increased	4 (1.2)	4 (1.2)	0	0
Respiratory, Thoracic And Mediastinal Disorders				
Pleural effusion	2 (0.6)	1 (0.3)	4 (1.2)	3 (0.9)
Dyspnoea	4 (1.2)	3 (0.9)	1 (0.3)	1 (0.3)

Source: ADAE.xpt

Dropouts and/or Discontinuations Due to Adverse Effects

Drug Discontinuation

Treatment-emergent adverse events (TEAEs) leading to drug discontinuation were more frequent in the ribociclib plus letrozole arm compared with the placebo plus letrozole arm

(15.0% vs. 3.0%, any grade). Grade 3 or 4 TEAEs leading to drug discontinuation were also more frequent in the ribociclib plus letrozole arm (11.4% vs. 1.8%). The most common TEAEs (any grade, >1% incidence) in the ribociclib plus letrozole arm requiring dose discontinuation were increased ALT (4.5%), increased AST (2.7%), and vomiting (2.4%). These are summarized in Table 36.

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Table 36. TEAEs Associated With Permanent Discontinuation by Preferred Term, Irrespective of Relationship to Study Drug

MedDRA Preferred Term	Ribociclib plus Letrozole N=334		Placebo plus Letrozole N=330	
	All Grades N	Grade 3/4 N	All Grades N	Grade 3/4 N
TOTAL	50	38	10	6
Alanine aminotransferase increased	15	12	1	0
Aspartate aminotransferase increased	9	7	2	2
Vomiting	8	4	0	0
Nausea	3	0	0	0
Neutropenia	3	3	0	0
Diarrhoea	2	0	0	0
Hepatotoxicity	2	2	0	0
Sepsis	2	2	0	0
Decreased appetite	2	2	0	0
Bone pain	2	2	0	0
Headache	2	1	0	0
Leukopenia	1	1	0	0
Atrial fibrillation	1	1	0	0
Pericardial effusion	1	0	0	0
Eye irritation	1	0	0	0
Duodenal perforation	1	1	0	0
Fatigue	1	1	0	0

Sudden death	1	1	0	0
Autoimmune hepatitis	1	1	0	0
Hepatocellular injury	1	1	0	0
Weight decreased	1	1	0	0
Joint stiffness	1	0	0	0
Bladder cancer	1	1	0	0
Sinus headache	1	0	0	0
Depression	1	0	0	0
Dyspnoea	1	1	0	0
Interstitial lung disease	1	1	0	0
Lung infiltration	1	1	0	0
Erythema	1	0	0	0
Pruritus	1	1	0	0
Rash	1	0	1	0
Skin burning sensation	1	0	0	0
Pleural effusion	0	0	1	1
Alcohol abuse	0	0	1	1
Renal failure	0	0	1	0
Hyperbilirubinemia	0	0	1	0
Atrial flutter	0	0	1	0
Hypertension	0	0	1	1
Epilepsy	0	0	1	1

Study drug discontinuation refers to discontinuation of ribociclib/placebo only or both ribociclib/placebo and letrozole
Source: ADAE.xpt, CSR Table 12-12

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Drug Interruption

TEAEs leading to drug interruption were more frequent in the ribociclib plus letrozole arm compared with the placebo plus letrozole arm (71.3% vs. 14.8%, any grade); these events are summarized in Table 37. Grade 3 or 4 TEAEs leading to drug interruption were also more frequent in the ribociclib plus letrozole arm (60.5% vs. 5.5%). The most common TEAEs (any grade, >5% incidence) in the ribociclib plus letrozole arm requiring dose interruption were neutropenia, decreased neutrophil count, vomiting, nausea, increased ALT, and decreased WBC. The most common Grade 3 or 4 TEAEs (>5% incidence) in the ribociclib plus letrozole arm requiring dose interruption were neutropenia (38.0%) and decreased neutrophil count (11.4%).

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Table 37. TEAEs leading to study drug interruption irrespective of causality, by preferred term (incidence >1.0% by preferred term in either group)

MedDRA Preferred Term	Ribociclib plus Letrozole N=334		Placebo plus Letrozole N=330	
	All grades N	Grade 3/4 N	All grades N	Grade 3/4 N
TOTAL	238	202	49	18
Neutropenia	131	127	2	1
Neutrophil count decreased	39	38	0	0
Vomiting	20	3	4	2
Nausea	18	4	3	1
Alanine aminotransferase increased	17	12	2	2
White blood cell count decreased	17	13	0	0
Diarrhoea	15	1	2	1
Aspartate aminotransferase increased	12	6	3	0
Leukopenia	12	10	0	0
Fatigue	7	1	4	1
Asthenia	6	1	3	1
Abdominal pain	5	2	1	0
Lymphopenia	5	3	0	0
Rash	5	1	3	0
Stomatitis	4	1	2	0
Pneumonia	4	0	0	0

Decreased appetite	4	1	0	0
Dehydration	4	1	0	0

Source ADAE.xpt, CSR Table 12-14

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Dose Reduction

TEAEs leading to dose reduction were more frequent in the ribociclib plus letrozole arm compared with the placebo plus letrozole arm (44.6% vs. 3.0%, any grade); these events are summarized in Table 38. Grade 3 or 4 TEAEs leading to drug interruption were also more frequent in the ribociclib plus letrozole arm (35.3% vs. 0.9%). The most common TEAEs (any grade, >5% incidence) in the ribociclib plus letrozole arm requiring dose interruption were neutropenia and decreased neutrophil count. The most common Grade 3 or 4 TEAEs (>5% incidence) in the ribociclib plus letrozole arm requiring dose reduction were neutropenia (22.8%) and decreased neutrophil count (7.2%).

Table 38. TEAEs leading to study drug reduction irrespective of causality, by preferred term (incidence >1.0% by preferred term in either group)

MedDRA Preferred Term	Ribociclib plus Letrozole N=334		Placebo plus Letrozole N=330	
	All grades N	Grade 3/4 N	All grades N	Grade 3/4 N
TOTAL	149	118	10	3
Neutropenia	79	76	0	0
Neutrophil count decreased	25	24	0	0
Alanine aminotransferase increased	10	6	1	0
Leukopenia	6	5	0	0
Diarrhoea	6	1	1	0
Nausea	6	1	1	0
Aspartate aminotransferase increased	5	2	1	0
Vomiting	4	0	0	0
Asthenia	4	1	0	0
Fatigue	4	1	2	0

Source ADAE.xpt, CSR Table 12-13

Significant Adverse Events

Adverse events of interest are described in section 7.4.5, Analysis of Submission-Specific Safety Issues. Specifically, the three adverse events of interest include: neutropenia, hepatotoxicity, and QT interval prolongation. Grade 3 -5 Adverse Events occurring up to 30-days after last dose of study therapy, with frequency greater than or equal to 2%, are described in Table 42 below in the Treatment Emergent Adverse Events and Adverse Reactions section.

Treatment Emergent Adverse Events and Adverse Reactions

TEAEs tabulated according to System Organ Class, High Level Group Term, and High Level Term are summarized in Table 39, Table 40, and Table 41 below.

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Table 39. TEAE Summary by System Organ Class (All Treated Population)

System Organ Class	Ribociclib + Letrozole N=334 n (%)	Placebo + Letrozole N=330 n (%)
Blood and lymphatic system disorders	227 (68.0)	38 (11.5)
Cardiac disorders	28 (8.4)	21 (6.4)
Ear and labyrinth disorders	25 (7.5)	17 (5.2)
Endocrine disorders	4 (1.2)	1 (0.3)
Eye disorders	74 (22.2)	37 (11.2)
Gastrointestinal disorders	265 (79.3)	207 (62.7)
General disorders and administration site conditions	217 (65.0)	186 (56.4)
Hepatobiliary disorders	14 (4.2)	7 (2.1)
Immune system disorders	11 (3.3)	8 (2.4)
Infections and infestations	168 (50.3)	140 (42.4)
Injury, poisoning and procedural complications	46 (13.8)	35 (10.6)
Investigations	189 (56.6)	77 (23.3)
Metabolism and nutrition disorders	116 (37.7)	98 (29.7)
Musculoskeletal and connective tissue disorders	199 (59.6)	216 (65.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	8 (2.4)	12 (3.6)
Nervous system disorders	150 (44.9)	138 (41.8)
Psychiatric disorders	91 (27.3)	80 (24.2)
Renal and urinary disorders	29 (8.7)	25 (7.6)
Reproductive system and breast disorders	42 (12.6)	50 (15.2)
Respiratory, thoracic and mediastinal disorders	145 (43.4)	112 (33.9)
Skin and subcutaneous tissue disorders	202 (60.5)	120 (36.4)
Social circumstances	1 (0.3)	0
Surgical and medical procedures	4 (1.2)	0
Vascular disorders	123 (36.8)	133 (40.3)

Source: ADAE.xpt, ADSL.xpt, analysis generated by MAED

Table 40. TEAE Summary (≥ 10%) by High Level Group Term (All Treated Population)

High Level Group Term	Ribociclib + Letrozole N=334 n (%)	Placebo + Letrozole N=330 n (%)
Gastrointestinal signs and symptoms	214 (64.1)	145 (43.9)
White blood cell disorders	211 (63.2)	22 (6.7)

General system disorders NEC	202 (60.5)	174 (52.7)
Gastrointestinal motility and defaecation conditions	169 (50.6)	121 (36.7)
Infections - pathogen unspecified	142 (42.5)	113 (34.2)
Epidermal and dermal conditions	139 (41.6)	73 (22.1)
Skin appendage conditions	127 (38.0)	64 (19.4)
Musculoskeletal and connective tissue disorders NEC	124 (37.1)	132 (40.0)
Respiratory disorders NEC	121 (36.2)	98 (29.7)
Haematology investigations (incl blood groups)	103 (30.8)	10 (3.0)
Joint disorders	100 (29.9)	98 (29.7)
Neurological disorders NEC	87 (26.1)	75 (22.7)
Headaches	77 (23.1)	66 (20.0)
Vascular disorders NEC	73 (21.9)	82 (24.9)
Hepatobiliary investigations	67 (20.1)	25 (7.6)
Appetite and general nutritional disorders	63 (18.9)	50 (15.2)
Anaemias nonhaemolytic and marrow depression	62 (18.6)	15 (4.6)
Oral soft tissue conditions	61 (18.3)	29 (8.8)
Vascular hypertensive disorders	49 (14.7)	49 (14.9)
Eye disorders NEC	46 (13.8)	20 (6.1)
Sleep disorders and disturbances	46 (13.8)	32 (9.7)
Body temperature conditions	42 (12.6)	18 (5.5)
Viral infectious disorders	41 (12.3)	28 (8.5)
Muscle disorders	40 (12.0)	45 (13.6)
Bone disorders (excl congenital and fractures)	39 (11.7)	43 (13.0)
Upper respiratory tract disorders (excl infections)	35 (10.5)	19 (5.8)
Salivary gland conditions	34 (10.2)	32 (9.7)

Source: ADAE.xpt, ADSL.xpt, analysis generated by MAED

Table 41. TEAE Summary (≥ 10%) by High Level Term (All Treated Population)

High Level Term	**Ribociclib + Letrozole N=334 n (%)**	**Placebo + Letrozole N=330 n (%)**
Neutropenias	206 (61.7)	14 (4.2)
Nausea and vomiting symptoms	187 (56.0)	107 (32.4)
Asthenic conditions	155 (46.4)	134 (40.6)
Musculoskeletal and connective tissue pain and discomfort	122 (36.5)	127 (38.5)
Diarrhoea (excl infective)	117 (35.0)	73 (22.1)
Alopecias	111 (33.2)	52 (15.8)

Joint related signs and symptoms	97 (29.0)	97 (29.4)
White blood cell analyses	96 (28.7)	10 (3.0)
Gastrointestinal atonic and hypomotility disorders NEC	87 (26.1)	71 (21.5)
Headaches NEC	76 (22.8)	64 (19.4)
Peripheral vascular disorders NEC	73 (21.9)	81 (24.6)
Coughing and associated symptoms	71 (21.3)	63 (19.1)
Rashes, eruptions and exanthems NEC	70 (21.0)	30 (9.1)
Upper respiratory tract infections	69 (20.7)	63 (19.1)
Liver function analyses	67 (20.1)	25 (7.6)
Appetite disorders	63 (18.9)	50 (15.2)
Anaemias NEC	62 (18.6)	15 (4.6)
Gastrointestinal and abdominal pains (excl oral and throat)	56 (16.8)	42 (12.7)
Leukopenias NEC	55 (16.5)	12 (3.6)
Pruritus NEC	50 (15.0)	22 (6.7)
Stomatitis and ulceration	48 (14.4)	26 (7.9)
Vascular hypertensive disorders NEC	48 (14.4)	49 (14.9)
Neurological signs and symptoms NEC	45 (13.5)	43 (13.0)
Oedema NEC	44 (13.2)	35 (10.6)
Breathing abnormalities	43 (12.9)	36 (10.9)
Urinary tract infections	43 (12.9)	30 (9.1)
Febrile disorders	42 (12.6)	18 (5.5)
Upper respiratory tract signs and symptoms	42 (12.6)	27 (8.2)
General signs and symptoms NEC	40 (12.0)	21 (6.4)
Lacrimation disorders	38 (11.4)	13 (3.9)
Sensory abnormalities NEC	36 (10.8)	21 (6.4)
Dermal and epidermal conditions NEC	35 (10.5)	16 (4.9)
Bone related signs and symptoms	34 (10.2)	39 (11.8)
Oral dryness and saliva altered	34 (10.2)	31 (9.4)

Source: ADAE.xpt, ADSL.xpt, analysis generated by MAED

All grade TEAEs were very commonly reported in the both the ribociclib plus letrozole (98.5%) and placebo plus letrozole (97.0%) groups, though Grade 3 and 4 TEAEs were much more common in the ribociclib plus letrozole group (81.1% vs. 32.7%). At the preferred term level, the most common Grade 3 and 4 TEAEs (where incidence exceeded that of the placebo plus letrozole arm) were neutropenia (48.2%), neutrophil count decreased (14.1%), white blood cell count decreased (12.9%), alanine aminotransferase Increased (9.3%), leukopenia (8.7%), aspartate aminotransferase increased (5.7%), lymphocyte count decreased (4.5%), and vomiting (3.6%). These are summarized in Table 42.

Table 42. Frequently reported Grade 3 and 4 TEAEs (those reported for all grades with incidence ≥10.0% or Grade 3 or 4 with incidence ≥2.0% of patients in the ribociclib arm)

System Organ Class **Adverse Event (preferred term)**	**Ribociclib plus Letrozole N=334**		**Placebo plus Letrozole N=330**	
	All Grades	**Grades 3/4**	**All Grades**	**Grades 3/4**
	n (%)	**n (%)**	**n (%)**	**n (%)**
Total Patients with TEAE	**329 (98.5)**	**271 (81.1)**	**320 (97.0)**	**108 (32.7)**
Blood and Lymphatic System Disorders				
Neutropenia	203 (60.8)	161 (48.2)	14 (4.2)	2 (0.6)
Leukopenia	52 (15.6)	29 (8.7)	9 (2.7)	1 (0.3)
Lymphopenia	14 (4.2)	8 (2.4)	4 (1.2)	1 (0.3)
Anaemia	61 (18.3)	4 (1.2)	15 (4.5)	4 (1.2)
Gastrointestinal Disorders				
Vomiting	98 (29.3)	12 (3.6)	51 (15.5)	3 (0.9)
Nausea	171 (51.2)	8 (2.4)	94 (28.5)	2 (0.6)
Diarrhoea	117 (35.0)	4 (1.2)	73 (22.1)	3 (0.9)
Constipation	83 (24.9)	4 (1.2)	63 (19.1)	0
Abdominal Pain	35 (10.5)	4 (1.2)	25 (7.6)	0
Stomatitis	41 (12.3)	1 (0.3)	22 (6.7)	0
General Disorders And Administration Site Conditions				

Fatigue	120 (35.9)	8 (2.4)	100 (30.3)	3 (0.9)
Asthenia	43 (12.9)	3 (0.9)	38 (11.5)	2 (0.6)
Pyrexia	42 (12.6)	1 (0.3)	18 (5.5)	0
Oedema Peripheral	41 (12.3)	0	33 (10.0)	0
Infections and Infestations				
Urinary Tract Infection	36 (10.8)	2 (0.6)	27 (8.2)	0
Upper Respiratory Tract Infection	35 (10.5)	0	35 (10.6)	0
Investigations				
Neutrophil Count Decreased	63 (18.9)	47 (14.1)	3 (0.9)	1 (0.3)
White Blood Cell Count Decreased	63 (18.9)	43 (12.9)	5 (1.5)	1 (0.3)
Alanine Aminotransferase Increased	52 (15.6)	31 (9.3)	14 (4.2)	4 (1.2)
Aspartate Aminotransferase Increased	50 (15.0)	19 (5.7)	13 (3.9)	4 (1.2)
Lymphocyte Count Decreased	21 (6.3)	15 (4.5)	3 (0.9)	2 (0.6)
Metabolism And Nutrition Disorders				
Hypophosphataemia	10 (3.0)	9 (2.7)	2 (0.6)	1 (0.3)
Decreased Appetite	61 (18.3)	5 (1.5)	50 (15.2)	1 (0.3)
Musculoskeletal And Connective Tissue Disorders				
Back Pain	66 (19.8)	7 (2.1)	58 (17.6)	1 (0.3)
Arthralgia	91 (27.2)	3 (0.9)	95 (28.8)	3 (0.9)
Pain In Extremity	35 (10.5)	0 (0)	40 (12.1)	1 (0.3)
Nervous System Disorders				
Headache	74 (22.2)	1 (0.3)	63 (19.1)	1 (0.3)
Dizziness	42 (12.6)	0	43 (13.0)	0
Psychiatric Disorders				
Insomnia	39 (11.7)	1 (0.3)	31	0

			(9.4)	
Respiratory, Thoracic And Mediastinal Disorders				
Cough	65 (19.5)	0	59 (17.9)	0
Dyspnoea	39 (11.7)	4 (1.2)	29 (8.8)	2 (0.6)
Skin And Subcutaneous Tissue Disorders				
Alopecia	111 (33.2)	0	52 (15.8)	0
Rash	57 (17.1)	2 (0.6)	27 (8.2)	0
Pruritus	45 (13.5)	2 (0.6)	19 (5.8)	0
Vascular Disorders				
Hypertension	48 (14.4)	33 (9.9)	49 (14.8)	36 (10.9)
Hot Flush	69 (20.7)	1 (0.3)	76 (23.0)	0

Source: AE Preferred Term Analysis by Toxicity Grade, ADAE.xpt

Reviewer comment*: Compared with the Prescribing Information, our review yielded slightly different adverse event frequencies as a result of differences in grouping of preferred terms. However we agree with the groupings used in the Prescribing Information and have verified the labeling for accuracy.*

Laboratory Findings

In MONALEESA-2, routine laboratory analyses (including hemoglobin, WBC, neutrophils, lymphocytes, platelet count. BUN (or urea), creatinine, albumin, AST/ALT, total bilirubin, alkaline phosphatase, LDH, sodium, potassium, calcium, magnesium, phosphorous, fasting glucose, coagulation panel) were obtained at screening (≤7 days prior to dosing), Day 15 of cycle 1, and Day 1 of cycles ≥2 and at the end of treatment visit. Urinalysis was performed at screening and Day 1 of cycles ≥2. Notable laboratory abnormalities are captured above in the TEAE investigations section as well as described in detail below as related to hepatotoxicity and neutropenia (Table 43).

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Table 43. Laboratory Abnormalities Occurring in ≥ 10% of Patients

	Ribociclib plus letrozole			Placebo plus letrozole		
	N=334			N=330		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Laboratory parameters	**%**	**%**	**%**	**%**	**%**	**%**
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

Source: CSR, ADAE.xpt

Vital Signs

Vital signs (body temperature, pulse rate, blood pressure) and physical exams were obtained at screening (Days -7 to -1), during each cycle, and at the study drug completion visit (within 15 days after last dose of study drug). Based on analyses of mean value and mean change from baseline at each cycle, no clinically meaningful differences in systolic blood pressure, diastolic blood pressure, heart rate, or temperature were observed during the course of treatment with either study group.

Electrocardiograms (ECGs)

Scheduled three consecutive (i.e. triplicate) 12-lead ECGs were performed approximately 2 minutes apart to determine the mean QTc interval.

Screening: 7 days prior to randomization (baseline)

Cycle 1: Day 15 (pre-dose and 2 hours post dose)
Cycles 2-3: Day 1 (pre-dose and 2 hours post dose)
Cycles 4-5: Day 1 (pre-dose)
Cycle 6: Day 1 (pre-dose and 2 hours post dose)
Cycles 7-8: Day 1 (pre-dose)
Cycle 9: Day 1 (pre-dose and 2 hours post dose)
All other cycles (for patients with mean QTcF ≥ 481 ms at any time prior to cycle 10): Day 1 (pre-dose and 2 hours post dose)

QT

For full details, see Clinical Pharmacology review, QT-IRC review, and section 7.5.4 clinical review of QT prolongation.

In the pooled analysis across clinical studies in 267 cancer patients receiving ribociclib (Study A2301 and Study X2107 for ribociclib 600 mg plus letrozole 2.5 mg combination therapy and Study X2101 and Study X1101 for ribociclib monotherapy studies), a significant positive relationship between ΔQTcF and concentrations of ribociclib was observed over doses ranging from 50 mg to 1200 mg. The estimated mean change from baseline in QTcF was 22.64 ms (90% CI: 20.19, 25.09) at the mean observed Cmax at steady state following administration at the recommended 600 mg dose. The impact of age, race, gender, body weight, hepatic and renal impairment, effect of genotype and drug-drug interactions are currently being evaluated; therefore, the extent that these factors will further increase the QTc interval though increases in exposure is not known at this time.

There was an imbalance in AEs related to QTc prolongation such as syncope, ventricular tachycardia and there was one sudden death. These AEs can signal potential proarrhythmic effects of ribociclib. The lack of torsades de pointes in this small clinical database (n=381) is not considered sufficient to dismiss possible arrhythmogenic risks.

In the combination therapy data (N=381), 15 patients (4.0%) experienced new QTcF >480 ms postbaseline, 1 patients (0.3%) of whom also had a new QTcF >500 ms. Furthermore, 12 patients (3.2%) had a change from baseline QTcF (ΔQTcF) >60 ms.

In the monotherapy pooled data (N=187), 16 patients (8.6%) experienced new QTcF >480 ms postbaseline, 6 patients (3.2%) of whom also had a new QTcF >500 ms. Furthermore, 20 patients (10.7%) had a change from baseline QTcF (ΔQTcF) >60 ms.

Immunogenicity

Not applicable as this was not assessed nor expected.

7.4.5 Analysis of Submission-Specific Safety Issues

Neutropenia

The Applicant presented grouped neutropenia AE analyses that included granulocytopenia, neutropenia, and neutrophil count decreased as preferred terms.

The reviewer expanded this analysis of neutropenia select AEs to include the following preferred terms: febrile neutropenia, granulocyte count decreased, granulocytes abnormal, granulocytopenia, neutropenia, neutropenic infection, neutropenic sepsis, neutrophil count abnormal, neutrophil count decreased, neutrophil function test abnormal, neutrophil percentage abnormal, and neutrophil percentage decreased up to 30-days after the last dose of study therapy. These are summarized in Table 44.

Table 44. Summary of Neutropenia Adverse Events (All Treated Population)

Adverse Event	**Ribociclib plus letrozole N=334 n (%)**	**Placebo plus letrozole N=330 n (%)**
Total Patients with Neutropenia AE	249 (74.6)	17 (5.2)
Febrile neutropenia	5(1.5)	0
Granulocyte count decreased	0	0
Granulocytes abnormal	0	0
Granulocytopenia	2 (0.6)	0
Neutropenia	203 (60.8)	14 (4.2)
Neutropenic infection	0	0
Neutropenic sepsis	0	0
Neutrophil count abnormal	0	0
Neutrophil count decreased	63 (18.9)	3 (0.9)
Neutrophil function test abnormal	0	0
Neutrophil percentage abnormal	0	0
Neutrophil percentage decreased increased	0	0

Source: ADAE.xpt, ADSL.xpt, analysis generated by MAED

In Study A2301, the select neutropenia AEs occurred in a higher proportion of patients in the ribociclib plus letrozole group (n=249, 74.6%) compared with the placebo plus letrozole group (n=17, 5.2%). Grade 3 or 4 grouped neutropenia events occurred in 199 patients (59.6%). The mean duration of neutropenia event was 27.5 days and the median duration was 15 days. There were three (0.9%) drug discontinuations attributable to neutropenia, all of which were Grade 3 or 4 adverse events.

There were 6 reported febrile neutropenia events in 5 patients (1.5%) who received ribociclib plus letrozole. All 6 of these were noted by the Investigators to be related to study treatment. Four patients required a dose reduction and/or drug interruption. None of these febrile neutropenia events resulted in drug discontinuation. These patients are summarized in Table 45 below.

Twenty-six (26, 7.8%) patients received colony stimulating factor in the ribociclib plus letrozole group compared with one patient (0.3%) in the placebo plus letrozole group.

Reviewer comment*:* Despite a high frequency of neutropenia, dose reductions were able to manage these laboratory findings and only 0.9% discontinued. Febrile neutropenia did not result in any dose discontinuations and the majority of patients recovered.

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Table 45. Ribociclib Plus Letrozole Patients with Febrile Neutropenia Adverse Event (All Treated Population)

Patient ID	Age	AE (Preferred Term)	Grade	Serious	Duration (days)	Action	Outcome
A2301-1700003	46	Febrile Neutropenia	3	Y	3	Drug Interrupted	R
A2301-3116002	81	Febrile Neutropenia	2	Y	5	Drug Interrupted	R
A2301-4100004	65	Febrile Neutropenia	3	N	8	Drug Interrupted	R
A2301-5063003	64	Febrile Neutropenia	3	Y	2	Dose Reduced	R
A2301-5091003	85	Febrile Neutropenia	4	Y	1	Dose Not Changed	O
		Febrile Neutropenia	3	N	2	Dose Not Changed	R

Source: ADAE.xpt

Abbreviations: AE, adverse event; O, recovering/resolving; R, recovered/resolved; N, not recovered / not resolved; U, unknown

Hepatotoxicity and Drug Induced Liver Injury (DILI)

The reviewer searched for hepatic select AEs including the following terms: acute hepatic failure, ALT increased, AST increased, bilirubin conjugated increased, blood bilirubin increased, blood alkaline phosphatase (ALP) increased, blood bilirubin increased, blood LDH increased, drug-induced liver injury, gamma-glutamyl-transferase (GGT) increased, hepatic enzyme increased, hepatic failure, hepatitis, hepatitis acute, hepatotoxicity, hyperbilirubinemia, hypertransaminemia, jaundice, liver disorder, liver function test (LFT) abnormal, liver injury, and transaminases increased up to 30-days after the last dose of study therapy. The select hepatic AEs occurred in 78 patients (23.4%) in the ribociclib plus letrozole compared with 40 (12.1%) patients in the placebo plus letrozole group. The most frequently occurring AEs (≥ 2% of patients), regardless of causality, were ALT increased, AST increased, blood ALP increased, GGT increased, and blood LDH increased. Table 46 summarizes the hepatic adverse events.

Table 46. Summary of Hepatic Adverse Events (All Treated Population)

Adverse Event	**Ribociclib plus letrozole N=334 n (%)**	**Placebo plus letrozole N=330 n (%)**
Total Patients with Hepatic AE	78 (23.4)	40 (12.1)
Acute hepatic failure	0	0
Alanine aminotransferase increased	52 (15.6)	13 (3.9)
Aspartate aminotransferase increased	50 (15.0)	12 (3.6)
Bilirubin conjugated increased	0	1 (0.3)
Blood alkaline phosphatase increased	15 (4.5)	18 (5.5)
Blood bilirubin increased	6 (1.8)	2 (0.6)
Blood lactate dehydrogenase increased	7 (2.1)	2 (0.6)
Drug-induced liver injury	0	0
Gamma-glutamyltransferase increased	9 (2.7)	3 (0.9)
Hepatic enzyme increased	1 (0.3)	1 (0.3)
Hepatic failure	2 (0.6)	0
Hepatitis	0	0
Hepatitis acute	0	0
Hepatotoxicity	3 (0.9)	0
Hyperbilirubinaemia	1 (0.3)	1 (0.3)
Hypertransaminasaemia	2 (0.6)	0
Jaundice	1 (0.3)	0
Liver disorder	1 (0.3)	1 (0.3)
Liver function test abnormal	0	1 (0.3)
Liver injury	0	0
Transaminases increased	3 (0.9)	3 (0.9)

Source: ADAE.xpt, ADSL.xpt, analysis generated by MAED

Thirty-seven (37) patients in the ribociclib plus letrozole group experienced at least one Grade 3 or Grade 4 hepatic select AE. These are summarized in Table 47 below. Of note, there were 12 Grade 4 hepatic select AE in the ribociclib plus letrozole group comprising a total of 6 patients.

Four patients (1.2%) in the ribociclib plus letrozole group met the biochemical definition of Hy's law; three cases were related to study treatment and none resulted in death. These are summarized and reviewed more closely in Table 48.

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Table 47. Ribociclib plus Letrozole Patients with Grade 3/4 Hepatic Adverse Events (All Treated Population)

Patient ID	Age	AE (Preferred Term)	Grade	Serious	Duration (days)	Action	Outcome
A2301-1001002	68	ALT Increased	3	N	22	Drug Interrupted	O
		ALT Increased	3	N	6	Dose Reduced	O
		AST Increased	3	N	8	Dose Reduced	O
		AST Increased	3	N	6	Drug Withdrawn	O
A2301-1001003	82	ALT Increased	3	N	20	Drug Withdrawn	R
		ALT Increased	3	N	37	Drug Interrupted	O
A2301-1001005	75	AST Increased	3	N	28	Not applicable	R
		ALT Increased	3	N	28	Not applicable	R
		AST Increased	3	N	11	Drug Interrupted	O
		ALT Increased	3	N	17	Drug Interrupted	O
A2301-1003010	71	ALT Increased	3	N	48	Drug Withdrawn	O
A2301-1301004	74	ALT Increased	3	N	16	Dose Reduced	O
		AST Increased	3	N	9	Dose Reduced	O

A2301-1700003	46	Transaminases Increased	3	Y	24	Dose Reduced	O
A2301-1902005	64	ALT Increased	3	Y	41	Drug Withdrawn	O
		AST Increased	3	N	41	Drug Withdrawn	O
		Hepatotoxicity	3	Y	42	Drug Withdrawn	R
A2301-2500002	57	ALT Increased	3	N	28	Dose Not Changed	O
		Blood Bilirubin Increased	3	N		Dose Not Changed	U
		ALT Increased	3	N		Dose Not Changed	N
		Blood ALP Increased	3	N		Dose Not Changed	N
		AST Increased	3	N		Dose Not Changed	N
A2301-2802005	59	ALT Increased	3	N	7	Dose Reduced	R
A2301-3004003	56	ALT Increased	4	Y	7	Drug Interrupted	O
		ALT Increased	4	N	10	Dose Not Changed	O
		AST Increased	4	N	5	Drug Interrupted	O
		AST Increased	3	N	6	Drug Interrupted	N
		AST Increased	4	N	10	Dose Not Changed	R

		GGT Increased	3	N	73	Dose Not Changed	R
		ALT Increased	3	N	22	Drug Interrupted	N
		AST Increased	3	N	22	Drug Interrupted	N
		Blood Bilirubin Increased	3	Y	42	Drug Interrupted	R
A2301-3004006	75	ALT Increased	3	N	12	Dose Reduced	N
A2301-3100003	71	ALT Increased	3	N	37	Not applicable	R
A2301-3101001	51	Blood ALP Increased	3	N	15	Dose Not Changed	R
A2301-3105001	57	Hepatotoxicity	3	N	7	Not applicable	N
		Hepatic Failure	3	Y	8	Not applicable	N
		Hepatotoxicity	3	N	22	Drug Interrupted	N
		Hepatotoxicity	3	Y	9	Drug Withdrawn	O
A2301-3109001	52	ALT Increased	3	N		Dose Not Changed	N
		AST Increased	3	N		Dose Not Changed	N
A2301-3110009	64	ALT Increased	3	N	29	Dose Not Changed	R
		ALT Increased	3	N		Dose Not Changed	N

		AST Increased	3	N		Dose Not Changed	N
A2301-3119006	50	ALT Increased	3	N	25	Dose Not Changed	N
		ALT Increased	4	Y	38	Drug Withdrawn	O
		Hepatotoxicity	3	Y	49	Not applicable	R
		AST Increased	3	N	8	Drug Interrupted	N
		AST Increased	4	Y	44	Drug Withdrawn	O
		Hepatic Failure	3	Y	28	Not applicable	R
		Blood Bilirubin Increased	4	N	24	Not applicable	O
		Blood Bilirubin Increased	3	N	19	Not applicable	O
A2301-3201003	62	ALT Increased	3	N	14	Drug Interrupted	O
A2301-3302002	82	ALT Increased	3	N	27	Dose Reduced	R
		ALT Increased	3	N	72	Drug Interrupted	O
		AST Increased	3	N	79	Drug Interrupted	O
A2301-3315002	63	ALT Increased	3	N	50	Drug Withdrawn	O
		AST Increased	3	N	19	Drug Withdrawn	O

A2301-3315003	72	ALT Increased	3	N	18	Drug Withdrawn	O
		AST Increased	3	N	5	Not applicable	O
A2301-3400002	61	Hepatic Enzyme Increased	3	N	38	Drug Interrupted	R
A2301-3400006	61	ALT Increased	4	N	3	Drug Withdrawn	O
		ALT Increased	3	N	50	Not applicable	R
		AST Increased	3	N	28	Drug Withdrawn	R
A2301-3500001	65	ALT Increased	4	Y	7	Drug Interrupted	N
		ALT Increased	3	Y	57	Drug Withdrawn	R
		ALT Increased	3	Y	61	Drug Interrupted	N
		AST Increased	3	Y		Drug Withdrawn	N
A2301-3501001	85	Blood ALP Increased	3	N	14	Dose Not Changed	O
A2301-3501007	50	ALT Increased	3	N	48	Drug Withdrawn	R
A2301-3700002	78	ALT Increased	3	N	56	Dose Not Changed	O
A2301-3802002	61	ALT Increased	3	N	16	Dose Not Changed	O
		ALT Increased	3	N	5	Drug Withdrawn	O

		ALT Increased	3	N	19	Drug Interrupted	O
		AST Increased	3	N	16	Dose Not Changed	O
A2301-3805002	63	ALT Increased	3	N	21	Drug Interrupted	R
A2301-5027003	40	ALT Increased	4	N	20	Drug Interrupted	O
		AST Increased	3	N	20	Drug Interrupted	R
A2301-5046001	54	ALT Increased	4	N	64	Drug Withdrawn	O
		AST Increased	3	N	8	Drug Withdrawn	N
		AST Increased	4	N	56	Not applicable	O
		Blood Bilirubin Increased	3	N	35	Not applicable	R
A2301-5614001	57	AST Increased	3	N	15	Dose Not Changed	O
A2301-5618002	79	ALT Increased	3	N	29	Drug Interrupted	O
		ALT Increased	3	N	27	Drug Interrupted	O
A2301-5630006	60	ALT Increased	3	N	16	Drug Interrupted	O
		ALT Increased	3	N	14	Drug Interrupted	O
		AST Increased	3	N	7	Dose Not Changed	O

		AST Increased	3	N	7	Drug Interrupted	O
A2301-5638002	71	ALT Increased	3	N	28	Dose Not Changed	R
A2301-6002003	65	ALT Increased	3	N	8	Dose Reduced	R
		Blood ALP Increased	3	N		Dose Not Changed	N
A2301-6008001	59	ALT Increased	3	N	14	Drug Withdrawn	N

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP: Alkaline Phosphatase, GGT: gamma-glutamyl transferase, F, female; Hosp, Hospitalized; N/A, not applicable; O, recovering/resolving; R, recovered/resolved; N, not recovered / not resolved; U, unknown
Source: ADAE.xpt

Table 48. Summary of patients who met biochemical definition of Hy's law in the ribociclib plus letrozole arm

Patient ID	Summary of Case	Hepatic AEs (listed as worst grade)	Reviewer Comment
A2301-5046-001	54 year old female with stage IV breast cancer with no liver metastases found to have LFTs within normal limits at baseline. Patient received first dose of ribociclib on 19 March 2014 (Day 1). On Day 111, she had Grade 3 elevated AST and Grade 4 increased ALT. She was on concurrent Tylenol, Vicodin, and ibuprofen. She was on a prohibited herbal medication with known hepatotoxicity (black cohosh). Study treatment was permanently discontinued on 8 July 2014. Her LFTs continued to worsen. On (b) (6), she had a liver biopsy consistent with autoimmune hepatitis. Her LFTs were WNL on 22 September 2014 (83 days after the last dose of ribociclib). She did not require prednisone.	Grade 4 increased ALT; grade 4 increased AST; grade 3 increase blood bilirubin; grade 3 hepatitis	The Investigator suspected a relationship between the abnormal LFTs and the study treatment. Notably, this patient had worsening LFTs in the setting of a known hepatotoxic herbal medication. It is thus unclear whether this case of Hy's Law is attributable to ribociclib.
A2301-3119-006	50 year old female with stage IV breast cancer found to have LFTs within normal limits at baseline. She received her first dose of ribociclib on 9 December 2014. On Day 85, she had both Grade 1 AST and ALT. On Day 102, she had both Grade 3 AST and ALT. On Day 113, she continued to have Grade 3 AST and ribociclib was interrupted while letrozole was continued. On Day 120, AST was Grade 4 and on Day 126 ALT was Grade 4. Ribociclib was permanently discontinued while letrozole was continued. On Day 137, in the setting of continued	Grade 4 increased AST, Grade 4 increased ALT, Grade 3 hepatotoxicity, Grade 4 increased blood bilirubin, Grade 3 hepatic failure	The Investigator suspected a relationship between the abnormal LFTs and the study treatment. The marked LFT abnormalities after beginning study treatment, together with biopsy findings, are consistent with drug-induced liver injury.

Patient ID	Summary of Case	Hepatic AEs (listed as worst grade)	Reviewer Comment
	LFT abnormality, letrozole was temporarily interrupted and later permanently discontinued. On [redacted] (b) (6) days after the last dose of ribociclib), the patient had a liver biopsy consistent with drug induced toxic hepatitis. She was treated with prednisone. By 21 August 2015 (151 days after the last dose of ribociclib), LFTs returned to normal range.		
A2301-3004-003	56 year old female with stage IV breast cancer found to have LFTs within normal limits at baseline. She received her first dose of ribociclib on 28 August 2014. On Day 141, she had Grade 1 ALT and AST elevation. On Day 169, ALT was improved yet still elevated and thus ribociclib was temporarily interrupted. On Day 197, ribociclib was restarted at the same dose until Day 201 in error. On Day 219, ALT and AST worsened to Grade 4. She was diagnosed with jaundice by Day 225. The patient had positive anti-actin antibodies and a liver biopsy consistent with autoimmune hepatitis. Ribociclib was discontinued (last dose 16 March 2015). Letrozole was continued. The patient was not treated with prednisone. Her LFTs gradually improved. On Day 338 (137 days after last dose of ribociclib), the autoimmune hepatitis resolved.	Grade 4 increased ALT, Grade 4 increased AST, Grade 3 increased bilirubin, grade 3 increased GGT, grade 2 jaundice, grade 3 autoimmune hepatitis, grade 1 hepatomegaly	The Investigator did not suspect a relationship between the abnormal LFTs, autoimmune hepatitis, and the study treatment. However, her LFTs and autoimmune hepatitis resolved after discontinuing ribociclib.
A2301-1902-005	64 year old female with stage IV breast cancer found to have LFTs within normal limits at baseline. She received her first dose of ribociclib on 17	Grade 3 increased ALT, Grade 3	The Investigator suspected a relationship between the abnormal LFTs,

Patient ID	Summary of Case	Hepatic AEs (listed as worst grade)	Reviewer Comment
	December 2014. On Day 85, she had Grade 3 increased ALT and Grade 2 increased AST. Ribociclib was interrupted from Day 87 and letrozole was interrupted from Day 94. LFTs were still abnormal on Day 99. Ribociclib was permanently discontinued. LFTs returned to WNL after 138 of discontinuation of ribociclib. No known history of herbal supplements or NSAIDs. No liver biopsy was performed. She did not receive treatment with prednisone.	increased AST, Grade 2 increased bilirubin, Grade 3 hepatotoxicity	hepatotoxicity, and the study treatment. No biopsy was performed. The marked LFT abnormalities after beginning study treatment are suspicious drug-related toxicity.

Source: CRFs, Narratives, CSR Table 12-26

***Reviewer comment**: Hepatobiliary toxicity was a substantial cause of Grade 3 and 4 toxicity among patients receiving ribociclib plus letrozole. Four patients (1.2%) in the ribociclib plus letrozole group met the biochemical definition of Hy's law; three cases were related to study treatment and none resulted in death. Adequate description of the risk is conveyed in the warnings and precautions section of labeling.*

QT Interval Prolongation

The reviewer searched for QT prolongation select AEs including the following terms: cardiac arrest, cardiac death, electrocardiogram abnormal, electrocardiogram change, electrocardiogram QT interval abnormal, electrocardiogram QT prolonged, loss of consciousness, presyncope, sudden cardiac death, sudden death, syncope, ventricular fibrillation, ventricular flutter, ventricular tachyarrhythmia, ventricular tachycardia up to 30-days after the last dose of study therapy. These are summarized in Table 49.

Table 49. Summary of QT Prolongation Adverse Events (All Treated Population)

Adverse Event	**Ribociclib + Letrozole N=334 n (%)**	**Placebo + Letrozole N=330 n (%)**
Total Patients with QT Prolongation AE	26 (7.8)	8 (2.4)
All AEs		
Cardiac arrest	0	1 (0.3)
Cardiac death	0	0
Electrocardiogram abnormal	0	0
Electrocardiogram change	0	0
Electrocardiogram QT interval abnormal	0	0
Electrocardiogram QT prolonged	15 (4.5)	4 (1.2)
Loss of consciousness	1 (0.3)	0
Presyncope	2 (0.6)	1 (0.3)
Sudden cardiac death	0	0
Sudden death	1 (0.3)	0
Syncope	9 (2.7)	3 (0.9)
Ventricular fibrillation	0	0
Ventricular flutter	0	0
Ventricular tachyarrhythmia	0	0
Ventricular tachycardia	1 (0.3)	0
Grade 3-4 AEs		
Syncope	6 (1.8)	2 (0.6)
Presyncope	1 (0.3)	1 (0.3)
Electrocardiogram QT prolonged	1 (0.3)	0

Loss of consciousness	1 (0.3)	0
Sudden death	1 (0.3)	0
SAEs		
Syncope	3 (0.9)	0
Sudden death	1 (0.3)	0
AEs leading to discontinuation		
Sudden death	1 (0.3)	0
AEs need dose adjustment or interruption		
Electrocardiogram QT prolonged	2 (0.6)	0
Syncope	1 (0.3)	0

QT interval prolongation events were more frequently reported in the ribociclib plus letrozole group compared with the placebo plus letrozole group (7.8% vs. 2.4%), with more grade 3/4 events reported in the patients treated with ribociclib plus letrozole (2.4% vs. 0.6%, respectively). The most frequent AEs reported in ribociclib plus letrozole group compared to placebo plus letrozole were electrocardiogram QT prolonged (4.5% vs 1.2%) and syncope (2.7% vs 0.9%).

Of the nine cases of syncope in the ribociclib plus letrozole group, five occurred at 600 mg, three occurred at 400 mg, and one occurred 8 cycles after stopping ribociclib.

Drug interruption / reduction was required for 0.9% of ribociclib plus letrozole group secondary to ECG QT prolonged and syncope. Discontinuation of treatment with ribociclib plus letrozole due to QT interval prolongation occurred only in one patient (0.3%), who experienced sudden death (subject A2301-4102-002, summarized above in the Death section).

Reviewer comment*: QT interval prolongation events were reported with greater frequency in the ribociclib plus letrozole group. As such, we have recommended, and agreed upon with the Applicant, a safety-related postmarketing requirement under FDAAA to explore whether an alternative dosing regimen will mitigate the risk of QT interval prolongation without compromising efficacy. Such a study is recommended to use safety QT prolongation as a primary safety endpoint, and also evaluate ORR as it related to the different doses proposed to determine if any detriment in activity is experienced due to a lower or different dose. In addition, at the current time, adequate description of the risk is conveyed in the warnings and precautions section of labeling and post-marketing surveillance will occur as is standard.*

7.4.6 Safety Analyses by Demographic Subgroups

Age

The majority of patients in both the ribociclib plus letrozole arm (184/334 [55.1%]) and the placebo plus letrozole arm (186/330 [56.4%]) of the MONALEESA-2 advanced breast cancer study were age < 65 years.

The overall incidence of SAEs was higher in patients ≥65 years (29.7%) than in patients <65 years (15.2%) in the ribociclib plus letrozole arm. The most frequently reported (≥20%) TEAEs in patients <65 years were neutropenia, nausea, fatigue, alopecia, diarrhea, arthralgia, hot flush, headache, neutrophil count decreased, vomiting, constipation, back pain, and white blood cell count decreased. The most frequently reported (≥20%) TEAEs in patients ≥65 years were neutropenia, nausea, diarrhea, fatigue, vomiting, alopecia, constipation, anemia, arthralgia, and decreased appetite (see Table 50).

Table 50. Age-stratified Summary of Treatment-Emergent AEs and SAEs

	Ribociclib plus letrozole N=334		**Placebo plus letrozole N=330**	
	<65 N=184	**≥65 N=150**	**<65 N=186**	**≥65 N=144**
Patients with AEs	181 (98.4%)	148 (98.7%)	181 (97.3%)	139 (96.5%)
Grade 3 or 4 AEs	141 (76.6%)	130 (86.7%)	52 (28.0%)	56 (38.9%)
SAE	33 (17.9%)	38 (25.3%)	22 (11.8%)	17 (11.8%)

Source: ADSL.xpt, ADAE.xpt

Race

The majority of patients in both the ribociclib plus letrozole arm (269/334 [80.5%]) and the placebo plus letrozole arm (276/330 [83.6%]) of the MONALEESA-2 advanced breast cancer study were Caucasian. In the ribociclib plus letrozole arm, only 28 patients (8.4%) were Asian and 10 patients (3.0%) were Black.

Gender
All patients in the MONALEESA-2 trial were female.

Reviewer Comment: *Patients aged 65 and greater who were treated with ribociclib accounted for 45% of the study population and no overall differences in safety (or effectiveness) were observed between these patients and younger patients. It is difficult to draw meaningful conclusions regarding the effect of race on the safety of ribociclib.*

7.4.7 Specific Safety Studies/Clinical Trials

Not applicable.

7.4.8 Additional Safety Explorations

Human Carcinogenicity or Tumor Development

See Pharmacology / Toxicology review.

Pediatrics and Assessment of Effects on Growth

Not applicable.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There are no known cases of overdose with ribociclib. There are no data available on the potential for drug abuse or dependence with ribociclib. A formal study has not been conducted by the applicant to investigate withdrawal.

7.4.9 Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Ribociclib is not marketed in the United States or other jurisdiction.

Expectations on Safety in the Postmarket Setting

Toxicities appear to have been adequately represented in MONALEESA-2 a large randomized study. The potential for QT prolongation as related to dose will be addressed with a safety PMR.

7.4.10 Integrated Assessment of Safety

In summary, the Applicant submitted safety data for 964 patients/subjects (industry-sponsored clinical studies) (original submission, 29 August 2016). We primarily based our safety review, as described above, on data from the Phase 3 registration Study A2301 (also referred to as MONALEESA-2) which enrolled 664 subjects (334 patients in the ribociclib plus letrozole arm, and 330 in the placebo plus letrozole arm) as the dose, schedule, and drug combination supported the proposed indication. There were 4 deaths (3 in the ribociclib plus letrozole group and 1 in the placebo plus letrozole group) within 30 days of study treatment. One subject in each group died from progression of breast cancer. The remaining 2 deaths in the ribociclib group were attributed to sudden death and death from unknown cause. In MONALEESA-2, the common preferred-term level TEAEs (i.e., ≥10% of patients) in the ribociclib plus letrozole arm were neutropenia (60.8%), nausea (51.2%), fatigue (35.9%), diarrhea (35.0%), alopecia (33.2), vomiting (29.3), and arthralgia (27.2%). Our review yielded three primary safety issues that warranted further analyses: neutropenia, hepatotoxicity, and QT interval prolongation. In MONALEESA-2, neutropenia AEs occurred in a higher proportion of patients in the ribociclib plus letrozole group (n=249, 74.6%) compared with the placebo plus letrozole group (n=17, 5.2%). Grade 3 or 4 grouped neutropenia events occurred in 199 patients (59.6%). There were 6 reported febrile neutropenia events in 5 patients (1.5%) who received ribociclib plus letrozole; all events were noted by the Investigators to be related to study treatment. Hepatotoxicity was more common in patients receiving ribociclib plus letrozole. Hepatic AEs occurred in 78 patients

(23.4%) in the ribociclib plus letrozole compared with 40 (12.1%) patients in the placebo plus letrozole group. Four patients (1.2%) in the ribociclib plus letrozole group met the biochemical definition of Hy's law; three cases were related to study treatment and none resulted in death. QT interval prolongation AEs were more frequently reported in the ribociclib plus letrozole group compared with the placebo plus letrozole group (7.8% vs. 2.4%), with more grade 3/4 events reported in the patients treated with ribociclib plus letrozole (2.4% vs. 0.6%, respectively). In consultation with clinical pharmacology, we have issued a Postmarketing Requirement for the Applicant to study an alternative dosing regimen which may mitigate the risks of QT interval prolongation while preserving treatment efficacy.

In mid-cycle communication dated January 9, 2017, FDA agreed with the Applicant to consider additional data in support of an indication expansion for ribociclib in combination with an aromatase inhibitor. To this end, the Applicant submitted supportive safety, efficacy, and PK data for ribociclib plus exemestane from Study X2106 and PK data for ribociclib plus anastrozole from Study E2301 (MONALEESA-7).

Briefly, Study X2106 is an ongoing open label, phase Ib, dose finding study, evaluating ribociclib plus exemestane (doublet) and ribociclib plus everolimus plus exemestane (triplet) combination treatments in patients with ER+/HER2- advanced breast cancer who were resistant to prior letrozole or anastrozole therapy. For all patients, the starting dose was ribociclib 600 mg 3 weeks on 1 week off with a standard dose of exemestane 25 mg daily, which was subsequently confirmed to be the RP2D. The Applicant submitted interim analysis results for key safety, efficacy and PK parameters from the doublet combination (ribociclib plus exemestane, n=14). The cut-off date for this analysis was November 3, 2016. No apparent drug-drug interactions have been reported between exemestane and ribociclib; the safety profile of the combination is consistent with the one reported for the combination of ribociclib plus letrozole. Compared with the ribociclib plus letrozole combination used in MONALEESA-2, no new safety signals were evident. The most common adverse events (all grade, >30%) were neutropenia, anemia, diarrhea, aspartate aminotransferase increased, nausea, constipation, fatigue and hyperglycemia. There were no events of febrile neutropenia. There were 3 on-treatment deaths attributable to gastrointestinal hemorrhage, aspiration, and acute respiratory failure. A review of the death narratives suggests that the first two deaths were attributable to disease progression, while the death associated with acute respiratory failure has an unknown etiology. Notably, the death of all three subjects occurred within 30 days after end of treatment.

Study E2301 (MONALEESA-7) is an on-going, double blind, Phase III trial comparing the combination of tamoxifen or non-steroidal aromatase inhibitor (letrozole or anastrozole) (plus goserelin) and ribociclib or placebo in premenopausal women with HR+, HER2-negative, advanced breast cancer who received no prior hormonal therapy for advanced disease. The Applicant submitted supportive PK data for 70 patients who are receiving/have received treatment with ribociclib/placebo and anastrozole (plus goserelin). To preserve data integrity of this ongoing blinded trial, an independent data monitoring committee, external to the Applicant, will review the PK data only. The Applicant notes that no unexpected safety findings

requiring a modification in the administration of ribociclib in combination with anastrozole have been reported.

This additional aromatase inhibitor data in combination with ribociclib support a broadened indication of ribociclib plus aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer as no new safety signals were identified and there was no clinically relevant drug drug interactions between ribociclib and the aromatase inhibitors.

Overall, the safety profile of ribociclib appears to be acceptable for the indicated population. Ribociclib did increase the incidence of neutropenia, hepatotoxicity, and QT interval prolongation. However, there is assurance given the data that the neutropenia and hepatotoxicity can be appropriately managed and is ultimately reversible. We have recommended a safety-related postmarketing requirement to explore whether an alternative dosing regimen will mitigate the risk of QT interval prolongation and adequate description of the risk is conveyed in the warnings and precautions section of labeling.

SUMMARY AND CONCLUSIONS

7.5 Statistical Issues

There are no major statistical issues with this application.

7.6 Conclusions and Recommendations

{See appended electronic signature page}

Erik Bloomquist, PhD
Primary Statistical Reviewer

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Statistical Team Leader

{See appended electronic signature page}

Anand Shah, MD
Primary Clinical Reviewer

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Clinical Team Leader

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8 Advisory Committee Meeting and Other External Consultations

No advisory committee meeting was required.

9 Pediatrics

Ribociclib was not studied in pediatric patients. The Applicant has submitted a PREA waiver and it will be reviewed prior to the action date.

10 Labeling Recommendations

10.2 Prescribing Information

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Proposed Labeling**	**Approved Labeling** ***(As of February 16, 2017)***
Highlights of Labeling		
Indications and Usage	KISQALI, a cyclin dependent kinase inhibitor (CDKi), is indicated in combination with letrozole for the treatment of 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. (1)	FDA revised the established pharmacologic class (EPC) to "kinase inhibitor"consistent with the FDA Guidance: Determining the EPC for Use in Highlights Guidance and current labeling practices. FDA revised "in combination with letrozole" to "in combination with an aromatase inhibitor as initial endocrine based therapy". *See Full Prescribing Information, 1. Indications and Usage below for more information.*
Contraindications	(b) (4)	FDA revised the contraindication to "None." to be consistent with current labeling practices. *See Full Prescribing Information, 4. Contraindications below for more information.*
Warnings and Precautions	(b) (4) toxicity: Can cause fetal harm (b) (4)	FDA revised to: "Embryo-Fetal Toxicity: Can

	(b) (4)	cause fetal harm. Advise patients of potential risk to a fetus and to use effective contraception during therapy. (5.4, 8.1, 8.3)"
Adverse Reactions	Most common adverse reactions (incidence ≥ 20%) are neutropenia, leukopenia, nausea, fatigue, diarrhea, alopecia, vomiting, constipation, headache, and back pain. (6)	FDA revised to provide adverse reactions in descending order based on incidence rates.
Use in Specific Populations	(not included)	FDA added this heading and the following statement: "Lactation: Advise not to breastfeed. (8.2)" to be consistent with current labeling practices.
Full Prescribing Information		
1. Indications and Usage	KISQALI® is a cyclin dependent kinase inhibitor (CDKi) indicated in combination with letrozole for the treatment of 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.	FDA removed the EPC from the Full Prescribing Information, Section 1 Indications and Usage since this is not required and to be consistent with current labeling practices. FDA revised "in combination with letrozole" to "in combination with an aromatase inhibitor as initial endocrine based therapy". *See Sections 1.3, 2.2, 6, 7.4.1, and 7.4.10 of this review for more information.*
2. Dosage and Administration	**Dose Modification for Strong CYP3A Inhibitors** Avoid concomitant use of KISQALI with strong CYP3A inhibitors and consider an alternative concomitant medication with less potential	FDA revised the Kisqali dose reduction when administered with a strong CYP3A inhibitor (b) (4) to "400 mg once daily" based on the FDA Clinical Pharmacology Reviewer findings. *See Section 6.2.2 of this review for more*

	for CYP3A inhibition *[see Drug Interactions (7.1)].* If a strong CYP3A inhibitor must be coadministered, reduce the KISQALI dose to (b) (4) mg once daily. …	*information.*
	(b) (4)	
	Hepatic Impairment …	FDA added the following to inform healthcare practitioners that dose modifications may be required for the aromatase inhibitor used in combination with Kisqali when patients have hepatic impairment (e.g., letrozole): "Review the Full Prescribing Information for the aromatase inhibitor for dose modifications related to hepatic impairment."
4. Contraindications	(b) (4)	FDA revised the contraindication to "None." to be consistent with current labeling guidance for

		hypersensitivity. *See FDA Guidance: Warnings and Precautions, Contraindications, and Boxed Warnings Sections of Labeling [III.A.2.] for more information.*
5. Warnings and Precautions	… **5.3 QT Interval Prolongation** (b) (4) study, one patient (0.3%) had >500 msec post-baseline QTcF value (average of triplicate), and nine patients out of 329 patients ((b) (4)%) had a >60 msec increase from baseline in QTcF intervals (average of triplicate). These ECG changes occurred within the first (b) (4) of treatment and were reversible with appropriate (b) (4). There were no reported cases of Torsade de Pointes. …	FDA revised the order of the numbered subsections in Section 5 to make QT prolongation 5.1, and neutropenia 5.3. This was reordered to reflect the clinical significance of the adverse reactions per the Section 5 FDA Labeling Guidance. FDA revised Section 5.3 to add the following statements: "Kisqali has been shown to prolong the QT interval in a concentration-dependent manner, with mean increase in QTc interval exceeding 20 ms at the 600 mg once daily dose."; "Syncope occurred in 9 patients (2.7%) in the Kisqali plus letrozole arm versus 3 (0.9%) in placebo plus letrozole arm."; and "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 Sections 7.4.4 and 7.4.5 of this review and the FDA Interdisciplinary Review Team (IRT) for QT review filed on January 4, 2017 for more information.*

6. Adverse Reactions	**6.1 Clinical Trial Experience** … The most common (b)(4)s leading to treatment discontinuation of (b)(4) KISQALI (b)(4) in patients receiving KISQALI plus letrozole were ALT increased ((b)(4)%), AST increased ((b)(4)%), vomiting ((b)(4)%).	Based on FDA safety analyses, FDA revised this statement to: "The most common ARs 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."
7. Drug Interactions	**7.1 (b)(4) That May Increase Ribociclib Plasma Concentrations** *CYP3A4 Inhibitors* … If coadministration of KISQALI with a strong CYP3A inhibitor cannot be avoided, reduce the dose of KISQALI to (b)(4) mg once daily (b)(4) . (b)(4)	**7.1 Drugs That May Increase Ribociclib Plasma Concentrations** *CYP3A4 Inhibitors* FDA revised the examples of strong CYP3A inhibitors by adding bocepravir, conivaptan, and grapefruit juice; and deleting (b)(4) . The Kisqali dose reduction when administered with a strong CYP3A inhibitor was revised (b)(4) to "400 mg once daily" as follows: "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)]."* *See Section 6.2.2 of this review for more information.*

	(b) (4)	
	7.3 (b) (4) *CYP3A substrates with narrow therapeutic index* (b) (4) **…**	**7.3 Effect of KISQALI on Other Drugs** *CYP3A substrates with narrow therapeutic index* … (b) (4)
8. Use in Specific Populations	**8.2 Lactation** … Because of the potential for serious adverse reactions in nursing infants from KISQALI, (b) (4)	FDA revised this subsection to advise lactating women not to breastfeed while taking Kisqali as follows: … "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." …

	…	
	8.5 Geriatric Use (b) (4) [redacted]	FDA moved and revised the following information from Section 12.3 to provide additional geriatric patient experience as follows: "Of 334 patients who received KISQALI in Study 1, 150 patients (45%) were ≥65 years of age and 35 patients (11%) were ≥75 years of age. No overall differences in safety or effectiveness of KISQALI were observed between these patients and younger patients."
	8.7 Renal Impairment …	**8.7 Renal Impairment** FDA moved this subsection (and the data from **8.6 Hepatic Impairment**) to subsection 12.3 per the FDA Guidance for the Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Considerations, Content, and Format [IV.C.4].
12. Clinical Pharmacology	**12.3 Pharmacokinetics** **Absorption** *Food Effect* …	FDA added the composition of the high-fat, high-calorie meal "(approximately 800 to 1000 calories with ~50% calories from fat, ~35% calories from carbohydrates, and ~15% calories from protein)" to this section.
	(**Specific Populations**) …	FDA added a subheading for Specific Populations per the

		Section 12 Guidance and consolidated the data for patients with hepatic impairment; renal impairment; and age, weight, gender, race in subsections (respectively).
	Geriatric Use **…**	FDA moved this information to section 8.5.
	(Drug Interaction Studies) …	FDA added the following information related to use with an additional aromatase inhibitors: "*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."
13. Nonclinical Toxicology	**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility** **…** **13.2 Animal Toxicology and/or Pharmacology** **…**	FDA revised 13.1 and 13.2 based on the FDA Pharmacology / Toxicology review findings related to fertility-related toxicity findings in animals. FDA added information to better describe ribociclib toxicology findings related to degeneration of seminiferous tubular epithelia in the testes, hypospermia, luminal cellular debris in the epididymides (rats and dogs) and vacuolation of epithelia in the epididymides (rats). *See the approved FPI Section 13.1 and 13.2; and Section 5.5.4 of this*

		review for more information.
14. Clinical Studies	**14 Clinical Studies** **…** **…**	FDA added the following information to describe the combination treatment regimen used in the clinical study and to provide the reasons for discontinuation (to be consistent with the Clinical Studies Section guidance): "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." For brevity and to reduce redundancy, FDA removed (b) (4) and replaced with the following: "The efficacy results from Study 1 are summarized in Table 8 and Figure 1."
	…	FDA added the following to better clarify the statistical analysis reported for Study 1: "The results shown are from a pre-planned interim efficacy analysis of PFS."
	Results were consistent across the subgroups of (b) (4) prior adjuvant or neo-adjuvant chemotherapy or	FDA revised the proposed statement referring to subgroups in Study 1 to include only those subgroups

	hormonal therapies, liver and/or lung involvement, bone only metastasis disease.	considered clinically relevant and/or were used as stratification factors: "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."
	(b) (4)	FDA revised this text to the following: "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 **…**	Table 8 was reformatted to be more consistent with previously approved labeling. FDA added the number and percentage of PFS events to improve interpretability of the PFS results. FDA removed the (b) (4)
16. How Supplied/Storage and Handling	**…**	FDA instructed the Applicant to add NDC numbers and to revise storage information to be consistent with USP controlled room temperature.

17. Patient Counseling Information	…	FDA revised the format for the subheadings in this Section to be consistent with the FDA Patient Counseling Information Guidance and revised the order of the counseling topics to align with new order for the Warnings and Precautions Section.

10.3 Patient Labeling

At the time of this labeling review (February 16, 2017), the Patient Information is under review.

{See appended electronic signature page}

William Pierce
Associate DirectorLabeling DOP1

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11 Risk Evaluation and Mitigation Strategies (REMS)

No REMS is recommended.

11.2 Safety Issue(s) that Warrant Consideration of a REMS

Not applicable

11.3 Conditions of Use to Address Safety Issue(s)

Not applicable

11.4 Recommendations on REMS

No REMS is recommended

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12 Postmarketing Requirements and Commitments

The following Postmarketing Requirements (PMR) were recommended and agreed upon with the Applicant:

1. Conduct a clinical trial to assess the efficacy and safety of an alternative dosing regimen 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).

   Timelines:
   Draft Protocol Submission: 06/2018
   Final Protocol Submission: 12/2018
   Trial Completion: 04/2022
   Final Report Submission: 10/2022

2. Complete ongoing clinical pharmacokinetic trial CLEE011A2116 (part 1) to determine an appropriate dose of ribociclib in patients with severe renal impairment.

   Timelines:
   Trial Completion: 10/2017
   Final Report Submission: 04/2018

The following Postmarketing Commitments (PMC) were recommended and agreed upon with the Applicant:

1. Submit the third overall survival (OS) interim data and analysis, and the final overall survival (OS) data and analysis from clinical trial entitled "MONALEESA-2" CLEE011A2301.

   Timelines:
   Interim Report Submission (Third OS Interim Data and Analysis): 12/2019
   Final Report Submission (OS Data and Analysis): 06/2022

2. Conduct additional in vitro studies to evaluate the discriminating ability of the dissolution acceptance criterion (Q = (b)(4)% at 45 min) using the approved dissolution method with a validated HPLC analytical method for drug quantification in combination with collecting in vivo PK data using film-coated tablet batches.

Timelines:
Final Report Submission: 09/2018

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13 Appendices

13.1 References

1. *Cancer statistics, 2017.* **Siegel, RL et al.** 2017, CA: Ca J for Clin, pp. 7-30.
2. SEER Cancer Statistics Database. 2017.
3. *Intrinsic breast tumor subtypes, race, and long-term survival in the Carolina Breast Cancer Study.* **O'Brien, KM et al.** 2010, Clin Cancer Research, pp. 6100-6110.
4. *NCCN Clinical Practice Guidelines in Oncology. Breast Cancer.* s.l. : NCCN, 2016, Vol. v2.2016.
5. *FDA Approval: Palbociclib for the Treatment of Postmenopausal Patients with Estrogen Receptor-Positive, HER2-Negative Metastatic Breast Cancer.* **Beaver, JA et al.** s.l. : Clin Cancer Res, 2015, pp. 4760-4766.
6. *Mammalian cyclin-dependent kinases.* **Malumbre, M and M Barbacid.** s.l. : Trends Biochem Sci, 2005, Vol. 30. 630-641.
7. *Regulation of the retinoblastoma tumor suppressor protein by cyclin/cdks.* **Adams, PD.** 1471, s.l. : Biochim Biophys Acta, 2001. 123-133.
8. *CDK inhibitors: positive and negative regulations of G1-phase progression.* **Sherr, CJ and JM Roberts.** s.l. : Gene Dev, 1999, Vol. 13. 1501-1502.
9. *The regulation of E2F by pRB-family proteins.* **Dyson, N.** s.l. : Genes Dev, 1998, Vol. 12. 2245-2262.
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14. *Mammalian cells cycle without the D-type cyclin-dependent kinases Cdk4 and Cdk6.* **Malumbres M, R Sotillo, D Santamaria, J Galan, A Cerezo, S Ortega, et al.** s.l. : Cell, 2004, Vol. 118. 493-504.
15. *Loss of Cdk4 expression causes insulin-deficient diabetes and Cdk4 activation results in beta-islet cell hyperplasia.* **Rane SG, P Dubus, RV Mettus, EJ Galbreath, G Boden, EP Reddy, M Barbacid.** 1, 1999, Vol. 22. 44-52.

13.2 Financial Disclosure

As agreed with FDA at the pre-NDA meeting of July 21, 2016, the following studies were considered as covered by the "Financial Disclosure for Clinical Investigators" rule: A2301 (MONALEESA-2) and X2107 (Phase IB multicenter study of ribociclib plus BYL719 with letrozole in adult patients with advanced ER+ breast cancer). All investigators were assessed for equity interest, significant payments, proprietary interests, and other compensation. Of the 2296 clinical investigators listed in the MONALEESA-2 study, certification was provided for 2288 (99.7%). Three of the 2296 clinical investigators listed in the MONALEESA-2 study report had financial information to disclose (0.1%); these investigators constituted 3 of the total 668 randomized patients in the trial (0.4%). These disclosures are summarized in Table 51 below. Of the 170 clinical investigators listed in the X2107 study, certification was provided for 169 (99.4%). No disclosable financial arrangements and interests were provided for Study X2107.

Table 51. Summary of Financial Disclosures from Study A2301 (MONALEESA-2)

Clinical Site Number	Investigator Name (PI or SI)	Disclosure
	(b) (6)	Equity interest totaling $79,680
		Husband working at (b) (6) (>$50,000)
		Providing nursing presentations for (b) (6) OPM programs and healing conversations but does not speak on the products (>$25,000 and <$50,000)

PI: Principle Investigator; SI: Sub-investigator. Source: NDA 209092 Financial Disclosure

Covered Clinical Study: MONALEESA-2

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 2296		
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): 3		
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: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in the Sponsor of covered study: 2		
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)

Reviewer Comment: *Investigators with significant disclosable interests enrolled approximately 0.4% (n=3) of the total number of patients in the MONALEESA-2 trial (N=668). This is unlikely to individually affect the results of the study.*

13.3. OCP Appendices (Technical documents supporting OCP recommendations)

13.3.1 Summary of Bioanalytical Method Validation and Performance

Were relevant metabolite concentrations measured in the clinical pharmacology and biopharmaceutics studies?

Yes, plasma and urine concentrations of the active parent, ribociclib and M4 (LEQ803, N-demethylation), were measured in the clinical pharmacology and biopharmaceutics studies. Based on the mass-balance Study A2012, ribociclib was the main circulating moiety in plasma (44%). The major circulating metabolites included metabolite M13 (CCI284, N-hydroxylation), M4, and M1 (secondary glucuronide), each representing an estimated 9%, 9%, and 8% of total radioactivity, and 22%, 20%, and 18% of ribociclib exposure. Numerous other metabolites were detected in plasma in minor amounts (≤ 4.15% of total radioactivity). Circulating metabolites have limited contribution to clinical efficacy and safety.

Ribociclib was extensively metabolized with unchanged drug accounting for 17% and 12% in feces and urine, respectively. M4 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).

For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

The total plasma concentration of ribociclib was measured in the clinical trials. This was appropriate due to the constant plasma protein binding of ribociclib over the clinically relevant concentration range studied. The average binding of ribociclib to proteins in human plasma was 70% and independent of concentration (10 to 10,000 ng/mL).

What bioanalytical methods are used to assess concentrations?

Five methods for the analysis of ribociclib and its metabolite, LEQ803 (N-demethylation) in human plasma (four methods) and urine (one method) samples collected during clinical studies are described below.

Ribociclib and LEQ803 Plasma Assays

An initial LC-MS/MS method was validated to measure ribociclib and LEQ803 in human plasma (validation report DMPK R1300147). The bioanalytical method was later revalidated at another bioanalytical site. The corresponding new validation results were reported under the report DMPK R1300457. A cross validation between both bioanalytical sites was successfully performed and results reported in the DMPK R1300457 report.

Under DMPK R1300457a, the method from DMPK R1300457 was further improved by changing the HPLC conditions and additional stability assessments.

Under DMPK R1300457b, the HPLC of the LC-MS/MS system was later changed to an UPLC, and a different quadrupole Mass spectrometer from another brand was used. These changes to the bioanalytical method were subsequently validated.

The first method (DMPK R1300147) was applied in Study X1102. The second method (DMPK R1300457) was applied in trials X1101, A2201, A2103, A2106, and A2111. The third method (DMPK R1300457a) was applied in trials X2107, A2201, A2301, A2101, A2103, and A2111. The fourth method (DMPK R1300457b) was applied in trials A2109, A2103, A2301 and X2107.

Ribociclib and LEQ803 Urine Assay

An initial LC-MS/MS method was validated for human urine (DMPK R1500013), and was applied to trial A2102. The long term stability were reported in amendment DMPK R1300013-01.

Letrozole Plasma Concentrations

Plasma samples obtained in protocol A2301 and X2107 were analyzed for letrozole concentrations by (b) (4) using LC-MS/MS in reports DMPK RCLEE011A2301 and DMPK RCLEE011X2107, respectively. The lower limit of quantitation (LLOQ) was 2.00 ng/mL and the linear calibration range was appropriate at 2.00 ng/mL to 200

ng/mL. The linearity of this method was evaluated by analyzing eight calibration standards over the nominal concentration range of 2.00 to 200 ng/mL using a linear regression algorithm to plot the peak area ratio of the analyte to its internal standard versus concentration.

Ritonavir and Rifampicin Plasma Concentrations

Plasma samples obtained in protocol A2101 were analyzed for ritonavir and rifampicin concentrations by (b) (4) using LC-MS/MS in reports DMPK RCLEE011A2101. The lower limit of quantitation (LLOQ) was 2.50 ng/mL for ritonavir and the linear calibration range was appropriate at 2.50 ng/mL to 2500 ng/mL. The linearity of this method was evaluated by analyzing seven calibration standards over the nominal concentration range of 2.50 ng/mL to 2500 ng/mL using a linear regression algorithm to plot the peak area ratio of the analyte to its internal standard versus concentration. The lower limit of quantitation (LLOQ) was 1.00 ng/mL for rifampin and the linear calibration range was appropriate at 1.00 ng/mL to 500 ng/mL. The linearity of this method was evaluated by analyzing seven calibration standards over the nominal concentration range of 1.00 ng/mL to 500 ng/mL using a linear regression algorithm to plot the peak area ratio of the analyte to its internal standard versus concentration.

Midazolam, 1'-hydroxymidazolam, and Caffeine Plasma Concentrations:

Plasma samples obtained in protocol A2106 were analyzed for midazolam , 1'-hydroxymidazolam, and caffeine concentrations by (b) (4) using LC-MS/MS in reports DMPK RCLEE011A2106. The lower limit of quantitation (LLOQ) was 50.0 pg/mL for midazolam and 1'-dydroxymidazolam, and the linear calibration range was

appropriate at 50 pg/mL to 50000 pg/mL. The linearity of this method was evaluated by analyzing seven calibration standards over the nominal concentration range of 50 pg/mL to 50000 pg/mL using a linear regression algorithm to plot the peak area ratio of the analyte to its internal standard versus concentration. The lower limit of quantitation (LLOQ) was 25.0 ng/mL for caffeine and the linear calibration range was appropriate at 25 ng/mL to 12500 ng/mL. The linearity of this method was evaluated by analyzing seven calibration standards over the nominal concentration range of 25 ng/mL to 12500 ng/mL using a linear regression algorithm to plot the peak area ratio of the analyte to its internal standard versus concentration.

13.3.2 Clinical PK

In health subjects, ribociclib PK were studied after single dose and after multiple doses (DDI Studies A2101 and A2106, food effect and/or BE Studies A2111 and A2103, an ADME Study A2102). The PK parameters are summarized in Table 52.

Table 52. Summary of ribociclib PK parameters in healthy subjects

Dose Study		Cmax (ng/mL)	Tmax (h)	AUC0-24h (hr•ng/mL)	AUCinf (hr•ng/mL)	T1/2 (h)	CL/F (L/h)
400 mg							
[Study A2101]	Single dose	n=24	n=24	n=24	n=24	n=24	n=24
		357 (42.5)	3.00 (1.00; 6.07)	3830 (38.9)	5840 (36.4)	30.6 (19.0)	68.5 (36.4)
[Study A2106]	Single dose	n=25	n=25	n=25	NE	NE	NE
		338 (38.3)	3.00 (1.00, 6.00)	3340 (35.2)			
	Multiple doses	n=25	n=25	n=25	NE	NE	NE
		823 (36.2)	3.00 (2.00, 6.00)	10600 (33.5)			
[Study A2109]	Single dose	n=11	n=11	n=11	n=11	n=11	n=11
	Normal liver function	303 (66.8)	4.00 (1.00, 6.00)	3410 (42.7)	6010 (35.5)	38.9 (18.9)	66.6 (35.5)
	Single dose	n=6	n=6	n=6	n=6	n=6	n=6
	Mild hepatic impairment	339 (24.2)	3.00 (1.00, 4.00)	3710 (33.1)	6330 (39.5)	44.2 (20.3)	63.2 (39.5)
	Single dose	n=6	n=6	n=6	n=6	n=6	n=6
	Moderate hepatic impairment	455 (18.2)	2.00 (2.00, 6.00)	4590 (27.0)	7920 (30.4)	36.8 (21.1)	50.5 (30.4)
	Single dose	n=5	n=5	n=5	n=5	n=5	n=5
	Severe hepatic impairment	407 (45.8)	1.00 (1.00, 2.03)	3940 (39.2)	7760 (33.0)	49.0 (40.8)	51.5 (33.0)
600 mg							
[Study A2101]	Single dose	n=24	n=24	n=24	n=24	n=24	n=24
		565 (57.4)	3.00 (1.00, 6.00)	5910 (51.4)	8940 (51.4)	31.5 (28.7)	67.1 (51.4)
[Study A2102]	Single dose	n=6	n=6	n=6	n=6	n=6	n=6
		507 (185) [1]	1.75 (1, 6)	8780 (3110) [1]	8880 (3100) [1]	54.7 (14.2) [1]	77.5 (28.9) [1]
[Study A2103]	Single dose	n=31	n=31	n=31	n=30	n=30	n=30
	Bioequivalence - DiC	596 (66.3)	3.00 (1.00, 8.00)	6880 (58.4) [2]	11400 (41.8)	29.7 (20.2)	52.7 (41.8)
	Single dose	n=31	n=31	n=31	n=31	n=31	n=31
	Bioequivalence - tablet	598 (36.3)	3.00 (1.00, 6.07)	7000 (33.8)	10700 (35.2)	30.6 (22.8)	55.8 (35.2)
	Single dose	n=23	n=23	n=23	n=23	n=23	n=23
	Food effect - without food	792 (35.0)	3.00 (2.00; 6.00)	9130 (32.8)	14300 (32.3)	32.0 (18.6)	42.0 (32.3)
	Single dose	n=24	n=24	n=24	n=24	n=24	n=24
	Food effect - with food	790 (33.2)	4.00 (1.08, 10.0)	9350 (28.0)	15000 (29.2)	33.6 (24.6)	39.9 (29.2)
[Study A2111]	Single dose	n=24	n=24	n=24	n=24	n=24	n=24
	Fasting	729 (64.8)	3.00 (1.00, 6.05)	7960 (59.6)	12100 (60.0)	31.5 (35.7)	49.8 (60.0)
	Single dose	n=23	n=23	n=23	n=23	n=23	n=23
	High-fat, high-calorie meal	558 (48.3)	6.00 (3.00, 8.02)	7310 (49.4)	11700 (50.7)	32.0 (28.3)	51.1 (50.7)

DiC: drug-in-capsule, n: number of healthy subjects with corresponding evaluable PK parameters; NE: not estimated; PK: pharmacokinetics.
Data are presented as geometric mean (CV% geo mean) for all parameters except for Tmax which is presented as median (range) or otherwise specified
[1] Arithmetic mean (standard deviation)
[2] Values reported as in the Clinical Study Report for Study A2103

Source: Table 2-1 of 2.7.2Addendum 2 for Summary of Clinical Pharmacology of Ribociclib in Combination with Letrozole in HR-positive, HER2-negative, Advanced Breast Cancer (Section 2.7.2)

In patients with cancer, ribociclib PK characteristics were evaluated after the first dose and after multiple doses (Studies X1101, X2101, and X2107). The PK parameters are summarized in Table 53 and Table 54. Only sparse PK data (Cycle 1 Day 15 pre-dose and 2 hours after dose) was collected in Study A2301. The PK data in Study A2301 were used for popPK model qualification.

Slightly lower exposure was observed for ribociclib in healthy subjects compared to patients with cancer. Following a single 600 mg dose, the geometric mean Cmax and AUC_{0-24h} in healthy subjects in studies ranged from 507 to 792 ng/mL and 5910 to 9350 h•ng/mL, respectively. The geometric mean Cmax and AUC_{0-24h} in patients with cancer ranged from 992 to 1260 ng/mL and 9700 to 14200 h•ng/mL, respectively. The differences are not clinically relevant considering the similar elimination noted between these populations and the high inter-patient variability (~ 60%) in ribociclib PK at the 600 mg daily dose. Following multiple 600 mg doses, similar as what observed in the cases in single dose, slightly lower exposure was observed for ribociclib in healthy subjects compared to patients with cancer.

Table 53. Summary of ribociclib PK parameters in patients with cancer after single dose

Dose Study		Cmax (ng/mL)	Tmax (h)	AUC0-24h (hr•ng/mL)
400 mg				
[Study X1101]	Single dose	n=4	n=4	n=3
		591 (26.4)	3.12 (1.97, 6.00)	6170 (25.9)
[Study X2101]	Single dose (pooled[1])	n=11	n=11	n=8
		559 (58.6)	4.00 (0.583, 4.20)	4900 (63.0)
600 mg				
[Study X1101]	Single dose	n=12	n=12	n=11
		1260 (38.3)	2.97 (1.92, 5.87)	14200 (35.1)
[Study X2101]	Single dose	n=8	n=8	n=7
	Oral solution formulation	1030 (86.4)	1.13 (1.08, 2.12)	7720 (97.2)
	Single dose	n=73	n=73	n=68
	Pooled[1]	992 (64.4)	2.08 (0.917, 7.95)	9700 (62.0)
[Study X2107]	Single dose	n=41	n=41	n=37
		1030 (46.3)	2.07 (0.983, 4.2)	10310 (37.2)

DiC: drug-in-capsule; n: number of patients with cancer with corresponding evaluable PK parameters; PK: pharmacokinetics.

Data are presented as geometric mean (CV% geo mean) for all parameters except for Tmax which is presented as median (range)

[1] Pooled data from patients with cancer receiving intermittent schedule (3 weeks on 1 week off) and patients with cancer with continuous dosing (once daily for 28 days)

Source: Table 2-5 of 2.7.2Addendum 2 for Summary of Clinical Pharmacology of Ribociclib in Combination with Letrozole in HR-positive, HER2-negative, Advanced Breast Cancer (Section 2.7.2)

Table 54. Summary of ribociclib PK parameters in patients with cancer after multiple doses

Dose Study		Cmax (ng/mL)	Tmax (h)	AUC0-24h (hr•ng/mL)	Racc (AUCtau)	T1/2,acc (h)	CL/F (L/h)
400 mg							
[Study X1101]	Multiple doses (C1, D21)	n=4	n=4	n=4	n=3	n=3	n=4
		2180 (15.8)	3.00 (1.98, 4.00)	27700 (15.8)	4.35 (8.1)	63.6 (9.2)	14.4 (15.8)
[Study X2101]	Multiple doses (C1, D18/21)	n=10	n=10	n=4	n=4	n=4	n=4
		1040 (49.3)	4.04 (1.00, 7.83)	11400 (57.8)	2.46 (24.6)	31.6 (33.2)	35.3 (59.2)
600 mg							
[Study X1101]	Multiple doses (C1, D21)	n=8	n=8	n=8	n=8	n=7	n=8
		3280 (59.9)	5.00 (4.00, 7.55)	51600 (59.2)	3.79 (37.6)	53.6 (44.8)	11.6 (59.2)
[Study X2101]	Multiple doses (C1, D18/21)	n=6	n=6	n=5	n=5	n=5	n=5
	Oral solution formulation	2530 (56.3)	1.69 (1.12, 6.00)	24400 (55.9)	4.09 (74.1)	57.6 (85.5)	24.6 (56.5)
	Pooled[1]	n=57	n=57	n=54	n=50	n=49	n=53
		1820 (62.4)	2.40 (0.683, 7.82)	23800 (66.0)	2.51 (45.6)	32.0 (63.2)	25.5 (65.7)
[Study X2107]	Multiple doses (C1 D21)	n=28	n=28	n=23	n=19	n=18	n=20
		1720 (44.6)	2.11 (1.05, 7.67)	23290 (52.2)	2.3 (38.7)	30.4 (38.7)	26.5 (53.2)

C: cycle; D: day; DiC: drug-in-capsule; n: number of patients with cancer with corresponding evaluable PK parameters; PK: pharmacokinetics.

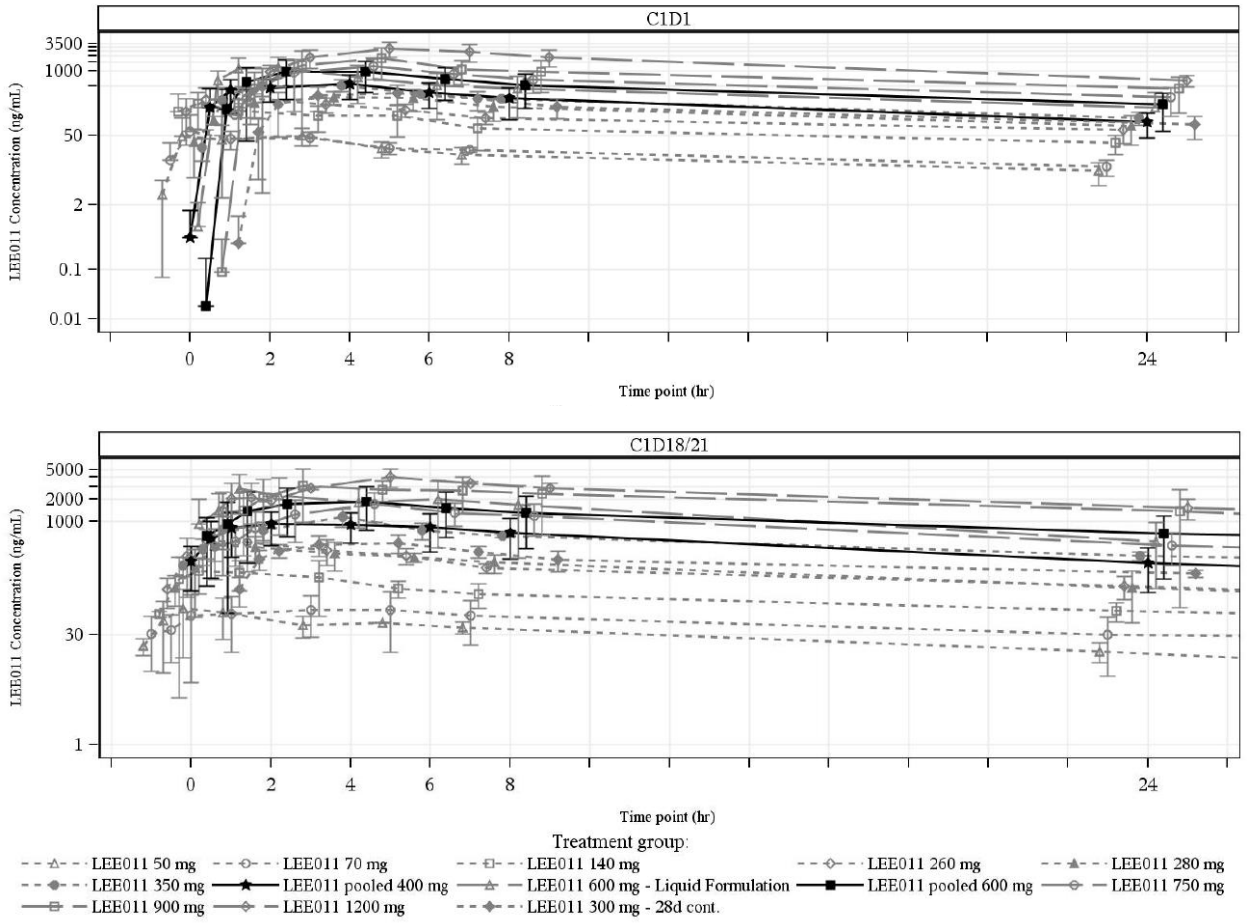
Data are presented as geometric mean (CV% geo mean) for all parameters except for Tmax which is presented as median (range)

Source: Table 2-5 of 2.7.2Addendum 2 for Summary of Clinical Pharmacology of Ribociclib in Combination with Letrozole in HR-positive, HER2-negative, Advanced Breast Cancer (Section 2.7.2)

In Study X2101, Ribociclib plasma concentration vs time profiles were measured after a single dose and after multiple doses across the dose range of 50 to 1200 mg in patients with cancer (Figure 10). A power model was applied to test the ribociclib dose proportionality in exposure in Study X2101 across the dose range of 50 to 1200 mg (Figure 11). The slopes of the power model on logarithmic scale (Cmax: 1.192 on C1D1 and 1.360 on C1D18/21; $AUC_{0\text{-}24h}$: 1.270 on C1D1 and 1.415 on C1D18/21) suggested over-proportional increases in exposure. Dose

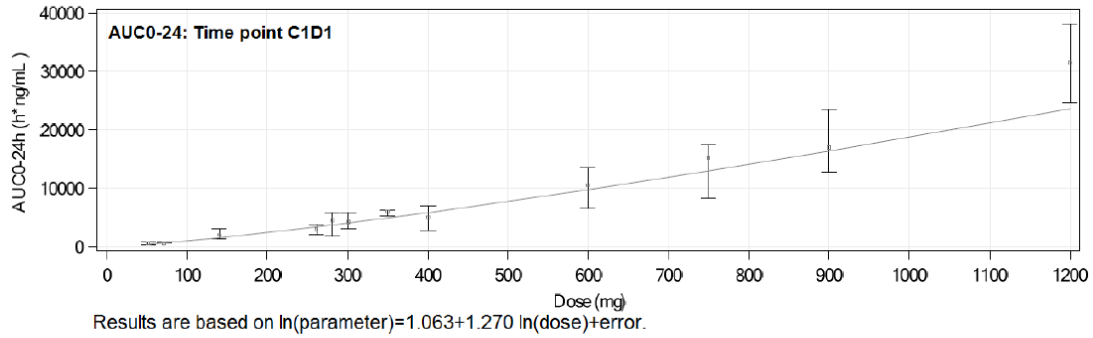
proportionality was not assessed for other studies in patients with cancer or in healthy subjects due to the narrow range of doses tested (400 mg or 600 mg).

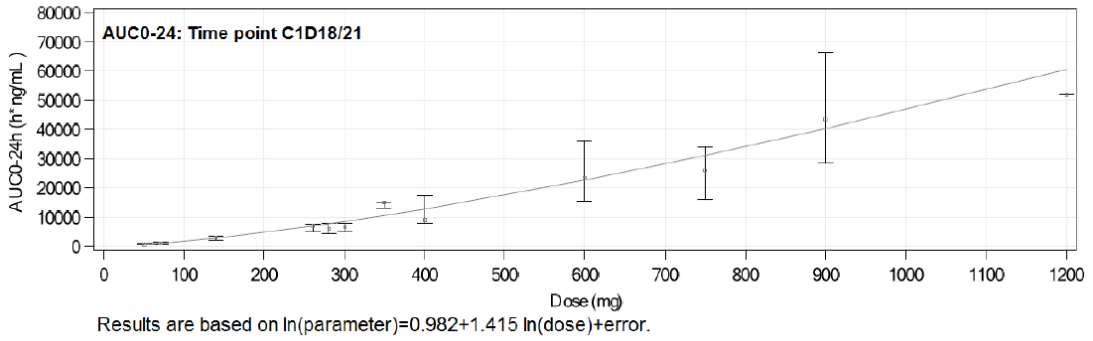
Figure 10. Semi-logarithmic arithmetic mean (SD) plasma concentration vs time profile of ribociclib after a single (C1D1, cycle 1 day 1; upper figure) and multiple (C1D18/21, cycle 1 day 18 or 21; lower figure) QD dose of ribociclib

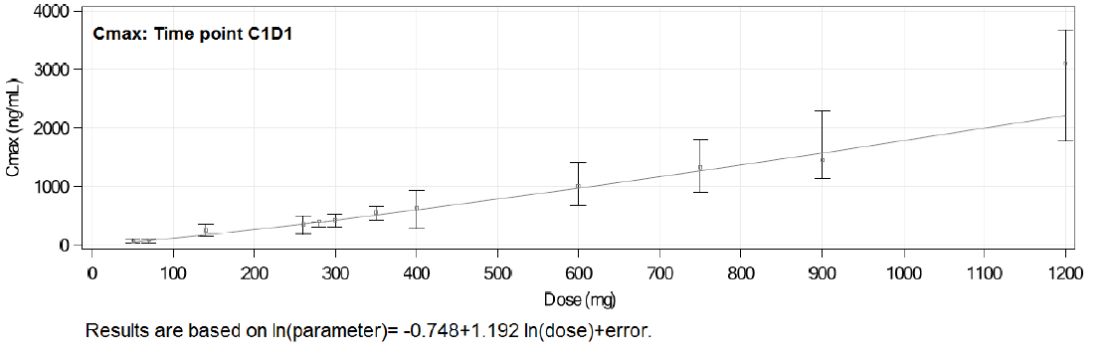


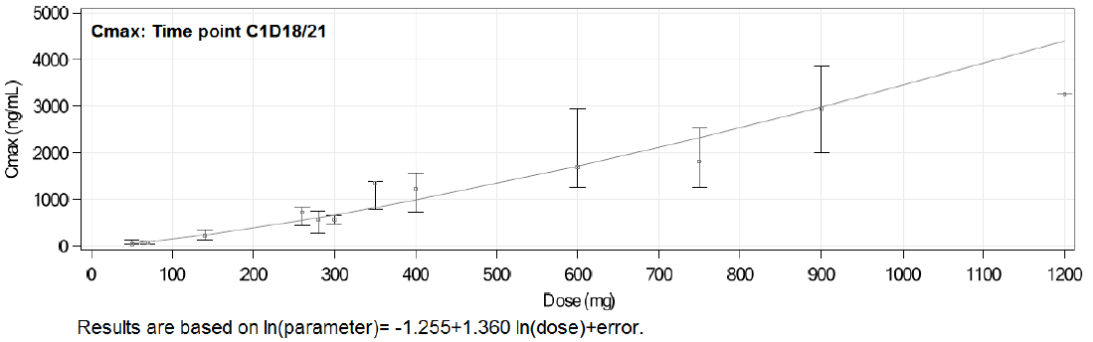
Source: Figure 14.2-2.1 of Interim clinical study report LEE011X2101

Figure 11. Dose proportionality for ribociclib PK parameters at Cycle 1 Day 1 (C1D1) and at steady state Cycle 1 Day 18 or Day 21 (C1D18/21) for Cmax and $AUC_{0\text{-}24h}$.









Source: Figure 3-1 of 2.7.2Addendum 2 for Summary of Clinical Pharmacology of Ribociclib in Combination with Letrozole in HR-positive, HER2-negative, Advanced Breast Cancer (Section 2.7.2)

13.3.3 Population PK and/or PD Analyses

13.4.3.1 Population PK analysis

Applicant's population PK analysis was based on pooled data (4731 non-missing PK samples available from 208 patients) from studies LEE011X1101, LEE011X2101 and LEE011X2107. PK data (175 evaluable PK samples from 93 patients) from pivotal phase III study LEE011A2301 were used for external model qualification. Ribociclib pharmacokinetic profile was adequately described using a two compartmental PopPK model with delayed zero-order oral absorption and linear clearance from the central compartment. Goodness-of-fit (GOF) plots and visual predictive check (VPC) (Figure 12, Figure 13) showed there is overall a good agreement between observations and model predictions. The parameter estimates of final population PK model were summarized in Table 55.

The final PopPK model was further externally validated to predict the ribociclib exposure at group level in Study A2301. Overall the simulation results were consistent with the observed data (Figure 14). At the 2h post-dose point, the mean was underpredicted by 15.6%. This underprediction, however, is not expected to be clinically consequential.

Applicant's conclusion based on population PK analysis

1. Dose was found to be a statistically significant and clinically important covariate on CL, Q and V2. It is consistent with the trend of more than dose-proportional increase in exposure previously observed.
2. Weight was found to be a statistically significant and clinically important covariate on CL, Q and V2. Simulation suggested a change of BW from 70 kg to 50 or 100 kg would cause up to 22% change in SS C_{max}, C_{trough} and AUC_{24h} at 600 mg QD. This covariate effect, however, was small relative to the inherent pharmacokinetic variability (IIV of CL: 51.3%).
3. There are no clinically relevant effects of age, gender or race on the systemic exposure of ribociclib that would require a dose adjustment. Gender (134 female and 74 male patients) and race (153 Caucasians, 23 Asians and 32 patients with other race) were removed from the final model due to their statistical insignificance. Age (median: 60, range: 23-84) was a statistically significant covariate on clearance but its simulated covariate effect on clearance was mild.
4. Co-administration of gastric pH-elevating agents PPIs (N=52) or letrozole (N=47) did not have a statistically significant and clinically important effect on ribociclib PK.
5. Mild hepatic impairment had no effect on the exposure of ribociclib (160 patients with normal liver function, 47 patients with mild hepatic impairment, 1 patient with moderate hepatic impairment). Therefore, no dose adjustment is recommended for patients with mild hepatic impairment.
6. No significant relationship was identified between clearance and eGFR (77 patients with normal renal function, 76 patients with mild renal impairment, 35 patients with moderate renal impairment and no patient with severe renal impairment). Therefore, no dose adjustment is recommended for patients with mild or moderate renal impairment.

Reviewer's Comments on population PK analysis

1. *Reviewer agrees with Applicant's conclusions in general. Goodness-of-fit plots and simulation-based diagnostics (VPC) showed final model adequately described the observed data. All PK parameters were estimated with acceptable precision. External validation in sparse PK data from study A2301 further confirmed the predictive capability of final PK model. Therefore, reviewer agrees that the final population PK model has sufficient predictive ability to simulate exposure of alternative dosing regimen of ribociclib treatment.*
2. *Applicant's conclusion regarding no dose adjustment for patients with mild or moderate renal impairment seems reasonable. This is consistent with renal elimination being a minor clearance pathway of ribociclib. However, the effect of severe renal impairment on ribociclib exposure is unknown.*
3. *The population PK model is not able to provide reliable post hoc exposure predictions in patients from pivotal study A2301 for the subsequent E-R analysis for efficacy (PFS or ORR) because of sparse PK sampling (175 observations available from 92 out of 334 patients receiving combination therapy of ribociclib and letrozole).*

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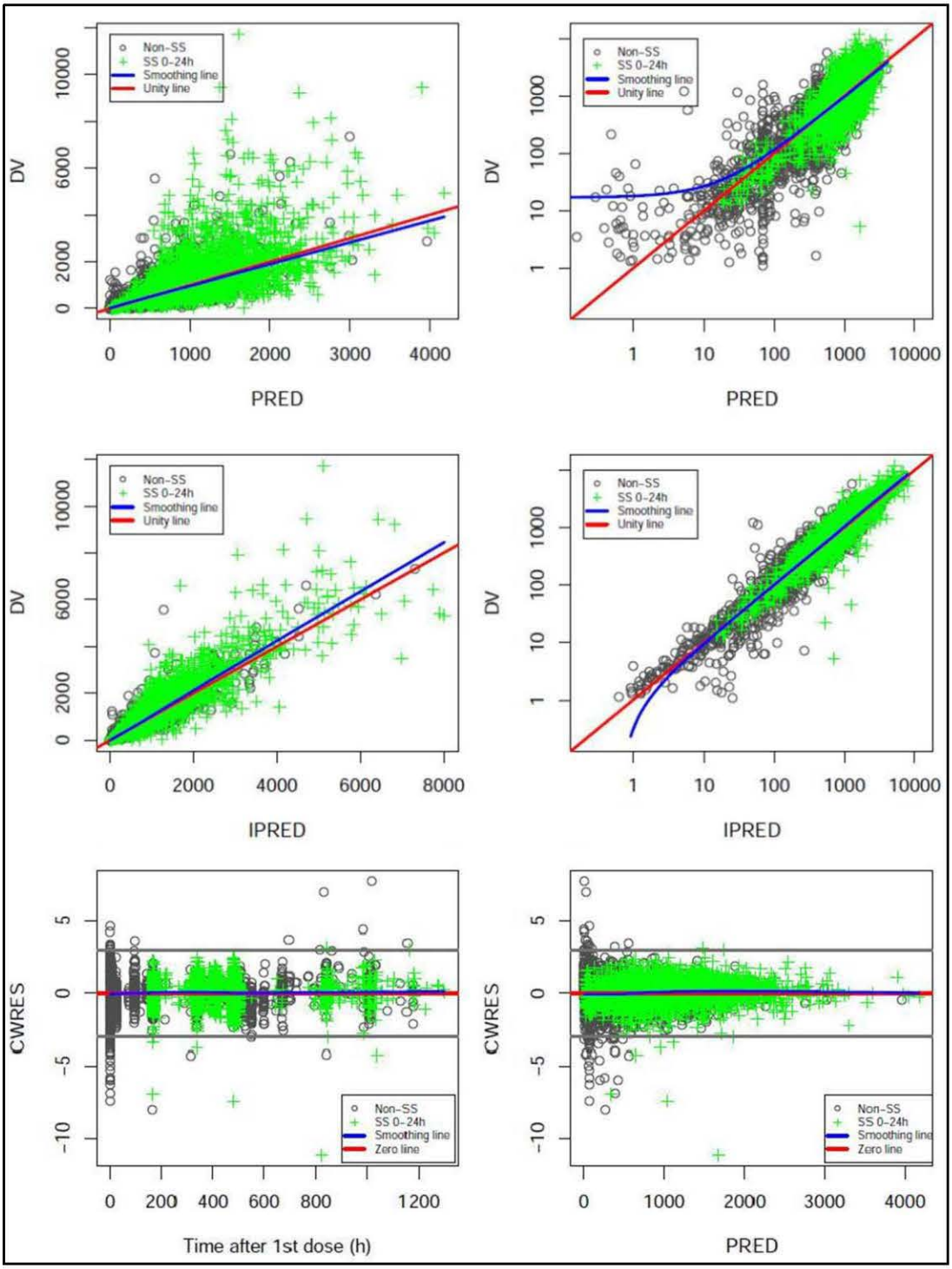
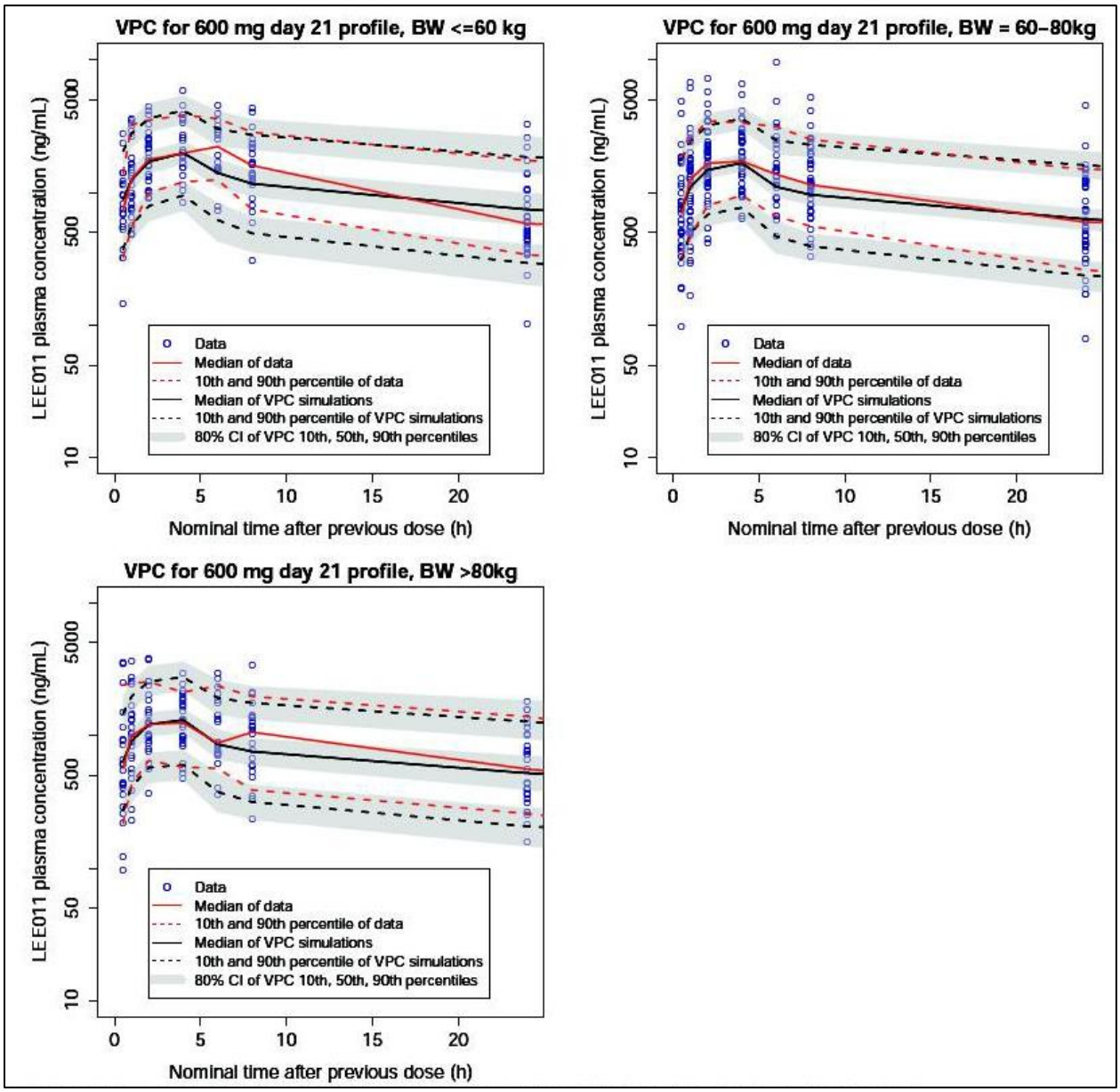
Figure 12: Goodness-of-fit plots from final PopPK model. **DV**: Observations; **PRED:** Population predictions; **IPRED:** Individual predictions; **CWRES:** Conditional weighted residuals; **IWRES:** Individual weighted residuals.



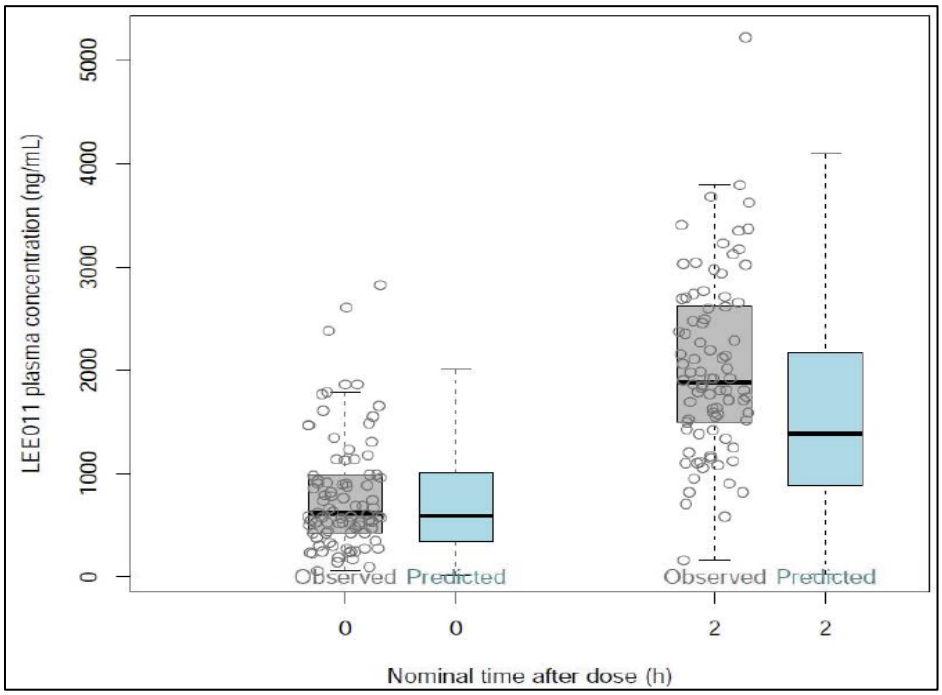
Source: *Applicant population pharmacokinetic modeling analysis report, Page 66-67, Figure 5-8, 5-9*

Figure 13: Body weight stratified VPC on Day 21 after 600mg QD using final PopPK model



Source: *Applicant population pharmacokinetic modeling analysis report, Page 69, Figure 5-11*

Figure 14: Observed and final PopPK model predicted ribociclib concentration in Study A2301



Sources: Applicant's Population PK analysis report, Page 70, Figure 5-12

Table 55: Parameter estimates of final population PK model

Parameter	Estimate	SE	RSE (%)	95% Confidence Interval	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
ω^2_{CL-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
ω^2_{CL-V2}	0.192	0.027	14.06	(0.139 - 0.245)	-
ω^2_{Q-V2}	0.213	0.046	21.6	(0.123 - 0.303)	-

Sources: Applicant's Population PK analysis report, Page 64, Table 5-7

13.4.3.2 PK/PD modeling for absolute neutrophil count

The PK/PD modeling analysis consisted of 1904 ANC observations in first 4 cycles of treatment pooled from 205 patients in studies LEE011X1101, LEE011X2101 and LEE011X2107. The

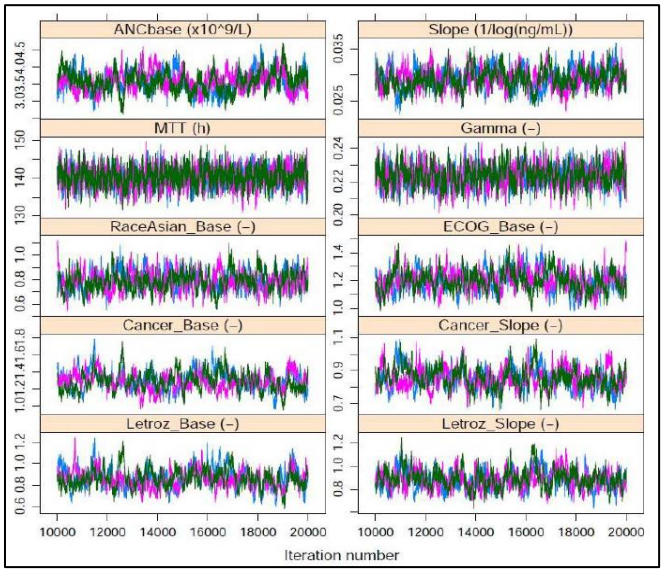
individual PK parameters obtained from population PK model were fixed to predict the individual PK profiles to drive the ANC reduction. ANC reduction with treatment of ribociclib was satisfactorily described with a physiological model coupled with a log-linear drug effect model using Bayesian estimation.

The MCMC (Markov Chain Monte Carlo) convergence of the final model was verified by inspection of trace plots (**Figure 15**). The parameter posteriors from the final model were shown in **Table 56**. The diagnostic plots suggested that final model described the observed ANC reduction well (
Figure 16**). VPC diagnostics demonstrated the model simulations were in line with the observations, further confirming the satisfactory performance of the final PK/PD model (Figure 17).**

The external model qualification (2090 ANC observations from 315 patients) showed the final PK/PD model can adequately predict the time course profile of ANC with ribociclib treatment of 600mg QD in the pivotal trial A2301 (22Figure 1822Figure **18**). Simulations indicate that a lower QD dose of ribociclib will lead to less ANC reduction (Figure 19).

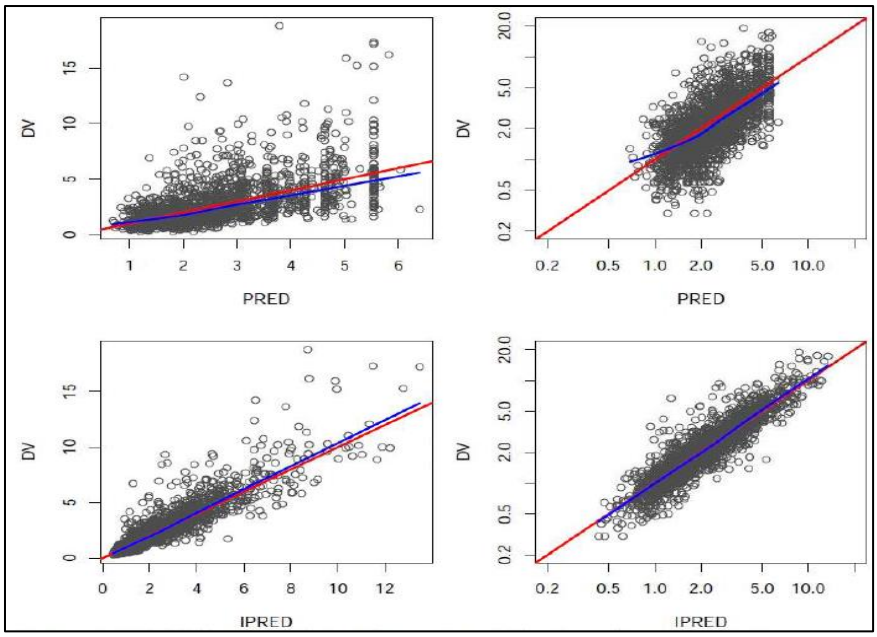
Reviewer's comments: The final PK/PD model adequately captured the observed ANC data and all the model parameters were estimated with acceptable precision. External validation confirmed the ability of the model in predicting time course profile of ANC reduction. The predicted probability of grade 3/4 neutropenia (44.8%) was comparable with the observed frequency of 600mg QD in the model qualification dataset (50.8%). The final Pop PK/PD model was shown to have sufficient predictive ability to assess the risks for neutropenia at alternative dose regimen of ribociclib treatment through model simulation.

Figure 15: Final ANC E-R model MCMC trace plots



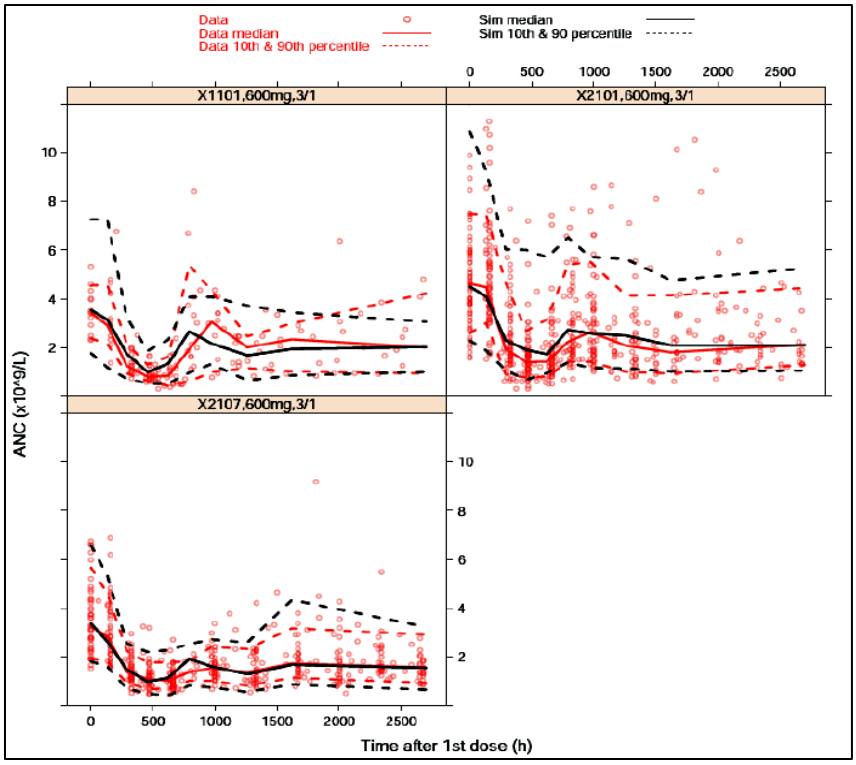
Sources: Applicant population pharmacokinetic modeling analysis report, Page 113, Figure 9-19

Figure 16: Goodness-of-fit plots of final Pop PK/PD model for ANC reductions. **DV**: Observations; **PRED:** Population predictions; **IPRED:** Individual predictions.

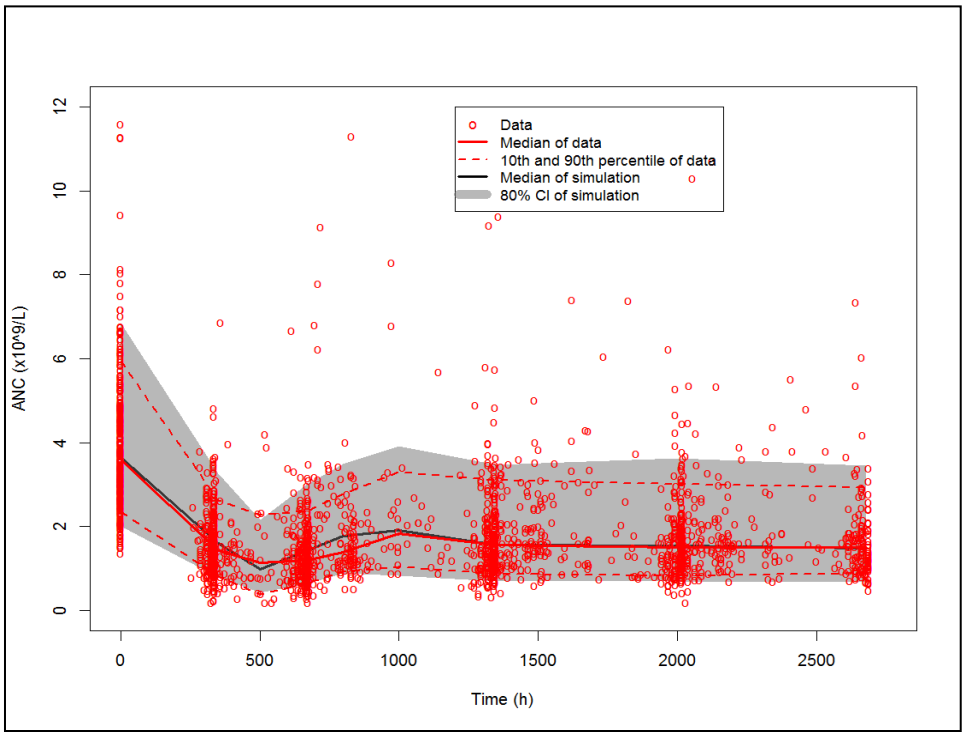


Sources: Applicant population pharmacokinetic modeling analysis report, Page 84, Figure 5-19

Figure 17: Final Pop PK/PD model VPC simulations consistent with ANC development dataset

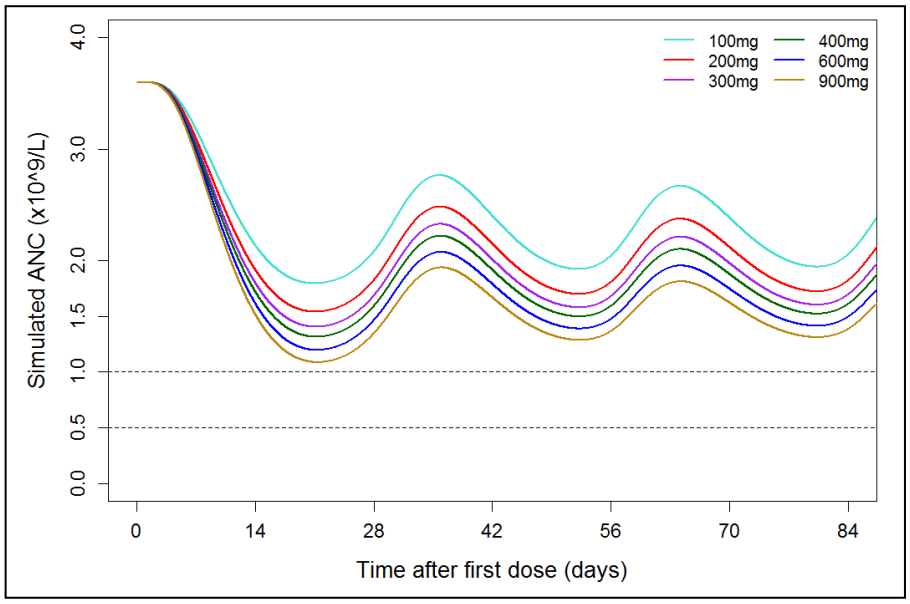


*Sources: Applicant population pharmacokinetic modeling analysis report, Page 87, Figure 5-22*Figure **18: ANC E-R model simulation consistent with qualification dataset from Study A2301**



Source: Applicant's response to FDA's IR 10, Figure 2-1, Page 5.

Figure 19: Simulated mean ANC profiles in cancer patients with various once daily treatments of ribociclib



Sources: Applicant population pharmacokinetic modeling analysis report, Page 90, Figure 5-25

Table 56: Parameter posteriors from final population PK/PD model for ANC reduction

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)
$\omega^2_{Base\sim Slope}$	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)

Sources: Applicant population pharmacokinetic modeling analysis report, Page 83, Figure 5-15

13.3.4 Exposure-Response Analyses

13.4.4.1 E-R for efficacy

In study A2301, the relationship between exposure (C_{trough}) and efficacy (PFS, TTR) was explored by Kaplan Meier (KM) analysis; however, as the number of subjects with events and concomitant exposure data included in the analyses was small (n=44 out 334), no definite conclusion can be drawn.

Distribution of dosing intensity (DI) was compared between patients having an event and all patients who are at risk at each PFS event time (Figure 20). Longer PFS was not clearly associated with high or low DI, with patients deriving PFS benefit across the range of DI studied.

In the cancer patient pool (Study A2301 and Study X2107), a relatively small number of patients (n=72 out of 434) have both data of ribociclib exposure (C_{trough}) and confirmed best response. Among these patients ribociclib exposures were similar between responders (BOR of CR/PR) and non-responders. The logistic regression indicated no relationship between ribociclib exposure and probability of responders (odds ratio: 0.923, 95% CI (0.819, 1.041); p=0.188).

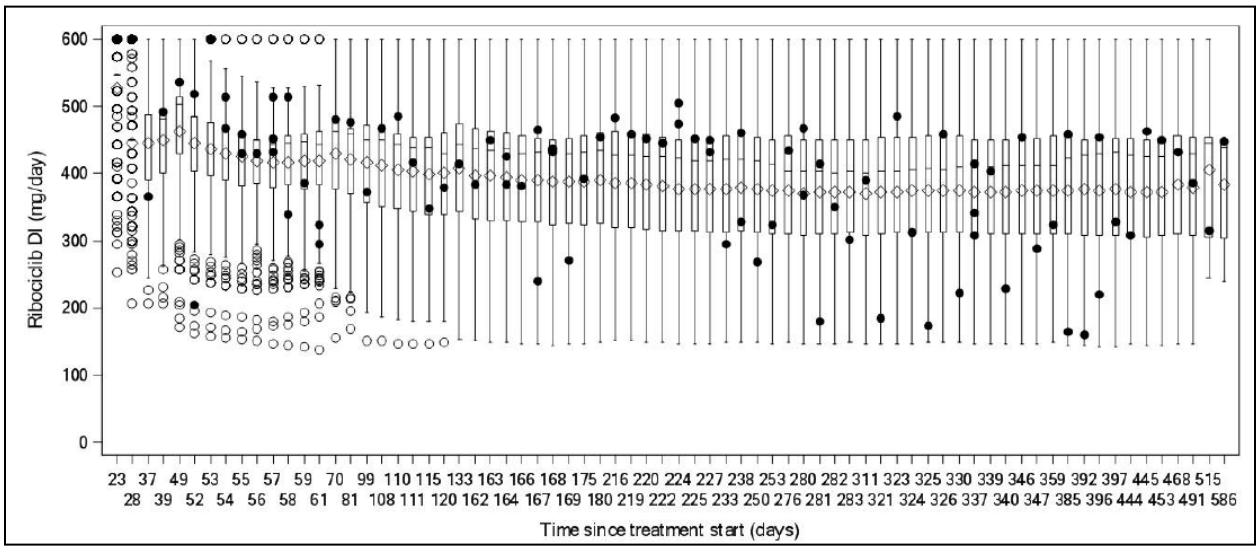
Reviewer's Comments:

The E-R relationship for efficacy remains inconclusive due to limited information of ribociclib exposure is available in Study A2301 and X2107. Only 44 patients were included in the E-R analysis for PFS and their collected exposures C_{trough} at Cycle 1 Day 15 (C1D15) may not represent the exposure associated with PFS events which usually happened later. Based on reviewer's analysis there is no clear trend of better PFS with increasing ribociclib exposure following the proposed dosing regimen 600mg QD (Figure 21). Similarly, no significant relationship was established between ribociclib exposure and probability of responders by Applicant's analysis using logistic regression.

Dosing intensity is a poor measure of drug exposure when there is high pharmacokinetic variability. It is also related to survival when the rate of dose reduction is high: patients who survived longer have higher probabilities of experiencing dose reductions and their dosing intensity tends to be lower, besides information of censoring is not present in the box plots of DI vs. PFS (Figure 20). No definite conclusion on E-R for PFS can be drawn from this analysis.

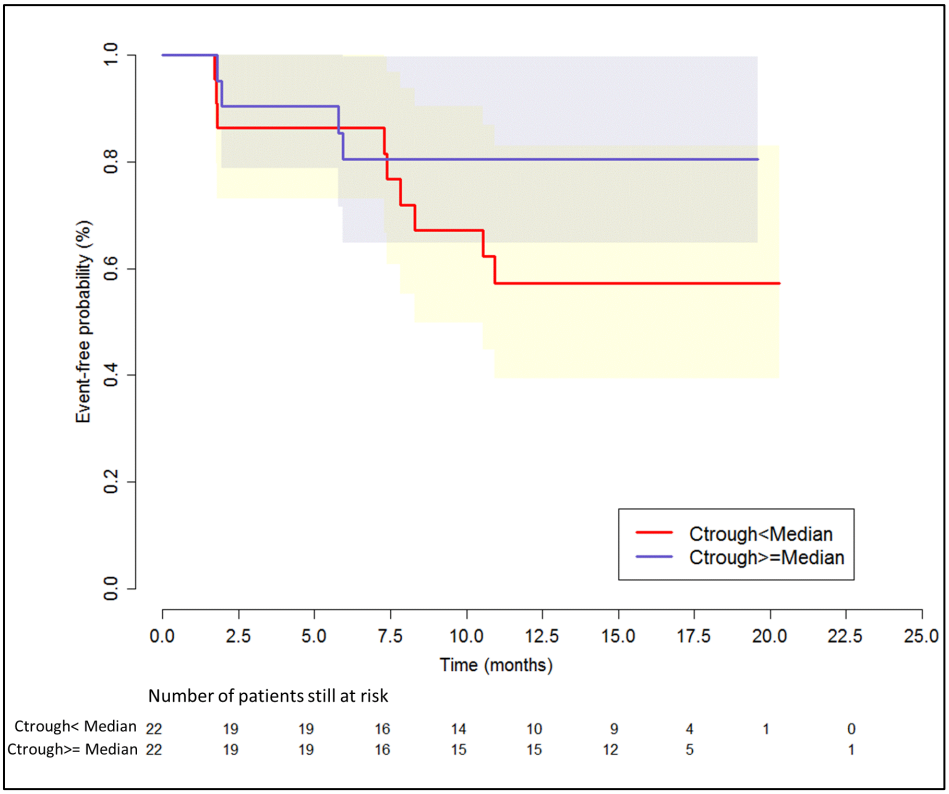
In summary due to limited data of drug exposure a reliable estimate of effect of ribociclib exposure on efficacy cannot be achieved and no definitive conclusion can be drawn with regard to the E-R relationship for efficacy (PFS or ORR) at this time.

Figure 20: Box plots of ribociclib DI vs PFS in Study A2301, FAS



Sources: Applicant population pharmacokinetic modeling analysis report, Page 58, Figure 3-5

Figure 21: Inconclusive E-R relationship for PFS based on Study A2301



13.4.4.2 E-R for safety

QT prolongation, hepatobiliary toxicity and neutropenia are important identified risks for ribociclib treatment.

13.4.4.2.1 QT prolongation

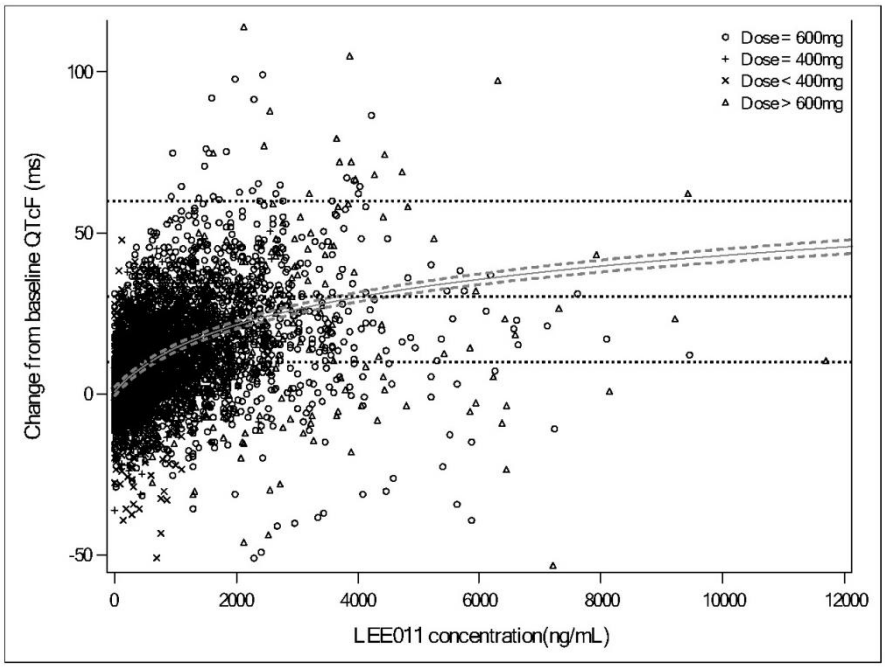
13.4.4.2.1.1 Applicant's C-QTc analyses

The concentration-QTc (C-QTc) analyses were assessed using 3848 time-matched ECG-concentration pairs in 267 cancer patients treated with single and multiple doses of ribociclib ranging from 50 to 1200 mg as a single agent and in combination with letrozole from studies A2301, X1101, X2101 and X2107. The distribution of baseline QTcF in patients was comparable across four studies. A log-linear mixed effect model identified concentration-dependent increases in change from baseline QTcF (ΔQTcF) (p-value<0.0001) (Figure 22). The fixed effect estimates from final model was listed in Table 57. The estimated mean ΔQTcF was 22.87 ms (90% CI: 21.6, 24.1) in patients at the mean steady-state C_{max} (2237 ng/mL) following a therapeutic dose of 600 mg QD. Based on the ER analysis large QTc prolongation (20 ms) is expected following 600mg QD and adequate ECG monitoring should be conducted.

Reviewer's comments: Independent analyses for the relationship between ΔQTcF and ribociclib concentrations were conducted by the reviewer (see details in QT-IRT review). Consistent with the Applicant's results, the relationship between ΔQTcF and ribociclib concentrations can be well

described with a log-linear mixed effect model with a significant slope (p<0.0001). This finding supports the dose modification plan to manage QT risks in the label.

Figure 22: Scatter Plot and Final Statistical Model of Ribociclib PK Concentration vs Change from Baseline QTcF for Patient Pool



Source: QT/QTc Safety Analysis Report, Figure 4-5, Page 47

Table 57: Fixed effect estimates and p-values from final model – patient pool

Effect	Estimated coefficient (SE)	p-value
Intercept	0.9104 (0.81178)	0.2631
Log(conc/median conc+1)	15.7117 (0.52421)	<.0001
Baseline QTcF-Median baseline QTcF	-0.1373 (0.03857)	0.0004

Median concentration=734.5ng/mL Median baseline QTcF=412.67ms
- The model is a linear mixed effects model with subject as a random effect, and mean function in the form of Delta QTcF = log (concentration/median concentration + 1) + (baseline QTcF – median baseline QTcF).

Source: Applicant's safety report for QT prolongation, page 45 ,Table 4-11

13.4.4.2.1.2 Reviewer's analysis: simulation of risks for QT prolongation at alternative dosing regimen

Introduction

Ribociclib can prolong the QT interval in a concentration-dependent manner, with mean increase in QTc interval exceeding 20ms at 600 mg once daily dose. Syncope and sudden death have occurred in patients taking ribociclib. Appropriate measures should be taken to mitigate the risks for QT prolongation. Under such circumstance additional analysis was conducted by reviewer to investigate the risk profiles for QT prolongation at alternative dosing regimen based on the established ER analysis.

Methods

The final PopPK model was used to simulate SS exposure metrics (C_{max}, C_{trough},and AUC_{tau}) after 21 days for alternative dosing regimen of ribociclib treatment. Alternative dosing regimens of interest include 400mg QD, 300mg BID and 400mg BID. Each simulation data file included a set of 5 patients with different body weights (50, 60, 70, 80 and 100 kg) for each regimen and was replicated for 1000 times.
A log-linear mixed effect model identified concentration-dependent increases in change from baseline QTcF (ΔQTcF) (Table 57). TheΔQTcF at simulated SS C_{max} of alternative dosing regimens of interest (300mg BID, 400mg BID, 400mg QD) were predicted using the established log-linear mixed effect model.

Data Sets

Data sets used are summarized in Table 58.

Table 58: Analysis datasets

Analysis	Data File	Link to EDR
Final Pop-PK	final.log.s3.k0.run09b2_ctl.txt	\\CDSESUB1\evsprod\NDA209092\0000\m5\datasets\lee011a-poppk\analysis\programs
C-QT analysis	adpceg.xpt	\\CDSESUB1\evsprod\NDA209092\0024\m5\datasets\scp\analysis\adam\datasets

Software

R 3.3.1 and NONMEM 7.3 were used for the analyses.

Results

The SS exposure metrics ($\boldsymbol{C_{max}}$, $\boldsymbol{C_{trough}}$,and $\boldsymbol{AUC_{tau}}$) of alternative dosing regimen 400mg QD, 300mg BID and 400mg BID were summarized in

Table 59 **Table 59**. The mean SS $\boldsymbol{C_{max}}$ for 300mg BID, 400mg BID and 400mg QD were 1150, 1700 and 1140 ng/mL respectively. The log-linear mixed effect model developed by Applicant to assess concentration-QT relationship is:

$\Delta QTCF_{ij} = 0.9104 + 15.7117 * \log\ (Concentration_{ij}/734.5 + 1) - 0.1373 * (baseline\ QTCF - 412.67)$

The simulated mean ΔQTCF at mean $SS\ C_{max}$ of alternative dosing regimen based on the established linear mixed effect model are summarized in

Table 60Table 60. A 26% relative reduction in QT prolongation is predicted in 300mg BID and 400mg QD compared to 600mg QD.
Reviewer believes appropriate measures should be taken to mitigate the risks for QT prolongation, which includes studying an alternative dosing regimen which targets lower risk for QT prolongation with comparable efficacy. e.g. Simulation shows that mean Δ QTcF at mean SS C_{max} of 300mg BID is reduced from 21.33 to 15.71ms compared to 600mg QD, while its AUC_{24h} is 79% of that of 600mg QD.

Table 59: Summary of SS exposure metrics ($\mathbf{C_{max}}$, $\mathbf{C_{trough}}$ and $\mathbf{AUC_{tau}}$) of alternative dosing regimen of ribociclib treatment.

Parameter	Statistics	300mgBID mg	400mgBID mg	400mgQD mg	600mgQD mg
Cmax	n	5000	5000	5000	5000
Cmax	Mean (SE)	1150 (8.05)	1700 (12)	1140 (7.59)	1960 (13.1)
Cmax	SD	569	848	537	923
Cmax	CV%	49.5	49.9	47.1	47.1
Cmax	Geo-Mean	1030	1530	1030	1770
Cmax	Median	1030	1520	1040	1770
Cmax	(Q1-Q3)	(753 - 1410)	(1130 - 2080)	(769 - 1390)	(1310 - 2410)
Cmax	(Min-Max)	(173 - 4980)	(340 - 8150)	(173 - 5810)	(274 - 8070)
Ctrough	n	5000	5000	5000	5000
Ctrough	Mean (SE)	692 (6.39)	1030 (9.5)	446 (4.29)	778 (7.41)
Ctrough	SD	452	672	303	524
Ctrough	CV%	65.3	65.2	67.9	67.4
Ctrough	Geo-Mean	574	860	366	631
Ctrough	Median	580	873	373	641
Ctrough	(Q1-Q3)	(380 - 876)	(575 - 1300)	(240 - 561)	(413 - 1020)
Ctrough	(Min-Max)	(27.5 - 4320)	(80.1 - 7240)	(35.7 - 3960)	(19.8 - 4670)
AUC_{24h}	n	5000	5000	5000	5000
AUC_{24h}	Mean (SE)	20700 (167)	30900 (247)	15100 (120)	26200 (206)
AUC_{24h}	SD	11800	17500	8490	14600
AUC_{24h}	CV%	57	56.6	56.2	55.7
AUC_{24h}	Geo-Mean	18000	26900	13200	22700
AUC_{24h}	Median	18200	26800	13200	22900
AUC_{24h}	(Q1-Q3)	(12500 - 25800)	(18900 - 38100)	(9270 - 18600)	(15800 - 33200)
AUC_{24h}	(Min-Max)	(2310 - 107000)	(5410 - 179000)	(2210 - 108000)	(1620 - 137000)

Table 60: Predicted ΔQTcF at simulated SS C_{max} of alternative dosing regimen of ribociclib treatment.

Dose	SS C_{max} ng/mL (mean)	Predicted **ΔQTcF** ms (90% CI)
600mg QD (observed)	2236.5	22.87 (21.61, 24.12)
600mg QD (sim)	1960	21.33 (20.11, 22.56)
400mg QD	1140	15.63 (14.48, 16.78)
400mg BID	1700	19.74 (18.54, 20.93)
300mg BID	1150	15.71 (14.56, 16.87)

13.4.4.2.2 Hepatobiliary toxicity
Evaluation of the exposure-response relationship of grade 3 or 4 liver function tests (LFTs) was limited by the low number of events (i.e. 5/240, 5/239, 7/240 for alanine aminotransferase, aspartate aminotransferase and total bilirubin, respectively), and as such, no correlation between ribociclib exposure and LFT increase was observed and no meaningful conclusion could be drawn.

Reviewer's comments: Reviewer agrees that no meaningful conclusion can be drawn on the E-R relationship for hepatobilitary toxicity because of low number of patients with LFT events and concomitant exposure data.

13.4.4.2.3 Neutropenia
13.4.4.2.3.1 PK/PD modeling for absolute neutrophil count
ANC reduction with treatment of ribociclib was satisfactorily described using a physiological model coupled with a log-linear drug effect model (see Section 4.3.2 for details about the PK/PD model). External model qualification showed the final PK/PD model can adequately predict the time course profile of ANC reduction with ribociclib treatment of 600mg QD in the Study A2301 (22Figure 18). Simulations using the PK/PD model were conducted to evaluate the dose dependency of neutropenia with ribociclib treatment in a simulated patient population. Results indicate that a lower QD dose of ribociclib will lead to less ANC reduction (Figure 19).
Reviewer's comments: The predicted probability of PK/PD model on grade 3/4 neutropenia was adequately validated. Simulation results suggested lowering dose/exposure might lead to slightly lower neutropenia risks. This finding supports the proposed dose modification plans for the neutropenia management in the label.

13.4.4.2.3.2 Logistic regression modeling for neutropenia
The analysis included a total of 196 patients treated with ribociclib at doses ranging from 50 to 1200 mg from 4 clinical studies. The ribociclib exposure variables used in the analysis included the geometric mean of all evaluable steady-state trough concentrations (C_{trough}, ss) prior to events, the geometric mean of all evaluable steady-state concentrations at 2 h post-dose (C2h)

prior to events and dosing intensity (DI) prior to events. The primary safety endpoint for neutropenia was newly occurring grade 2 or worse neutropenia.

Logistic regression analysis indicated that a higher probability of grade 2 or worse neutropenia was associated with higher ribociclib exposure, after taking into account the effect of baseline weight and prior chemotherapy. The odds ratio for having grade 2 or worse neutropenia from a 100 ng/mL change in C_{trough}, ss was 1.05 (95% CI: 0.993, 1.105; p=0.087). Similar findings were also observed in the logistic regression using C2h and DI.

Reviewer's comments: While a trend of higher probability of grade 2 or worse neutropenia with higher ribociclib exposure is observed, this relationship is not statistically significant (p>0.05). Besides the exposure metrics used in the analysis (C_{trough}, C2h) doesn't necessarily represent the exposure related to the neutropenia event. Given neutropenia is an event of abnormally low level of neutrophils, a population PK/PD model that simultaneously described the relationship between longitudinal change in ANC and ribociclib concentrations in section 4.4.2.3.1 is a better approach to analyze E-R relationship for neutropenia.

13.4.4.2.3.3 Simulation of neutropenia events for alternative dosing regimen
The established PK/PD model is suitable for prediction of neutropenia risks. With incorporation of relevant study conditions and patient characteristics, the predicted probability of grade 3/4 neutropenia in the first 4 cycles for 600mg QD was 44.8%. This prediction is comparable to the observed frequency (50.8%) of grade 3/4 neutropenia summarized from the same 315 patients.

Simulations using the PK/PD model were conducted to evaluate the dose dependency of neutropenia with ribociclib treatment in a simulated patient population. In the simulation, all patients have a typical body weight (70kg) and the baseline ANC for each subject was sampled from the distribution that consisted of all available baseline observations in Study A2301. With inclusion of residual errors the simulated probabilities of grade 3/4 neutropenia for 400mg QD, 300mg BID, and 400mg BID (3 weeks on/1 week off) in the simulated patient population are 35.7%, 38.8 and 45.1% respectively (
Table 61

Table 61).

Reviewer's comments: The VPC (22Figure 18) showed the final PK/PD model adequately captured the observed ANC data. The predicted probability of grade 3/4 neutropenia (44.8%) was comparable with the observed frequencies of 600mg QD in the model qualification dataset (50.8%). Reviewer agrees that the simulation using the developed PK/PD model is suitable to evaluate the dose dependency of neutropenia with ribociclib treatment. Based on simulation, the predicted probability of patients experiencing grade 3/4 neutropenia was similar between 300mg BID and 600mg QD.

Table 61: Simulated probability (%) of Grade 3/4 neutropenia with various ribociclib dosing regimens (3 weeks on/1 week off) in a simulated patient population

Dosing Regimen	Grade 3	Grade 4	Grade 3/4

300mg BID	32.2	6.6	38.8
400mg BID	37.6	7.5	45.1
400mg QD	30.7	5.0	35.7
600mg QD	34.1	7.3	41.4

APPEARS THIS WAY ON ORIGINAL

13.3.5 PBPK Analysis

13.3.5.1 Objectives

The main objectives of this review are to 1) evaluate the adequacy of applicant's conclusions regarding the ability of a physiologically-based pharmacokinetic (PBPK) model to predict the drug-drug interaction (DDI) potential of ribociclib as a victim and a perpetrator of the CYP metabolic pathway; 2) provide a dosing recommendation based on the predicted DDI potential; 3) evaluate the adequacy of the applicant's conclusions regarding the ability of a PBPK to predict the impact of stomach pH on the absorption of ribociclib. To support its conclusions the applicant provided the following PBPK modeling and simulation reports and updates:

1. Under study report DMPK R1400619 entitled "Predictions of interactions between LEE011 and typical CYP substrates and perpetrators using Simcyp" [1].
    - A PBPK model using first order absorption and considering the CYP3A auto-inhibition was built and verified using clinical DDI study results.
    - The effects of strong CYP3A inhibitors (ritonavir, ketoconazole), strong CYP3A inducers (rifampicin, carbamazepine), a moderate CYP3A inhibitor (erythromycin), a moderate CYP3A inducer (efavirenz), and a weak CYP3A inhibitor (fluvoxamine) on exposure of ribociclib were simulated. These simulations were performed to support ribociclib dosing recommendations when given in combination with CYP3A modulators not evaluated clinically.
    - The net effects of ribociclib on exposure of a CYP3A probe substrate (midazolam) and a CYP1A2 probe substrate (caffeine) were simulated.
2. Under study report DMPK R1600364 entitled "In silico evaluation of the impact of stomach pH on the absorption of LEE011 in humans" [2].
    - A human advanced compartment and transit (ACAT) absorption model and an advanced dissolution, absorption, and metabolism model (ADAM) absorption model were built in ribociclib PBPK models to simulate the impact of stomach pH on absorption of ribociclib in humans.
3. Under study report DMPK R1500700 entitled "Predictions of LEE011 pharmacokinetics after intravenous infusion using Simcyp" [3].
    - The absolute oral bioavailability (F) of ribociclib was predicted using the ribociclib PBPK model developed in [1] above.
4. Under study report DMPK R1600433 entitled "Prediction of systemic exposure of LEE011 when coadministered with strong CYP3A inhibitors" [4]
    - The PK of 200 mg, 400 mg and 600 mg single or multiple once daily (QD) dose regimen of ribociclib with and without ritonavir was predicted using the ribociclib PBPK model developed in [1] above.
5. Response to FDA Information Request (IR-14) Received on November 4, 2016 and Response to FDA Information Request (IR-25) Received on January 3, 2017 [5].

13.3.5.2 Background

Ribociclib (LEE011) is an irreversible CDK4/6 inhibitor developed in combination with an aromatase inhibitor for the treatment of postmenopausal women with HR+, HER2- advanced or metastatic breast cancer as initial endocrine-based therapy [6]. The proposed dosing regimen of ribociclib is 600 mg orally QD for 21 consecutive days followed by 7 days off treatment resulting in a 28-day treatment cycle.

After initial review of the PBPK study reports summarized in Section 1 above [1-3], the FDA reviewers issued three information requests (IRs) to the applicant on September 30, 2016, on November 04, 2016, and on January 03, 2017 (09302016IR, 11042016IR and 01032017IR. Section 0). In the responses to these IRs, applicant provided updated simulations of ribociclib PK in the presence and in the absence of CYP3A modulators. [5]

Ribociclib DDI potentials as a CYP3A victim, a CYP3A perpetrator and a CYP1A2 perpetrator under clinically untested scenarios were predicted using Simcyp models [1]. The effects of stomach pH on absorption of ribociclib were evaluated in both GastroPlus and Simcyp models [2].

This review evaluates the adequacy of applicant's ribociclib PBPK models to predict the DDI potential for ribociclib after oral administration as well as the impact of stomach pH on the absorption of ribociclib, and provides dosing recommendations based on the predictions.

13.3.5.3 Methods

Population based PBPK software packages Simcyp® (A Certara Company, Sheffield, UK) version 13 (V13) and GastroPlus® (Simulations Plus, Inc. Lancaster, CA) version 9.0 (V9.0) were used by the applicants to develop Ribociclib PBPK models assessed in this review [7,8, 9]. Ribociclib DDI potentials as a victim and a perpetrator of CYPs were studied using a Simcyp model considering first order absorption [1,4]. The effects of stomach pH on absorption of ribociclib were studied using mechanistic absorption models: an ACAT model in GastroPlus and an ADAM model in Simcyp [2]. The absolute oral bioavailability of ribociclib was predicted using the PBPK model considering first order absorption[3].

Simcyp models for CYP-based DDI predictions

The Simcyp ribociclib PBPK model assumed full PBPK distribution [7]. Software's built-in "Healthy Volunteer" virtual population was used for all simulations because the applicant justified that there is no clinically relevant ribociclib PK difference between health subjects and patients with cancer [6]. Parameters and their sources are summarized in Appendix Table A 1.

Perpetrator models fluvoxamine, erythromycin, ketoconazole, carbamazepine and victim models midazolam, caffeine from the Simcyp V13 drug model library were directly used. Perpetrator models for ritonavir and rifampicin were modified from Simcyp V13. The perpetrator efavirenz and itraconazole (including its inhibitory metabolite hydroxyitraconazole) Simcyp V13 models were built by transferring respective parameters from software's version 15 (V15) drug model library.

Applicant's PBPK modeling of ribociclib can be summarized in three parts.

(A). Model building: Updated results of in vitro experiments and physicochemical properties, and in vivo PK studies (Table 62) were used to describe absorption, distribution, metabolism, and excretion (ADME) characteristics in the model (Appendix Table A 1).

(B). Model verification: Results of clinical PK study of ribociclib and clinical DDI studies with a strong CYP3A inhibitor or inducer (ritonavir or rifampicin, respectively) , a sensitive CYP3A substrate (midazolam) and a sensitive CYP1A2 substrate (caffeine) were used to verify ribociclib PBPK model (Table 62).

(C). Model applications: The applicant conducted simulations to prospectively predict the PK of following (Table 62):

- 200, 260, 400 and 600 mg single oral dose or QD oral of ribociclib in the presence of a strong CYP3A modulator ritonavir or rifampicin.
- 400 mg or 600 mg single oral dose of ribociclib in the presence of a moderate CYP3A inhibitor erythromycin, a weak CYP3A inhibitor fluvoxamine, or strong CYP3A inhibitor ketoconazole.
- 600 mg single oral dose of ribociclib in the presence of a moderate CYP3A inducer efavirenz or a strong CYP3A inducer carbamazepine.
- 5 mg single oral dose midazolam in the presence of 600 mg QD oral dose of ribociclib.
- 100 mg single dose caffeine in the presence of 600 mg QD oral dose of ribociclib.

Table 62. Summary of the design of simulations and clinical studies for the development, verification, and application of ribociclib PBPK model using Simcyp

Interacting drugs (purposes)	**Simulation Design**	**Clinical Study Design**
None (model development)	Ribociclib simulations Simulations were done using 1 trial with 24 subjects (n=24). Healthy Volunteers. Age 20-65 years, 50% females. Ribociclib single oral dose or QD oral doses under fasted state : 50 mg, 70 mg, 140 mg, 260 mg, 280 mg, 350 mg, 400 mg, 600 mg, 750 mg, 900 mg and 1200 mg	Total 134 patients were included in Study CLEE011X2101: The median age of the population was 58.6 years with most patients (64.4%) aged between 22 and 84 years. Majority of the patients (80.5%) were female. Ribociclib single oral dose or QD oral doses administered irrespective of food : 50 mg, 70 mg, 140 mg, 260 mg, 280 mg, 300mg, 350 mg, 400 mg, 600 mg, 750 mg, 900 mg and 1200 mg
Ritonavir (model verification (single dose ribociclib) and prediction (QD ribociclib))	Simulations were done using 1 trial with 24 subjects (n=24). Healthy Volunteers. Age 27-54 years, 20.8% females. Dosing: Crossover design Ribociclib single oral dose simulations: • Ribociclib 200mg, 260 mg, 400 mg and 600 mg single oral dose on day 2 • Ritonavir oral 100 mg twice daily (BID) day 1 - 14. Ribociclib multiple doses • Ribociclib 260 mg, 400 mg and 600 mg QD oral	A Phase I, single center, open label, randomized, two-period, fixed-sequence, drug-drug interaction study to assess the effect of ritonavir (a CYP3A4 inhibitor) and rifampicin (a CYP3A4 inducer) on the pharmacokinetics of a single oral dose of LEE011 in healthy volunteers Total 48 patients were included in two treatment arms. Treatment arm 1 (n=24, with ritonavir): The median age of the population was 34.5 years (range: 21 to 53 years). Majority of the patients (79.2%) were female. • Ribociclib 400 mg single dose on day 1 • Ribociclib 400 mg single dose on day 14 • Ritonavir 100 mg BID dosing for 14 days (day 13 - 26)

	doses day 1 - 14 • Ritonavir oral 100 mg BID, day 1 - 14. •	Treatment arm 2: See rifampicin row below.
Ketoconazole (model prediction)	Simulations were done using 1 trial with 24 subjects (n=24). Healthy Volunteers. Age 20-65 years, 50% females. Ketoconazole oral 200 mg BID for 14 days, Ribociclib 400 mg or 600 mg single dose on day 7 together with ketoconazole under fasted state.	Not applicable
Itraconazole (model prediction)	Simulations were done using 1 trial with 24 subjects (n=24). Healthy Volunteers. Age 27-54 years, 20.8% females. Dosing: Crossover design Ribociclib multiple doses • Ribociclib 200 mg, 400 mg or 600 mg QD oral doses day 1-14 • Itraconazole oral 200 mg BID day 1 - 14.	Not applicable
Rifampicin (model verification (ribociclib single dose) and prediction)	Simulations were done using 1 trial with 24 subjects (n=24). Healthy Volunteers. Age 27-54 years, 20.8% females. Ribociclib single dose simulations: • Oral ribociclib 200mg, 260 mg, 400 mg and 600 mg single dose on day 2 • Rifampicin oral 600 mg QD day 1 - 14 Ribociclib multiple doses • Oral ribociclib 200mg, 260 mg, 400 mg and 600 mg QD day 1 - 14 • Rifampicin oral 600 mg QD day 1 - 14 •	A Phase I, single center, open label, randomized, two-period, fixed-sequence, drug-drug interaction study to assess the effect of ritonavir (a CYP3A4 inhibitor) and rifampicin (a CYP3A4 inducer) on the pharmacokinetics of a single oral dose of LEE011 in healthy volunteers Total 48 patients were included in two treatment arms. Treatment arm 1: See ritonavir row above. Treatment arm 2 (n=24, with rifampicin): The median age of the population was 38 years (range: 27 to 54 years). Majority of the patients (79.2%) were female. • Ribociclib 600 mg single dose on day 1 • Ribociclib 600 mg single dose on day 17 • Rifampicin 600 mg QD dosing for14 days (day 13 - 26)
Erythromycin (model prediction)	Simulations were done using 1 trial with 24 subjects (n=24). Healthy Volunteers. Age 20-65 years, 50% females. Erythromycin oral 500 mg BID day 1 - 14. Ribociclib 400 mg or 600 mg single oral dose on day 7 together with erythromycin under fasted state.	Not applicable
Fluvoxamine (model prediction)	Simulations were done using 1 trial with 24 subjects (n=24). Healthy Volunteers. Age 20-65 years, 50% females. Fluvoxamine oral 50 mg QD day 1 – 14. Ribociclib 400 mg or 600 mg single oral dose on day 7 together with fluvoxamine under fasted state	Not applicable
Carbamazepine (model prediction)	Simulations were done using 1 trial with 24 subjects (n=24). Healthy Volunteers. Age 20-65 years, 50% females. Dosing: Crossover design Carbamazepine oral 400 mg BID for 14 days, Ribociclib 400 mg or 600 mg single oral dose on day 5 together with carbamazepine under fasted state.	Not applicable

Efavirenz (model prediction)	Simulations were done using 1 trial with 24 subjects (n=24). Healthy Volunteers. Age 20-65 years, 50% females. Dosing: Crossover design Efavirenz oral 400 mg QD day 1 - 14. Ribociclib 600 mg single oral dose on day 7 together with efavirenz under fasted state.	Not applicable
Midazolam (model verification)	Simulations were done using 1 trial with 25 subjects (n=25). Healthy Volunteers. Age 20-65 years, 50% females. Ribociclib oral 400 mg QD day 1 - 8, Midazolam 5 mg single oral dose on day 8 together with ribociclib under fasted state.	A Phase I, single center, open label, two-period, fixed-sequence, drug-drug interaction study in healthy volunteers Total 25 patients were included. The median age of the population was 38 years (range: 21 to 55 years). Majority of the subjects (72%) were male. • Midazolam 5 mg single dose on day 1, 3 and 10 • Caffeine 100 mg single dose on day 1, 3 and 10 • Rifampicin 400 mg QD dosing for 8 days (day 3 - 10)
Caffeine (model verification)	Simulations were done using 1 trial with 25 subjects (n=25). Healthy Volunteers. Age 20-65 years, 50% females. Ribociclib oral 400 mg QD day 1 - 8, Midazolam Caffeine 100 mg single oral dose on day 8 together with ribociclib under fasted state.	Same as Above

GastroPlus model for predictions of the effect of change in stomach pH

Permeability (human effective permeability or P_{eff}) and solubility (solubility and dissolution at physiologically relevant pH range) parameters are critical for a PBPK model to predict the oral absorption of a drug.

The permeability and solubility parameters in the GastroPlus ACAT model are summarized below. Other parameters are listed in Appendix Table A 2.

- Permeability: in vitro Caco-2 of 0.1833×10^{-5} cm/sec was used to convert to human P_{eff} of 0.9023×10^{-4} cm/sec.
- Solubility: solubility of 0.3 mg/mL at pH 7.5 determined in vitro and a solubility factor of 110 for base pKas of 8.6 and 5.5 (based on solubility vs pH profile)
- Dissolution: Takano model [11] pH-dependent z-factors is determined by calculation from in vitro dissolution data: Z-factors (mL/mg/s) were 0.000173, 0.000233, 0.000229, and 0.00042 for pH 1.0, 2.0, 4.5, and 6.8, respectively (*Data source: Table 4-3 of [2])*

13.3.5.4 Results

Can Ribociclib PBPK Model be Used to Predict Ribociclib Exposure after Single or Multiple Dose of Ribociclib?

Yes. The applicant's ribociclib model incorporated CYP3A4 time dependent inhibition (TDI) parameters ($K_{app,u}$ and K_{inact}, unbound apparent inactivation constant and maximal inactivation rate constant, respectively, Appendix Table 1) to describe observed nonlinear PK profiles of the drug. In general, the predicted AUC, C_{max} and T_{max} after single or QD oral administration of ribociclib in the dosing amount ranging from 50-1200 mg were comparable to the observed results in cancer patients in Study X2101 (Table 63 and Table 64).

Table 63. The observed and model simulated ribociclib exposure following single oral dose administration

Treatment	Dose (mg)	N		Cmax (ng/mL)		AUC(0-24h) (ng·h/mL)		Tmax (h)	
		Simcyp	Observed	Predicted	Observed	Predicted	Observed	Predicted	Observed
LEE011, single dose, q.d.	50	24	3	71.3 (36.7-155)	42.1 (25.3-64.5)	671 (268-2104)	402 (249-563)	1.91 (1.01-2.87)	4 (3.93-4.03)
	70	24	2	101 (52.1-219)	62 (34.9-110)	953 (379-3000)	570 (451-721)	1.91 (1.01-2.87)	2.75 (1.25-4.25)
	140	24	4	208 (109-453)	227 (101-431)	1989 (777-6348)	1850 (913-3180)	1.94 (0.99-2.90)	1.06 (0.633-6)
	260	24	4	402 (214-874)	300 (134-552)	3930 (1497-12774)	2810 (1600-4050)	1.94 (0.99-2.95)	2.07 (1-3.95)
	280	24	4	436 (232-946)	336 (191-411)	4272 (1622-13920)	3650 (1880-5680)	1.94 (0.99-2.95)	3.92 (2-6.03)
	350	24	4	555 (297-1202)	602 (342-1260)	5509 (2067-18088)	7300 (5170-14500)	1.97 (1.04-3.00)	3.96 (2-4.08)
	400	24	5	642 (345-1388)	582 (267-1150)	6430 (2393-21203)	5840 (2680-13500)	1.99 (1.04-3.05)	4 (1.17-4)
	600	24	16-17	1004 (547-2154)	933 (340-3200)	10413 (3769-34623)	9720 (3860-34300)	2.02 (1.04-3.09)	2.08 (1-4.12)
	750	24	10-11	1289 (708-2746)	1090 (214-2880)	13702 (4873-45472)	12100 (3030-28300)	2.06 (1.04-3.19)	4 (1-4.03)
	900	24	13	1582 (876-3349)	1560 (693-4790)	17234 (6039-56783)	18300 (8790-52100)	2.06 (1.09-3.24)	4 (2-26.2)
	1200	24	3	2193 (1229-4580)	2730 (1790-3670)	24972 (8556-80266)	36900 (24600-53200)	2.12 (1.09-3.34)	4.02 (4-4.1)

Pharmacokinetic data are presented as geometric means with range in parentheses except for Tmax (median with range). Observed values were taken from CLEE011X2101. Trial design parameters for the simulation were taken from Table 3-1.

Data source: Table 6-4 of DMPK R1400619

Table 64. The observed and model simulated ribociclib exposure following multiple (QD) oral administration

Treatment	Dose (mg)	At Day X	N		Cmax (ng/mL)		AUC(0-24h) (ng·h/mL)	
			Simcyp	Observed	Predicted	Observed	Predicted	Observed
LEE011, after multiple dose, q.d.	50	18	24	2-3	83.2 (39.0-223)	67.5 (46.4-129)	820 (275-3272)	770 (574-998)
	70	18	24	2	121 (55.9-336)	62 (38.9-99.5)	1217 (391-5095)	1000 (604-1660)
	140	18	24	3	270 (120-825)	224 (131-539)	2869 (821-13687)	2490 (1780-3840)
	260	18	24	4	569 (244-1857)	569 (250-837)	6483 (1638-33030)	5990 (3690-7420)
	280	18	24	3	623 (266-2039)	511 (303-768)	7168 (1784-36498)	6600 (4770-7910)
	350	18	24	4	821 (347-2685)	1280 (799-1820)	9732 (2316-48867)	15300 (13200-18000)
	400	18	24	4	969 (408-3153)	1020 (486-1660)	11705 (2717-57839)	14700 (8010-25200)
	600	21	24	12-14	1607 (661-5042)	1940 (859-5860)	20550 (4500-94180)	26600 (9960-89600)
	750	18	24	4-6	2121 (863-6466)	1700 (841-2740)	27982 (6026-121597)	22300 (13900-37100)
	900	18	24	10-11	2657 (1077-7891)	3090 (1940-7930)	35958 (7715-149044)	43500 (20100-135000)
	1200	18	24	1	3777 (1534-10742)	3240 (3240-3240)	53138 (11554-203927)	51800 (51800-51800)

Pharmacokinetic data are presented as geometric means with range in parentheses. Observed values were taken from CLEE011X2101. Trial design parameters for the simulation were taken from Table 3-1.

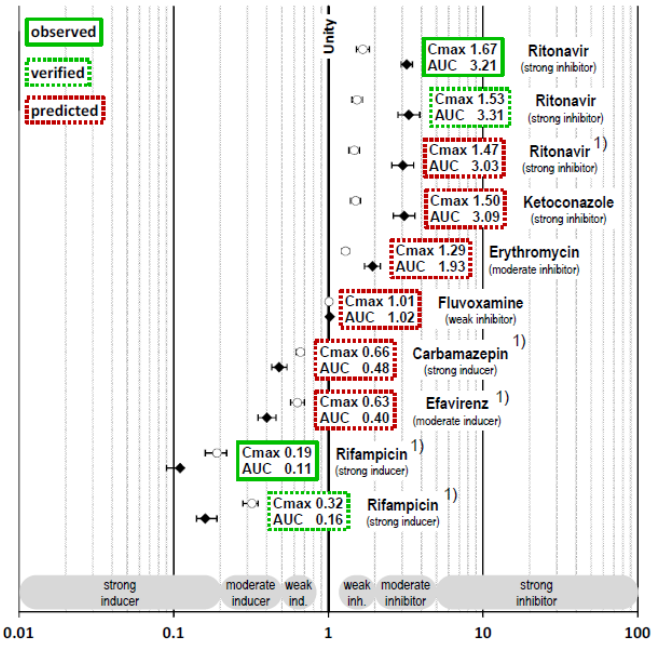
Data source: Table 6-5 of DMPK R1400619

Can Ribociclib PBPK Model be Used to Predict the Effect of CYP3A Modulation on Ribociclib Exposure?

Yes. Two major factors are critical for a substrate PBPK model to predict the effect of CYP inhibition or induction on its PK: quantitative determination of the contribution of the CYP pathway that is modulated by co-medication (e.g., assumption of $f_{m,CYP3A}$ for ribociclib), and

ability of the model to predict the PK profile. The ability of the model to predict ribociclib PK profiles was already discussed in section above.
By using CYP3A4 enzyme kinetic parameters (unbound Michaelis Menten constant $K_{m,u}$ = 6.67 µM; maximal reaction velocity V_{max} = 284 pmol/min/mg) and TDI parameters ($K_{app,u}$ = 13.44 µM and K_{inact} = 1 hr^{-1}), the applicant defined $f_{m,CYP3A}$ to be approximately 0.71 in the ribociclib model after single oral 600 mg administration of ribociclib. This is verified using clinical drug-drug interaction data when ribociclib was co-administered with ritonavir (a strong CYP3A inhibitor, Figure 4) and rifampicin (a strong CYP3A inducer, Figure 4). The PBPK model reasonably predicted mean AUC and Cmax ratios by with/without ritonavir or rifampicin. Of note, because TDI of CYP3A is likely responsible for the observed nonlinear PK of ribociclib and its effect on the PK of other CYP3A substrates, simulation results discussed in section above (PK simulations) and in section below regarding midazolam-ribociclib DDI support parameterization of CYP3A mediated metabolism and TDI mechanism within ribociclib PBPK model.

Figure 23. Forest plot to summarize the DDI effects of ribociclib as a CYP3A victim drug



Data source: Figure 7-9 of DMPK R1400619

Several prospective predictions of the effect of CYP modulators on ribociclib PK, as summarized in Table 62 were conducted. The results can be found in Table 65 (effect of strong CYP3A inhibitor ritonavir on steady state PK of ribociclib, see discussion in next section below), Table 66 (effect of strong CYP3A inhibitor itraconazole on steady state PK of ribociclib, see discussion in next section below), and Figure 23 (effects of strong CYP3A inhibitor ketoconazole, and other moderate and weak modulators of CYP3A on single dose PK of ribociclib). For ribociclib as a victim, simulations showed that co-administration with a strong CYP3A inhibitor ketoconazole increased mean AUC and Cmax of single oral dose of ribociclib by 3.09 fold and 1.50 fold, respectively; co-administration with a moderate CYP3A inhibitor erythromycin increased mean

AUC and Cmax of single oral dose of ribociclib by 1.93 fold and 1.29 fold, respectively; co-administration with a weak CYP3A inhibitor fluvoxamine had minimal effect on ribociclib exposure; and co-administration with a moderate CYP3A inducer efavirenz decreased mean AUC and Cmax of single oral dose of ribociclib by 60% and 37%, respectively.

Table 65. Model predicted ribociclib exposures with or without concomitant use of ritonavir under different dosing regimens

Victim	Day	Dose (mg)	Inhibition	N	Cmax (ng/mL)		AUC [1)] (ng·h/mL)		AUCi/AUC	
					Predicted	Observed	Predicted	Observed	Predicted	Observed
LEE011, multiple dose, p.o., q.d.	8	200	Without inhibitor	24	356 (95.1-924)	NA	3955 (758-16491)	NA	-	-
	8	200	+ ritonavir (100 mg, b.i.d., for 14 days)	24	675 (273-1421)	NA	10746 (3319-28230)	NA	2.72 (1.27-8.31)	NA
	8	400	Without inhibitor	24	847 (214-2290)	NA	10290 (1759-43375)	NA	-	-
	8	400	+ ritonavir (100 mg, b.i.d., for 14 days)	24	1354 (546-2850)	NA	21586 (6651-56663)	NA	2.10 (1.08-6.58)	NA
	8	600	Without inhibitor	24	1416 (354-3739)	NA	18234 (3021-72270)	NA	-	-
	8	600	+ ritonavir (100 mg, b.i.d., for 14 days)	24	2036 (821-4286)	NA	32498 (9993-85240)	NA	1.78 (1.05-5.13)	NA

NA: not available; the predicted Cmax and AUC are mean with 95% confident intervals in parentheses.
1) AUC: AUC_{INF} on single dosing mode; AUC0-24h at the last dose on multiple dosing mode
Data source: Table 6-3 of DMPK R1400433

Table 66. Ribociclib exposures with or without concomitant use of itraconazole

Victim	Day	Dose (mg)	Inhibition	AUC0-24h (ng•hr/mL) [a] AUCR with and without itraconazole [b]	
				Fasted	Fed
LEE011 (multiple dose, p.o., q.d.)	14	200	Without inhibitor	3926 (612-17488)	3931 (619-17519)
	14	200	+ itraconazole (200 mg b.i.d. x 14 days)	10563 (2231-32636) AUCR: 2.69 (1.20-7.96)	10251 (2235-32573) AUCR: 2.61 (1.19-7.55)
	14	400	Without inhibitor	10084 (1374-45774)	10072 (1377-45850)
	14	400	+ itraconazole (200 mg b.i.d. x 14 days)	21283 (4513-65406) AUCR: 2.11 (1.09-6.36)	20924 (4522-65393) AUCR: 2.08 (1.09-6.32)
	14	600	Without inhibitor	17678 (2270-75997)	17649 (2267-76134)
	14	600	+ itraconazole (200 mg b.i.d. x 14 days)	32007 (6813-98186) AUCR: 1.81 (1.05-4.99)	31762 (6827-98229) AUCR: 1.80 (1.05-5.01)

Trial design parameters for the simulation were the same as for the ritonavir DDI simulation [DMPK R1600433-Table 3-1].
[a] Geometric mean (range) for N=24 subjects
[b] AUCR: AUC ratio with and without inhibitor

Data source: Table 2-2 of Response to FDA Information Request (IR-14) Received November 4, 2016

What is the dosing recommendation of ribociclib when the drug has to be co-administered with a strong CYP3A inhibitor?

In its draft US prescription information, the applicant proposed that concomitant use of ribociclib with strong CYP3A inducers or strong CYP3A inhibitors should be avoided. If strong inhibitors cannot be avoided, reduce ribociclib dose [redacted] (b) (4). However, based on the simulation results in Table 65, the predicted mean AUC (10746 ng·h/mL) of 200 mg QD

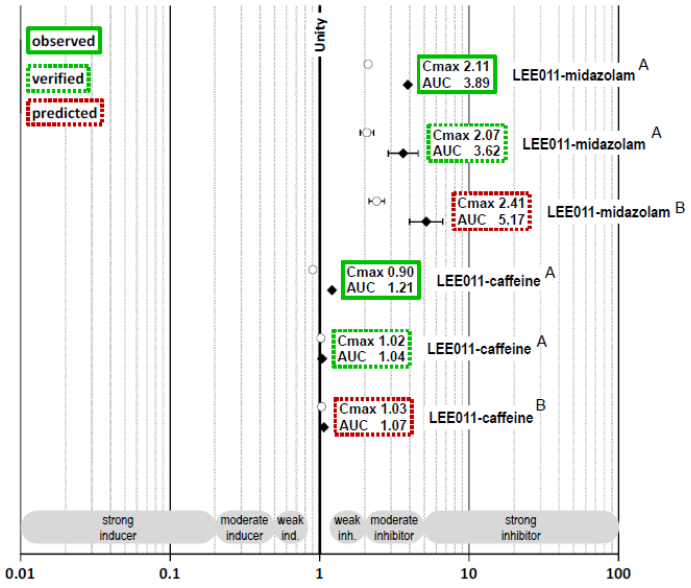
ribociclib coadministered with ritonavir is about 40% lower than the mean AUC (18234 ng·h/mL) of 600 mg QD ribociclib administrated without a CYP3A inhibitor. Instead, a dose reduction to 400 mg QD in combination with ritonavir provided a comparable ribociclib exposure (mean AUC = 21586 ng·h/mL and mean Cmax = 1354 ng/mL, Table 4) with those from 600 mg QD administration without a CPY3A inhibitor (mean AUC = 18234 ng·h/mL and mean Cmax = 1416 ng/mL), especially for Cmax. In response to FDA's 11042016IR, the applicant provided additional simulations of DDI with another strong CYP3A inhibitor itraconazole (Table 66). The simulated DDIs appeared to be similar regardless which strong inhibitor was used (comparing predicted mean or geometric AUC values in the presence of inhibitor at different ribociclib doses in Table 65 and Table 66). The applicant believed that reduction ribociclib to (b) (4) when in combination with a strong CYP3A inhibitor can balance therapeutic benefit (PFS) and risk (QTc prolongation and neutropenia). In support of its proposed dose reduction to (b) (4) when in combination with a strong CYP3A inhibitor, the applicant stated that PFS benefit was observed across the dose range of an analysis of ribociclib dose intensity (DI) and PFS in clinical Study A2301 [5a]. However, the DI analysis is biased due to patients responded to the treatment can stay in the clinical study longer and may have more chance to receive dose reduction. To date, there is no clinical data to support an alternative dosing regimen with no inferior therapeutic benefit comparing to that from 600 mg QD administration (see discussions under section 13.4.4). To date, impact of the predicted 40% decrease in ribociclib AUC on the efficacy of the drug has not been elucidated. As such, based on predicted similarity in ribociclib exposure after 400 mg QD with a strong inhibitor and after 600 mg QD without inhibitor, the FDA reviewers proposed the dose reduction to 400 mg QD when ribociclib is concomitantly used with a strong CYP3A inhibitor.

It has to be noted that all simulations were conducted in health volunteer with a male to female ratio range from 0.5 to 0.8, yet the target population for this NDA is postmenopausal women with HR+, HER2- advanced or metastatic breast cancer. Because the simulations assumed no gender difference in CYP3A metabolism, this simulation design (male to female ratio of 0.5 to 0.8) is considered acceptable to address the ribociclib exposure changes caused by CYP3A modulators.

Can Ribociclib PBPK Model be Used to Predict the Effect of Ribociclib as a CYP3A and CYP1A2 inhibitor?

Yes. Two major factors are critical for a perpetrator PBPK model to predict the CYP inhibition effect: quantitative determination of the inhibition parameters (reversible inhibition constant Ki and/or TDI inhibition parameters $K_{app,u}$ and K_{inact} for a mechanism-based inhibitor), and capability of the model to predict the PK profile of the perpetrator. The ability of the model to predict ribociclib PK profiles was already discussed.

Figure 24. Forest plot to summarize the DDI effects of ribociclib as a perpetrator drug on sensitive CYP1A2 and CYP3A substrates



Data source: Figure 7-5 of DMPK R1400619

In vitro, ribociclib was identified as a competitive inhibitor of CYP1A2 and a competitive as well as a TDI of CYP3A4/5. By using CYP1A2 (Ki =13.1 µM) and CYP3A4/5 (Ki =35 µM; $K_{app,u}$ = 13.44 µM and K_{inact} = 1 hr^{-1}) inhibition parameters, the PBPK model reasonably predicted mean AUC and Cmax ratio of caffeine (a sensitive CYP1A2 substrate) and midazolam (a sensitive CYP3A substrate) in the presence of ribociclib vs in the absence of ribociclib (Figure 24). Again, the midazolam-ribociclib DDI simulation and above simulations describing ribociclib nonlinear PK and the effect of CYP modulators together support the parameterization of CYP3A mediated metabolism and TDI mechanism in ribociclib PBPK model. Besides using ribociclib PBPK model to predict the clinical observed DDI of 400 mg QD administration of ribociclib with caffeine and midazolam, the applicant applied ribociclib model to predict caffeine and midazolam exposure with 600 mg QD administration of ribociclib (Figure 24). Simulations showed that there is more than 5 fold increase in midazolam exposure but no clinical significant exposure change for caffeine (geometric mean AUC increased by 21% and Cmax decreased by 10%). A simulation by FDA reviewer using applicant's models showed that there is no clinical significant change for exposure of another CYP1A2 substrate theophylline with 600 mg oral QD of ribociclib (Appendix Table A 3). Based on simulated exposure change in midazolam co-adminisered with ribociclib 600 mg QD, , caution should be exercised when ribociclib is administered with CYP3A substrates with narrow therapeutic index.

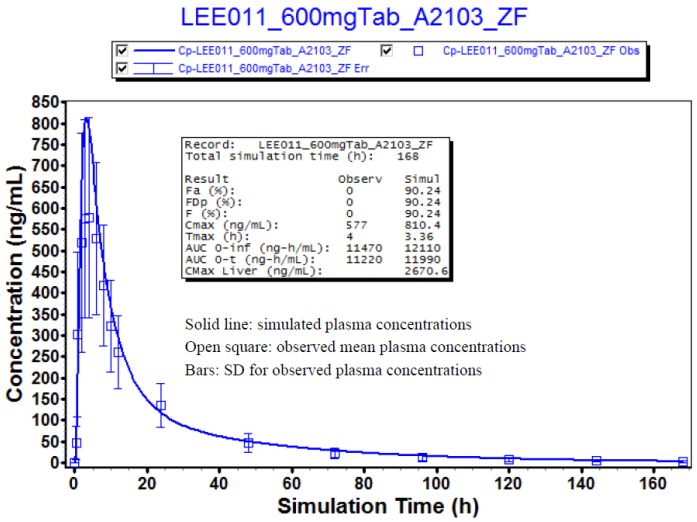
All simulations were conducted in health volunteers with a male to female ratio of 0.5, yet the target population for this NDA is postmenopausal women with HR+, HER2- advanced or metastatic breast cancer. Because the simulations assumed no gender difference in CYP1A2 and CYP3A metabolism and inhibition, this simulation design (male to female ratio of 1:1) is

considered acceptable to address the caffeine and midazolam exposure changes caused by ribociclib.

Can Ribociclib PBPK Model be Used to Predict the Impact of Stomach pH on the Absorption of Ribociclib?

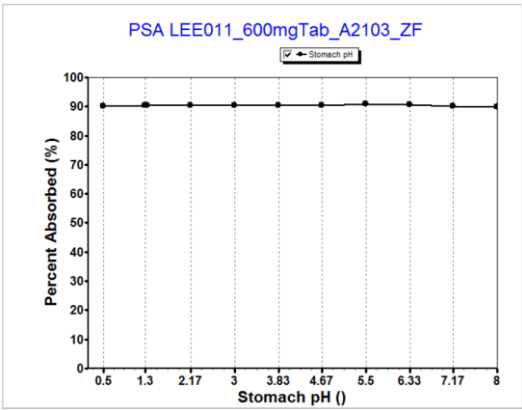
At present, prospective prediction of the effect of change in stomach pH on drug absorption and PK is not mature. In a population PK analysis, the ratio of the relative bioavailability in patients on proton pump inhibitors (PPIs) to that in patients not on PPIs was estimated to be 0.95 (95% CI: 0.818, 1.087) [**6]. The PBPK modeling results described below appear to mechanistically support the absence of PPI based DDIs.**
This review will only focus on the ACAT model since the applicant only provided detailed information on its ACAT model [2], and claimed that both **ACAT (Gastroplus) and ADAM (Simcyp) models reached the same conclusion that changing stomach pH from 0.5 – 8.0 would not affect the absorption ribociclib.**
The PBPK model developed in Gastroplus can describe the observed human PK profile (Figure 25). The predicted percent absorption of 600 mg ribociclib was not impacted by stomach pH (ranging from 0.5 to 8.0) in human (Figure 26). The simulation results suggested gastric pH-elevating agents would not affect the absorption of ribociclib.

Figure 25. Simulated vs observed mean PK profiles of 600 mg ribociclib administrated as tablet formulation



Data source: Figure 8-12 of DMPK R1600364

Figure 26. Predicted percent absorption of 600 mg ribociclib tablet formulation vs stomach pH



Data source: Figure 8-15 of DMPK R1600364

13.3.5.5 Conclusion

The applicant's PBPK models of ribociclib are considered sufficient to predict ribociclib PK, ribociclib DDI potentials as a victim with CYP3A modulators and as a perpetrator with CYP3A and CYP1A2 substrates**. The model predictions also support the minimal effect of change in stomach pH on ribociclib absorption.**

For ribociclib as a victim of CYP3A inhibitors, simulations show that co-administration with a strong CYP3A inhibitor ritonavir increased ribociclib exposure for 600 mg single dose (increased AUC ~ 3 fold and Cmax ~ 1.5 fold) and multiple QD doses (increased AUC~ 1.8 fold and Cmax ~ 1.4 fold). At steady state after QD administration of ribociclib, the simulations show 400 mg administration with a strong CYP3A inhibitor has similar exposure comparing to exposure from 600 mg administration without inhibitor, whereas a lower exposure (b) (4) Based on these simulations, the FDA reviewers proposed that the dose of ribociclib should be reduced to 400 mg QD, (b) (4) proposed by the applicant, when ribociclib is concomitantly used with a strong CYP3A inhibitor. Co-administration with a moderate CYP3A inhibitor erythromycin increased mean AUC and Cmax of single 600 mg dose ribociclib by 1.93 fold and 1.29 fold, respectively; co-administration with a weak CYP3A inhibitor fluvoxamine increased mean AUC and Cmax of single 600 mg dose ribociclib by less than 10%.

For ribociclib as a victim of CYP3A inducers, co-administration with a moderate CYP3A inducer efavirenz decreased mean AUC and Cmax of a single dose ribociclib by **60% and 37%, respectively.**

For ribociclib as an inhibitor of CYP3A, simulations show that there is more than 5 fold increase in midazolam exposure when midazolam coadministrated with 600 mg QD administration of ribociclib. **Caution should be exercised when ribociclib is administered with CYP3A substrates with narrow therapeutic index. For ribociclib as an inhibitor of CYP1A2, simulations show that**

there is no clinical significant exposure change for caffeine when the drug is coadministrated with 600 mg QD administration of ribociclib.
The predicted percent absorption of 600 mg ribociclib was not impacted by change in stomach pH. The simulation results suggested gastric pH-elevating agents would not affect the absorption of ribociclib.

13.3.5.6 Appendices for PBPK analysis

Abbreviations

BID, twice daily dosing; B/P, blood to plasma ratio; AUC, area under the concentration-time profile; Cmax, maximal concentration in plasma; CL, clearance; CL_{int}, intrinsic clearance; DDI: drug-drug interaction; f_{mj}, fraction of total clearance mediated by j CYP isoform or renal elimination; $fu_{,mic}$, fraction unbound in microsomes; $fu_{,inc}$, fraction unbound in (hepatocyte) incubation; $I_{nd,max}$, maximal fold induction; $I_{nd,50}$, concentration causing half-maximal fold induction; K_i, reversible inhibition constant; K_I, inactivation constant, inhibitor concentration resulting in half maximal inactivation; K_m, Michaelis-Menten Constant; k_{inact}, maximal inactivation rate constant; NA, not applicable; NDA: new drug application; Human P_{eff}, effective passive permeability in man; PBPK: Physiological-based Pharmacokinetic; P-gp: P-glycoprotein; QD, once daily dosing.

Information Request

1). Clinical Pharmacology September 30, 2016 (09302016IR, Reference ID 3993005 in DARRTs) Please reference NDA 209092 Kisqali (ribociclib) submitted on 8/29/2016. Please address the following information request. **Respond no later than 3 pm, Tuesday, October 4, 2016.** Please acknowledge receipt of this information request.

- Reference the PBPK analyses. Provide model files used to generate final PBPK simulations in the following PBPK reports:
  - Executable Gastroplus model files for Study 1600364. These files include, but are not limited to model compound file (.mdb), solubility vs pH (.spd), particle size distribution (.psd), tissue/plasma conc. vs. time data: other dosage forms (.opd), and user-defined ACAT model (.cat).
  - Executable Simcyp model files for Study 1400619, Study 1500700, Study 1600364, and Study 1600433. These files include, but are not limited to drug model files, population files, and workspace files (e.g., .cmp, .lbr, and .wks). Software specific excel files such as parameter estimation data files and simulation outputs should be submitted as MS Excel files.

2). Clinical Pharmacology November 10, 2016 (11102016IR, Reference ID 4009744 in DARRTs) Please reference NDA 209092 Kisqali (ribociclib) submitted on 8/29/2016. Please address the following information request. **Respond no later than 3 pm, Thursday, November 10, 2016.** Please acknowledge receipt of this information request.

1. Justify current dose adjustment in the event of concomitant use of a strong CYP inhibitor. Your proposed to reduce ribociclib to (b) (4) mg once daily dose if coadministration of ribociclib with a strong CYP3A inhibitor cannot be avoided. Your simulated AUC0-24h (on day 8) for 200 mg ribociclib once daily co-administrated with ritonavir was lower than the steady-state AUC0-24h for 600 mg ribociclib once daily without co-administrated with a CYP3A inhibitor.
2. We request that you simulate DDI between ribociclib (200 mg, 400 mg, and 600 mg once daily) and itraconazole (200 mg twice daily) after multiple dosing for 14 days.
3. Provide executable Simcyp model files for these simulations. These files include, but are not limited to drug model files, population files, and workspace files (e.g., .cmp, .lbr, and .wks). Software specific excel files such as parameter estimation data files and simulation outputs should be submitted as MS Excel files.

3). Clinical Pharmacology January 3, 2017 (01032017IR, Reference ID 4036135 in DARRTs)
In your PBPK report (DMPK R1400619) you stated that you have modified and validated Simcyp rifampicin and ritonavir models by referencing DMPK R1400692 and DMPK R1400693.

1. Provide study reports DMPK R1400692 and DMPK R1400693.
2. Provide model executable Simcyp model files used to generate final PBPK simulations in the above PBPK reports. These files include, but are not limited to drug model files, population files, and workspace files (e.g., .cmp, .lbr, and .wks). Software specific excel files such as parameter estimation data files and simulation outputs should be submitted as MS Excel files.

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Appendices Tables and Figures

Appendix Table A 1. Physicochemical parameters of ribociclib PBPK model (Simcyp version 13)

Input parameters	Description	Units	Value	Reference
1.Physicochemical and binding properties				
MW	Molecular weight	g/mol	434.54	
Log P	Octanol-water partition	-	1.954	
Compound type	Acid,base or neutral	-	Diprotic base	
pKa		-	8.52/5.63	
B/P ratio	Blood to plasma drug concentration ratio	-	1.01	(DMPK R0800276)
fu	Fraction unbound in plasma	-	0.3	(DMPK R0800276)
HSA or AGP	Main plasma binding protein	-	HSA	Assumption
2.Absorption [1]				
Absorption model	First order absorption model			
fa	Fraction available from dosage form	-	0.96	[2] Prediction
CV fa	Coefficient of variation fa	%	30	[2]
ka	Absorption rate constant	1/h	1.536	(CLEE011X2101)
CV ka	Coefficient of variation ka	%	30	[2]
fu(gut)	Unbound fraction in enterocytes	-	1	Assumption
Q(gut)	Nominal flow in gut model	L/h	11.0	[2] Prediction
CV Q(gut)	Coefficient of variation Q(gut)	%	30	[2]
P Caco-2	Caco-2 permeability	10^{-6}cm/s	1.833	(DMPK R0800504)
P propranolol	Reference compound permeability	10^{-6}cm/s	3.5	
3.Distribution				
Distribution model	Minimal PBPK model			
Tissue model	Perfusion limited model			
Vss	Volume of distribution at steady-state	L/kg	4.04	[3] Prediction
CV Vss	Coefficient of variation Vss	%	30	[2]
4.Enzyme/transporter phenotyping				
Human liver microsomes				
CLint (CYP3A4)	*In vitro* clearance	µL/min/mg	42.6	Optimized based on (DMPK R0800536; CLEE011A2101) [4]
Vmax (CYP3A4)	*In vitro* maximum velocity	pmol/min/mg	284	
Km (CYP3A4)	*In vitro* Michaelis-Menten constant	µM	6.67	
fu(inc) (CYP3A4)	Fraction unbound *in vitro*	-	1.00	
5.Other Distribution and Elimination property				
5-1. *In vivo* CL				
CLr	Renal clearance in 20-30yr healthy male	L/h	1.22	(DMPK R0800526; CLEE011A2102) [5]
5-2. *In vitro* CL				
Uptake hep	Total hepatic uptake clearance/passive diffusion (suspended hepatocytes)	-	1.00	Assumption based on (DMPK R1400554) [5]
HLM CLint	Additional undefined HLM CLint	µL/min/mg	11.7	Optimized based on (DMPK R0800536; CLEE011A2101) [4]
CV HLM CLint	Coefficient of variation HLM CLint	%	30	[2]

Input parameters	Description	Units	Value	Reference
fu(mic)	Unbound fraction in HLM	-	1	Optimized based on (DMPK R0800536; CLEE011A2101) 4)
CLint(hep)	Overall biliary clearance	µL/min/10^6 cells	0	Assumption based on (DMPK R0800526) 5)
CV CLint(hep)	Coefficient of variation CLint(hep)	%	30	2)
6.Interaction				
CYP inhibition (competitive)				(DMPK R0800459)
Ki (CYP1A2)	Inhibition constant	µM	13.1	
fu(mic) (CYP1A2)	Fraction unbound *in vitro*	-	1.0	
Ki (CYP2E1)	Inhibition constant	µM	31	=IC50/2 6)
fu(mic) (CYP2E1)	Fraction unbound *in vitro*	-	0.8	
Ki (CYP3A4/5)	Inhibition constant	µM	35	
fu(mic) (CYP3A4/5)	Fraction unbound *in vitro*	-	0.86	
CYP inhibition (mechanism-based)				Optimized based on (DMPK R0800196; CLEE011A2106) 7)
Kapp (CYP3A4/5)	Inhibition constant	µM	13.4	
kinact (CYP3A4/5)	Inactivation rate of enzyme	1/h	1.00	
fu(mic) (CYP3A4/5)	Fraction unbound *in vitro*	-	1.00	

Date source: Table 6-1 of DMPK R1400619

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Appendix Table A 2. Physicochemical parameters of ribociclib PBPK model (GastroPlus V09)

Parameter	Used value	Source
Molecular Formula	$C_{23}H_{30}N_8O$	-
Molecular Weight	434.55 g/mol	-
logP	1.954	-
pH logP	-1 (indicating neutral species)	-
pK_a	pKa1: 8.6 (base); pKa2: 5.5 (base)	Report PHAD002190B
Solubility factor	110 (pKa1); 110 (pKa2)	Adjusted to solubility vs pH profile
Reference solubility	0.3 mg/mL at pH 7.5	Report PHAD002190B
Mean Precipitation Time	900 sec	Default value in G+
Diffusion Coefficient	0.6297 * 10^{-5} cm^2/sec	Calculated from molecular weight in GastroPlus™ v9.0
Drug Particle Density	1.2	Default value in G+
Particle Size radius [µm]	60 µm	analysis report of DS batch 1010005102 used for HGC batch 1010005955
Caco-2 [10^{-5} cm/sec]	0.1833	DMPK R0800504
Human Peff [10^{-4} cm/sec]	0.9023	Converted from Permeability on Caco2

Parameters	Automatic estimation using PK Plus Module	Final 2 compartmental model
CL/F (L/h/kg)	0.596	0.596
Vc/F (L) central compartment	7.63	5 (optimized)
K12 (h^{-1})	0.041	0.07 (optimized)
K21 (h^{-1})	0.041	0.041

Data source: Table 3-1 and Table 4-1 of MDPK R1600364

Appendix Table A 3. FDA simulation of theophylline steady state after multiple TID doses exposure ratio (with/without ribociclib 600 mg QD)[a]

	Mean	Median	Geometric mean	95% Confidence Interval	
$AUC_{ss,0-8hr}$ Ratio	1.04	1.04	1.04	1.03	1.04
Cmax Ration	1.03	1.03	1.03	1.03	1.04

[a] Simulation using Simcyp Version 15.1. Applicant's ribociclib model, KU-LEE011 (v2.1), and SV-Theophylline in Simcyp model library were used. Study Design: Simulations were done using 10 trial with 10 subjects (n=100). Healthy Volunteers. Age 20-50 years, 50% females. Theophylline 125 mg TID dose on day 8 to 14. Ribociclib 600 mg TID dose on day 1 to 14.

13.3.5.7 References for PBPK Analysis

1. Novartis. Umehara K. MDPK R1400619. Predictions of interactions between LEE011 and typical CYP substrates and perpetrators using Simcyp. May 04, 2016.
2. Novartis. Laisney M. MDPK R1600364. In silico evaluation of the impact of stomach pH on the absorption of LEE011 in humans. July 01, 2016.
3. Novartis. Umehara K. MDPK R1500700. Predictions of LEE011 pharmacokinetics after intravenous infusion using Simcyp. May 04, 2016.
4. Novartis. Umehara K. MDPK R1600433. Prediction of systemic exposure of LEE011 when coadministered with strong CYP3A inhibitors July 18, 2016.
5. a. Novartis. Ribociclib RRT. Response to FDA Information Request (IR-14) Received November 4, 2016. November 10, 2016.
   b. Novartis. Ribociclib RRT. Response to FDA Information Request (IR-25) Received January 3, 2017. January 5, 2017.
6. Novartis: Clinical Development 2.7.2 Summary of Clinical Pharmacology of Ribociclib in Combination with Letrozole in HR-positive, HER2-negative Advanced Breast Cancer, August 04, 2016.
7. Simcyp manual: A Guide for IVIVE and PBPK/PD Modeling using the Simcyp Population-based Simulator version 12, CERTARA™ 2013.
8. GastroPlus manual. version 9.0, Simulations Plus, Inc. 2013
9. Jamei M, Marciniak S, Feng K, Barnett A, Tucker G, Rostami-Hodjegan A. The Simcyp population-based ADME simulator. Expert Opin Drug Metab Toxicol 2009 5(2):211-23.
10. a. Novartis. Umehara K., Huth F. MDPK R1400692. Simcyp model improvement for rifampicin. January 12, 2015.
    b. Novartis. Umehara K. MDPK R1400693. Simcyp model improvement for ritonavir. October 01, 2014.
11. Takano, R., Sugano, K., et al. Oral absorption of poorly water-soluble drugs: computer simulation of fraction absorbed in humans from a miniscale dissolution test. Pharm Res 2006 23(6):1144-56.

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Richard Pazdur, MD

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/s/

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NAM ATIQUR RAHMAN
03/10/2017
I support the review team's conclusions and recommendations.

ERIK W BLOOMQUIST
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03/10/2017

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RICHARD PAZDUR
03/13/2017

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 209092 **Applicant: Novartis** **Stamp Date:**

Drug Name: ribociclib **NDA/BLA Type: 1 (NME)**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic common technical document (eCTD).	X			Electronic
2.	Is the clinical section legible and organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
LABELING					
6.	Has the applicant submitted a draft prescribing information that appears to be consistent with the Physician Labeling Rule (PLR) regulations and guidances (see http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm	X			
SUMMARIES					
7.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
8.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
9.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
10.	Has the applicant submitted a benefit-risk analysis for the product?	X			2.5 Clinical Overview > 6.5 Overall benefit-risk balance
11.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).	X			505(b)(1)
505(b)(2) Applications					
12.	If appropriate, what is the relied upon listed drug(s)?			X	
13.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the listed drug(s)/published literature?			X	
14.	Describe the scientific bridge (e.g., BA/BE studies)			X	
DOSAGE					
15.	If needed, has the applicant made an appropriate attempt to determine the correct dosage regimen for this product (e.g., appropriately designed dose-ranging studies)? Study Number: CLEE011X2101 Study Title: A phase I multicenter, open label, dose escalation study of oral LEE011 in patients with advanced solid tumors or lymphomas Sample Size: 134 Treatment Arms: Dose-escalation study	X			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Location in submission: Section 11.4.3.2				
EFFICACY					
16.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1: CLEE011A2301 Indication: Postmenopausal women with HR-positive, HER2-negative, advanced breast cancer, who received no prior therapy for advanced disease Pivotal Study #2: CLEE011X2107 Indication: Adult post-menopausal women with locally advanced or metastatic ER+/HER2-negative breast cancer. In the dose escalation part of the study, patients could have any number of prior lines of endocrine therapy with up to one prior cytotoxic regimen in the metastatic or locally advanced setting, whereas in the dose expansion patients should not have received prior systemic treatment for advanced setting with the exception of therapy with letrozole in advanced setting for a maximum duration of one month prior to starting study treatment.	X			
17.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
18.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
19.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		X		32% (213/668) was enrolled in the U.S., and the remainder in ex-U.S. sites with same standards of care, and according to GCP
SAFETY					
20.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
21.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			
22.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
23.	For chronically administered drugs, have an adequate	X			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	number of patients (based on ICH guidelines for exposure[1]) been exposed at the dosage (or dosage range) believed to be efficacious?				
24.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
25.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			MedDRA 18.1
26.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
27.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			X	
OTHER STUDIES					
28.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
29.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
30.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Request for waiver
PREGNANCY, LACTATION, AND FEMALES AND MALES OF REPRODUCTIVE POTENTIAL USE					
31.	For applications with labeling required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, has the applicant submitted a review of the available information regarding use in pregnant, lactating women, and females and males of reproductive potential (e.g., published literature, pharmacovigilance database, pregnancy registry) in Module 1 (see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307 htm)?	X			
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		X		32% (213/668) was enrolled in the U.S., and the remainder in ex-U.S. sites with same standards of

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
					care, and according to GCP
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
37.	Are all datasets to support the critical safety analyses available and complete?	X			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			2.5 Clinical Overview > 1.2.1

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___Yes____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Reviewing Medical Officer Date

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Clinical Team Leader Date

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/s/

ANAND SHAH
09/27/2016

JULIA A BEAVER
09/27/2016

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA

NDA Number: 209092 **Applicant: Novartis** **Stamp Date: 8/29/16**

Drug Name: Ribociclib **NDA Type: 505(b)(1)**

On **initial** overview of the NDA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required and requested IND studies (in accord with 505 (b)(1) and (b)(2) including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	X		
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	X		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			N/A

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m^2 or comparative serum/plasma levels) and in accordance with 201.57?	X		The agreement to specific language in the label will be determined during the review of the NDA.
10	Have any impurity, degradant, extractable/leachable, etc. issues been addressed? (New toxicity studies may not be needed.)	X		
11	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			N/A
12	If the applicant is entirely or in part supporting the safety of their product by relying on nonclinical information for which they do not have the right to the underlying data (i.e., a 505(b)(2) application referring to a previous finding of the agency and/or literature), have they provided a scientific bridge or rationale to support that reliance? If so, what type of bridge or rationale was provided (e.g., nonclinical, clinical PK, other)?			N/A

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? __Yes_____

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

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CHING-JEY G CHANG
09/29/2016

TODD R PALMBY
09/29/2016

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**209092**	**Brand Name**	**Kisqali**
OCP Division (I, II, III, IV, V)	**V**	**Generic Name**	**Ribociclib**
Medical Division	**DOP1**	**Drug Class**	**Cyclin dependent kinase inhibitor**
OCP Reviewer	**Wentao Fu**	**Indication(s)**	**In combination with letrozole for the treatment of postmenopausal women with HR+, HER2- advanced or metastatic breast cancer as initial endocrine-based therapy**
OCP Team Leader	**Qi Liu**	**Dosage Form**	**200 mg tablets**
Pharmacometrics Reviewer	**Youwei Bi**	**Dosing Regimen**	**Ribociclib 600 mg orally (3 x 200 mg tablets) taken once daily with or without food for 21 consecutive days followed by 7 days off treatment in combination with letrozole 2.5 mg once daily.**
Pharmacometrics Team Leader	**Jingyu (Jerry) Yu**	**Date of Submission**	**August 29, 2016**
Genomics Reviewer		**Estimated OCP Due Date**	**February 24, 2017**
Genomics Team Leader		**Medical Division Due Date**	**March 14, 2017**
Sponsor	**Novartis**	**PDUFA Due Date**	**April 29, 2017**
Priority Classification	**Priority**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:	**X**	**1**		CLEE011A2102
Isozyme characterization:	**X**			
Blood/plasma ratio:	**X**			
Plasma protein binding:	**X**			
Pharmacokinetics (e.g., Phase I) -	**X**	**10**	**10**	**See details below for studies in Healthy Volunteers and Patients**
Healthy Volunteers-	**X**	**6**		CLEE011A2101: A Phase 1 DDI trial. Single dose (SD) 400 mg ribociclib with ritonavir (CYP3A4 inhibitor); SD 600 mg ribociclib with rifampicin (CYP3A4 inducer) CLEE011A2102: A Phase 1 ADME trial. SD 600 mg [14C]ribociclib. CLEE011A2103: A Phase 1 trial. SD ribociclib 600 mg. BE of table as compared to drug in-capsule (DiC). Tablets food effect . CLEE011A2106: A Phase 1 DDI trial. Multiple daily dose ribociclib 400 mg with midazolam (CYP3A4 substrate); multiple daily dose ribociclib 600 mg with caffeine (CYP1A2 substrate); CLEE011A2109: A Phase 1 trial. SD ribociclib 600 mg. Hepatic imparied study. CLEE011A2111: A Phase 1 trial. SD ribociclib 600 mg. DiC food effect
single dose:	**X**	**5**		

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

multiple dose:	**X**	**1**		
Patients-	**X**	**4**		CLEE011X1101: A Phase 1 trial at dose levels of ribociclib 400 mg and 600 mg QD 3 weeks on/1 week off in Asian patients with advanced solid tumors CLEE011X2101 :A Phase 1 trial in patients with advanced solid tumors or lymphoma. Dose escalation phase: dose levels of ribociclib 50 to 1200 mg QD 3 weeks on/1 week off or continuous QD. CLEE011X2107: A Phase 1b/II trial at dose level of ribociclib 600 mg (QD 3 weeks on/1 week off)+ letrozole (2.5 mg QD) in postmenopausal women with advanced ER+, HER2- advanced Breast Cancer CLEE011A2301: A Phase 3 trial at dose level of ribociclib 600mg (QD 3 weeks on/1 week off)+ letrozole (2.5 mg QD) in postmenopausal women with advanced ER+, HER2- advanced Breast Cancer
single dose:				
multiple dose:	**X**	**4**		CLEE011X1101 CLEE011X2101 CLEE011X2107 CLEE011A2301
Dose proportionality -	**X**	**1**		CLEE011X2101: slightly over-proportional increases in exposure (Cmax and AUC0-24h) after a single dose and after multiple doses across the dose range tested (50 to 1200 mg) in patients with cancer.
fasting / non-fasting single dose:	**X**	**1**		CLEE011X2101
fasting / non-fasting multiple dose:	**X**	**1**		CLEE011X2101
Drug-drug interaction studies -	**X**	**2**		CLEE011A2101 CLEE011A2106
In-vivo effects on primary drug:	**X**	**1**		CLEE011A2101
In-vivo effects on other drugs:	**X**	**1**		CLEE011A2106

In-vitro:	**X**	**39**	**39**	• R0800196: Comparative inhibition of CYPs (1A2, 2D6 and 2C9) • R0800264: Metabolism in human liver microsomes and hepatocytes • R0800276: protein binding and blood/plasma concentration ratio • R0800459: Inhibition of CYPs (1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4) • R0800504: Efflux transport of ribociclib using Caco-2 cell line • R0800505:Inhibition of efflux transporter (MDR1, MXR, MRP2) • R0800525: in vitro metabolism • R0800536: CYP phenotyping (HLM, chemical inhibitors, rCYPs) • R0800585: Efflux transporter phenotyping (MDR1, MXR, MRP2) • R0800782: Hepatocytes uptake • R0900249: Efflux transporter(MDR1, MXR, MRP2) inhibition • R1300155: induce CYPs (1A2, 2B6, 2C9 and 3A4) in mRNA and hepatocytes • R1300586: Uptake transporter (OATP1B1, 1B3) inhibition • R1300587: Uptake transporter (OCT1, OCT2) inhibition • R1300588: Uptake transporter (OAT1, OAT3) inhibition • R1300602: Human hepatocytes uptake • R1400554: Efflux transporter (OATP1B1, 1B3) phenotyping • R1400619: Simcyp PBPK modeling with CYP substrates and perpetrators • R1500585: UGT2B7 inhibition by ribociclib and its metabolite LEQ803 • R1500598: CYP inhibition by LEQ803 • R1500624: LEQ803 as inducer in hepatocytes • R1500643: LEQ803 inhibition of efflux transporter (MDR1, MXR) • R1500644: LEQ803 inhibition of SLC transporter (MATE1, MATE2K) • R1500645: LEQ803 inhibition of uptake transporter (OAT1, OAT3) • R1500646: LEQ803 inhibition of uptake transporter (OCT1, OCT2) • R1500647: LEQ803 inhibition of uptake transporter (OATP1B1, 1B3) • R1500648: LEQ803 inhibition of efflux transporter (BSEP, MRP2) • R1500700: Simcyp PBPK modeling of PK after IV infusion • R1500857: Riociclib metabolite CCI284 inhibition of CYPs • R1500858: CCI284 induction of CYPs • R1500875: CCI284 inhibition of efflux transporter (BSEP, MRP2) • R1500876: CCI284 inhibition of efflux transporter (MDR1, MXR) • R1500877: CCI284 inhibition of SLC transporter (MATE1, MATE2K) • R1500878: CCI284 inhibition of uptake transporter (OAT1, OAT3) • R1500880: CCI284 inhibition of uptake transporter (OATP1B1, 1B3) • R1500983: LEQ803, CCI284 protein binding • R1501054: UGTs involved in formation of ribociclib M1 and M6 • R1600364: G+ and Simcyp PBPK models for impact of pH on ribociclib absorption. • R1600443: Simcyp PBPK modeling with strong CYP3A inhibitors

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Subpopulation studies -	**X**	**1**		CLEE011A2109. Dose adjustment is not recommended for patients with mild hepatic impairment. A dose reduction to 400 mg is recommended for patients with moderate or serval hepatic impairment. In population analysis, Body weight was found to be a statistically significant and a clinically important covariate. The effect of body weight, however, that body weight based dose adjustment is not warranted. Additional intrinsic (age, sex, race, baseline hepatic function, renal function, and baseline ECOG status) and extrinsic factors (use of letrozole, proton-pump inhibitors, CYP3A4/5 inhibitors) were evaluated for effects, but were not found to be statistically significant nor clinically important.
ethnicity:				
gender:				
pediatrics:				The safety and effectiveness of ribociclib in pediatric patients have not been studied.
geriatrics:				
renal impairment:				Dose adjustment is not recommended for patients with mild and moderate renal impairment based on a population PK analysis. An appropriate dose has not been established for patients with severe renal impairment
hepatic impairment:	**X**	**1**		CLEE011A2109 Dose adjustment is not recommended for patients with mild hepatic impairment. A dose reduction to 400 mg is recommended for patients with moderate or serval hepatic impairment.
PD -				
Phase 2:				
Phase 3:				
PK/PD -	**X**	**2**		1) E-R analyses based on study CLEE011X1101,CLEE011X2101, and CLEE011X2107 • absolute neutrophil count 2) QT/QTc Safety Analysis Report
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -	**X**	**4**	**4**	CLEE011X1101 (N =17) CLEE011X2101 (N=144) CLEE011X2107 (N =47) CLEE011A2301 (N = 93)
Data rich:	**X**	**3**	**3**	CLEE011X1101 CLEE011X2101 CLEE011X2107
Data sparse:	**X**	**1**	**1**	CLEE011A2301
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -	**X**	**1**		CLEE011A2103
solution as reference:				
alternate formulation as reference:	**X**	**1**		CLEE011A2103
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies	**X**	**2**	**2**	CLEE011A2103 CLEE011A2111
Bio-waiver request based on BCS				
BCS class	**X**			IV by the applicant
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**49**	**49**	

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

On **initial** review of the NDA/BLA application for filing:

Criteria for Refusal to File (RTF): This OCP checklist applies to NDA, BLA submissions and their supplements					
No	**Content Parameter**	**Yes**	**No**	**N/A**	**Comment**
1	Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			To be marketed tablets formulation was compared with capsule formulation used in the Phase 3 pivotal trial.
2	Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	X			
3	Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	X			
4	Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?			X	An NME
5	Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	X			
6	Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	X			
7	Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	X			
8	Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	X			
9	Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	X			
	Complete Application				
10	Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	X			

File name: 5_Clinical Pharmacology Filing Form/Checklist for NDA208542 Rociletinib

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	N/A	Comment
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
1	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
2	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	X			
	Studies and Analyses				
3	Is the appropriate pharmacokinetic information submitted?	X			
4	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
5	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
6	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
7	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
8	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
9	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
10	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
11	Was the translation (of study reports or other study information) from another language needed and provided in this submission?		X		

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
___Yes_____

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Wentao Fu, Ph.D. 09/29/2016
Reviewing Clinical Pharmacologist Date

Qi Liu, Ph. D. 09/29/2016
Team Leader Date

File name: 5_Clinical Pharmacology Filing Form/Checklist for NDA208542 Rociletinib

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

/s/

WENTAO FU
10/03/2016

YOUWEI N BI
10/03/2016

JINGYU YU
10/04/2016

PING ZHAO
10/04/2016

QI LIU
10/04/2016