

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209092Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for **each** PMR/PMC in the Action Package.

NDA# 209092
Product KISQALI(Ribociclib)
Name:

PMR Description: 3868-1 Conduct a clinical trial to assess the efficacy and safety of an alternative dosing regimen after evaluation of ECG, PK and efficacy data from 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 safety assessments should include QT prolongation, hepatobiliary toxicities and neutropenia. The primary efficacy endpoint should be objective response rate (ORR).

PMR Schedule Milestones:	Draft Protocol Submission:	06/2018
	Final Protocol Submission:	12/2018
	Trial Completion:	04/2022
	Final Report Submission:	10/2022

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☒ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

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.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

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.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☒ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- ☐ Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- ☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Conduct an open-label, randomized, parallel trial to compare the efficacy and safety of an alternative dosing regimen (such as 300mg BID or 400mg QD) to the proposed 600mg QD ribociclib dose. The goal of conducting this clinical trial is to find an alternative dosing regimen which is able to mitigate the risks for QT prolongation without compromising efficacy.

The primary objective should compare the overall response rate (ORR) between tested dosing regimen to the proposed 600mg QD dose. The ORR is defined as the percentage of subjects with a confirmed response (CR) or partial response (PR) by local investigator assessment as per RECIST criteria. PFS and OS should be included as exploratory endpoints for efficacy.

The secondary objective should evaluate the safety and tolerability of the tested dose, including QT prolongation, hepatobiliary toxicity and neutropenia. Adequate ECG monitoring should be conducted to ensure the correct assessment of risks for QT prolongation.

The trial should include a minimum sample size of 100 total subjects per arm. The protocol and statistical analysis plan should be submitted prior to initiation of the study for full Agency review.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☒ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials

Continuation of Question 4

- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
- ☐ Immunogenicity as a marker of safety
- ☐ Other (provide explanation)

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- ☐ Dose-response study or clinical trial performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)
- ☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- ☐ There is a significant question about the public health risks of an approved drug
- ☐ There is not enough existing information to assess these risks
- ☐ Information cannot be gained through a different kind of investigation
- ☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- ☐ The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

- ☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA # 209092
Product Name: KISQALI(ribociclib)
PMR Description: Complete on-going clinical pharmacokinetic trial CLEE011A2116 (part 1) to determine an appropriate dose of ribociclib in patients with severe renal impairment.
3168-2

PMR Schedule Milestones:

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

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
Life-threatening condition
☐ Long-term data needed
☐ Only feasible to conduct post-approval
☐ Prior clinical experience indicates safety
☒ Small subpopulation affected
☐ Theoretical concern
☐ Other

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/1.73m²).

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

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

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☐ Pediatric Research Equity Act
- ☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
- ☒ Assess signals of serious risk related to the use of the drug?
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- ☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- ☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☒ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials

Continuation of Question 4

- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
 - ☐ Immunogenicity as a marker of safety
 - ☐ Other (provide explanation)
-

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- ☐ Dose-response study or clinical trial performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)

-
- ☐ Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- ☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- ☐ There is a significant question about the public health risks of an approved drug
- ☐ There is not enough existing information to assess these risks
- ☐ Information cannot be gained through a different kind of investigation
- ☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- ☐ The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

- ☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for **each** PMR/PMC in the Action Package.

NDA # 209092
Product Name: KISQALI (ribociclib)
PMC Description: 3168-3 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.

PMC Schedule Milestones:	Third OS Interim Data and Analysis:	12/2019
	Final Report of OS Data and Analysis:	06/2022

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☒ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

The secondary objective of Trial CLEE011A2301 was to compare the two treatment arms with respect to overall survival (OS). At the interim analysis, OS data were immature with a total of only 43 deaths at the time of the data cut-off and the median OS was not reached for either treatment arms.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The PMC is recommended for submission of the third interim and final OS data/results and analysis of Trial CLEE011A2301 to provide long-term data on the efficacy of ribociclib. This OS data may be used to update the ribociclib label and provide prescribers with important information.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☐ Pediatric Research Equity Act
- ☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
- ☐ Assess signals of serious risk related to the use of the drug?
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- ☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Submit the final OS data from Trial CLEE011A2301, a randomized double-blind, placebo-controlled study of LEE011 in combination with letrozole for the treatment of postmenopausal women with hormone receptor positive, HER2-negative, advanced breast cancer who received no prior therapy for advanced disease.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials

☐ Immunogenicity as a marker of safety

☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)

☐ Pharmacoeconomic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

☒ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

☐ Dose-response study or clinical trial performed for effectiveness

☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?

☒ Are the objectives clear from the description of the PMR/PMC?

☒ Has the applicant adequately justified the choice of schedule milestone dates?

☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug

☐ There is not enough existing information to assess these risks

☐ Information cannot be gained through a different kind of investigation

☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

☐ The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template: Product Quality (Biopharmaceutics)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA # 209092-ORIG-1
Product Name: Kisqali® (ribociclib) film-coated tablets

PMC Description: 3168-4 Conduct additional in vitro studies to evaluate the discriminating ability of the dissolution acceptance criterion ($Q = \text{(b) (4)}\%$ 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.

PMC Schedule Milestones: Final Report Submission: 09/30/2018

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- ☒ Need for drug (unmet need/life-threatening condition)
- ☐ Long-term data needed (e.g., stability data)
- ☐ Only feasible to conduct post-approval
- ☐ Improvements to methods
- ☐ Theoretical concern
- ☐ Manufacturing process analysis
- ☒ Other

Original NDA 209092 for ribociclib film-coated tablets is a Priority NDA with Break Through Therapy designation.

2. Describe the particular review issue and the goal of the study.

The additional data requested will be useful in supporting the adequacy of the dissolution acceptance criterion for routine QC testing of ribociclib tablets at batch release and during stability testing.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- ☒ Dissolution testing
- ☐ Assay
- ☐ Sterility
- ☐ Potency
- ☐ Product delivery
- ☐ Drug substance characterization
- ☐ Intermediates characterization
- ☐ Impurity characterization
- ☐ Reformulation
- ☐ Manufacturing process issues
- ☐ Other

Describe the agreed-upon study:

- i. *In vitro* dissolution profile data and the corresponding *in vivo* PK data from batches of the film-coated tablets used in an ongoing clinical study will be provided. The *in vitro* and the *in vivo* data generated will be used to validate the current PBPK model.
- ii. The current (or a suitable alternative) HPLC analytical method for dissolution testing of ribociclib film-coated tablets will be validated. The analytical method validation will evaluate the robustness of both the dissolution and drug quantification methods (e.g., with respect to type of sampling technique, paddle speed, pH of the dissolution medium, Normality and volume of the dissolution medium, UV wavelength, replacement of media withdrawn during dissolution testing), in addition to precision, specificity, linearity, range, accuracy, solution stability, and filter compatibility.
- iii. Batch release testing of the intended commercial drug product batches will be performed by the approved QC dissolution method. In parallel, data will be collected on commercial batches (1) tested by the modified QC dissolution method (by HPLC), using the existing HPLC methodology until the method is validated, and (2) a comparison of the dissolution profiles of the commercial batches to the BE batch will be performed using the modified QC dissolution method (by HPLC).
- iv. Long-term stability testing on the commercial batches will be conducted for up to 12 months; dissolution data at 30 min and 45 min using the modified QC dissolution method (by HPLC) will be collected.

5. To be completed by ONDQA/OBP Manager:

- ☒ Does the study meet criteria for PMCs?
- ☒ Are the objectives clear from the description of the PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- ☐ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs only)

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

/s/

CHRISTINA D MARSHALL
03/09/2017

KATHERINE M FEDENKO
03/09/2017

Clinical Inspection Summary

Date	February 21, 2017
From	Lauren Iacono-Connors, Reviewer Susan Thompson, M.D., Team Leader Kassa Ayalew, M.D., M.P.H, Branch Chief Division of Clinical Compliance Evaluation (DCCE)
To	Elleni Alebachew, Regulatory Project Manager Anand Shah, Clinical Reviewer Division of Oncology Products 1
NDA #	209092
Applicant	Novartis Pharmaceuticals Corporation
Drug	Kisqali® (Ribociclib, LEE011)
NME	Yes
Therapeutic Classification	Priority
Proposed Indication	Kisqali® is indicated for use in combination with letrozole for the treatment of postmenopausal women with HR-positive, HER2-negative, advanced or metastatic breast cancer as initial endocrine-based therapy
Consultation Request Date	September 19, 2016
Summary Goal Date	February 24, 2017
Action Goal Date	Updated to Mid-March 2017 (Original date: April 22, 2017)
PDUFA Date	April 29, 2017

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The data from Study CLEE011A2301 were submitted to the Agency in support of NDA 209092. Four clinical sites, Dr. Lowell Hart (Site 5044), Dr. Gabriel Hortobagyi (Site 5095), Dr. Cristian Villanueva (Site 3004), Dr. Salomon Stemmer (Site 1302) and the study sponsor, Novartis Pharmaceuticals Corporation, were selected for audit.

The primary efficacy endpoint, Progression Free Survival (PFS) as determined by the clinical investigators, was verified with the source records generated at the inspected clinical sites. There were no significant inspectional findings for clinical investigators Dr. Gabriel Hortobagyi, Dr. Cristian Villanueva, and Dr. Salomon Stemmer. The inspection of the study sponsor, Novartis Pharmaceuticals Corporation (Novartis), is scheduled to begin on February 23, 2017. At this time, there is no information from the sponsor inspection on the sponsor's conduct and oversight of Study CLEE011A2301.

II. BACKGROUND

Novartis Pharmaceuticals Corporation (Novartis) seeks approval of Ribociclib tablets, 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. This clinical inspection summary is based on the results from primarily Study CLEE011A2301.

The following overview of the Study CLEE011A2301 is intended as background context for interpreting the inspectional findings. Study CLEE011A2301 is a Phase 3, randomized, double-blind, placebo controlled 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 disease. The study randomized 668 subjects at 223 clinical centers in 29 countries.

Study Period: Study initiation date (first subject enrolled): December 17, 2013
Data cut-off date for analysis: January 29, 2016

Primary efficacy endpoint: PFS as determined by the Clinical Investigator review of radiology data using RECIST version 1.1 criteria. PFS was defined as the time from the date of randomization to the date of the first documented disease progression or death due to any cause.

Inspections of clinical sites were considered essential to verify the quality of conduct of the studies for this NME application.

Objectives of Inspections:

- a. Verify PFS as assessed by the investigator using RECIST Version 1.1.
- b. Identification, documentation, and reporting of adverse events (AEs) for a sample of enrolled subjects.
- c. General compliance with the investigational plan.

III. RESULTS (by site):

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	Preliminary Classification NAI
CI #2: Gabriel Hortobagyi (Site 5095) 1515 Holcombe Boulevard - 1354 Houston, TX 77030	Protocol: CLEE011A2301 Subjects: 15	February 13- 16, 2017	Preliminary Classification NAI

Name of CI, Site #, Address	Protocol # and # of Subjects	Inspection Date	Final Classification
CI #3: Cristian Villanueva (Site 3004) 3, bd Alexandre Fleming Besancon Cedex, 25030 France	Protocol: CLEE011A2301 Subjects: 10	January 16- 23, 2017	Preliminary Classification 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	Preliminary Classification NAI
Sponsor: Novartis Pharmaceuticals Corp. One Health Plaza East Hanover, NJ 07936-1080	Protocol: CLEE011A2301 Site Numbers: TBD	<i>Planned Start Date: 02/23/17</i>	<i>Preliminary Classification TBD</i>

Key to Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

1. Dr. Lowell Hart, M.D. (Site 5044)

The site screened 14 subjects and nine subjects were enrolled. A complete record review was done for enrolled subjects. At the time of this inspection, no subject had completed the study. Three subjects continue on active treatment, five subjects discontinued due to disease progression, and one subject withdrew from the study to start an approved therapy. Study subject source documents/records were compared to the eCRF and data listings submitted to NDA 209092, focusing on inclusion/exclusion criteria compliance, adverse events, randomization, and efficacy endpoint verification.

The inspection revealed no significant deficiencies. The primary efficacy endpoint, PFS per the investigator, was verifiable. There was no evidence of under-reporting AEs.

The data from Site 5044, associated with Study CLEE011A2301 appear reliable.

2. Dr. Gabriel Hortobagyi, M.D. (Site 5095)

The site screened 21 subjects and enrolled 15 subjects. At the time of this inspection,

six subjects were still on study receiving either ribociclib or placebo, and five subjects were in long term follow-up and were being followed for survival. One subject had expired. Three subjects transferred to a different study site and were still active at those sites. A comprehensive record review was done for all 15 enrolled subjects.

Study subject source documents/records were compared to the eCRF and data listings submitted to NDA 209092.

The inspection revealed no significant deficiencies. The source data were compared to the sponsor's data listings and no discrepancies were noted. There was no evidence of under-reporting of AEs. The primary endpoint, PFS, data were verified. Six subjects have had a partial response and five subjects experienced progressive disease and are no longer on study. Records were very organized and complete. All protocol deviations were reported to the sponsor and the IRB as necessary. No additional protocol deviations were noted during this inspection. Signed informed consent was obtained from each subject prior to the performance of any study related procedures. The informed consent process was also well documented in the subject case history records.

The data from Site 5095, associated with Study CLEE011A2301, appear reliable.

3. Dr. Cristian Villanueva, M.D. (Site 3004)

The site screened 13 subjects and enrolled 10 subjects. A complete record review was done for 12 subjects; three of which were screen failures and nine of which were enrolled subjects. The record review included informed consent, entry criteria satisfaction, randomization, assessments of primary and secondary efficacy data, adverse events and serious adverse events. The inspection also considered monitoring, test article accountability, delegation of authority, and overall good clinical practice compliance.

The inspection revealed no significant deficiencies. The primary efficacy endpoint, PFS per the investigator, was verifiable. There was no evidence of under-reporting of AEs.

The data from Site 5044, associated with Study CLEE011A2301 appear reliable.

4. Dr. Salomon Stemmer, M.D. (Site 1302)

The site screened 18 subjects, four subjects were screen failures and 14 subjects were enrolled. At the time of this inspection three subjects were still on study and taking study drug. A complete record review was done for all enrolled subjects. The inspection focused on comparison of subject source documents/records to the eCRF and data listings submitted to NDA 209092.

The inspection revealed no significant deficiencies. The primary efficacy endpoint, PFS per the investigator, was verifiable. There was no evidence of under-reporting AEs. There were several observations that were discussed with the site. There were transcription errors in the

investigational product return records. Specifically, there were a few instances where study drug kit numbers were not recorded as returned and other kit numbers had been recorded twice. A second item was related to reminding study subjects to complete the dosing diaries contemporaneously. These observations were not systemic and should not impact data integrity or subject safety.

The data from Site 1302, associated with Study CLEE011A2301 appear reliable.

5. Sponsor: Novartis Pharmaceuticals Corp.

The inspection of the sponsor, Novartis, of Study CLEE011A2301 is scheduled to begin on February 23, 2017. As soon as the inspection is completed, an assessment of preliminary findings will be conducted. The Clinical Inspection Summary will be amended to reflect the preliminary inspectional findings.

A recommendation regarding data reliability of the data submitted by Novartis to the Agency associated with Study CLEE011A2301 will be provided in an addendum to the CIS.

{See appended electronic signature page}

Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan Thompson, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
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Kassa Ayalew, M.D., M.P.H
Branch Chief
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Office of Scientific Investigations

CC:

Central Doc. Rm. NDA #209092
DOP1/Division Director/Geoffrey Kim
DOP1/Clinical Team Leader/Julia Beaver
DOP1/Project Manager/Elleni Alebachew
DOP1/Medical Officer/Anand Shah
OSI/Office Director (Acting)/David Burrow
OSI/DCCE/ Division Director/Ni Khin
OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/Susan D. Thompson
OSI/DCCE/GCP Reviewer/Lauren Iacono-Connors
OSI/ GCP Program Analysts/Joseph Peacock/Yolanda Patague
OSI/Database PM/Dana Walters

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/s/

LAUREN C IACONO-CONNORS
02/21/2017

SUSAN D THOMPSON
02/21/2017

KASSA AYALEW
02/21/2017

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 17, 2017

TO: Geoff Kim, M.D.
Director
Division of Oncology Products (DOP1)
Office of Hematology and Oncology Products

Ann Farrell, M.D.
Director
Division of Hematology Products (DHP)
Office of Hematology and Oncology Products

Jean-Marc Guettier, M.D.
Director
Division of Metabolism and Endocrinology Products
(DMEP)
Office of Drug Evaluation II (ODEII)

FROM: Xikui Chen, Ph.D.
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance
Office of Translational Sciences

THROUGH: Sally Choe, Ph.D.
Deputy Director
Office of Study Integrity and Surveillance
Office of Translational Sciences

SUBJECT: Review of inspection of (b) (4)
(b) (4) covering NDA 209092 (ribociclib), NDA (b) (4)

Summary:

The Office of Study Integrity and Surveillance (OSIS) conducted a surveillance inspection at (b) (4)
(b) (4) covering the analytical portion of (b) (4) No bioequivalence studies under NDAs 209092, (b) (4) No significant deficiencies were observed and Form FDA 483 was not issued at the close of the inspection. The final classification of the inspection is No Action Indicated (NAI). Based on the inspection findings, these reviewers recommend that data from the following studies be accepted for further Agency review.

Table 1.

NDA	Study #	Study title	Clinical Study Dates	Analytical Study Dates
209092	14BAS324	"Determination of the concentration of LEE011 and its metabolite LEQ803 in human plasma by LC-MS/MS, in support of clinical study referenced CLEE011A2103"	August 01, 2014 (First patient enrolled) to October 22, 2015 (Last patient completed)	June 11, 2015 to October 28, 2015

(b) (4)

OSIS investigators, Seongeun (Julia) Cho and Xikui Chen, conducted an audit of (b) (4) at (b) (4)

The audit of the studies listed in **Table 1** included a thorough review of method validations, study records, facility equipment, and original laboratory worksheets, and interviews with the firm's management and staff.

Conclusion:

Based on the inspectional findings and overall evaluation of bioanalytical study conduct at (b) (4) the OSIS reviewers conclude that data from the studies listed in Table 1 are reliable. Therefore, these reviewers recommend that the analytical portion of the studies listed in Table 1 be accepted

for further Agency review.

Final Site Classification:

NAI [REDACTED] (b) (4)
FEI: [REDACTED]

DARRTS CC:
OTS/OSIS/Kassim/Choe/Taylor/Haidar/Miller/Nkah/Kadavil
OTS/OSIS/DGDBE/Cho/Skelly/Choi/Au
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas
CDER/OND/Kim/Farrell/Guettier
Draft: XC 2/16/17
Edits: MFS 2/17/2017; JC 2/17/2017

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Labora [REDACTED] (b) (4) ance/INSPECTIONS/BE Program/ANALYTICAL
SITES/ [REDACTED] (b) (4)

[REDACTED] (b) (4) BE7308 (NDA 209092) and [REDACTED] (b) (4)
[REDACTED] (b) (4)
FACTS: [REDACTED] (b) (4)

Xikui Chen, Ph.D.
OSIS, DGDBE

Sally Choe, Ph.D.
Deputy Director
OSIS

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/s/

XIKUI CHEN
02/17/2017

SEONGEUN CHO
02/17/2017

SALLY Y CHOE
02/17/2017

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 17, 2017

TO: Geoff Kim, M.D.
Director
Division of Oncology Products (DOP1)
Office of Hematology and Oncology Products

Ann Farrell, M.D.
Director
Division of Hematology Products (DHP)
Office of Hematology and Oncology Products

Jean-Marc Guettier, M.D.
Director
Division of Metabolism and Endocrinology Products
(DMEP)
Office of Drug Evaluation II (ODEII)

FROM: Xikui Chen, Ph.D.
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance
Office of Translational Sciences

THROUGH: Seongeun (Julia) Cho, Ph.D.
Director
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance
Office of Translational Sciences

SUBJECT: tion of (b) (4)
(b) (4)
(b) (4)

Summary:

The Office of Study Integrity and Surveillance (OSIS) conducted a surveillance inspection at (b) (4) covering the analytical portion of (b) (4) bioequivalence studies under NDAs 209092, (b) (4). No significant deficiencies were observed and Form FDA 483 was not issued at the close of the inspection. The final classification of the inspection is No Action Indicated (NAI). Based on the inspection findings, these reviewers recommend that data from the following studies be accepted for further Agency review.

Table 1.

NDA	Study #	Study title	Clinical Study Dates	Analytical Study Dates
209092	14BAS324	"Determination of the concentration of LEE011 and its metabolite LEQ803 in human plasma by LC-MS/MS, in support of clinical study referenced CLEE011A2103"	August 01, 2014 (First patient enrolled) to October 22, 2015 (Last patient completed)	June 11, 2015 to October 28, 2015

(b) (4)

OSIS investi

ucted

(b) (4)

(b) (4)

The audit of the studies listed in **Table 1** included a thorough review of method validations, study records, facility equipment, and original laboratory worksheets, and interviews with the firm's management and staff.

Conclusion:

Based on the inspectional findings and overall evaluation of bioanalytical study conduct at (b) (4) the OSIS reviewers conclude that data from the studies listed in Table 1 are reliable. Therefore, these reviewers recommend that the

analytical portion of the studies listed in Table 1 be accepted for further Agency review.

Final Site Classification:

NAI (b) (4)
FEI:

DARRTS CC:
OTS/OSIS/Kassim/Choe/Taylor/Haidar/Miller/Nkah/Kadavil
OTS/OSIS/DGDBE/Cho/Skelly/Choi/Au
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas
CDER/OND/Kim/Farrell/Guettier
Draft: XC 2/16/17
Edits: MFS 2/17/2017; JC 2/17/2017

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/INSPECTIONS/BE Program/ANALYTICAL
SITES (b) (4)

OSI file #: (b) (4) BE7308 (NDA 209092) and (b) (4)
(b) (4)
FACTS: (b) (4)

Xikui Chen, Ph.D.
OSIS, DGDBE

Seongeun (Julia) Cho, Ph.D.
Director
OSIS, DGDBE

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/s/

XIKUI CHEN
02/17/2017

SEONGEUN CHO
02/17/2017

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

******Pre-decisional Agency Information******

Memorandum

Date: February 3, 2017

To: Elleni Alebachew, MS, RAC
Senior Regulatory Health Project Manager
Division of Oncology Products 1 (DOP1)
Office of Hematology and Oncology Products

From: Kevin Wright, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **KISQALI®** (ribociclib) tablets, for oral use
NDA 209092

Office of Prescription Drug Promotion comments on proposed
prescribing information (PI), blister card label, sleeve and carton
labeling

Office of Prescription Drug Promotion (OPDP) has reviewed the draft prescribing information (PI) and proposed blister card labels, blister sleeve and carton labeling for KISQALI® (ribociclib) tablets, for oral use (Kisqali) as requested by DOP1 in the consult dated October 5, 2016.

OPDP's review of the proposed PI is based on the draft PI titled, "NDA 209092 – Proposed PI-FDA Revised 1.19.20(3)" sent by electronic mail on January 23, 2017, to OPDP (Kevin Wright) from DOP1 (Elleni Alebachew). OPDP comments are listed on the attached PI.

OPDP also reviewed the proposed blister card labels and blister sleeve and carton labeling submitted to the electronic document room on December 20, 2016. OPDP has no comments for the proposed labels and labeling.

The combined OPDP and Division of Medical Policy Programs (DMPP) review of the patient package insert (PPI) will be provided under a separate cover.

If you have any questions, please feel free to contact, Kevin Wright at (301) 796-3621 or kevin.wright@fda.hhs.gov. OPDP appreciates the opportunity to provide comments on these materials. Thank you!

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/s/

KEVIN WRIGHT
02/03/2017

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: February 3, 2017

To: Geoffrey Kim, MD
Director
Division of Oncology Products 1 (DOP1)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Shawna Hutchins, MPH, BSN, RN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Rowell Medina, PharmD, BCPS
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Kevin Wright, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): KISQALI (ribociclib)

Dosage Form and Route: tablets, for oral use

Application Type/Number: NDA 209092

Applicant: Novartis Pharmaceuticals Corporation

1 INTRODUCTION

On August 29, 2016, Novartis Pharmaceuticals Corporation submitted for the Agency's review a New Drug Application (NDA) 209092 for KISQALI (ribociclib) tablets. The Applicant proposed the following indication: 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.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology Products 1 (DOP1) on October 5, 2016 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for KISQALI (ribociclib) tablets.

2 MATERIAL REVIEWED

- Draft KISQALI (ribociclib) tablets PPI received on August 29, 2016, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on January 23, 2017.
- Draft KISQALI (ribociclib) tablets Prescribing Information (PI) received on August 29, 2016, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on January 27, 2017.
- Approved IBRANCE (palbociclib) capsules comparator labeling dated February 19, 2016.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

ROWELL MEDINA
02/03/2017

KEVIN WRIGHT
02/03/2017

SHAWNA L HUTCHINS
02/03/2017

LASHAWN M GRIFFITHS
02/03/2017

Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

IND or NDA	NDA 209092
Brand Name	KISQALI
Generic Name	Ribociclib (LEE011)
Sponsor	Novartis Pharmaceuticals
Indication	Indicated, in combination with letrozole, 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
Dosage Form	Tablets
Drug Class	A cyclin dependent kinase inhibitor (CDKi)
Therapeutic Dosing Regimen	600 mg plus letrozole 2.5 mg QD, 3 weeks on/1 week off
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	900 mg QD, 3 weeks on/1 week off
Submission Number and Date	001 and 8/29/2016
Review Division	DOP1

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1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

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 Δ QTcF 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 C_{max} 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.

For E14 central tendency analysis, our review focused on the data for the proposed ribociclib 600 mg therapeutic dose. The largest upper bounds of the 2-sided 90% CI for the mean differences Ribociclib 600 mg with or without Letrozole 2.5 mg are all exceeded 20 ms (with point estimates also around 20 ms or higher) as shown in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Ribociclib 600 mg with or without Letrozole 2.5 mg (FDA Analysis)

Study Treatment	Cycle/Day	Mean	Std Dev	90% CI for Mean
Phase 3 Registration Study				
[A2301] Placebo + Letrozole 2.5 mg	C7D1	6.9	16.1	(1.0, 12.8)
[A2301] Ribociclib 600 mg + Letrozole 2.5 mg	C1D15	19.6	16.4	(18.0, 21.2)
[A2107] Ribociclib 600 mg + Letrozole 2.5 mg	C1D21	24.6	21.3	(18.9, 30.3)
Monotherapy Studies				
[X1101] Ribociclib 600 mg	C1D15	25.0	14.6	(17.4, 32.6)
[X2101] Ribociclib 600 mg	C1D15	27.3	21.0	(21.8, 32.7)

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.

Appropriate risk mitigation strategies for QTc prolongation are needed in product labeling to reduce risk of torsades de pointes. We recommend the following to be considered:

- a warning/precautionary statement about the risk;
- use of monitoring of ECGs and electrolytes;
- a precautionary statement to avoid concomitant drugs that also cause QTc prolongation;
- instructions for dose reductions in patients that have intrinsic/extrinsic factors that increase exposure; and
- a plan for management of patients with QT/QTc prolongation or symptoms suggestive of an arrhythmia.

The benefit/risk profile of this product should be considered in patients with increased risk of arrhythmias such as those patients with congenital long QT syndrome, bradyarrhythmias, structural heart disease, and congestive heart failure.

2 PROPOSED LABEL

The following is the sponsor's proposed labeling language related to QT. Our suggested changes to the proposed label are shown below in Review's Comments. We defer to the Division for final labeling language.

Highlights of Prescribing Information:

2.2 Dose Modifications

Table 4: Dose Modification and Management for QT Prolongation

ECGs with QTcF > 480 msec	1. Interrupt KISQALI Treatment 2. If QTcF prolongation resolves to < 481 msec, resume treatment at the same dose level; 3. If QTcF $\geq$ 481 msec recurs, interrupt dose until QTcF resolves to < 481 msec; then resume KISQALI at next lower dose level.
ECGs with QTcF > 500 msec	1. Interrupt KISQALI treatment if QTcF greater than 500 msec on at least 2 separate ECGs (within the same visit). 2. If QTcF prolongation resolves to < 481 msec, resume treatment at the next lower dose level Permanently discontinue KISQALI if QTcF interval prolongation is either greater than 500 msec or greater than 60 msec change from baseline AND associated with any of the following: Torsade de Pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia.
Electrocardiograms (ECGs) should be assessed prior to initiation of treatment. Repeat ECGs at approximately Day 14 of the first cycle and at the beginning of the second cycle, then as clinically indicated. In case of (QTcF) prolongation at any given time during treatment, more frequent ECG monitoring is recommended.	

Reviewer's comment: The Division may want to consider discontinuation if patient experiences unexplained syncope in the presence of QTc prolongation >500 ms.

5.3 QT Interval Prolongation

In the Phase III study, one patient (0.3%) had >500 msec post-baseline QTcF value (average of triplicate), and nine patients out of 329 patients (2.7%) 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 (b) (4). There were no reported cases of Torsade de Pointes.

ECG (b) (4) prior to initiation of treatment. Treatment with KISQALI (b) (4) only in patients with QTcF values less than 450 msec. Repeat ECG at approximately Day 14 of the first cycle and the beginning of the second cycle, (b) (4) as clinically indicated.

(b) (4) monitor (b) (4) serum electrolytes (including potassium, calcium, phosphorous and magnesium) (b) (4) prior to the initiation of treatment, at the beginning of the first 6 cycles, (b) (4) as clinically indicated. (b) (4) correct (b) (4) before start (b) (4) KISQALI therapy [see Dosage and Administration (2.2)].

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

- long QT syndrome

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

Avoid using KISQALI with drugs known to prolong QTc interval and/or strong CYP3A inhibitors as this may lead to prolongation of the QTcF interval [see Clinical Pharmacology (12.3)].

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

Reviewer's comment: The first paragraph minimizes the risk of QTc prolongation. We recommend the following changes to the first paragraph:

KISQALI can prolong the QT interval in a concentration-dependent manner, with mean increases in QTc interval exceeding 20 ms [See Clinical Pharmacology (12.2)]. Syncope, ventricular tachycardia and sudden death have occurred in patients taking KISQALI.

7.4 Drugs That Prolong the QT Interval

Avoid coadministration of KISQALI with medicinal products with a known potential to prolong QT such as antiarrhythmic medicines (including, but not limited to amiodarone, disopyramide, procainamide, quinidine and sotalol), and other drugs that are known to prolong the QT interval (including, but not limited to, chloroquine, halofantrine, clarithromycin, haloperidol, methadone, moxifloxacin, bepridil, pimozide and ondansetron (i.v)) [see Warnings and Precautions (5.2) and Clinical Pharmacology (12.3)].

Reviewer's comment: The Division may want to consider including QT prolong drugs that this specific patient population would be likely taking such as antiemetics (e.g., ondansetron, dolasetron), antibiotics (e.g., clarithromycin, ciprofloxacin, levofloxacin), antidepressants (e.g., citalopram, paroxetine), and other oncology medications. A full listing of QT prolonging medications can be found at www.crediblemeds.org.

12.2 Pharmacodynamics

Cardioelectrophysiology

Serial, triplicate ECGs were collected following a single dose and at steady-state to evaluate the effect of ribociclib on the QTc interval in patients with advanced cancer. A pharmacokinetic-pharmacodynamic analysis included a total of 267 patients treated with ribociclib at doses ranging from 50 to 1200 mg, including 193 patients treated with ribociclib 600 mg. The analysis suggested that ribociclib causes concentration-dependent increases in the QTc interval. The estimated mean change from baseline in QTcF was 22^{(b) (4)} ms (90% CI: 21.6, 24.1) at the mean observed C_{max} at steady state following administration at the recommended 600 mg dose.

Reviewer's comments: Section 12.2 is acceptable.

3 BACKGROUND

3.1 PRODUCT INFORMATION

Ribociclib is an orally bioavailable, highly-selective small molecule inhibitor of CDK4/6 enzyme complexes. It is being developed for 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.

3.2 MARKET APPROVAL STATUS

Ribociclib is not approved for marketing in any country

3.3 PRECLINICAL INFORMATION

QT interval prolongation was observed in vivo in dogs at ribociclib and LEQ803 (a prominent metabolite) plasma concentrations that occur in patients on a therapeutic dose of 600 mg, and are consistent with inhibition of the hERG channel.

See Appendix 6.1 for more details.

3.4 PREVIOUS CLINICAL EXPERIENCE

See Appendix 6.1

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of ribociclib's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT previously reviewed the sponsor's QT assessment and ECG monitoring plan in a type C meeting under IND 117796. The sponsor submitted the safety analysis report for the study drug, including electronic datasets and waveforms to the ECG warehouse.

4.1 TQT STUDY

4.1.1 Title

QT/QTc Safety Analysis Report

4.1.2 Protocol Number

LEE011/ribociclib

4.1.3 Objectives

The primary objective of this analysis was to evaluate the potential of ribociclib to delay cardiac repolarization as measured by QTc prolongation.

4.1.4 Study Description

4.1.4.1 Design

This safety data included combination therapy and monotherapy studies. The combination therapy included studies LEE011A2301 and LEE011X2107 and the dose is ribociclib 600 mg plus letrozole 2.5 mg. The monotherapy studies include studies LEE011X2101, LEE011XUS03, and LEE011X1101 and doses are ranged from 50 mg to 1200 mg. The Table below overview of clinical studies included to support the safety assessment (QT/QTc effect) of ribociclib when used in combination with letrozole.

Table 3-1 Overview of clinical studies included

Studies	Population	Comment	Ribociclib/Dose schedule ¹	Total patients and number of patients in the safety set
Combination therapy studies				
Study A2301	Postmenopausal patients with advanced metastatic or recurrent HER+, HER2-neg breast cancer	Phase III registration study	Ribociclib 600 mg once daily taken on Days 1-21 of a 28-day cycle plus once daily letrozole 2.5 mg	Total patients: N=668 Ribociclib 600 mg: 334 patients Placebo: 330 patients
Study X2107 ²	Dose escalation: postmenopausal patients with ER+ / HER2 negative breast cancer who received prior treatment Dose expansion: patients with advanced breast cancer who received no prior treatment	Phase Ib dose escalation and expansion phase	Ribociclib 600 mg once daily taken on Days 1-21 of a 28-day cycle plus once daily letrozole 2.5 mg	Total patients: N=47 Ribociclib 600 mg: 19 patients Dose escalation: 19 patients Dose expansion: 28 patients
Monotherapy studies				
Study X2101	Patients with advanced solid tumors or lymphomas	Phase I First in human dose escalation	Ribociclib once daily ³ : 50 mg, 70 mg, 140 mg, 260 mg, 280 mg, 350 mg, 400 mg, 600 mg, 750 mg, 900 mg, and 1200 mg taken on Days 1-21 of a 28-day cycle	Total patients: N=134 Ribociclib: <400 mg: 23 patients 400 mg: 5 patients 600 mg: 68* patients 600 mg liquid: 8 patients >600 mg: 30 patients
Study XUS03	Patients with solid tumors and/or hematologic malignancies	Phase II Interventional study	Ribociclib: 600 mg once daily taken on Days 1-21 of a 28-day cycle	Total patients: N=106 Ribociclib 600 mg: 106 patients
Study X1101 ⁴	Japanese patients with advanced solid tumors	Phase I Dose escalation in Japanese patients	Ribociclib once daily 400 mg (4 patients) and 600 mg taken on Days 1-21 of a 28-day cycle	Total patients completed: N = 13 Ribociclib 600 mg: 13 patients

¹ Only ribociclib 600 mg is included in the monotherapy pool. Safety data from other doses of ribociclib are discussed in Study X2101 CSR. Patients who received ribociclib on a continuous dosing schedule are not included in this Summary of Safety.

² This study also evaluated a triple combination of ribociclib plus alpelisib in combination with letrozole.

³ Doses of 600 mg are included in the monotherapy pool. Safety data from dosing with ribociclib 400 mg are discussed in Study X1101 CSR.

⁴ Pooled ribociclib 600 mg includes the following: 68 subjects who received the 600-mg capsule.

Source: Study A2301, Study X2107, Study X2101, Study XUS03, and Study X1101

4.1.4.2 Controls

Placebo control was included in Study A2301.

4.1.5 Treatment Regimen

4.1.5.1 Treatment Arms

An overview of these studies is presented in the sponsor's Table 3-1. Both the intermittent dosing schedule (once daily, 3 weeks on/1 week off) at a range of doses from 50 to 1200 mg and the continuous dosing schedule (once daily) at doses of 300, 400 and 600 mg were included in the analysis.

4.1.5.2 Sponsor's Justification for Doses

Reviewer's Comment: The maximum tolerated dose (MTD) of 900 mg and the recommended dose of 600 mg were all evaluated.

4.1.5.3 Instructions with Regard to Meals

Ribociclib tablets can be taken orally with or without food in combination with letrozole.

Reviewer's Comment: The effect of food on the peak plasma concentrations of ribociclib is mild.

4.1.5.4 ECG and PK Assessments

A summary of ECG and PK assessments is provided in the following table.

Table 2: PK and ECG Assessment Schedules in Studies Included in C-QT Analysis

Study	Timing of PK collection (Protocol planned)	Timing of ECG assessments (Protocol planned)
Studies in patients		
LEE011A2301 (A2301)	C1D15: 0h C1D15: 2h	Screening (- D7,D1), C1D15, C2D1: 0, 2 h post-dose C3D1: 0 h Unscheduled as clinically indicated
LEE011X1101 (X1101)	C1D1: 0h, 0.5h, 1h 2h, 4h, 6h, 8h C1D2: 24h C1D8: 0h, 1h, 2h, 4h C1D15: 0h, 1h, 2h, 4h C1D21***: 0h, 0.5, 1h 2h, 4h, 6h, 8h C1D22: 24h C1D23: 48h C1D24: 72h C2D1: 0h C2D8: 2h	Screening C1D1, C1D21: same time as PK C1D8, C1D15: same time as PK C1D2: 0 hr C2D1: 0 hr C2D8, C2D15: 4-hr intensive x ≥ 3: CxD1: pre-dose CxD15: 4-hr intensive Unscheduled: as clinically indicated EOT
LEE011X2101 (X2101)	Escalation: C1D1: 0h, 0.5h, 1h 2h, 4h, 6h, 8h C1D2: 0h C1D8: 0h, 1h, 2h, 4h C1D15: 0h, 1h, 2h, 4h C1D21: 0h, 0.5, 1h 2h, 4h, 6h, 8h C1D22: 0h C1D23: 48h C1D24: 72h C2D1: 0h C2D8: 2h Expansion: C1D1, C1D21: 8h intensive C1D8, C1D15: 6h intensive C1D2, C1D22: 0h C2D1, C2D8, C2D15: 0h C2D8, C2D15: 4h Unscheduled as clinically indicated	Screening C1D1, C1D21: same time as PK C1D8, C1D15: same time as PK C1D2: 0 hr C1D22: 0 hr C2D1**: 0 hr C2D8, C2D15: 4-hr intensive CxD1, CxD15: x ≥ 3: same as C2 As clinically indicated EOT Day -1: 8h intensive C1D1, C1D21: same time as PK C1D8, C1D15: same time as PK C2D1: 0h C2D8, C2D15: 4h regular CxD1, CxD15: x ≥ 3: same as C2 As clinically indicated EOT
LEE011X2107 (X2107)	All patients: C1D1: 0h, 0.5h, 1h C1D1: 2h, 4h, 8h C1D2: 0h C1D8: 0h C1D15: 0h C1D21: 0h, 0.5h, 1h C1D21: 2h, 4h, 8h C1D22: 0h C2D15: 0h C3D15: 0h C4D15: 0h C5D15: 0h C6D15: 0h	Screening C1D1: 4h regular, 8 C1D8: 0, 4h C1D15: 4h regular C1D21: 4h regular C2D1: 0h C2D15: anytime C3-6D15: anytime C7-nD1: anytime Unscheduled: as clinically indicated EOT

Reviewer's Comment: Overall, the timing of the ECGs and PK collection is acceptable to capture the drug effect around Tmax after first dose and at steady state.

4.1.5.5 Baseline

For both the patient and healthy subject pool, the baseline ECG interval measurement was defined as the last ECG measurement taken prior to study drug administration on Study Day 1.

For Day 1 ECGs, if dosing time was not available to determine if an ECG measurement was taken pre-dose or post-dose, then only the screening and the scheduled pre-dose measurements were considered for baseline.

4.1.6 ECG Collection

Combination therapy pool: Standard, triplicate 12 lead ECG assessments were performed. All ECGs including unscheduled measurements collected were transmitted to a central laboratory and were centrally reviewed by an independent reviewer. Analyses of ECG data were based on the average of all available ECG measurements at a particular time point for each patient.

Monotherapy pool: Standard 12 lead ECG assessments were performed in all the three studies. For studies X2101 and X1101, all ECGs were transmitted to a central laboratory and were centrally reviewed by an independent reviewer. For Study XUS03, the machine read ECG intervals were interpreted by a qualified physician. The average of all available ECG measurements at a particular time point was calculated to provide a single value for each patient.

4.1.7 Sponsor's Results

4.1.7.1 Study Subjects

Pooled safety data from monotherapy and combination studies are included in this report to support the safety assessment (QT/QTc effect) of ribociclib when used in combination with letrozole (see sponsor's Table 3-1).

Combination therapy pool (N=381): The combination therapy pool is based on safety data from the combination therapy studies, Study A2301 and Study X2107 in the targeted indication. The primary safety evaluation of ribociclib and letrozole combination is based upon data from Study A2301, the registration study, in post-menopausal women with HR+, HER2-negative advanced breast cancer who received no prior therapy for advanced breast cancer. Furthermore, safety data from Study A2301 have been pooled with safety data from Study X2107 to provide a more comprehensive evaluation of the safety profile of ribociclib used in combination with letrozole.

Monotherapy pool (N=187): The monotherapy pool consists of Study X2101, Study XUS03, and Study X1101 in the targeted dosing regimen of ribociclib (600 mg on Days 1-21 of a 28-day cycle). The monotherapy studies are open-label, non-randomized, single-agent studies.

In total, 45 patients on ≤ 400 mg, 217 patients on 600 mg, and 30 patients on >600 mg were included in the PK/ECG set. Most of the patients from the individual studies were included in the PK/ECG set, except for study A2301, which only collected PK data in a subset of patients (51/331 (15.4%) in the 600 mg group).

4.1.7.2 Statistical Analyses

4.1.7.2.1 Central Tendency Analysis

The primary endpoint is change from baseline in QTcF. For study A2301, the largest upper bounds of the 2-sided 90% CI for the mean difference Ribociclib 600 mg plus Letrozole 2.5 mg over 20 ms at C1D15 (see Table below).

Table 4-8 Study A2301-Changes from baseline in QTcF by treatment and time point (Safety set)

Visit	Change from baseline			
	Ribociclib 600 mg plus letrozole 2.5 mg		Placebo plus letrozole 2.5 mg	
	n	Mean (95% CI)	n	Mean (95% CI)
C1D15 - pre-dose	308	13.5 (11.8, 15.1)	313	1.7 (0.3, 3.1)
C1D15 - 2 hour post-dose	277	19.6 (17.6, 21.5)	307	1.8 (0.5, 3.2)
C2D1 - pre-dose	312	5.1 (3.5, 6.8)	319	2.7 (1.2, 4.1)
C2D1 - 2 hour post-dose	264	11.8 (10.1, 13.6)	297	3.2 (1.7, 4.7)
C3D1 - pre-dose	302	6.1 (4.4, 7.9)	295	2.9 (1.3, 4.5)
C3D1 - 2 hour post-dose	1	5.3	3	1.8 (-15.7, 19.3)
C9D1 - pre- dose	53	5.7 (1.7, 9.8)	54	6.7 (3, 10.3)
C9D1 - 2 hour post-dose	41	11.6 (6.9, 16.4)	44	4.9 (0.7, 9)

C = Cycle; D = Day

Source: [\[Study A2301-Table 14.3-5.1\]](#)

Reviewer's Comments: We provided our independent analysis result in Section 5.2. Our results are similar as those reported by the sponsor for study A2301.

4.1.7.2.2 Assay Sensitivity

No positive control arm included and no assay sensitivity established.

4.1.7.2.3 Categorical Analysis

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

Sponsor's Categorical Analysis of Combination Therapy Study

	Study A2301		Study X2107	Pooled combination therapy
	RIBO+LET	PBO+LET	RIBO+LET	RIBO+LET
	N=334	N=330	N=47	N=381
	n/m (%)	n/m (%)	n/m (%)	n/m (%)
QTcF (ms) (n)				
New >450	96/323 (29.7)	27/327 (8.3)	25/ 46 (54.3)	121/369 (32.8)
New >480	11/329 (3.3)	1/330 (0.3)	4/ 47 (8.5)	15/376 (4.0)
New >500	1/329 (0.3)	0/330 (0)	0/ 47 (0)	1/376 (0.3)
Increase from baseline >30	101/329 (30.7)	27/330 (8.2)	32/ 47 (68.1)	133/376 (35.4)
Increase from baseline >60	9/329 (2.7)	0/330 (0)	3/ 47 (6.4)	12/376 (3.2)

Source: Safety Report, Table 3-4, page 17/51

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

Sponsor's Categorical Analysis of Monotherapy Therapy Study

	Study X2101	Study XUS03	Study X1101	Pooled monotherapy
	RIBO	RIBO	RIBO	RIBO
	N=68	N=106	N=13	N=187
	n/m (%)	n/m (%)	n/m (%)	n/m (%)
QTcF (ms) (n)				
New >450	32/ 67 (47.8)	41/105 (39.0)	8/ 12 (66.7)	81/184 (44.0)
New >480	8/ 68 (11.8)	5/106 (4.7)	3/ 13 (23.1)	16/187 (8.6)
New >500	1/ 68 (1.5)	3/106 (2.8)	2/ 13 (15.4)	6/187 (3.2)
Increase from baseline >30	42/ 68 (61.8)	49/106 (46.2)	10/ 13 (76.9)	101/187 (54.0)
Increase from baseline >60	10/ 68 (14.7)	7/106 (6.6)	3/ 13 (23.1)	20/187 (10.7)
Heart rate (bpm)				
Increase from baseline >25% to a value >100	8/ 68 (11.8)	7/106 (6.6)	1/ 13 (7.7)	16/187 (8.6)
Decrease from baseline >25% to a value <50	2/ 68 (2.9)	0/106 (0.0)	0/ 13 (0.0)	2/187 (1.1)
QRS (ms)				
Increase from baseline >25% to a value >110	0/ 68 (0.0)	1/106 (0.9)	0/ 13 (0.0)	1/187 (0.5)

N: Total number of patients in the treatment group in this analysis set.

n: Number of patients who meet the designated criterion.

m: Number of patients at risk for a specific category. For new abnormality post-baseline values, this is the number of patients with both baseline and post-baseline evaluations, and baseline not meeting the criteria. For abnormal change from baseline, it is the number of patients with both baseline and post-baseline evaluations.

All scheduled and unscheduled visits are included in this output.

RIBO=ribociclib

Source: Safety Report, Table 3-5, page 19/51

4.1.7.3 Safety Analysis

The overall safety evaluation of ribociclib presented in this report is based on data from the Safety set in 381 patients from the combination therapy studies with ribociclib 600 mg plus letrozole 2.5 mg (Study A2301 and Study X2107) and 187 patients from the monotherapy studies (Study X2101, Study XUS03, and Study X1101).

In Study A2301, QTc prolongation grouped events were more frequently reported in the ribociclib plus letrozole arm compared with the placebo plus letrozole arm (7.5% vs. 2.4%), with

more grade 3/4 events reported in the patients treated with ribociclib plus letrozole arm (2.4% vs. 0.6%, respectively). Dose interruptions/adjustments were required for only 0.9% of ribociclib plus letrozole arm. Discontinuation of treatment with ribociclib plus letrozole due to QTc interval prolongation events occurred in just one patient (0.3%).

The most frequent AEs reported in ribociclib plus letrozole arm compared to placebo plus letrozole arm were electrocardiogram QT prolonged (4.5% vs 1.2%), and syncope (2.7% vs 0.9%). None of the patients had ECGs at the same time or day as the syncopal event.

Ventricular tachycardia was reported as an adverse event in 1 patient on ribociclib combination. Re-assessment of the ECGs by the independent ECG core laboratory showed sinus tachycardia, not ventricular tachycardia. The patient had grade 3 anorexia, which led to permanent discontinuation of ribociclib combination.

One patient (A2301-4102-002) died while on treatment with ribociclib 600 mg and letrozole 2.5 mg with no apparent symptoms suggesting the cause of death. Sudden death was assessed by the Investigator as suspected to be related to the study drug. This 53-year-old, obese (BMI=30.9 kg/sqm) female had no medical or family history of QT interval prolongation or arrhythmia. The patient took methadone, a prohibited medication with a known risk for QT interval prolongation, prior to and during the first cycle of study treatment. Methadone was stopped three weeks before the death occurred. The ECGs prior to the start of study treatment were abnormal with flat T-waves and premature ventricular complexes (PVCs). QTcF was measured and reported to be 413-447 ms. ECG at Cycle 1 Day 15 showed flat T waves and QTcF values of 443-487 ms. At the last visit, on Cycle 2 Day 1, (i.e. 10 days before the patient died), the patient had grade 2 QTc interval prolongation on the ECGs and grade 2 hypokalemia (3.1 mEq/L) based on local laboratory data (central data showed grade 3 hypokalemia). The average of triplicate QTcF was determined as 483 ms pre-dose and 475 ms approximately 6.5 hours post-dose.

In Study X2107, 'QTc interval prolongation' events occurred in two patients (4.3%) treated with ribociclib plus letrozole (Table 3-6). 'QTc interval prolongation' events determined by the Investigators to be related to ribociclib combination were reported in 1 patient (2.1%). No grade 3/4, serious adverse events (SAEs), AEs, dose leading to adjustments/interruptions, or discontinuations from ribociclib plus letrozole treatment occurred in the study.

In the monotherapy pool, 'QTc interval prolongation' events were reported in 33 patients (17.6%). Discontinuation of therapy with ribociclib due to 'QTc interval prolongation' occurred in only in 1 patient (0.5%).

Sponsor's Table of Clinical Impact of QTc Interval Prolongation Events— Combination Therapy

	Study A2301		Study X2107	Pooled combination therapy
	RIBO+LET	PBO+LET	RIBO+LET	RIBO+LET
	N=334	N=330	N=47	N=381
QT interval prolongation AEs	n (%)	n (%)	n (%)	n (%)
All grades	25 (7.5)	8 (2.4)	2 (4.3)	27 (7.1)
Grade 3	7 (2.1)	2 (0.6)	0	7 (1.8)
Grade 4	1 (0.3)	0	0	1 (0.3)
All AEs	25 (7.5)	8 (2.4)	2 (4.3)	27 (7.1)
Electrocardiogram QT prolonged	15 (4.5)	4 (1.2)	2 (4.3)	17 (4.5)
Syncope	9 (2.7)	3 (0.9)	0	9 (2.4)
Loss of consciousness	1 (0.3)	0	0	1 (0.3)
Sudden death	1 (0.3)	0	0	1 (0.3)
Ventricular tachycardia	1 (0.3)	0	0	1 (0.3)
Cardiac arrest	0	1 (0.3)	0	0
CTC grade 3/4	8 (2.4)	2 (0.6)	0	8 (2.1)
Syncope	6 (1.8)	2 (0.6)	0	6 (1.6)
Electrocardiogram QT prolonged	1 (0.3)	0	0	1 (0.3)
Loss of consciousness	1 (0.3)	0	0	1 (0.3)
Sudden death	1 (0.3)	0	0	1 (0.3)
Suspected AEs	17 (5.1)	3 (0.9)	1 (2.1)	18 (4.7)
Electrocardiogram QT prolonged	14 (4.2)	3 (0.9)	1 (2.1)	15 (3.9)
Syncope	3 (0.9)	0	0	3 (0.8)
Sudden death	1 (0.3)	0	0	1 (0.3)
SAEs	4 (1.2)	0	0	4 (1.0)
Syncope	3 (0.9)	0	0	3 (0.8)
Sudden death	1 (0.3)	0	0	1 (0.3)
AEs leading to discontinuation	1 (0.3)	0	0	1 (0.3)
Sudden death	1 (0.3)	0	0	1 (0.3)
AEs needing dose adjustment or interruption	3 (0.9)	0	0	3 (0.8)
Electrocardiogram QT prolonged	2 (0.6)	0	0	2 (0.5)
Syncope	1 (0.3)	0	0	1 (0.3)

Let=letrozole; PBO=placebo; RIBO=ribociclib
Source: [SCS-Appendix 1-Table 3-18a](#)

Source: Safety Report, Table 3-4, page 17/51

4.1.7.4 Clinical Pharmacology

4.1.7.4.1 Pharmacokinetic Analysis

The PK results are presented in Table 3, Table 4 and Figure 1. Ribociclib exhibited slightly over-proportional increases in exposure (C_{max} and AUC) across the dose range tested (50 to 1200mg). Steady-state was generally reached by Day 8 and the steady-state *geometric mean* C_{max} of therapeutic dose 600mg QD is 1820 ng/ml.

Table 3: Summary of Ribociclib PK Parameters across Studies with Cancer Patients after Single Dose

Dose		Cmax (ng/mL)	Tmax (h)	AUC0-24h (hr•ng/mL)
Study				
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: Clinical Pharmacology Report NDA209092, Page 31

Table 4: Summary of Ribociclib PK Parameters across Studies with Cancer Patients 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
[Study X2107]	Multiple doses (C1 D21)	1820 (62.4)	2.40 (0.683, 7.82)	23800 (66.0)	2.51 (45.6)	32.0 (63.2)	25.5 (65.7)
		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)

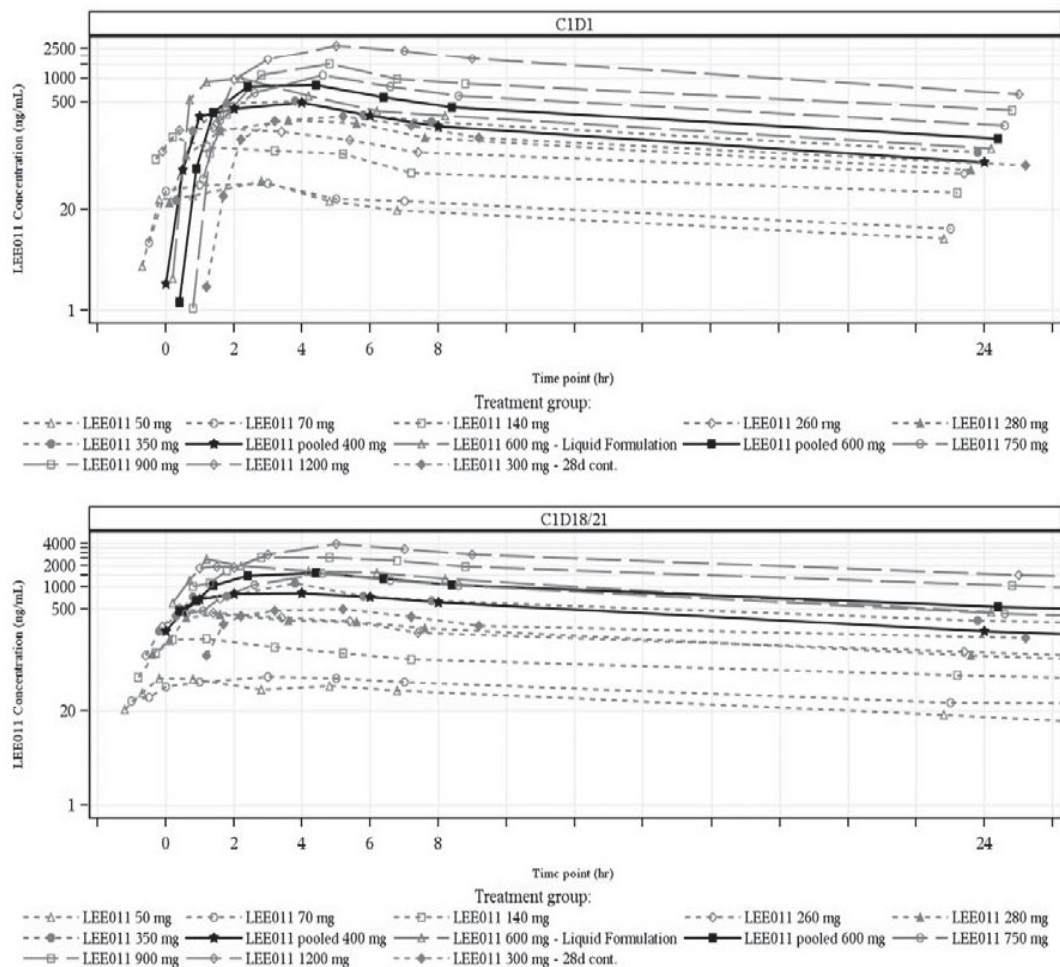
C: cycle; D: day; DiC: drug-in-capsule; n: number of patients with cancer with corresponding evaluable PK parameters; PK: pharmacokinetics.

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

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: Clinical Pharmacology Report NDA209092, Page 33

Figure 1: Geometric Mean Plasma Concentration-Time Profiles of Ribociclib after a Single (Day 1) and Repetitive (Day 18/21) Oral Daily Dose of Ribociclib by Treatment

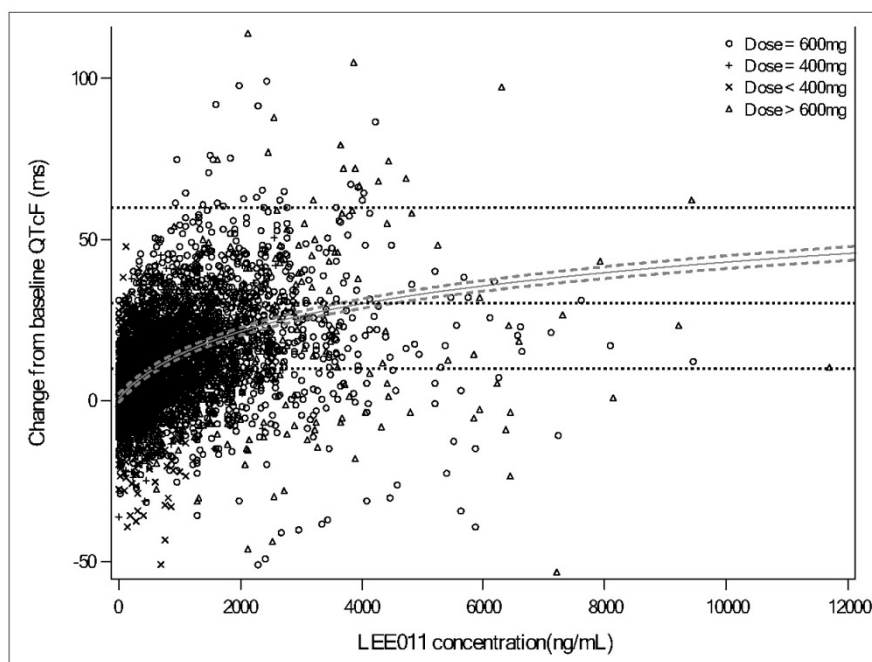


Source: Clinical study report for LEE011X2101, Page 97

4.1.7.4.2 Exposure-Response Analysis

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 4 clinical studies. The distribution of baseline QTcF in patients was comparable across four studies conducted in patients. A log-linear mixed effect model identified concentration-dependent increases in change from baseline QTcF (Δ QTcF). The estimated mean Δ QTcF 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.

Figure 2: 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 5: Summary of Estimated Ribociclib QTc Effect at Steady State C_{max} of Different Dose Groups in Cancer Patients

Dose group	Concentration level*	Concentration (ng/mL)	Estimated mean QTcF change from baseline (ms)	90% CI (ms)
400 mg	Mean C _{max}	1443.2	17.99	(16.8,19.2)
	25% quantile of C _{max}	848	12.97	(11.8,14.1)
	Median of C _{max}	1500	18.39	(17.2,19.6)
	75% quantile of C _{max}	1820	20.49	(19.3,21.7)
600 mg	Mean C _{max}	2236.5	22.87	(21.6,24.1)
	25% quantile of C _{max}	1300	16.92	(15.8,18.1)
	Median of C _{max}	1850	20.68	(19.5,21.9)
	75% quantile of C _{max}	2860	25.86	(24.5,27.2)
900 mg	Mean C _{max}	3460	28.29	(26.9,29.7)
	25% quantile of C _{max}	2000	21.56	(20.3,22.8)
	Median of C _{max}	2930	26.16	(24.8,27.5)
	75% quantile of C _{max}	3860	29.72	(28.3,31.2)

Median concentration=734.5 ng/mL Median baseline QTcF=412.67 ms

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

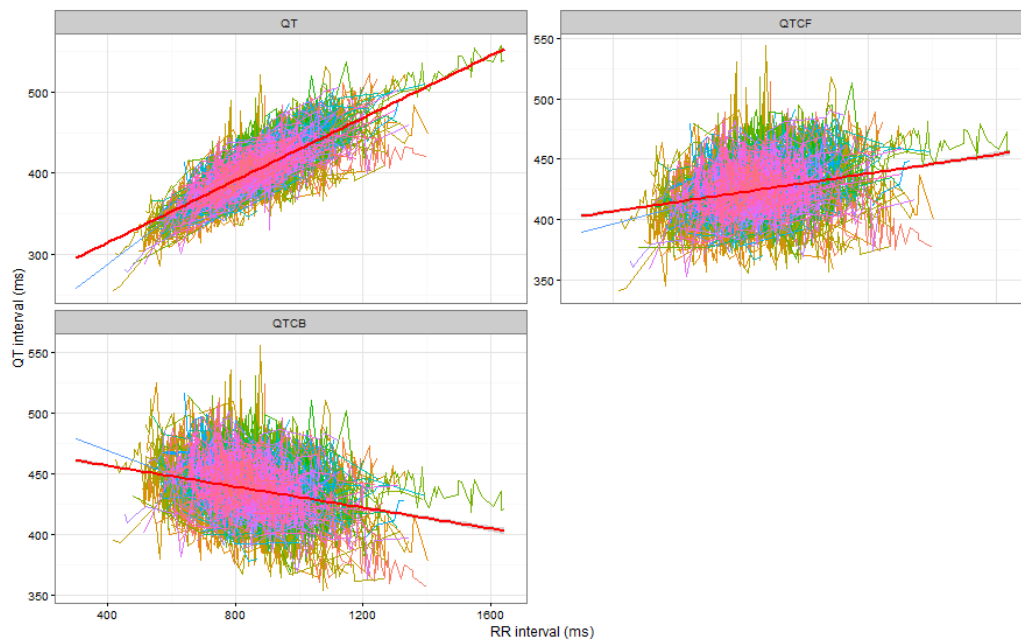
Reviewer's comments: Independent analyses for the relationship between $\Delta QTcF$ and ribociclib concentrations were conducted by the reviewer (Figure 5). Consistent with the sponsor's results,

the relationship between $\Delta QTcF$ and ribociclib concentrations can be well described with a log-linear mixed effect model with a significant slope ($p < 0.0001$).

5 REVIEWERS' ASSESSMENT

This review did not evaluate of the QT/RR correction method because the sponsor provided only QTcB and QTcF correction intervals. QTcF was used in the primary statistical analysis. The relationship between different correction methods and RR is presented in Figure 3.

Figure 3: QT, QTcB and QTcF vs. RR (Each Subject's Data Points are Connected with a Line)



5.1 STATISTICAL ASSESSMENTS

The submitted pooled analysis dataset contains clinical studies in 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).

5.1.1 QTc Analysis

5.1.1.1 The Central Tendency Analysis for Ribociclib (LEE011)

The primary endpoint is change from baseline in QTcF. The analysis results are listed in Table 6 and Table 7 for combination therapy study, and Table 8 and Table 9 for monotherapy study. The largest upper bounds of the 2-sided 90% CI for the mean differences Ribociclib 600 mg with or without Letrozole 2.5 mg are over 20 ms.

Table 6: Analysis Results of Δ QTcF with Largest Upper Bound for Ribociclib 600 mg plus Letrozole 2.5 mg by Dose Level (Combination Therapy Study)

Treatment	Cycle/Day	Mean	Std Dev	90% CI for Mean
[A2301] Placebo + Letrozole 2.5 mg	C7D1	6.9	16.1	(1.0, 12.8)
[A2301] Ribociclib 600 mg + Letrozole 2.5 mg	C1D15	19.6	16.4	(18.0, 21.2)
[A2107] Ribociclib 600 mg + Letrozole 2.5 mg	C1D21	24.6	21.3	(18.9, 30.3)

Table 7: Analysis Results of Δ QTcF by Treatment, Visit and Time (Combination Therapy Study)

Doses	Cycle/Day	Time	N	Mean	Std Dev	90% CI for Mean
[A2301] Placebo + Letrozole 2.5 mg	C1D15	0 hours pre dose	313	1.7	12.5	(0.5, 2.8)
		2 hours post dose	307	1.8	12.4	(0.7, 3.0)
	C2D1	0 hours pre dose	319	2.7	13.1	(1.4, 3.9)
		2 hours post dose	297	3.2	13.2	(2.0, 4.5)
	C3D1	0 hours pre dose	295	2.9	13.9	(1.5, 4.2)
	C7D1	0 hours pre dose	22	6.9	16.1	(1.0, 12.8)
	C8D1	0 hours pre dose	37	4.9	11.9	(1.6, 8.2)
	C9D1	0 hours pre dose	54	6.7	13.4	(3.6, 9.7)
[A2301] Ribociclib 600mg + Letrozole 2.5 mg	C1D15	0 hours pre dose	308	13.5	14.7	(12.1, 14.9)
		2 hours post dose	277	19.6	16.4	(18.0, 21.2)
	C2D1	0 hours pre dose	312	5.1	14.8	(3.7, 6.5)
		2 hours post dose	264	11.8	14.7	(10.3, 13.3)
	C3D1	0 hours pre dose	302	6.1	15.3	(4.7, 7.6)
	C6D1	0 hours pre dose	11	4.9	16.1	(-3.9, 13.7)
	C7D1	0 hours pre dose	23	9.4	9.6	(5.9, 12.8)
	C8D1	0 hours pre dose	42	8.9	13.7	(5.3, 12.4)
	C9D1	0 hours pre dose	53	5.7	14.8	(2.3, 9.1)
		2 hours post dose	41	11.6	15.0	(7.7, 15.6)

Doses	Cycle/Day	Time	N	Mean	Std Dev	90% CI for Mean
[X2107] Ribociclib 600mg + Letrozole 2.5 mg	C1D1	2 hours post dose	46	5.9	10.7	(3.3, 8.6)
		4 hours post dose	46	12.3	11.8	(9.4, 15.3)
	C1D8	0 hours pre dose	46	10.6	12.8	(7.4, 13.7)
		4 hours post dose	46	19.3	15.4	(15.5, 23.1)
	C1D15	0 hours pre dose	46	11.5	16.7	(7.4, 15.6)
		2 hours post dose	42	23.0	14.9	(19.1, 26.9)
		4 hours post dose	42	21.5	16.8	(17.1, 25.9)
		8 hours post dose	43	20.3	14.8	(16.5, 24.1)
	C1D21	0 hours pre dose	43	14.3	12.4	(11.1, 17.5)
		2 hours post dose	39	21.7	15.2	(17.6, 25.8)
		4 hours post dose	40	24.6	21.3	(18.9, 30.3)

Table 8: Analysis Results of $\Delta Q T c F$ with Largest Upper Bound for Ribociclib 600 mg (Monotherapy Study)

Study Treatment	Cycle/Day	Mean	Std Dev	90% CI for Mean
[X1101] Ribociclib 600 mg	C1D15	25.0	14.6	(17.4, 32.6)
[X2101] Ribociclib 600 mg	C1D15	27.3	21.0	(21.8, 32.7)

Table 9: Analysis Results of $\Delta Q T c F$ for Ribociclib 600 mg by Treatment, Visit and Time (Monotherapy Study)

Doses	Cycle/Day	Time	N	Mean	Std Dev	90% CI for Mean
X1101_RIBO600	C1D1	1 hours post dose	13	-2.1	7.7	(-5.9, 1.7)
		2 hours post dose	13	5.3	7.4	(1.6, 8.9)
		4 hours post dose	13	11.2	9.1	(6.7, 15.7)
		6 hours post dose	13	9.0	5.4	(6.3, 11.7)
		8 hours post dose	13	8.9	10.4	(3.8, 14.1)
	C1D8	0 hours pre dose	13	2.4	8.1	(-1.6, 6.4)
		1 hours post dose	13	8.7	13.0	(2.3, 15.2)
		2 hours post dose	13	17.9	13.0	(11.4, 24.3)
		4 hours post dose	13	24.3	11.4	(18.7, 30.0)
	C1D15	0 hours pre dose	13	11.6	19.2	(2.1, 21.1)
		1 hours post dose	12	6.2	13.4	(-0.8, 13.1)
		2 hours post dose	12	15.2	17.9	(6.0, 24.5)
		4 hours post dose	12	25.0	14.6	(17.4, 32.6)
X2101_RIBO600	C1D1	1 hours post dose	67	5.9	10.6	(3.8, 8.1)
		2 hours post dose	67	10.0	11.4	(7.7, 12.3)
		4 hours post dose	65	7.4	11.6	(5.0, 9.8)
		6 hours post dose	67	7.2	13.5	(4.5, 10.0)
		8 hours post dose	66	7.3	12.6	(4.7, 9.9)
	C1D8	0 hours pre dose	66	11.4	16.6	(8.0, 14.9)
		1 hours post dose	61	17.0	18.3	(13.1, 20.9)
		2 hours post dose	63	20.6	19.6	(16.5, 24.7)
		4 hours post dose	65	20.5	18.5	(16.7, 24.4)
	C1D15	6 hours post dose	44	20.0	18.5	(15.3, 24.7)
		0 hours pre dose	64	11.2	14.4	(8.2, 14.2)
		1 hours post dose	60	18.6	18.8	(14.6, 22.7)
		2 hours post dose	61	22.9	18.0	(19.1, 26.8)
	C1D21	4 hours post dose	62	21.5	23.1	(16.6, 26.4)
		6 hours post dose	42	27.3	21.0	(21.8, 32.7)
		0 hours pre dose	56	11.8	12.1	(9.1, 14.5)
		1 hours post dose	49	18.6	14.4	(15.1, 22.0)
		2 hours post dose	49	21.8	15.2	(18.2, 25.4)
		4 hours post dose	49	22.2	17.3	(18.0, 26.3)

Doses	Cycle/Day	Time	N	Mean	Std Dev	90% CI for Mean
		6 hours post dose	48	18.3	18.1	(13.9, 22.6)
		8 hours post dose	49	18.1	14.3	(14.7, 21.5)

5.1.1.2 Assay Sensitivity Analysis

Not applicable.

5.1.1.3 Categorical Analysis

Table 10 and Table 11 lists the number of subjects whose QTcF values are ≤ 450 ms, between 450 ms and 480 ms, between 480 ms and 500 ms, and >500 ms. One subjects' QTcF are above 500 ms from combination therapy or monotherapy studies.

**Table 10: Categorical Analysis for QTcF
(Combination Therapy Studies)**

Doses	Total N	Value $\leq$ 450 ms	450 ms<Value $\leq$ 480 ms	480 ms<Value $\leq$ 500 ms	Value $>$ 500
[A2301] Placebo + Letrozole 2.5 mg	322	309 (96.0%)	13 (4.0%)	0 (0.0%)	0 (0.0%)
[A2301] Ribociclib 600mg + Letrozole 2.5 mg	311	236 (75.9%)	69 (22.2%)	5 (1.6%)	1 (0.3%)
[X2107] Ribociclib 600mg + Letrozole 2.5 mg Escalation + Expansion	47	24 (51.1%)	20 (42.6%)	3 (6.4%)	0 (0.0%)

**Table 11: Categorical Analysis for QTcF
(Monotherapy Study)**

Treatment Group	Total N	Value $\leq$ 450 ms	450 ms<Value $\leq$ 480 ms	480 ms<Value $\leq$ 500 ms	Value $>$ 500
X1101_RIBO600	13	4 (30.8%)	6 (46.2%)	3 (23.1%)	0 (0.0%)
X2101_RIBO600	68	35 (51.5%)	26 (38.2%)	6 (8.8%)	1 (1.5%)

Table 12 and Table 13 list the categorical analysis results for Δ QTcF. One subject change from baseline is above 90 ms from monotherapy study.

**Table 12: Categorical Analysis of Δ QTcF
(Combination Therapy Studies)**

	Total N	Value $\leq$ 30 ms	30 ms<Value $\leq$ 60 ms	60 ms<Value $\leq$ 90 ms	Value>90 ms
[A2301] Placebo + Letrozole 2.5 mg	322	316 (98.1%)	6 (1.9%)	0 (0.0%)	0 (0.0%)
[A2301] Ribociclib 600mg + Letrozole 2.5 mg	311	236 (75.9%)	71 (22.8%)	4 (1.3%)	0 (0.0%)
[X2107] Ribociclib 600mg + Letrozole 2.5 mg Escalation + Expansion	47	17 (36.2%)	27 (57.4%)	3 (6.4%)	0 (0.0%)

**Table 13: Categorical Analysis of Δ QTcF
(Monotherapy Study)**

Treatment Group	Total N	Value $\leq$ 30 ms	30 ms<Value $\leq$ 60 ms	60 ms<Value $\leq$ 90 ms	Value>90 ms
X1101_RIBO600	13	3 (23.1%)	8 (61.5%)	2 (15.4%)	0 (0.0%)
X2101_RIBO600	68	27 (39.7%)	33 (48.5%)	7 (10.3%)	1 (1.5%)

5.1.2 HR Analysis

The change from baseline in HR was evaluated using similar methods as described for QTc section 5.1.1. No effect of ribociclib on HR interval was detected.

5.1.3 PR Analysis

The change from baseline in PR was evaluated using similar methods as described for QTc section 5.1.1. No effect of ribociclib on PR interval was detected.

5.1.4 QRS Analysis

The change from baseline in QRS was evaluated using similar methods as described for QTc section 5.1.1. No effect of ribociclib on QRS interval was detected.

5.2 CLINICAL PHARMACOLOGY ASSESSMENTS

The mean concentration-time profile of ribociclib is illustrated in Figure 1.

The relationship between Δ QTc and ribociclib was investigated by a log-linear mixed-effects model with QTcF change from baseline (Δ QTcF) as the dependent variable and log transformed concentrations as the predictor (Figure 4). The final C-QTc model was a log-linear model with random effect on the intercept and slope, an effect of baseline QTcF, Study and time of data collection on the intercept. Including study and time of data collection as categorical factors in the final model and random effect on the slope was able to fit data better (Δ AIC= -399)

compared to the model proposed by the sponsor. Summary of results of the final ribociclib concentration-ΔQTcF analysis is shown in Table 14.

According to the final model, a significant relationship between ΔQTcF and ribociclib concentrations was observed ($p < 0.0001$) and the mean (90% CI) ΔQTcF at mean steady-state C_{max} of 2236.5 ng/ml following therapeutic dosing regimen 600 mg QD is estimated to be 22.64 (20.19, 25.09) ms. At the mean steady-state C_{max} of 3460 ng/ml with the suprathreshold dosing regimen of 900mg QD, the mean ΔQTcF (90% CI) of 27.75 (24.74, 30.75) ms is estimated. The risks for QT prolongation were also predicted for alternative dosing regimen (300mg BID, 400mg BID and 400mg QD according to the review team's interest). The predicted ΔQTcF at estimated steady-state C_{max} for 300mg BID, 400mg BID and 400mg QD were 15.8, 15.9 and 19.7 ms respectively (Table 15). A relative reduction of 13% to 30% in QT prolongation was predicted compared to 600mg QD.

Table 14: Fixed Effect Estimates and P-values of Final Ribociclib Concentration-ΔQTcF Analysis

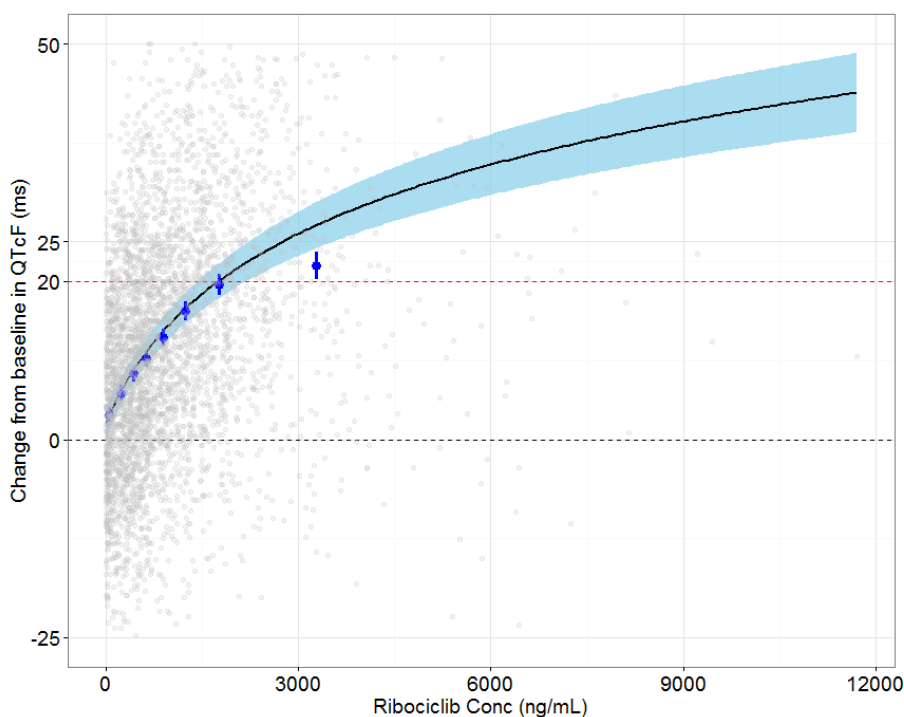
Effect	Estimates (SE)	P-value
Intercept	6.724 (2.202)	0.002337
Log(conc/median conc+1)	15.757 (0.973)	<0.0001
Baseline QTcF-Median baseline QTcF	-0.108 (0.031)	0.000613
Study effect		
X1101	-11.653 (3.011)	0.000124
X2101	-6.655 (2.209)	0.002698
X2107	-3.509 (2.557)	0.170521
Time of data collection		
30 minutes post dose	2.113 (0.922)	0.022069
1 hour post dose	0.459 (0.658)	0.485576
2 hour post dose	1.178 (0.669)	0.078141
4 hour post dose	1.675 (0.662)	0.011463
6 hour post dose	1.385 (0.746)	0.063481
8 hour post dose	2.588 (0.804)	0.001303
24 hour post dose	-2.950 (1.203)	0.014215

Table 15: Summary of Estimated Ribociclib QTc Effect at Steady State C_{max} of Alternative Dose Groups

Dose groups	Steady-state C_{max} (ng/mL)	Estimated mean ΔQTcF (ms)	90% CI (ms)
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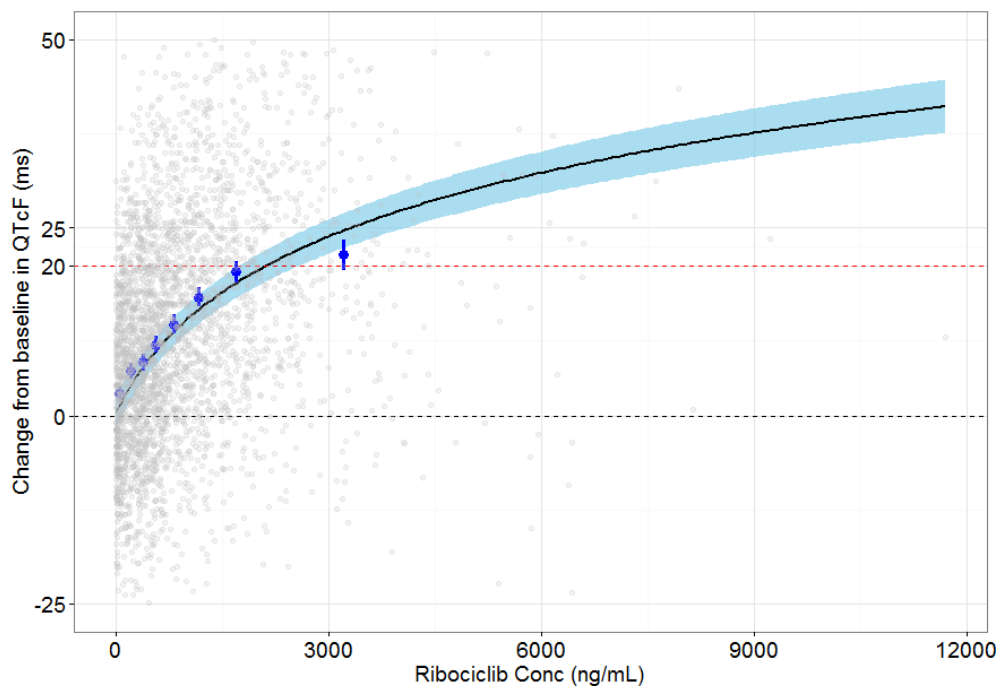
600mg QD	2236.5	22.64	20.19, 25.09
900mg QD	3460	27.75	24.74, 30.75
400mg QD	1141.6	15.84	13.96, 17.73
300mg BID	1150.8	15.91	14.02, 17.80
400mg BID	1703.7	19.72	17.55, 21.90

Figure 4: Δ QTcF vs. Ribociclib Concentration



A separate C-QT analysis was also conducted in study X2101 because it studied a wide range of ribociclib doses from 50 to 1200 mg and consisted of the majority of concentration-QTc data (3224 out of 3848 (83.8%) time-matched C-QT pairs were collected from study X2101). A significant relationship between Δ QTcF and ribociclib concentrations was observed ($p < 0.0001$). The mean (90% CI) Δ QTcF at mean steady-state C_{max} of 2236.5 ng/ml following 600 mg QD is predicted to be 20.56 (18.43, 22.68) ms. At the mean steady-state C_{max} of 3460 ng/ml with the suprathreshold dosing regimen of 900mg QD, the mean Δ QTcF (90% CI) of 25.52 (23.13, 27.90) ms is estimated (Figure 5).

Figure 5: Δ QTcF vs. Ribociclib Concentration in Study X2101



5.3 CLINICAL ASSESSMENTS

5.3.1 Safety assessments

Ribociclib prolong the mean QTc interval by >20 ms at therapeutic exposures and has substantial increased likelihood of being proarrhythmic. Sponsor's summary of AEs related to QTc interval prolongation is described in section 4.1.7.3. There was an imbalance of AEs related to QTc prolongation such as syncope, ventricular tachycardia and 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.

5.3.2 ECG assessments

Overall ECG acquisition and interpretation in 4 studies submitted (A2301, X1101, X2101, and X2107) appears acceptable.

5.3.3 Other ECG Interval

No clinical relevant effect on heart rate, PR or QRS intervals.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose and exposure* *All values are geometric mean (CV% geometric mean) from Study [X2101] [SCP-Table 2-3, Table 2-5]	Maximum proposed clinical dosing regimen: 600 mg QD, 3 weeks on/1 week off Single maximum proposed clinical dose: C_{max} (n=73): 992 ng/mL (64.4% CV) AUC_{0-24h} (n=68): 9700 hr*ng/mL (62.0% CV) Steady-state for maximum proposed clinical dosing regimen: C_{max} (n=57): 1820 ng/mL (62.4% CV) AUC_{0-24h} (n=54): 23800 hr*ng/mL (66.0% CV)	
Maximum tolerated dose (MTD)	900 mg QD, 3 weeks on/1 week off (n=13)	
Principal adverse events Source: [X2101 CSR]	In the first-in-human Phase I dose escalation study, 126 patients were treated in the dose determining set using an intermittent dosing schedule with increasing doses of ribociclib, taken orally (118 patients treated at doses between 50 and 1200 mg), or as a liquid formulation (8 patients at 600 mg), once daily on Days 1-21 in a 28-day cycle. Fourteen patients (11.1%) experienced at least one DLT during the first 28 days of treatment. DLTs in order of frequency: • Thrombocytopenia (n=4, 3.2%: 1 at 600mg; 3 at doses higher than 600 mg) • Neutropenia (n=3, 2.4%: 1 at 400 mg, 2 at 600 mg) • Febrile neutropenia (n=2; 1.6%: 1 at 600 mg and 1 at doses higher than 600 mg) • Electrocardiogram QT prolonged (n=2, 1.6%: 1 at 600 mg and 1 at doses higher than 600 mg). All other DLTs (platelet count decreased, stomatitis, herpes simplex, and pulmonary embolism) occurred in one patient each, with an incidence of 0.8%). All occurred at doses lower than 600 mg except the platelet count decreased event that occurred at 600 mg [X2101 CSR section 12.2.1] and [Table 12-3]. Among the 68 patients who received ribociclib 600 mg (3 weeks on/1 week off), the most frequently reported AEs (occurring in ≥ 30% patients) regardless of study treatment relationship were (all grades, Grade 3/4): • Nausea (54.4%, 4.4%) • Vomiting (39.7%, 2.9%) • Fatigue (39.7%, 0%) • Diarrhea (35.3%, 2.9%) • White blood cell count decreased (33.8%, 13.2%) • Neutropenia (32.4%, 23.5%)	
Maximum dose tested [Study X2101]	Single Dose	1200 mg QD, 3 weeks on/1 week off
	Multiple Dose	1200 mg QD, 3 weeks on/1 week off

Exposures* Achieved at Maximum Tested Dose [Study X2101- Table 14.2-2.1] *All values are geometric mean (CV% geometric mean); limited exposure data were available at maximum tested dose (1200 mg), exposure data at MTD (900 mg) is also provided.	Single Dose	1200 mg QD, 3 weeks on/1 week off Cmax (n=3): 2730 ng/mL (38.8% CV) AUC0-24h (n=2): 30700 hr*ng/mL (31.7% CV) 900 mg QD, 3 weeks on/1 week off Cmax (n=12): 1600 ng/mL (62.8% CV) AUC0-24h (n=12): 18200 hr*ng/mL (54.7% CV)
	Multiple Dose	1200 mg QD, 3 weeks on/1 week off Cmax (n=1): 3240 ng/mL AUC0-24h (n=1): 51800 hr*ng/mL 900 mg QD, 3 weeks on/1 week off Cmax (n=11): 3090 ng/mL (49.9% CV) AUC0-24h (n=9): 44600 hr*ng/mL (64.4% CV)
Range of linear PK [Study X2101-Table 14.2-2.8a]	Single dose: Slightly greater than dose-proportional increase in Cmax and AUC at doses ranging from 50-1200 mg (slope: 1.19 and 1.26, respectively) Multiple dose: Slightly greater than dose-proportional increase in Cmax and AUC after repeat daily doses ranging from 50-1200 mg (slope: 1.37 and 1.42, respectively)	
Accumulation at steady state [SCP-Table 2-5]	600 mg QD, 3 weeks on/1 week off: 2.51 (45.6% CV)	

Metabolites [SCP-Section 3.7]	LEQ803 (N-demethylation), CCI284 (N-hydroxylation), M1 (secondary glucuronide), each representing ≤10% of total radioactivity. Clinical activity (pharmacological and safety) primarily due to parent compound, with negligible contribution from metabolites • LEQ803 and CCI284 were approximately 5-fold (IC50: 0.24 μM) and 20-fold (IC50: 1.137 μM) less potent, respectively, compared to ribociclib (IC50: 0.053 μM) for G1 arrest of cellular activity. • LEQ803 had hERG channel activity (IC50 values ranged from 4.5 μM and 15.8 μM depending on the assay), however the concentrations observed clinically for LEQ803 (Cmax at 600 mg: 116 ng/mL or 0.3 μM) were >15-fold lower than the lowest IC50 value measured.	
Absorption	Absolute/Relative Bioavailability [SCP-Section 3.5]	Moderate absorption (~60% based on human ADME at 600 mg); absolute oral bioavailability is not known in humans
	Tmax [SCP-Table 2-3, Table 2-4, Table 2-5, Table 2-6]	• Median (range) for parent: 2.08 h (0.917-7.95 h) after single dose (n=73); 2.40 h (0.683-7.82 h) after multiple doses (n=57) • Median (range) for metabolite LEQ803: 3.83 h (1.00-8.00 h) after single dose (n=73); 4.00 (0.683-8.03 h) after multiple doses (n=58)

Distribution	Vd/F [SCP-Section 3.6]	1090 L based on population PK estimation of V1=239.492L (RSE% 7.98) and V2=850.144 (RSE%
	% bound [DMPK R0800276]	Mean bound: 70.3% Mean (SD) unbound: 29.7% (1.7%)
Elimination	Route [SCP-Section 3.8]	- Primary route: hepatic metabolism, mainly via CYP3A4 69.1% of dose excreted in feces; 22.6% of dose excreted in urine
	Terminal t _{1/2} * [SCP-Table 2-5, Table 2-6] *Effective t _{1/2} in patients based on drug accumulation	- Parent: 32.0 h (63.2% CV) - Metabolite LEQ803: 31.4 h (64.3% CV)
	CL/F [SCP-Table 2-5]	25.5 L/h (65.7% CV)
Intrinsic Factors	Age* [SCP-Section 3.9.5] *Based on simulations using full population PK model	No statistically significant effect 75 years old (approximately 95th percentile in the analysis dataset) vs. 60 years old (reference): - C_{max,ss}: 1.06 - AUC_{ss}: 1.11 40 years old (approximately 5th percentile in the analysis dataset) vs. 60 years old (reference): - C_{max,ss}: 0.91 - AUC_{ss}: 0.83
	Sex* [SCP-Section 3.9.2] *Based on simulations using full population PK model	No statistically significant effect Male vs. female (reference) - C_{max,ss}: 0.98 - AUC_{ss}: 0.96
	Race* [SCP-Section 3.9.4] *Based on simulations using full population PK model	Minor effect on CL/F, but not considered clinically relevant for dose adjustment; limited number of Asian patients in analysis (n=23) Asian vs Caucasian (reference) - C_{max,ss}: 1.08 - AUC_{ss}: 1.15 Others/unknown vs Caucasian (reference) - C_{max,ss}: 1.00 - AUC_{ss}: 1.00

	Hepatic* & Renal Impairment** *All values are GMR (90% CI) **Based on simulations using full population PK model; clinical study is ongoing	[Study A2109]: Hepatic impairment [SCP-Section 2.2.3] Mild (n=6) vs normal (n=11) □ LEE011 Cmax: 1.12 (90% CI: 0.756, 1.66) □ LEE011 AUCinf: 1.05 (90% CI: 0.785, 1.42) Moderate (n=6) vs normal (n=11) □ LEE011 Cmax: 1.50 (90% CI: 1.01, 2.22) □ LEE011 AUCinf: 1.32 (90% CI: 0.982, 1.77) Severe (n=5) vs normal (n=11) □ LEE011 Cmax: 1.34 (90% CI: 0.883, 2.03) □ LEE011 AUCinf: 1.29 (90% CI: 0.945, 1.77) Renal impairment [SCP-Section 3.9.6] eGFR 150 (approximately 95th percentile in the analysis dataset) vs. 90 mL/min/1.73m² (reference): • Cmax,ss: 0.95 • AUCss: 0.91 eGFR 50 (approximately 5th percentile in the analysis dataset) vs. 90 mL/min/1.73m² (reference): • Cmax,ss: 1.06 • AUCss: 1.12
Extrinsic Factors	Drug interactions* [SCP-Section 3.10] *All values are GMR (90% CI)	[Study A2101](Arm 1): DDI with strong CYP3A4 inhibitor (ritonavir) □ LEE011 Cmax: 1.67 (90% CI: 1.52, 1.84) □ LEE011 AUCinf: 3.21 (90% CI: 2.95, 3.49) [Study A2101](Arm 2): DDI with strong CYP3A4 inducer (rifampicin) □ LEE011 Cmax: 0.190 (90% CI: 0.164, 0.219) □ LEE011 AUCinf: 0.107 (90% CI: 0.0945, 0.120) [Study A2106]: DDI study with sensitive CYP3A4 substrate (midazolam) and sensitive CYP1A2 substrate (caffeine), administered as a cocktail Following single dose ribociclib (400 mg): □ Midazolam Cmax: 0.990 (90% CI: 0.927, 1.06) □ Midazolam AUCinf: 1.26 (90% CI: 1.20, 1.34) Following multiple dose ribociclib (400 mg x 8 days): □ Midazolam Cmax: 2.05 (90% CI: 1.88, 2.23) □ Midazolam AUCinf: 3.75 (90% CI: 3.41, 4.11) Following single dose ribociclib (400 mg): □ Caffeine Cmax: 0.912 (90% CI: 0.871, 0.956) □ Caffeine AUCinf: 1.25 (90% CI: 1.18, 1.34) Following multiple dose ribociclib (400 mg x 8 days): □ Caffeine Cmax: 0.897 (90% CI: 0.864, 0.931) □ Caffeine AUCinf: 1.17 (90% CI: 1.10, 1.24)

	Food Effects* [SCP-Section 3.2]	[Study A2111]: Food effect with capsule formulation Fed (high-fat, high-calorie meal) vs fasted:
	*All values are GMR (90% CI)	☐ LEE011 Cmax: 0.775 (90% CI: 0.700, 0.858) ☐ LEE011 AUCinf: 0.994 (90% CI: 0.925, 1.07) [Study A2103](Part 2): Food effect with tablet formulation Fed (high-fat, high-calorie meal) vs fasted: ☐ LEE011 Cmax: 1.00 (90% CI: 0.90, 1.11) ☐ LEE011 AUCinf: 1.06 (90% CI: 1.01, 1.12)
Expected High Clinical Exposure Scenario	- Co-administration with a strong CYP3A4 inhibitor [Study A2101] represents the worst-case scenario where ribociclib Cmax increased 1.67-fold and AUCinf increased 3.21-fold following a single dose of ribociclib. - At the clinically relevant dose (600 mg), the geometric mean Cmax and AUC0-24h at steady-state were 1820 ng/mL and 23800 hr*ng/mL, respectively, and the maximum Cmax and AUC0-24h observed was 6170 ng/mL and 90600 hr*ng/mL, respectively [Study X2101-Table 14.2-2.1]. - Using the worst-case increase observed from Study A2101 and the geometric mean exposures at 600 mg, a 1.67-fold increase in Cmax and a 3.21-fold increase in AUC would result in exposures below the maximum exposures observed at 600 mg. - In addition, at the MTD (900 mg), the maximum Cmax and AUC0-24h observed were 7930 ng/mL and 135000 hr*ng/mL, respectively, providing an additional safety margin in the scenario of co-administration of a strong CYP3A4 inhibitor. - Concomitant use of ribociclib should be avoided with strong CYP3A4 inhibitors. If co-administration of ribociclib with a strong CYP3A4 inhibitor cannot be avoided, a dose (b) (4) [SCP-Section 3.10.1.1.1].	
Preclinical Cardiac Safety Source: [nonclinical-overview]	<u>In Vitro</u> <u>Ribociclib:</u> - hERG channel activity: IC50 values ranged from 5.5 to 53 µM, depending on the assay. - Nav1.5 patch clamp assay: IC50 = 24 µM. - Ribociclib had no effect on hERG trafficking. <u>LEQ803</u> (metabolite of ribociclib representing between 6 to 10 % of parent drug in dogs): - hERG channel activity: IC50 values ranged from 4.5 µM to 15.8 µM depending on the assay. - LEQ803 had no effect on hERG trafficking.	

	<u>In Vivo</u> <u>Ribociclib</u> Dog (GLP) telemetry study: • Ribociclib caused dose-dependent prolongation of QTc intervals when compared to vehicle. • Mean changes of QTc interval at ribociclib doses of 20, 50 and 100 mg/kg were +12.1 ms (+5.3 %), +23.4 ms (+10.2 %), and +37.9 ms (+16.5 %), respectively. • No other ECG findings and no effects on heart rate, blood pressure or core body temperature. • The lowest ribociclib Cmax following 20 mg/kg where QTc interval prolongation was observed was 929 ng/mL. At 100 mg/kg, the Cmax range was 2570 to 7250 ng/mL. Dog (non-GLP) non-invasive telemetry study: • A single dose of ribociclib 100 mg/kg produced QTc interval prolongation (up to 31 ms, or 12%) when compared to vehicle. • One dog did exhibit QRS prolongation (up to 13 ms or 33%), heart rate increase and an increase in the incidence of premature ventricular contractions (PVCs) (isolated or bigeminal; total of 45 PVCs/ 24 h period). • The Cmax in the single dog dosed at 100 mg/kg, and in which an increased incidence of PVCs was observed, was 9720 ng/mL; exposure in this dog was 2-fold higher than those observed in the GLP study dosed with 100 mg/kg ribociclib. LEQ803 Dog (non-GLP) non-invasive telemetry study: • LEQ803 prolonged mean QTc intervals (up to 16%) at 5 mg/kg after single oral administration in a non-GLP study. • LEQ803 had no effect on heart rate, RR, PR and QRS intervals of the ECG and no arrhythmias were observed. • At 5 mg/kg, LEQ803 Cmax ranged from 13.4 to 86.6 ng/mL. At 600 mg in patients, for LEQ803, total Cmax at steady-state was 116 ng/mL [SCP-Table 2-6]. <u>Conclusion</u> In vivo cardiac safety studies in dogs demonstrated dose and concentration-related QTc interval prolongation at an exposure that would be expected to be achieved in patients following the recommended dose of 600 mg. There is the potential to induce incidences of PVCs at elevated exposures (~ 5-fold the clinical Cmax). There were no effects on heart rate, blood pressure, core body temperature, or other ECG findings.
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Clinical Cardiac Safety	Clinical cardiac safety assessment of ribociclib (QTc categorical analyses, QTc interval prolongation AEs) is based on the following data: • 381 patients from combination therapy (ribociclib 600 mg plus letrozole 2.5 mg) (studies A2301 and X2107) • 187 patients from the monotherapy studies X2101, XUS03, and X1101. Pooled safety data from monotherapy and combination studies are included in the QT/QTc Safety Analysis Report within the NDA submission and in (Table 2-2) displaying the clinical trials and number of patients at each ribociclib dose level. In accordance with the International Conference on Harmonisation E14 Guidance “Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs” (FDA 2005 Guidance for Industry), cardiac safety events per this Guidance (e.g., QT prolongation, syncope, seizures, ventricular arrhythmias, ventricular tachycardia, ventricular fibrillation, flutter, torsades de pointes, or sudden deaths) have been summarized in the following sections. There were no reported cases of Torsades de Pointes, ventricular fibrillation, ventricular flutter, or seizure in any of the studies. Cases of QT prolongation, syncope, ventricular tachycardia, and sudden death, were reported and are summarized below and as patient narratives in the QT/QTc Safety Analysis Report [QT/QTc Safety Analysis Report, Appendix 4]
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/s/

JIANG LIU
01/03/2017
Youwei is the primary Clinical Pharmacology reviewer.

YOUWEI N BI
01/03/2017

MOH JEE NG
01/04/2017

QIANYU DANG
01/04/2017

MICHAEL Y LI
01/04/2017

CHRISTINE E GARNETT
01/04/2017

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	December 2, 2016
Requesting Office or Division:	Division of Oncology Products 1 (DOP1)
Application Type and Number:	NDA 209092
Product Name and Strength:	Kisqali (ribociclib) film-coated tablets, 200 mg
Product Type:	Single ingredient product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Novartis Pharmaceuticals Corporation
Submission Dates:	August 29, 2016 November 1, 2016 November 4, 2016 November 7, 2016
OSE RCM #:	2016-1971
DMEPA Primary Reviewer:	Tingting Gao, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

Novartis Pharmaceuticals Corporation submitted Kisqali (ribociclib) container labels, carton labeling, and prescribing information (PI) for NDA 209092. The Division of Oncology Products 1 (DOP1) requested that we review the submitted Kisqali container labels, carton labeling, and PI for areas of vulnerability that could lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We evaluated the proposed Kisqali container labels and carton labeling and noted that all packaging configurations are labeled with a prominent “200 mg per tablet” strength statement. This may lead to wrong selection errors because it is not obvious which Kisqali blister pack should be chosen for a patient’s prescribed dose. We recommend revising the container labels and carton labeling to prominently display the daily dose followed by the quantity of tablets required for the dose (e.g., “600 mg daily dose (three 200 mg tablets)”, “400 mg daily dose (two 200 mg tablets)”, and “200 mg daily dose (one 200 mg tablet)”) to prevent wrong selection errors. We also noticed that NDC numbers are presented as placeholders (0000-0000-00). Similarly, to prevent wrong selection errors, we recommend the Applicant to consider using different and non-sequential product code (middle four digits -0000-) for the NDC number to differentiate the different package configurations (“600 mg daily dose”, “400 mg daily dose”, and “200 mg daily dose”), and to ensure that the package code (last two digits -00) of the NDC number is different for including taking into account the blister cards of 21 or 14 tablets and the carton that contains 3 blister packs. Additionally, the dosing instructions on the container label and carton labeling should be improved to ensure patients take the correct number of tablets per day for their intended dose.

We reviewed the proposed PI and noticed the use of “x” in the Dosage and Administration section of the PI, and recommend to revise the statement “600 mg (3 x 200 mg film-coated tablets)” to “600 mg (three 200 mg film-coated tablets)” for clarity and to prevent misinterpretation and confusion. We also noticed that NDC numbers weren’t provided in the How Supplied/Storage and Handling Section of the full PI and recommend Applicant to provide the NDC number information in this section.

We noticed the use of “film-coated tablets” throughout labels and labeling, and we defer to Office of Pharmaceutical Quality (OPQ) for the determination of the appropriate dosage form for the product on labels and labeling.

4 CONCLUSION & RECOMMENDATIONS

The proposed Kisqali container labels (pull out blister cards), carton labeling (blister card sleeves, and carton boxes), and prescribing information may be improved to ensure safe product use. We provide specific recommendations in Section 4.1 and 4.2 below.

4.1 RECOMMENDATIONS FOR THE DIVISION

- A. Prescribing Information (PI)
 - a. Dosage and Administration Section, Highlights of PI and Full PI
 - i. Revise the statement “600 mg (3 x 200 mg film-coated tablets)” to “600 mg (three 200 mg film-coated tablets)” for clarity and to prevent misinterpretation and confusion.
 - b. Dosage and Administration Section, Full PI
 - i. Revise the statement “# x 200 mg tablets” in Table 1 to “Three/Two/One 200 mg tablet(s)” for clarity and to prevent misinterpretation and confusion.
 - c. How Supplied/Storage and Handling, Full PI
 - i. Please provide NDC number for each package configuration.

4.2 RECOMMENDATIONS FOR NOVARTIS

We recommend the following be implemented prior to approval of this NDA:

- A. General recommendation
 - 1. Since the proposed blister packs are intended for unit of dispensing (21 day supply for a complete 28 day cycle), labeling all packaging configurations with a prominent “200 mg per tablet” strength statement may lead to wrong selection errors because it is not obvious which Kisqali blister pack should be chosen for a patient’s prescribed dose. We recommend revising the container labels and carton labeling to prominently display the daily dose followed by the quantity of tablets required for the dose (e.g., “600 mg daily dose (three 200 mg tablets)”, “400 mg daily dose (two 200 mg tablets)”, and “200 mg daily dose (one 200 mg tablet)”) to prevent wrong selection errors.

For example, see the 600 mg daily dose carton labeling below. Please note that the example layout below is just to demonstrate our recommendations above.

Kisqali		NDC 0000-0000-00
(ribociclib)		Rx only
Tablets		600 mg daily dose (three 200 mg tablets)
63 Film-coated tablets	Contents: 3 individual weekly blister packs. Each blister pack contains 21 tablets (200 mg per tablet).	

2. We noticed that the NDC number on the container labels and carton labeling are presented as placeholders (0000-0000-00).
 - i. To prevent wrong selection errors between the daily dose blister packs, consider using different and non-sequential product code (middle four digits -0000-) for the NDC number to differentiate the different package configurations (“600 mg daily dose”, “400 mg daily dose”, and “200 mg daily dose”), and ensure that the package code (last two digits -00) of the NDC number is different for the blister cards of 21 or 14 tablets and the carton that contains 3 blister packs.

B. Container Labels – Pull Out Blister Cards

1. On the front and back panel of each blister card, we recommend adding a statement “**Take # tablets once a day**” in bold and black font to instruct the patients to take the correct number of tablets per day.
2. For the 400 mg and 600 mg daily dose blister cards, relocate the days of the week above the top blister cell row (similar to the 200 mg daily dose blister card). We recommend this change to ensure the patients will understand that they will need to take 2 or 3 tablets for that day.
3. As currently presented on the blister card for the 400 mg daily dose, the two blister cells for each daily dose are spaced apart, and patients may mistake this as to take 1 tablet twice daily instead of 2 tablets once a day. Therefore, consider moving the top blister cell row closer to the bottom blister cell row so that the tablets will be located closer together.
4. For the 200 mg daily dose pull out blister card, as currently presented, the text “Week 1”, “Week 2”, and “Week 3” is hidden in the pouch and not visible when the blister card is pulled out. Consider redesign the label so that the text is visible.

C. Carton Labeling – Blister Card Sleeves

1. Revise the Dosage statement on the principal display panel for “600 mg daily dose”, “400 mg daily dose”, and “200 mg daily dose” from “(b) (4)” to “**Usual Dosage:** Take [three/two/one] 200 mg tablets at the same time once daily, with or without food. Swallow tablets whole. **DO NOT** chew, crush, or split tablets.” Ensure there is adequate white space between this

statement and the storage statement to improve readability and reduce visual clutter.

2. On the back panel, consider bolding the “once a day” in the statement “Take your dose of Kisqali once a day at approximately the same time for three weeks, followed by a one-week break.” This will ensure the patients understand that they need to take 2 or 3 tablets all at once.

D. Carton Labeling – Carton boxes containing 3 weekly blister card sleeves

1. Principal Display Panel
 - i. Remove the statement “(b) (4) ”.
2. Back Panel
 - i. See C.1.
 - ii. Consider grouping the two bulletins related to “Take Kisqali exactly as directed...” and “Use the dose calendar...” with the Usual Dosage statement since this information is related.
 - iii. Revise the statement “Use the dose calendar located on each weekly pack inside to keep track of your treatment.” to “Use the dose calendar located on the back of each weekly pack to keep track of your treatment.”

For example, see the 600 mg daily dose carton labeling below. Please note that the example layout below is just to demonstrate our recommendations above.

Usual Dosage: Take three 200 mg tablets at the same time once daily, with or without food. Swallow tablets whole. **DO NOT** chew, crush, or split tablets.

- Take Kisqali exactly as directed by your prescriber.
- Use the dose calendar located on the back of each weekly pack to keep track of your treatment.

Store at 25°C (77°F); excursion permitted to 15°C to 30°C (59°F to 86°F).

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Kisqali that Novartis Pharmaceuticals Corporation submitted on August 29, 2016 and November 4, 2016.

Table 2. Relevant Product Information for Kisqali															
Initial Approval Date	N/A														
Active Ingredient	ribociclib														
Indication	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.														
Route of Administration	Oral														
Dosage Form	Tablets														
Strength	200 mg														
Dose and Frequency	KISQALI tablets are taken orally with or without food in combination with letrozole. 600 mg (3 x 200 mg film-coated tablets) taken orally, once daily for 21 consecutive days followed by 7 days off treatment resulting in a complete cycle of 28 days. <table><thead><tr><th>Level</th><th>Dose</th><th>Number of Tablets</th></tr></thead><tbody><tr><td>Starting dose</td><td>600 mg/day</td><td>3 × 200 mg tablets</td></tr><tr><td>First dose reduction</td><td>400 mg/day</td><td>2 × 200 mg tablets</td></tr><tr><td>Second dose reduction</td><td>200 mg/day*</td><td>1 × 200 mg tablets</td></tr></tbody></table> *If further dose reduction below 200 mg/day is required, discontinue the treatment.			Level	Dose	Number of Tablets	Starting dose	600 mg/day	3 × 200 mg tablets	First dose reduction	400 mg/day	2 × 200 mg tablets	Second dose reduction	200 mg/day*	1 × 200 mg tablets
Level	Dose	Number of Tablets													
Starting dose	600 mg/day	3 × 200 mg tablets													
First dose reduction	400 mg/day	2 × 200 mg tablets													
Second dose reduction	200 mg/day*	1 × 200 mg tablets													
How Supplied	Blister pack (21 tablets) – each blister pack contains 21 tablets (200 mg per tablet) (b) (4) 600 mg dose) - Outer container - 3 Blister packs per outer container Blister pack (14 tablets) – each blister pack contains 14 tablets (200 mg per tablet) (b) (4) 400 mg dose) - Outer container - 3 Blisters packs per outer container Blister pack (21 tablets) – each blister pack contains 21 tablets (200 mg per tablet) (b) (4) 200 mg dose) - Outer container – 1 Blister pack per outer container														
Storage	Store at 25°C (77°F); excursions permitted between 15°C to 30°C (59°F to 86°F). Store in the original package.														
Container Closure	Ribociclib 200 mg film-coated tablet for primary stability studies were packaged in the followings: (b) (4)														

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/s/

TINGTING N GAO
12/02/2016

CHI-MING TU
12/02/2016

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 209092 BLA#	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Animal Rule Confirmatory Study (SE10)
Proprietary Name: Kisqali® Established/Proper Name: Ribociclib Dosage Form: Tablets Strengths: 200 mg		
Applicant: Novartis Pharmaceuticals Corporation Agent for Applicant (if applicable): N/A		
Date of Application: August 29, 2016 Date of Receipt: August 29, 2016 Date clock started after Unacceptable for Filing (UN): N/A		
PDUFA/BsUFA Goal Date: April 29, 2017		Action Goal Date (if different): April 21, 2017
Filing Date: October 28, 2016		Date of Filing Meeting: September 29, 2016
Chemical Classification (original NDAs only) : ☒ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☐ Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☐ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch ☐ Type 9-New Indication or Claim (will <u>not</u> be marketed as a separate NDA after approval) ☐ Type 10-New Indication or Claim (will be marketed as a separate NDA after approval)		
Proposed indication(s)/Proposed change(s): 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.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2) N/A
<i>If 505(b)(2)NDA/NDA Supplement: Draft the “505(b)(2) Assessment” review found at:</i>		

Type of BLA		☐ 351(a) ☐ 351(k) N/A		
<i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>				
Review Classification: <i>The application will be a priority review if:</i> <i>A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)</i> <i>The product is a Qualified Infectious Disease Product (QIDP)</i> <i>A Tropical Disease Priority Review Voucher was submitted</i> <i>A Pediatric Rare Disease Priority Review Voucher was submitted</i>		☐ Standard ☒ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher		
Resubmission after withdrawal? ☐		Resubmission after refuse to file? ☐		
Part 3 Combination Product? ☐ <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)		
☐ Fast Track Designation ☒ Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:		☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)		
Collaborative Review Division (if OTC product): N/A				
List referenced IND Number(s): IND 117796				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in the electronic archive? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	☒	☐		
Are the established/proper and applicant names correct in electronic archive?	☒	☐		

<i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into electronic archive.</i>					
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm <i>If no, ask the document room staff to make the appropriate entries.</i>		☒	☐	☐	
Application Integrity Policy		YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm		☐	☒		
If yes, explain in comment column.					N/A
If affected by AIP, has OC been notified of the submission? If yes, date notified:		☐	☐		N/A
User Fees		YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?		☒	☐		
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.</i>		Payment for this application (<i>check daily email from UserFeeAR@fda.hhs.gov</i>): ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Contact the User Fee Staff. If appropriate, send UN letter.</i>		Payment of other user fees: ☒ Not in arrears ☐ In arrears			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf		Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> ☒ Yes ☐ No			

505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment																
Is the application a 505(b)(2) NDA? (Check the 356h form, cover letter, and annotated labeling). If yes , answer the bulleted questions below:	☐	☒																		
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☐		N/A																
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].	☐	☐		N/A																
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]? <i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i>	☐	☐		N/A																
Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm If yes, please list below: <table border="1"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration													☐	☐		N/A
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>																				
Exclusivity	YES	NO	NA	Comment																
Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/ood/index.cfm	☐	☒																		
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?	☐	☐	☒																	
<i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>																				
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?	☒	☐	☐																	

If yes, # years requested: 5				
<i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?	☐	☐	☒	
<i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>				
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act?	☐	☐	☒	
<i>If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager</i>				
<i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>				

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?	N/A			
Overall Format/Content	YES	NO	NA	Comment
If electronic submission , does it follow the eCTD guidance? ¹ If not , explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21	☒	☐		

¹ <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm333969.pdf>

CFR 601.2 (BLAs/BLA efficacy supplements) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?	☐	☐	☒	
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included.</i> Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	☒	☐		
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	☒	☐		
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	☒	☐		
<i>If yes, ensure that the application is also coded with the</i>				

<i>supporting document category, "Form 3674."</i> <i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i>	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	☐	☐	☒	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>	☐	☐	☒	
Pediatrics	YES	NO	NA	Comment

<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	☒	☐		
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	☒	☐	☐	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	☐	☐	☒	
<u>BPCA:</u> Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required³</i>	☐	☒		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	☒	☐	☐	
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	☐	☒	☐	
Prescription Labeling	☐ Not applicable			
Check all types of labeling submitted.	☒ Package Insert (Prescribing Information)(PI) ☒ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide)			

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027829.htm>

3

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027837.htm>

	☒ Carton labeling ☒ Immediate container labels ☐ Diluent labeling ☐ Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format?	☒	☐		
<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in Physician Labeling Rule (PLR) format? ⁴	☒	☐		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	☐	☐	☒	
For applications submitted on or after June 30, 2015: Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format? Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?	☒ ☒	☐ ☐	☐ ☐	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLLR format before the filing date.</i>	☐	☐	☒	
Has all labeling [(PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP?	☒	☐	☐	
Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? (send WORD version if available)	☒	☐	☐	
Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☒	☐	☐	
OTC Labeling	☒ Not Applicable			

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/LabelingDevelopmentTeam/ucm025576.htm>

Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted?	☐	☐		
<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?	☐	☐	☒	
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?	☐	☐	☒	
<i>If no, request in 74-day letter.</i>				
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☒	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	☒	☐	☐	
<i>If yes, specify consult(s) and date(s) sent:</i> QT-IRT				10/5/2016
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): 10/2/2014, 3/26/2015	☒	☐		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 7/21/2016	☒	☐		
Any Special Protocol Assessments (SPAs)? Date(s):	☐	☒		

ATTACHMENT

MEMO OF FILING MEETING

DATE: September 29, 2016

BACKGROUND: Novartis Pharmaceuticals Corporation submitted NDA 209092 pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Kisqali® (ribociclib), 200 mg Tablets, on August 29, 2016, for the following indication:

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.

Kisqali® (ribociclib) is a new chemical entity (b) (4) In June 2013 a new IND (IND 117796) was initiated specifically for the breast cancer indication. Kisqali® (ribociclib) is not approved or marketed in any country.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Tracy Cutler	Y
	CPMS/TL:	Christy Cottrell	N
Cross-Discipline Team Leader (CDTL)	Julia Beaver		Y
Division Director/Deputy	Geoffrey Kim		Y
	Amna Ibrahim		N
Office Director/Deputy	Richard Pazdur		N
	Amy McKee		N
Clinical	Reviewer:	Anand Shah	Y
	TL:	Julia Beaver	Y
Social Scientist Review (for OTC products)	Reviewer:	N/A	
	TL:	N/A	
OTC Labeling Review (for OTC products)	Reviewer:	N/A	
	TL:	N/A	

Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	N/A	
	TL:	N/A	
Clinical Pharmacology	Reviewer:	Wentao Fu	Y
	TL:	Qi Liu	Y
• Genomics	Reviewer:	N/A	
• Pharmacometrics	Reviewer:	Youwei Bi	Y
Biostatistics	Reviewer:	Erik Bloomquist	Y
	TL:	Shenghui Tang	N

Nonclinical (Pharmacology/Toxicology)	Reviewer:	George Chang	Y
	TL:	Todd Palmby	Y
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:	N/A	
Product Quality (CMC) Review Team:	ATL:	Xiao-Hong Chen	Y
	RBPM:	Kristine Leahy	Y
• Drug Substance	Reviewer:	Ray Frankenwich	N
• Drug Product	Reviewer:	Paresma Patel	N
• Process	Reviewer:	Sung Kim	N
• Microbiology	Reviewer:	Julie Nemecek	N
• Facility	Reviewer:	Marion Michaelis	N
• Biopharmaceutics	Reviewer:	Ta-Chen Wu	N
• Immunogenicity	Reviewer:	N/A	
• Labeling (BLAs only)	Reviewer:	N/A	
• Other (e.g., Branch Chiefs, EA Reviewer)	Anamitro Banerjee		Y
OMP/OMPI/DMPP (MedGuide, PPI, IFU)	Reviewer:	N/A	
	TL:	N/A	
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)	Reviewer:	N/A	
	TL:	N/A	
OSE/DMEPA (proprietary name, carton/container labeling)	Reviewer:	Tingting Gao	Y
	TL:	Alice Tu	N
OSE/DRISK (REMS)	Reviewer:	Till Olickal	Y
	TL:	Naomi Redd	N
OC/OSI/DSC/PMSB (REMS)	Reviewer:	N/A	
	TL:	N/A	

Bioresearch Monitoring (OSI)	Reviewer:	Lauren Iacono-Conner	Y
	TL:	Susan Thompson	N
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:	N/A	
Other reviewers/disciplines			
• Discipline	Reviewer:	N/A	
	TL:	N/A	
Other attendees	Frances Fahnbulleh		Y
	Christina Marshall		Y
	William Pierce		Y
	Pritpal Singh		Y
	Carolyn McCloskey		Y
	Peter Waldron		Y
	Joshua Meinert		Y

FILING MEETING DISCUSSION:

GENERAL 505 b)(2) filing issues: - Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? - Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
Per reviewers, are all parts in English or English translation? If no, explain:	☒ YES ☐ NO
Electronic Submission comments	☐ Not Applicable ☒ No comments

List comments:	
CLINICAL	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE
Comments:	☐ Review issues for 74-day letter
Clinical study site(s) inspections(s) needed? If no, explain:	☒ YES ☐ NO
- Advisory Committee Meeting needed? Comments: <i>If no, for an NME NDA or original BLA, include the reason. For example:</i> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i>	☐ YES Date if known: ☒ NO ☐ To be determined Reason: - This drug is not first in its class - The clinical study was acceptable - The application did not raise significant safety/efficacy issues - The application did not raise significant public health questions on the role of the drug in the diagnosis, cure, mitigation, treatment or prevention of disease.
If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? Comments:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE
Abuse Liability/Potential Comments:	☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE
Comments:	☐ Review issues for 74-day letter

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CLINICAL PHARMACOLOGY Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Clinical pharmacology study site(s) inspections(s) needed?	☒ YES ☐ NO
BIOSTATISTICS Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>New Molecular Entity (NDAs only)</u> Is the product an NME?	☒ YES ☐ NO
<u>Environmental Assessment</u> Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? Comments:	☒ YES ☐ NO ☐ YES ☐ NO
<u>Facility Inspection</u> Establishment(s) ready for inspection? Comments:	☐ Not Applicable ☒ YES ☐ NO

<u>Facility/Microbiology Review (BLAs only)</u> Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>CMC Labeling Review (BLAs only)</u> Comments:	N/A ☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☐ N/A ☒ YES ☐ NO ☒ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	N/A
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☒ YES ☐ NO

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Richard Pazdur, MD Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): 12/13/2016 21st Century Review Milestones (see attached) Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. <u>Review Classification:</u> ☐ Standard Review ☒ Priority Review
ACTION ITEMS	
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☒	If priority review, notify applicant in writing by day 60 (see CST for choices)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☒	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRA's completed: April 2016

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

/s/

TRACY L CUTLER
10/26/2016

CHRISTY L COTTRELL
10/26/2016

REGULATORY PROJECT MANAGER PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 209092

Application Type: New NDA

Drug Name(s)/Dosage Form(s): Kisqali® (ribociclib), 200 mg Tablets

Applicant: Novartis Pharmaceuticals

Receipt Date: August 29, 2016

Goal Date: April 29, 2017

1. Regulatory History and Applicant's Main Proposals

Novartis Pharmaceuticals submitted NDA 209092 pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Kisqali® (ribociclib) on August 29, 2016 for the following indication:

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.

Kisqali® (ribociclib) is an orally bioavailable, highly-selective, small-molecule inhibitor of cyclin-dependent kinase (CDK) 4 and 6, which induces G1 arrest at submicromolar concentrations in a variety of retinoblastoma protein (pRb)-positive cancer cells in vitro. (b) (4)

(b) (4)
In June 2013, a new IND (IND 117796) was initiated specifically for the breast cancer indication. Kisqali® (ribociclib) is not approved or marketed in any country.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies, see Section 4 of this review.

In addition, the following labeling issues were identified:

1. In the Highlights section, Contraindications subsection, remove the period after the section reference.

RPM PLR Format Review of the Prescribing Information

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by November 4, 2016. The resubmitted PI will be used for further labeling review.

Selected Requirements of Prescribing Information

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement.
Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

Comment:

- YES** 3. A horizontal line must separate:
- HL from the Table of Contents (TOC), **and**
 - TOC from the Full Prescribing Information (FPI).

Comment:

- YES** 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment:

- NO** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

Comment: *Insert a space before each major heading listed in the highlights section.*

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

- YES** 7. Headings in HL must be presented in the following order:

Heading	Required/Optional
• Highlights Heading	Required

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• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading, “**HIGHLIGHTS OF PRESCRIBING INFORMATION**” must be **bolded** and should appear in all UPPER CASE letters.

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: “**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**” The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

Comment:

- N/A** 13. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. Even if there is more than one warning, the term

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“**WARNING**” and not “**WARNINGS**” should be used. For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings. The BW title should be centered.

Comment:

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

Comment:

- N/A** 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement “*See full prescribing information for complete boxed warning.*”)

Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015.”

Comment:

- N/A** 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

- N/A** 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Contraindications in Highlights

- YES** 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word “None.”

Comment:

Selected Requirements of Prescribing Information

Adverse Reactions in Highlights

- YES** 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**”

Comment:

Patient Counseling Information Statement in Highlights

- YES** 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**
- **See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**

Comment:

Revision Date in Highlights

- YES** 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 8/2015** ”).

Comment:

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Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

- YES** 24. The TOC should be in a two-column format.
Comment:
- YES** 25. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS.**” This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- N/A** 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].
Comment:
- YES** 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading “**FULL PRESCRIBING INFORMATION: CONTENTS***” must be followed by an asterisk and the following statement must appear at the end of the TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "Labor and Delivery")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "Nursing Mothers")
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, "[see *Warnings and Precautions (5.2)*]."

Comment:

Selected Requirements of Prescribing Information

- N/A** 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 34. The following heading “**FULL PRESCRIBING INFORMATION**” must be **bolded**, must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A** 35. All text in the BW should be **bolded**.

Comment:

- N/A** 36. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. (Even if there is more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used.) For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

- N/A** 37. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 38. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

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

Comment:

- N/A** 39. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

YES 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment:

YES 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use **PROPRIETARY NAME** safely and effectively. See full prescribing information for **PROPRIETARY NAME**.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING

See full prescribing information for complete boxed warning.

- Text (4)
- Text (5.x)

RECENT MAJOR CHANGES

Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

INDICATIONS AND USAGE

PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for ... (1)

Limitations of Use: Text (1)

DOSAGE AND ADMINISTRATION

- Text (2.x)
- Text (2.x)

DOSAGE FORMS AND STRENGTHS

Dosage form(s): strength(s) (3)

CONTRAINDICATIONS

- Text (4)
- Text (4)

WARNINGS AND PRECAUTIONS

- Text (5.x)
- Text (5.x)

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are text (6.x)

To report **SUSPECTED ADVERSE REACTIONS**, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Text (7.x)
- Text (7.x)

USE IN SPECIFIC POPULATIONS

- Text (8.x)
- Text (8.x)

See 17 for **PATIENT COUNSELING INFORMATION** and FDA-approved patient labeling **OR** and Medication Guide.

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: TITLE OF WARNING

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Subsection Title

2.2 Subsection Title

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Subsection Title

5.2 Subsection Title

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Immunogenicity

6.2 or 6.3 Postmarketing Experience

7 DRUG INTERACTIONS

7.1 Subsection Title

7.2 Subsection Title

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation (if not required to be in PLLR format use Labor and Delivery)

8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format use Nursing Mothers)

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Subpopulation X

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 Subsection Title

14.2 Subsection Title

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

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

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/s/

TRACY L CUTLER
10/26/2016

CHRISTY L COTTRELL
10/26/2016

MEMORANDUM**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: 11/23/2016

TO: Division of Oncology Products (DOP1)
Office of Hermatology and Oncology Products

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: NDA 209092

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

Rationale

OSIS recently inspected the site listed below. The inspectional outcome from the inspection was classified as No Action Indicated (NAI).

Inspection Site

Facility Type	Facility Name	Facility Address
Clinical	PPD Phase I Clinic	7551 Metro Center Drive, Suite 200, Austin, TX

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/s/

SHILA S NKAH
11/23/2016