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RESEARCH**

APPLICATION NUMBER:

207997Orig1s000

207997Orig2s000

OTHER REVIEW(S)



U.S. FOOD & DRUG
ADMINISTRATION

**Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research| Office of Surveillance and Epidemiology (OSE)**

**Epidemiology: Pregnancy Registry ARIA Sufficiency Template
Version: 2017-02-08**

Date: April 24, 2017

Reviewer(s): Kate Gelperin, MD, MPH
Division of Epidemiology-1

Team Leader: Steven Bird, PharmD, PhD
Division of Epidemiology-1

Division Director: Simone Pinheiro, PhD
Division of Epidemiology-1

Subject: ARIA Sufficiency Memo

Drug Name(s): RYDAPT (Midostaurin)

Application Type/Number: NDA 207997

Applicant/sponsor: Novartis

OSE RCM #: 2017-710



1. Why is pregnancy safety a safety concern for this product?

- ☐ Specific FDA-approved indication in pregnant women exists and exposure is expected
- ☐ No approved indication, but practitioners may use product off-label in pregnant women
- ☐ No approved indication, but there is the potential for inadvertent exposure before a pregnancy is recognized
- ☒ No approved indication, but use in women of child bearing age is a general concern

2. Types of evidence supporting safety concern, if any:

- ☐ Spontaneous reports
- ☐ Pre-clinical studies
- ☐ Clinical studies
- ☒ Therapeutic mechanism of action
- ☐ Class-based effect
- ☐ Other, please specify: *Enter text on supporting evidence*

For any checked boxes above, please describe briefly the supporting evidence:

Based on its mechanism of action and findings from animal reproduction studies, midostaurin may cause fetal harm when administered to pregnant women. In animal studies, midostaurin caused embryo-fetal toxicities, including late embryo-fetal death and reduced fetal birth weight, with delays in fetal growth at doses lower than the recommended human dose.

3. Describe the Safety Concern

- ☐ Specific pregnancy safety concern.
** If checked, please complete standard ARIA sufficiency template*
- ☒ No specific pregnancy safety concern, but broad based surveillance of all pregnancy outcomes is desired (e.g., pregnancy registry)

4. Regulatory Goal

- ☒ *Signal detection* – Nonspecific safety concern with no prerequisite level of statistical precision and certainty
- ☐ *Signal refinement of specific outcome(s)* – Important safety concern needing moderate level of statistical precision and certainty
** If checked, please complete standard ARIA sufficiency template*
- ☐ *Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review)
** If checked, please complete standard ARIA sufficiency template*



Midostaurin is a kinase inhibitor with proposed indications for the treatment of adult patients with:

- Newly diagnosed acute myeloid leukemia (AML) that is FLT3 mutation-positive as detected by an FDA-approved test, in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation.
- Aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated hematological neoplasm (SM-AHN), or mast cell leukemia (MCL).

Because the indicated conditions (ASM and AML) occur rarely, it will not be feasible for a US-based pregnancy registry to enroll adequate numbers of exposed pregnancies to provide sufficient power for rigorous statistical comparison with similar unexposed controls. The incidence of AML is 3 to 5 cases per 100,000 in the United States and Europe, and the median age at diagnosis is approximately 65 years.¹ Based on these data, exposure to midostaurin during pregnancy is likely to occur very rarely. Measures such as expanding registry enrollment to additional countries still may not achieve an adequately powered study. We also note that ARIA is not sufficient because it lacks a mother infant linkage and the requisite analysis tools to analyze the data. Nonetheless, it is important to capture clinically relevant data on any pregnancy exposures that may occur with midostaurin, even though formal inferential testing is not feasible.

We recommend the following PMR for a worldwide Pregnancy Surveillance Program with midostaurin:

Establish a worldwide Pregnancy Surveillance Program (enhanced pharmacovigilance) to collect and analyze information for a minimum of 10 years on pregnancy complications and birth outcomes in women exposed to midostaurin during pregnancy. Add notice of the Pregnancy Surveillance Program and telephone contact number (and/or website) to the prescribing information. Provide a complete protocol which includes details regarding how you plan to encourage patients and providers to report pregnancy exposures (e.g. telephone contact number and/or website in prescribing information); (b)(4)

measures to ensure complete data capture regarding pregnancy outcomes and any adverse effects in offspring; and plans for comprehensive data analysis and yearly reporting. Submit yearly reports on the cumulative findings and analyses from the Pregnancy Surveillance Program.

¹ Schiffer CA, Anastasi J. Clinical manifestations, pathologic features, and diagnosis of acute myeloid leukemia. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on April 21, 2017.)

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/s/

KATE GELPERIN
04/24/2017

STEVEN BIRD
04/24/2017

SIMONE P PINHEIRO
04/24/2017

JUDITH W ZANDER
04/24/2017

MICHAEL D NGUYEN
04/25/2017

ROBERT BALL
04/25/2017

PMR/PMC Development Template

NDA # 207997
Product: Rydapt (midostaurin)

PMC Description: To corroborate your assertion that midostaurin induces a treatment benefit in the overall population of patients with FLT3 mutations rather than in only a subset of patients with a mutation in a different kinase inhibited by the drug, provide subgroup analyses for CR, OS and EFS by genomic mutations that occurred concurrently with FLT3 for randomized subjects who consented for additional molecular studies in the RATIFY trial. Submit a data file with results of the full mutational profiling at baseline performed by Novartis in close collaboration with Alliance and RATIFY Cooperative Groups / Investigators in addition to the full study report.

Schedule Milestones:	Draft Protocol Submission	06/2017
	Final Protocol Submission	12/2017
	Study Completion	04/2018
	Final Report Submission	10/2018

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

Acute myeloid leukemia is a life-threatening disease with limited treatment options.

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

AML is a heterogeneous disorder genomically. Mutations in numerous kinases have been associated with the disease, and a single AML can have more than one such mutations. Midostaurin is a multikinase inhibitor which inhibits several of the kinases known to be active in AML, including mutant and wild type FLT3. The sponsor conducted Study A2301 (RATIFY) to test the efficacy of midostaurin in combination with standard chemotherapy in patients with newly diagnosed AML having a FLT3 mutation. They demonstrated a small effect on CR rate, event-free survival and overall survival. Since only FLT3 mutations were assessed at study start, and efficacy in patients with AML having mutations other than FLT3 have not been studied systematically, it is not clear that inhibition of mutant FLT3 is mediating the effect of midostaurin. A study of clinical outcomes by concurrent mutation should be performed to exclude the possibility that treatment benefit was mediated by inhibition of an alternative target of midostaurin, such a KIT, that occurred in only a subgroup of the proposed intended population.

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

If not a PMR, skip to 4.

- ☐ 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.

See PMC description

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
- ☐ 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 or 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.

PMR/PMC Development Template

NDA # 207997
Product: Rydapt (midostaurin)

PMC Description: To demonstrate that the treatment effect of midostaurin is consistent across prognostic subgroups, provide subgroup analyses for randomized subjects with cytogenetic/molecular prognostic information in the RATIFY trial for CR, OS and EFS by cytogenetic/molecular prognostic category using an accepted consensus prognostic classification, such as that published in 2016 or later by the European Leukemia Net (ELN) or the National Comprehensive Cancer Network (NCCN). Submit a data file with results of the full karyotype description at baseline performed by Alliance and/or Novartis in addition to the full study report.

Schedule Milestones:	Draft Protocol Submission	06/2017
	Final Protocol Submission	12/2017
	Study Completion	04/2018
	Final Report Submission	10/2018

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.

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

Acute myeloid leukemia is a life-threatening disease with limited treatment options.

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

Genomic lesions arising from gene mutations or chromosomal translocations are the main indicator of outcome for patients with AML. The sponsor conducted Study A2301 (RATIFY), a randomized trial of standard chemotherapy with midostaurin vs placebo in patients with newly diagnosed AML having a FLT3 mutation. At randomization, patients were stratified solely by FLT3-mutation type. The case report form showed that the karyotype description was collected by Alliance, but this information was not conveyed to the Applicant. The Applicant did not show that the two study arms were balance for prognostic markers, nor did the Applicant show that the treatment effect was consistent across prognostic subgroups.

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

If not a PMR, skip to 4.

- ☐ 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)

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- ☐ 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?

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See PMC description

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- ☐ Observational pharmacoepidemiologic study
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- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials
- ☐ 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)
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5. Is the PMR/PMC clear, feasible, and appropriate?

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PMR/PMC Development Coordinator:

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/s/

BARRY W MILLER
04/18/2017

PMR/PMC Development Template

NDA # 207997

Product: Rydapt (midostaurin)

PMR Description: Establish a worldwide Pregnancy Surveillance Program (enhanced pharmacovigilance) to collect and analyze information for a minimum of 10 years on pregnancy complications and birth outcomes in women exposed to midostaurin during pregnancy. Add notice of the Pregnancy Surveillance Program and telephone contact number (and/or website) to the prescribing information. Provide a complete protocol which includes details regarding how you plan to encourage patients and providers to report pregnancy exposures (e.g. telephone contact number and/or website in prescribing information), measures to ensure complete data capture regarding pregnancy outcomes and any adverse effects in offspring, and plans for comprehensive data analysis and yearly reporting. Submit yearly reports on the cumulative findings and analyses from the Pregnancy Surveillance Program.

Schedule Milestones: Draft Protocol Submission: 6/2017
Final Protocol Submission: 8/2017
Revised Prescribing Information: 12/2017
Interim Report #1: June/2018
Interim Report #2: June/2019
Interim Report #3: June/2020
Interim Report #4: June/2021
Interim Report #5: June/2022
Interim Report #6: June/2023
Interim Report #7: June/2024
Interim Report #8: June/2025
Interim Report #9: June/2026
Study Completion: April/2027
Final Report Submission: June/2027

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.

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- ☐ Long-term data needed
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- ☒ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

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

Midostaurin is a multiple kinase inhibitor under review for treatment of patients with advanced systemic mastocytosis (ASM) and for patients with newly diagnosed acute myeloid leukemia (AML) that is FLT3 mutation positive. Treatment of ASM will be single agent. Treatment of AML will be in combination with cytarabine and an anthracycline (7+3 chemotherapy).

Available experience using 7+3 cytotoxic chemotherapy for treatment of AML suggests that the risks to the fetus are greatly outweighed by the benefit of chemotherapy during the second and third trimester. Based on this experience, it is common practice and a consensus recommendation (Milojkovic and Apperley 2014; Ali et al. 2015) to consider use of 7+3 for treatment of pregnant patients with AML during the second and third trimesters despite warnings in labeling regarding the embryo-fetal toxicity of daunorubicin and cytarabine. However, the findings of embryo-fetal and post-fetal toxicities in the nonclinical studies of midostaurin raised questions about safe use of this drug during pregnancy, including during the second and third trimesters. Given the major difference in mechanism of action between midostaurin and cytotoxic chemotherapy, the safety of use of midostaurin during pregnancy cannot be imputed from the experience with 7+3. The Applicant identified 7 (~2%) pregnancies among the 398 females participating in Study A2301, but none of the pregnancies during exposure to midostaurin had information on fetal outcome. The high level of uncertainty regarding the risks from use of midostaurin during pregnancy will be communicated in labeling to allow the healthcare provider and patient to have an informed discussion about risks and benefit. Given the common practice described above, a boxed warning for embryo-fetal toxicity was recommended by some reviewers. A final decision was made for a warning in the label and a pregnancy registry or enhanced pharmacovigilance program as a post-marketing requirement.

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

If not a PMR, skip to 4.

- ☐ 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)

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- ☒ 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?
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- ☐ 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.

A worldwide Pregnancy Surveillance Program (enhanced pharmacovigilance) to collect and analyze information for a minimum of 10 years on pregnancy complications and birth outcomes in women exposed to midostaurin during pregnancy.

Required

- ☒ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☐ Primary safety study or clinical trial
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- ☐ Thorough Q-T clinical trial
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- ☐ Immunogenicity as a marker of safety
- ☐ Other (provide explanation):

Agreed upon:

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

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

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/s/

BARRY W MILLER
04/18/2017

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 # 207997 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: RYDAPT® Established/Proper Name: Midostaurin Dosage Form: capsules Strengths: 25 mg		
Applicant: Novartis Pharmaceuticals Corporation Agent for Applicant (if applicable):		
Date of Application: August 29, 2016 Date of Receipt: August 29, 2016 Date clock started after Unacceptable for Filing (UN):		
PDUFA/BsUFA Goal Date: April 28, 2017		Action Goal Date (if different):
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): Original 1: The treatment of adult patients with advanced systemic mastocytosis (Advanced SM) Original 2: The treatment of patients with newly diagnosed FLT3 mutation positive acute myeloid leukemia (AML)		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
<i>If 505(b)(2)NDA/NDA Supplement: Draft the “505(b)(2) Assessment” review found at:</i>		

http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499				
Type of BLA		☐ 351(a) ☐ 351(k)		
<i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i> Review Classification:		☐ Standard ☒ Priority		
<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>		☐ 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):				
List referenced IND Number(s): IND 057120				
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,</i>				

ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into electronic archive.				
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.				
If affected by AIP, has OC been notified of the submission? If yes, date notified:	☐	☐		
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 (check daily email from UserFeeAR@fda.hhs.gov): ☐ 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?	☐	☐		
• 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)].	☐	☐		
• 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>				
• 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:				
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)]?	☐	☒	☐	Orphan Designation AML: 7/7/09 MCL: 4/30/10
<i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>				
NDA/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?	☒	☐	☐	
If yes , # years requested: 5 years (new chemical entity)				

<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				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	☐ 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?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance? ¹ <i>If not, explain (e.g., waiver granted).</i>	☒	☐	☐	
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 CFR 601.2 (BLAs/BLA efficacy supplements) including:	☒	☐		

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

☐ 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> <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.</i>				
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 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, <u>both</u> 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</i>	☒	☐		Orphan designation

meeting²				
<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)?	☐	☐	☒	Orphan designation
<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?	☒	☐	☐	10/04/2016 acknowledgement letter sent
<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) ☒ Carton labeling ☐ Immediate container labels ☐ Diluent labeling ☐ Other (specify)			
	YES	NO	NA	Comment

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

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

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? (<i>send WORD version if available</i>)	☒	☐	☐	
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			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL)			

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

	☐ 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)	☒	☐	☐	QT consult September 13, 2016
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): October 11, 2011	☒	☐		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): September 2, 2015; May 24, 2016	☒	☐		
Any Special Protocol Assessments (SPAs)? Date(s):	☐	☒		

ATTACHMENT

MEMO OF FILING MEETING

DATE: September 28, 2016

BACKGROUND: Midostaurin received fast track designation on January 20, 2016 for the treatment of patients with aggressive systemic mastocytosis or mast cell leukemia with or without an associated hematologic non-mast cell lineage disorder. In addition, midostaurin was granted breakthrough therapy designation for the treatment of adult patients with newly diagnosed acute myeloid leukemia (AML) who are Fms-like Tyrosine Kinase 3 (FLT3) mutation-positive as detected by an FDA-approved test and who are eligible to receive standard induction and consolidation chemotherapy on January 29, 2016.

Novartis submitted NDA 209707 under rolling submission on April 5, 2016, and final module was received on August 29, 2016. The proposed indications for midostaurin included:

- Original 1: the treatment of patients with aggressive systemic mastocytosis (ASM)
- Original 2: the treatment of patients with mast cell leukemia (MCL)

This application will be reviewed under the PDUFAV “Program”.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Kimberly Scott	Y
	CPMS/TL:	Donna Przepiorka	Y
Cross-Discipline Team Leader (CDTL)	Donna Przepiorka		Y
Division Director/Deputy	Ann Farrell		Y
Office Director/Deputy	Albert Deisseroth		Y
Clinical	Reviewer: Original 1	Yvette Kasamon	Y
	Reviewer: Original 2	Ashley Ward	Y
	TL:	Donna Przepiorka	Y
Clinical Pharmacology	Reviewer:	Sriram Subramaniam	Y
	TL:	Stacy Shord	Y
	Primary	Yuching Yang	N

	Reviewer PBPK:		
	Secondary Reviewer PBPK:	Ping Zhao	N
	TL:	Nitin Mehrotra	Y
• Pharmacometrics	Reviewer:	Jee Eun Lee	Y
	TL:	Lian Ma	
Biostatistics	Reviewer:	Chia-Wen Ko	N
	TL:	Lei Nie	Y

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Natalie Simpson	Y
	TL:	Christopher Sheth	Y
Product Quality (CMC) Review Team:	ATL:	Sherita McLamore-Hines	Y
	RBPM:	Rabiya Laiq	Y
• Drug Product	Reviewer:	Nina Ni	Y
• Drug Substance	Reviewer:	Gene Holbert	N
• Process	Reviewer:	Zhaoyang Meng	N
• Microbiology	Reviewer:	Zhaoyang Meng	N
• Facility	Reviewer:	Ruth Moore	N
	TL:	Steven Hertz	N
• Biopharmaceutics	Reviewer:	Ta Chen Wu	Y
	TL:	Okpo Eradin	Y
• QT/IRT	Reviewer:	Devi Kozeli	Y
• Other (e.g., Branch Chiefs, EA Reviewer)			
OMP/OMPI/DMPP (MedGuide, PPI, IFU)	Reviewer:	Rowe Medina	N
	TL:	Barbara Fuller	N
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)	Reviewer:	Rachel Conklin	Y
	TL:	Susannah O'Donnell	Y
OSE/DMEPA (proprietary name, carton/container labeling)	Reviewer:	Hina Mehta	Y
	TL:	Leeza Rahimi	Y
	RPM:	Neil Vora	Y
OSE/DRISK (REMS)	Reviewer:	Mei-Yean Chen	Y
	TL:	Naomi Redd	Y
OSE/OPE/DPVII(pharmacovigilance)	Reviewer:	Afrouz Nayernama	Y
	TL:	Steven Bird	
OSE/OPE/DEPII	Reviewer:	Kate Gelperin Carolyn McCloskey	Y
	TL:	Steven Bird	N
	Reviewer:		Y
	TL:		Y

Clinical Outcomes Assessment	Reviewer:	Wen-Hung Chen	Y
	TL:	Selena Daniels	Y
Bioresearch Monitoring (OSI)	Reviewer:	Lu Min	Y
	TL:	Anthony Orencia	Y
DPMH (maternal)	Reviewer:	Jane Liedtka	Y
	TL:	Miriam Dinatale	Y
	RPM:	Denise Johnson-Lyles	Y
Other reviewers/disciplines			
• CDRH	Reviewer:	Allen Williams Karen Bijwaard	Y
	TL:	Donna Roscoe	
Other attendees	Kelly Norsworthy		Y
	Karen Boyd		Y
	Virginia Kwitkowski		Y
	Angelo de Claro		Y
	Diane Leaman		Y
	Sarah Harris		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	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
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described in published literature):	
Per reviewers, are all parts in English or English translation? If no, explain:	☒ YES ☐ NO
Electronic Submission comments List comments: sent list of eCTD deficiencies on 9/29/16, and Applicant to respond by 10/20/16	☐ Not Applicable ☐ No comments

CLINICAL Comments: Review issues sent with Day 60 letter	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ 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: 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.
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 Abuse Liability/Potential Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CLINICAL PHARMACOLOGY Comments: Review issues sent with Day 60 letter Clinical pharmacology study site(s) inspections(s) needed?	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter ☐ 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:	☐ 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?	
• 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: Ann T. Farrell Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): November 30, 2016 21st Century Review Milestones (see attached) (listing review milestones in this document is optional): 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

Version: 4/12/2016

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

/s/

KIMBERLY L SCOTT
04/11/2017

THERESA A CARIOTI
04/11/2017

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

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

Memorandum

Date: 04/06/17

To: Kimberly Scott, Regulatory Project Manager
Division of Hematology Products (DHP)

From: Rachael Conklin, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Comments on draft labeling (Package Insert, Carton/Container Labeling) for RYDAPT (midostaurin) capsules, for oral use NDA 207997

In response to your labeling consult request dated September 13, 2016, we have reviewed the draft Package Insert for RYDAPT (midostaurin) capsules, for oral use (Rydapt). This review is based upon the version of the draft PI emailed to OPDP on March 23, 2017 and the versions of the Carton/Container labeling accessed from the shared drive on April 6, 2017.

If you have any questions, please contact Rachael Conklin at (240) 402-8189 or Rachael.Conklin@fda.hhs.gov.

PI

<u>Section</u>	<u>Statement from Draft (if applicable)</u>	<u>OPDP Comment</u>
2.4 Recommended Administration	"Consider interval assessments of QT by EKG if RYDAPT is taken concurrently with medications that can prolong the QT interval."	(b) (4)
14.1 Acute Myeloid Leukemia	Patients were randomized (1:1) to receive RYDAPT 50 mg twice daily (n=360) or placebo (n=357) with food on days 8-21 in combination with standard daunorubicin	(b)(4)

	(60 mg/m² daily on days 1 to 3) / cytarabine (200 mg/m² daily on days 1 to 7) for up to two cycles of induction and high dose cytarabine (3 g/m² every 12 hours on days 1, 3 and 5) for up to four cycles of consolidation, followed by continuous RYDAPT or placebo treatment according to initial assignment for up to 12 additional 28-day cycles.	(b)(4) (b) (4)
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Carton/Container Labeling

OPDP acknowledges and concurs with the November 8, 2016, review of the carton and container labeling by the Division of Medication Error Prevention and Analysis (DMEPA) and has no additional comments on the carton and container labeling.

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/s/

RACHAEL E CONKLIN
04/06/2017

**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: April 6, 2017

To: Ann Farrell, MD
Director
Division of Hematology Products (DHP)

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

Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

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

Rachael Conklin, MS, RN
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

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

Drug Name (established name): RYDAPT (midostaurin)

Dosage Form and Route: capsules, for oral use

Application Type/Number: NDA 207997

Applicant: Novartis Pharmaceuticals Corporation

1 INTRODUCTION

On August 29, 2016, Novartis Pharmaceuticals Corporation submitted for the Agency's review the fourth and final part of a rolling submission for New Drug Application (NDA) 207997 for RYDAPT (midostaurin) capsules. The proposed indication for RYDAPT (midostaurin) capsules is for the treatment of patients with newly diagnosed FLT3 mutation positive acute myeloid leukemia (AML) and patients with advanced system mastocytosis (Advanced SM).

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 Hematology Products (DHP) on February 21, 2017, and September 13, 2016, respectively, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for RYDAPT (midostaurin) capsules.

2 MATERIAL REVIEWED

- Draft RYDAPT (midostaurin) capsules PPI received on August 29, 2016, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 23, 2017.
- Draft RYDAPT (midostaurin) capsules Prescribing Information (PI) received on August 29, 2016, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 23, 2017.

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)

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
04/06/2017

RACHAEL E CONKLIN
04/06/2017

BARBARA A FULLER
04/06/2017

LASHAWN M GRIFFITHS
04/06/2017

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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)

Date of This Memorandum:	March 06, 2017
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	NDA 207997
Product Name and Strength:	Rydapt (midostaurin) capsules, 25 mg
Submission Date:	February 16, 2017
Applicant/Sponsor Name:	Novartis
OSE RCM #:	2016-1821-1
DMEPA Primary Reviewer:	Leeza Rahimi, Pharm.D.
DMEPA Team Leader:	Hina Mehta, Pharm.D.

1 PURPOSE OF MEMO

The Division of Hematology Products (DHP) requested that we review the revised commercial carton, containers and, professional sample labels for Rydapt (midostaurin) capsules (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The carton and containers for Rydapt is acceptable from a medication error perspective. The term “soft” on the carton and container labels was not removed to be consistent with the prescribing information. The sample labels have not been revised per our recommendation. Novartis has agreed to implement our recommendation of increasing the font size for the term “Sample-Not for Sale” in their next printing cycle which is acceptable. We have no further recommendations at this time.

^a Rahimi, L. Label and Labeling Review for RYDAPT (midostaurin) (NDA 207997). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 Nov 08. 10 p. OSE RCM No.: 2016-1821.

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/s/

LEEZA RAHIMI
03/06/2017

HINA S MEHTA
03/07/2017

CLINICAL INSPECTION SUMMARY

Date	February 24, 2017
From	Anthony Orenca, M.D., F.A.C.P., GCPAB Medical Officer Janice Pohlman, M.D., M.P.H., GCPAB Team Leader Kassa Ayalew, M.D. M.P.H., GCPAB Branch Chief Division of Clinical Compliance Evaluation/OSI
To	Donna Przepiorka, M.D., Ph.D., CDTL Yvette Kasamon, M.D., Medical Officer Ashley Ward, M.D., Medical Officer Ann Farrell, M.D., Division Director Kimberly Scott, RN, BSN, Regulatory Project Manager Division of Hematology Products/OHOP
NDA	207997
Applicant	Novartis Pharmaceuticals Corporation
Drug	midostaurin
NME	Yes (PDUFA)
Therapeutic Classification/Review	Priority Application
Proposed Indication	(1) systemic mastocytosis (2) acute myeloid leukemia
Consultation Request Date	September 14, 2016 (signed)
Summary Goal Date	Original: February 1, 2017 Revised: March 1, 2017
Action Goal Date	March 1, 2017
PDUFA Date	April 29, 2017

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The study data derived from these clinical sites as reported by the sponsor to the NDA are considered reliable in support of the requested indication.

The final classification for the domestic inspection of Dr. Kolitz is NAI. The preliminary classification for the foreign inspections of Drs. Kluin-Nelemens, Ganser, Reiter, and Doehner is (b) (5). The preliminary classification of the sponsor, Novartis, Form FDA 483 issued at the close of the inspection, and the sponsor's written response to the 483 is (b) (5).

2. BACKGROUND

Midostaurin (PKC412) is an inhibitor of all major isoforms of protein kinase C, the tyrosine kinase associated with the vascular endothelial growth factor (VEGF) receptor, and most importantly, class III tyrosine protein kinases involved in hematopoiesis and leukemia, such as FLT3. Midostaurin is an oral agent that has been shown to inhibit FLT3 kinase, both *in vitro* and *in vivo* studies, as well as clinically in patients with both the ITD FLT3 and TKD FLT3 mutations. Midostaurin also potently inhibits multiple other molecular targets (e.g., VEGFR-1) thought to be important for the pathogenesis of acute myeloid leukemia. Midostaurin can also exert inhibitory activity on other mutated tyrosine kinases implicated in a variety of diseases (systemic mast cell disease, gastrointestinal stromal tumors or myeloproliferative disorder).

The Division of Hematology Products (DHP) selected two randomized clinical trials submitted in support of the applicant's NDA for inspection: one study of proposed treatment of adult patients with aggressive systemic mastocytosis (ASM) and another study of proposed treatment of adult patients with acute myeloid leukemia (AML). The review division requested inspections of two clinical sites for Study PKC412D2201 (ASM indication) and three clinical sites for Study PKC412A2301 (AML indication).

Study PKC412D2201 (Aggressive Systemic Mastocytosis)

Study PKC412D2201 was a non-randomized, single arm, open-label, multi-center Phase 2 study followed by an extension phase. This study was submitted in support of the aggressive systemic mastocytosis (ASM) indication.

The primary study objective was to determine the efficacy of midostaurin when administered orally at a dose of 100 mg bid continuously for 6 cycles (of 4 weeks each) in patients with aggressive systemic mastocytosis or mast cell leukemia as measured by overall treatment response rate (ORR). The ORR was defined as the percentage of patients classified as confirmed responders (major response [MR] or partial response [PR]) adjudicated by the Study Steering Committee, according to response assessment criteria specified in the protocol. This Study Steering Committee (SSC) adjudicated eligibility for every enrolled patient, performed a pathologic review of tissue specimens, adjudicated response assessments at regular intervals, and reviewed and provided input into the study protocol, protocol amendments, and scientific aspects of the trial.

The primary efficacy was overall treatment response rate (ORR), defined as the proportion of patients with a best response of major or partial response, that initially occurred in the first 6 cycles of treatment using modified Valent/Cheson criteria and that was confirmed at least 56 days later.

The first subject was enrolled on January 6, 2009. The analysis cut-off date was December 1, 2014. Approximately 45% of the trial subjects were enrolled in Germany. A minority of the subjects were enrolled in the United States (about 29%), and foreign data thus contributed heavily to the observed treatment effect as well as safety findings.

Study PKC412A2301 (Acute Myeloid Leukemia)

Study PKC412A2301 was a Phase 3, randomized, double-blind, placebo-controlled study examining the efficacy, PK, and safety of midostaurin in combination with induction therapy (daunorubicin/cytarabine), remission-consolidation treatment (high-dose cytarabine) and as a single agent continuation therapy (midostaurin/placebo) in patients <60 years of age with FLT3-mutated AML (Note: this study addresses principally two types of FLT3 mutations: ITD and TIKD). Study PKC412A2301 is a multicenter, international Phase 3 trial sponsored by a cooperative group that is being submitted as the primary data source for the AML indication. The study is known to have several limitations, including failure to collect Grade 1 and Grade 2 adverse events, as well as detailed information about drug exposure.

Patients were randomized to receive midostaurin or placebo in addition to the standard of care chemotherapy during the induction and consolidation phases followed by monotherapy midostaurin or placebo during the continuation phase. The primary objective of this study was to determine if the addition of midostaurin to daunorubicin/cytarabine induction, high-dose cytarabine consolidation, and continuation therapy improves overall survival (OS) in both the mutant FLT3-ITD and the mutant FLT3-TKD AML patients. The primary efficacy endpoint was overall survival. This evaluation tested the superiority of midostaurin compared to placebo on overall survival, using an analysis non-censoring at the time of stem cell transplant.

The first subject was enrolled on July 1, 2008. The cut-off date for the primary analysis was April 1, 2015. The clinical cutoff date was January 11, 2016. Study PKC412A2301 was conducted cross 13 countries at 177 study centers (58 study centers were located in the U.S.)

3. RESULTS (by site):

Name of CI, Address	Protocol #, Site #, and # of Enrolled Subjects	Inspection Date	Classification
J-C Kluin-Nelemans, M.D. Universitair Medisch Centrum Groningen UMCG The Academisch Ziekenhuis Groningen and Faculteit der Medische Wetenschappen Hanzeplein 1 Groningen, 9713 GZ Netherlands	Protocol PKC412D2201 Site 180 (Netherlands) 10 Subjects	January 16 to 20, 2017	Pending: Preliminary (b) (5)
Andreas Reiter, M.D. Univ. Klinikum Mannheim TheodorKutzer Ufer 13, Gebäude 27, Ebene 4 Mannheim, 68135 Germany	Protocol PKC412D2201 Site 150 (Germany) 21 Subjects	January 23 to 27, 2017	Pending: Preliminary (b) (5)

Name of CI, Address	Protocol #, Site #, and # of Enrolled Subjects	Inspection Date	Classification
Hartmut Doehner, M.D. Universitätsklinikum Ulm, Albert-Einstein-Allee 23 Ulm, Germany 89081	Protocol PKC412A2301 Site 2937 (Germany) 21 Subjects	January 16 to 20, 2017	Pending: Preliminary (b) (5)
Arnold Ganser, M.D. Kliniken der Med. Hochschule Hannover Hämostaseologie und Onkologie, Carl-Neuberg-Str. 1 Hanover, Germany 30625	Protocol PKC412A2301 Site 2941 (Germany) 17 Subjects	January 9 to 13, 2017	Pending: Preliminary (b) (5)
Jonathan Kolitz, M.D. North Shore-Long Island Jewish Health System/Monter Cancer Center 450 Lakeville Road Lake Success, NY 11042	Protocol PKC412A2301 Site 0177/0234 (US) 12 Subjects	October 13 to 18, 2016	NAI
Sponsor: Novartis Pharmaceuticals Corporation One Health Plaza, Bldg. 337/B01-6A East Hanover, NJ 07936-1080	Study Protocols: Protocol PKC412D2201 Protocol PKC412A2301	January 10 to 24, 2017	Pending: Preliminary (b) (5)

Key to Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data are 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.

Clinical Investigator**1. J-C Kluin-Nelemans, M.D., Groningen, Netherlands (Study PKC412D2201)**

The inspection was conducted from January 16 to 20, 2017. A total of 11 subjects were screened, and 10 subjects enrolled and were randomized. Two study subjects had progressive disease. There were seven study subjects who died in this study. One study subject remains in follow-up. An audit of 10 subjects' records was conducted (Note: only three subjects' records (003, 010 and 012) were reviewed for SAE occurrences.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (Inspectional Observations) was not issued.

However, the following items were discussed at the inspection close out meeting:



OSI reviewer comments:



Data submitted by this clinical site appear acceptable in support of this specific indication.

2. Andreas Reiter, M.D., Mannheim, Germany (Study PKC412D2201)

The inspection was conducted from January 23 to 27, 2017. A total of 23 subjects were screened, 21 subjects were enrolled and 19 study subjects randomized. Eleven study subjects died in this study. Two study subjects withdrew from the study after randomization. One study subject had disease progression. Five study subjects remain in follow-up. An audit of the 21 enrolled subjects' records was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (Inspectional Observations) was not issued. Data submitted by this clinical site appear acceptable in support of this specific indication.

3. Hartmut Doehner, M.D., Ulm Germany (PKC412A2301)

The inspection was conducted from January 16 to 20, 2017. A total of 89 subjects were screened, 21 subjects were enrolled, and 21 subjects were randomized. Ten study subjects died in this study. Eleven study subjects are currently in follow-up. An audit of 21 subjects' records was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (Inspectional Observations) was not issued. Data submitted by this clinical site appear acceptable in support of this specific indication.

4. Arnold Ganser, M.D., Hanover Germany (PKC412A2301)

The inspection was conducted from January 9 to 13, 2017. A total of 59 subjects were screened and 17 subjects were enrolled and randomized. Four subjects withdrew study consent. Five study subjects died in this study. Eight subjects are currently in follow-up. An audit of the 17 subjects' records was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (Inspectional Observations) was not issued. Data submitted by this clinical site appear acceptable in support of this specific indication.

5. Jonathan Kolitz, M.D., Lake Success, NY (A2301)

The inspection was conducted from October 13 to 18, 2016. A total of 53 subjects were screened and 12 subjects were enrolled and randomized. Four subjects died. One study subject was transferred to another CI site in Florida. Seven study subjects remain in follow-up. An audit of the 12 subjects' records was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. There were no limitations during conduct of the clinical site inspection.

At the inspection close-out meeting, a deficiency regarding [REDACTED] was discussed. [REDACTED]

(b) (5)

(b) (5)

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (Inspectional Observations) was not issued. Data submitted by this clinical site appear acceptable in support of this specific indication.

SPONSOR-CRO

6. Novartis Pharmaceuticals Corp., East Hanover, NJ

This sponsor inspection was conducted from January 10 to 24, 2017. This sponsor inspection was requested to ensure that there were no monitoring concerns for this NME application. The inspection evaluated the following: documents related to study monitoring visits and correspondence, Institutional Review Board (IRB) approvals, completed Form FDA 1572s, monitoring reports, drug accountability, training of staff and site monitors; review of controls and security of electronic systems; and data collection and handling procedures; adequacy of

monitoring and corrective actions taken by the sponsor/monitor for the studies; clinical site study personnel training in GCP, and memorandum documents and reporting updates to clinical site investigators regarding serious unexpected adverse events.

In general, this site appeared to be in compliance with Good Clinical Practices. However, a Form FDA 483 was issued at the end of the sponsor inspection.

Specifically, the following regulatory deficiencies were observed:



GCPAB Reviewer's Comment:



(b) (5)

The sponsor, in a written communication dated February 8, 2017, provided an adequate response to the observations listed on the Form FDA 483, Inspectional Observations. Specifically, (b) (5)

Notwithstanding the observed regulatory deficiencies at the sponsor, data submitted by this sponsor appear acceptable in support of the requested indication.

{See appended electronic signature page}

Anthony Orencia, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Janice Pohlman, M.D., M.P.H.
Team Leader, Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

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

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/s/

JANICE K POHLMAN

02/24/2017

Signing for primary author, Anthony Orencia, MD, and myself

KASSA AYALEW

02/27/2017

Division of Hematology Products (DHP) Labeling Review

Application Number	NDA 207997
Application Type	New Molecular Entity
Proprietary Name (nonproprietary name)	Rydapt (midostaurin)
Receipt Date	04/05/2016-08/29/16 (rolling submission)
PDUFA Goal Date	03/01/17
Review Classification	Priority
Proposed Indication (or current indication if unchanged)	For the treatment of patients with newly diagnosed FLT3 mutation positive acute myeloid leukemia (AML) and patients with advanced systemic mastocytosis (Advanced SM).
Dosing Regimen	AML: 50 mg orally twice daily ASM, SM-AHN, and MCL: 100 mg orally twice daily
From	Virginia Kwitkowski, MS, ACNP-BC Associate Director for Labeling, DHP

Background of Application:

In this review, I propose labeling recommendations and edits in the RYDAPT (midostaurin) labeling to ensure that the prescribing information is a useful communication tool for healthcare providers and uses clear, concise language; is based on regulations and guidances; and conveys the essential scientific information needed for the safe and effective use of RYDAPT (midostaurin).

The following pages contain the working version of the RYDAPT (midostaurin) labeling with recommended edits and comments identified as 'VK1' through 'VK105'. This labeling version also includes comments from other members of the review team. Given that the scientific review of the labeling is ongoing, my labeling recommendations in this review should be considered preliminary and may not represent DHP's final recommendations for the RYDAPT (midostaurin) labeling.

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/s/

VIRGINIA E KWITKOWSKI
02/17/2017



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Memorandum

Date: January 27, 2017 **Date Consulted:** September 13, 2016

From: Jane Liedtka M.D., Medical Officer, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Miriam Dinatale, DO, Acting Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, Director
Division of Pediatric and Maternal Health

To: Kimberly Scott, Regulatory Project Manager (RPM)
Office of Hematology and Oncology Products (OHOP)/
Division of Hematology Products (DHP)

Drug: RYDAPT (Midostaurin)

NDA: NDA 207997

Indication: RYDAPT is a protein kinase inhibitor indicated for the treatment of adult patients with:

- Newly diagnosed acute myeloid leukemia (AML) that is Fms-like Tyrosine Kinase 3 (FLT3) mutation-positive as detected by an FDA-approved test.
- Aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated hematological neoplasm (SM-AHN), or mast cell leukemia (MCL).

Applicant: Novartis Pharmaceuticals Corp

Subject: Pregnancy and Lactation labeling

Materials Reviewed:

- Applicant's submitted background package for NDA 207997

- Applicant's revised label, literature review and summary of pharmacovigilance database submitted via email on October 28, 2016.

Consult Question: Labeling Review

INTRODUCTION

On September 13, 2016, DHP consulted DPMH to provide input for appropriate format and content of the pregnancy and lactation sections of RYDAPT (Midostaurin) labeling to be in compliance with the Pregnancy and Lactation Labeling (PLLR) format.

REGULATORY HISTORY

On December 22, 2015, Novartis Pharmaceuticals Corp submitted a new drug application (NDA) for RYDAPT (Midostaurin), a new molecular entity (NME), NDA 207997.

RYDAPT is a protein kinase inhibitor indicated for the treatment of adult patients with:

- Newly diagnosed acute myeloid leukemia (AML) that is Fms-like Tyrosine Kinase 3 (FLT3) mutation-positive as detected by an FDA-approved test.
- Aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated hematological neoplasm (SM-AHN), or mast cell leukemia (MCL).

On October 6, 2016, the Agency sent the Applicant an email requesting that they submit a review and summary of the available published literature and a summary of the Applicant's pharmacovigilance database regarding midostaurin use in pregnant and lactating women. On October 28, 2016, the Applicant submitted the revised labeling and the requested supporting information which was adequate.

BACKGROUND

Midostaurin and Drug Characteristics¹

Midostaurin is a multi-kinase inhibitor. *In vitro* biochemical or cellular assays have shown that midostaurin or its major human active metabolites CGP62221 and CGP52421 inhibit the activity of FLT3 (wild type (b) (4) KIT (wild type and D816V mutant), (b) (4) (PDGFR α), (b) (4) (PDGFR β), (b) (4)

Midostaurin demonstrated the ability to inhibit FLT3 receptor signaling and cell proliferation and induce apoptosis in leukemic cells expressing ITD and TKD mutant FLT3 receptors or overexpressing wild type FLT3 and PDGF receptors. Midostaurin also demonstrated the ability to inhibit KIT signaling, cell proliferation and histamine release or induce apoptosis in mast cells.

The median terminal half-life lives of midostaurin, CGP62221 and CGP52421 in plasma are $\approx$ 20.5, 32.3 and (b) (4) hours. The molecular weight of midostaurin is $\approx$ 571 Daltons.

¹RYDAPT proposed package insert

Midostaurin is greater than (b)(4)% bound to plasma protein, mainly to α 1-acid glycoprotein (AGP).

The most common adverse reactions ($\geq 20\%$) observed in clinical trials for AML were febrile neutropenia, nausea, (b)(4), vomiting, headache, petechiae, (b)(4). The most common adverse reactions ($\geq 20\%$) observed in clinical trials for ASM, SM-AHN or MCL were nausea, vomiting, diarrhea, constipation, abdominal pain, edema, fatigue, upper respiratory tract infection, pyrexia, (b)(4), headache, and dyspnea.

AML and Pregnancy

Acute leukemias rank third after breast and cervical cancer in association with pregnancy.² However, the association of leukemia and pregnancy is uncommon. Its incidence is estimated to be 1 in 75 000–100,000 pregnancies.^{2,3,4} During pregnancy, most leukemias are acute: two-thirds are myeloid and one-third are lymphoblastic. Pregnancy often results in a delay in diagnosis. Because the early symptoms are non-specific, it is estimated that 23% of acute leukemias diagnosed during pregnancy are detected in the first trimester, 37% in the second trimester, and 40% in the third trimester.⁵ Treatment delay until the postpartum period is associated with an increased maternal mortality.^{6,7} Retrospective data suggest that treatment outcomes might be adversely affected when time from diagnosis to start of treatment increases beyond 5 days.⁸ Similarly, modifications of therapy to try to ensure the birth of a healthy infant may adversely affect maternal prognosis.⁹ Remission rates of 70–75% are currently reported for pregnant women.¹⁰ Survival was shown to be significantly longer in the patients whose induction therapy was started before delivery than in those treated after delivery.¹¹

With regard to infant outcomes, chemotherapy during pregnancy has been associated with congenital malformations, increased risk of miscarriage and neonatal bone marrow suppression.^{12,13} The risk of birth defects may also vary according to the time at which the

² Pavlidis NA. Coexistence of pregnancy and malignancy. *Oncologist* 2002;7:279–87.

³ Haas VA. Pregnancy in association with newly diagnosed cancer: a population-based epidemiological assessment. *Int J Cancer* 1984;34:229–35.

⁴ Lichtman MA, Liesveld JL. Acute myelogenous leukemia. In: Beutler E, Lichtman MA, Coller BS, Kipps TJ, Seligsohn U, eds. *Williams Hematology*, 6th edn. New York: McGraw-Hill; 2001.

⁵ Caligiuri MA, Mayer RJ. Pregnancy and leukemia. *Semin Oncol* 1989;16:388–96.

Greenlund LJ, Letendre L, Tefferi A. Acute leukemia during pregnancy: a single institutional experience with 17 cases. *Leuk Lymphoma* 2001;41:571–7.⁶

⁷ Kawamura S, Yoshike M, Shimoyama T, et al. Management of acute leukemia during pregnancy: from the results of a nationwide questionnaire survey and literature survey. *Tohoku J Exp Med* 1994;174:167–75.

⁸ Sekeres MA, Elson P, Kalaycio ME, et al. Time from diagnosis to treatment initiation predicts survival in younger, but not older, acute myeloid leukemia patients. *Blood*. 2009;113:28–36.

⁹ Iseminger KA, Lewis MA. Ethical challenges in treating mother and fetus when cancer complicates pregnancy. *Obstet Gynecol Clin North Am* 1998;25:273–85.

¹⁰ Chelghoum Y, Vey N, Raffoux E, et al. Acute leukemia during pregnancy: a report on 37 patients and a review of the literature. *Cancer* 2005;104:110–7.

¹¹ Kawamura S, Suzuki Y, Tamai Y, Itoh J, Fukushima K, Takami H. Pregnancy outcome among long-term survivors with acute leukemia. *Int J Hematol* 1995;62:157–61.

¹² Cardonick E, Iacobucci A. Use of chemotherapy during human pregnancy. *Lancet Oncol* 2004;5:283–91.

drug is administered during pregnancy and with the dose.¹⁴ The risk of fetal injury induced by the administration of cytotoxic chemotherapy during the first trimester of pregnancy is real but actually occurs in a minority of patients.¹⁵ Teratogenic potential of chemotherapeutic agents is highest between the fifth and 10th week of gestation and then decreases until organogenesis is completed in the 13th week of pregnancy. According to Avivi, “therapeutic abortion should therefore be offered to all patients developing AML during the first semester”.¹⁶ However, successful treatment of AML in pregnant mothers is possible with the fetus *in utero*. Cytotoxic agents appear to be increasingly safer as the pregnancy approaches its term. Chemotherapy after the second trimester is not associated with an increased rate of fetal malformations.^{15,17, 18, 19} From the second trimester onwards, growth restriction is the main risk of chemotherapy. Fetal hematopoiesis was not adversely affected and no malformations were observed when chemotherapy was administered during the third trimester.²⁰

Pregnancy and Lactation Labeling

On June 30, 2015, the “*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,”²¹ also known as the Pregnancy and Lactation Labeling Rule (PLLR) went into effect. The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) are removed from all prescription drug and biological product labeling and a new format is required for all products that are subject to the 2006 Physicians Labeling Rule²² format to include information about the risks and benefits of using these products during pregnancy and lactation.

¹³ Zemlickis D, Lishner M, Degendorfer P, et al. Maternal and fetal outcome after breast cancer in pregnancy. *Am J Obstet Gynecol* 1992;166:781–7.

¹⁴ Thomas, X. Review Article: Acute myeloid leukemia in the pregnant patient. *European Journal of Haematology* . 2015; 95: 124–136.

¹⁵ Doll DC, Ringenberg S, Yarbrow JW. Management of cancer during pregnancy. *Arch Intern Med* 1988;148:2058–64.

¹⁶ Avivi, I and Brenner, B. Management of acute myeloid leukemia during pregnancy. *Future Oncol*. 2014; 10(8): 1407-1415.

¹⁷ Feliu J, Suarez S, Ordonez A, Garcia-Paredes LM, Gonzales- Baron M, Montero JM. Acute leukemia and pregnancy. *Cancer* 1988;61:580–4.

¹⁸ Schafer AI. Teratogenic effects of antileukemic chemotherapy. *Arch Intern Med* 1981;141:514–5.

¹⁹ Buekers TE, Lallas TA. Chemotherapy in pregnancy. *Obstet Gynecol Clin North Am* 1998;25:323–9.

²⁰ Morishita S, Imai A, Kawabaa I, Tamaya T. Acute myelogenous leukemia in pregnancy: fetal blood sampling and early effects of chemotherapy. *Int J Gynaecol Obstet* 1994;44:273–7.

²¹ *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).

²² *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).

REVIEW

Pregnancy

Nonclinical Experience

In animal reproduction studies, oral administration of midostaurin to pregnant rats and rabbits during organogenesis caused embryo-fetal toxicities, including late embryo-fetal death and reduced fetal birth weight, with delays in fetal growth at doses lower than the recommended human dose.

For further details, the reader is directed to the Nonclinical Review by Natalie Simpson, PhD.

Applicant's Review of Literature

A review of the literature was not requested by the Agency.

DPMH's Review of Literature

DPMH conducted a search of published literature in PubMed and Embase using the search terms “midostaurin and pregnancy,” “midostaurin and pregnant women,” “midostaurin and pregnancy and birth defects,” “midostaurin and pregnancy and congenital malformations,” “midostaurin and pregnancy and stillbirth,” “midostaurin and spontaneous abortion” and “midostaurin and pregnancy and miscarriage.” No reports of adequate and well-controlled studies of midostaurin use in pregnant women were found. No published case reports involving pregnancy in midostaurin patients were identified.

The only notation regarding midostaurin in Micromedex²³ was under “Investigational Drugs - New Drug Application (NDA) Status” which contains only a brief summary of proposed indication, date application was filed with the FDA and sponsor's name.

Pharmacovigilance Database Summary

The following table provides all of the available information (according to the applicant) on subjects in midostaurin clinical trials who became pregnant:

²³ Truven Health Analytics information, <http://www.micromedexsolutions.com/>. Accessed 7/1/16.

Table 1: Pregnancies in Subjects in Midostaurin Clinical Trials

Subject # /patient ID	Exposure	Dates	Pregnancy Outcomes	Fetal Outcomes	Comments
#1 114290	Yes	1/19/09- 11/6/09	Elective abortion at week 12	Not reported	31-year-old patient on study drug for about 9 months; an abortion was done at 12 weeks of pregnancy and she received re-induction chemotherapy as she had blast crisis secondary to AML relapse
#2 ADE02T	Yes – pregnancy was 50 days post treatment	12/17/14- 12/22/14	Elective abortion at week 5	Not reported	28-year-old patient became pregnant about 50 days after the last intake of midostaurin; she had intentional abortion upon diagnosis at 5 weeks of gestation
#3 117819	Unclear – pregnancy occurred at an unknown time post treatment	10/22/09- 5/17/11	Planned abortion at week 8	Not reported	43-year-old became pregnant after midostaurin treatment was completed; No other details were provided
#4 119815	No – pregnancy was 2 years post treatment	3/25/10- 9/6/11	(labor - 6 hours and 50 minutes) at 40 weeks	neonate (height 53 cm, weight 3.6 kg, Apgar score 9,10,10 and head circumference 35cm.	32-year-old patient delivered a healthy on term baby 2 years after the last intake of midostaurin; the pregnancy was voluntary
#5 127134	No –treated after delivery	Not reported	Not reported	Not reported	31-year-old patient with AML detected at 30weeks of gestation. The patient started study treatment 4 days after delivering her baby.
#6 126089	No-placebo	Not reported	Loss of pregnancy at 8 weeks	Not reported	35-year-old patient became pregnant during study treatment, however the exact details of the drug intake were not provided
#7 118033	No-placebo	4/11/09- 5/25/11	Post mature male infant (41+4), C section delivery	Not reported	37-year-old patient gave birth 4.5 years after stopping midostaurin
#8 119003	No-placebo	1/26/10- 9/4/11	Elective abortion	Not reported	33-year-old patient who became pregnant more than one year after study

Summary

Human pregnancy outcome data for midostaurin were not found in the published literature. There were no cases of midostaurin exposure during pregnancy with fetal outcome information available from the applicant's pharmacovigilance database. The findings in animal studies did demonstrate risk to the fetus. Since there is a concern for fetal risk based on mechanism of action

and animal studies, DPMH recommends that a boxed warning for embryofetal toxicity be added to labeling for midostaurin and recommends verification of pregnancy status prior to treatment in females of reproductive potential. DPMH also recommends effective contraception during treatment and for 4 months following the last dose.

Lactation

Nonclinical Experience

There is no information regarding the presence of midostaurin in human milk. Midostaurin is present in the milk of lactating rats.

For further details, the reader is directed to the Nonclinical Review by Natalie Simpson, PhD.

Applicant's Review of Literature

A review of the literature was not requested by the Agency.

DPMH Review of Literature

DPMH conducted a search of *Medications and Mother's Milk*²⁴, the Drugs and Lactation Database (LactMed),²⁵ Micromedex²⁶, and of published literature in PubMed and Embase using the search terms "midostaurin and lactation" and "midostaurin and breastfeeding." No reports of adequate and well-controlled studies of midostaurin use in lactating women were found. No published case reports involving lactation in midostaurin patients were identified.

No mention of midostaurin was found in *Medications and Mother's Milk*¹⁴. Midostaurin is not referenced in LactMed.

Summary

There are no data on the presence of midostaurin or its active metabolites in human milk, the effect on the breastfed infant, or the effect on milk production. Orally administered midostaurin and its active metabolites pass into the milk of lactating rats. Because of the potential for serious adverse reactions in breastfed infants from RYDAPT, including neutropenia and infection, advise women not to breastfeed during treatment with RYDAPT and for at least 4 months following the last dose.

²⁴ Hale, Thomas (2012) *Medications and Mothers' Milk*. Amarillo, Texas Hale Publishing, pg. 422-423.

²⁵ <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

²⁶ Truven Health Analytics information, <http://www.micromedexsolutions.com/>. Accessed 7/1/16.

Use in Females and Males of Reproductive Potential

Nonclinical Experience

Carcinogenicity studies have not been performed with midostaurin. Midostaurin was not mutagenic or clastogenic.

Reproductive toxicity was observed in a fertility study, in which treated female rats were mated with treated males at oral doses of 10, 30 and 60 mg/kg/day of midostaurin (approximately 0.02, 0.11, and 0.13 times, respectively, the AUC in patients with cancer at the recommended human dose of 50 mg BID). In males, testicular degeneration and atrophy was observed at doses greater than or equal to 10 mg/kg/day and reduced and reduced sperm count and motility, and a decrease in reproductive organ weights were observed at 60 mg/kg/day. In females, increased resorptions (including total resorption of litter), decreased pregnancy rate, number of implants and live embryos were observed at 60 mg/kg/day. When F1 generation males were mated with F1 females from dams treated with 30 mg/kg/day midostaurin in an oral pre- and postnatal development study in the rat, the number of implantation sites and live fetuses/litter were reduced. In a 3-month toxicology study in dogs, there was inhibition of spermatogenesis was seen in dogs at doses greater than or equal to 3 mg/kg/day (approximately 0.012 times the exposure measured by AUC in patients with cancer at the recommended human dose).

For further details, the reader is directed to the Nonclinical Review by Natalie Simpson, PhD.

Applicant's Review of Literature

A review of the literature was not requested by the Agency.

DPMH's Review of Literature

DPMH conducted a search of published literature in PubMed and Embase regarding midostaurin and its effects on fertility and found no relevant articles regarding the topic.

Summary

Based on findings in animals, midostaurin may impair fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible. There are no human data available on the effect of midostaurin on fertility. Therefore, section 8.3 will also contain a section describing the potential for midostaurin to impair female and male fertility.

CONCLUSIONS

Based on the literature review and review of the pharmacovigilance database, DPMH has the following recommendations for RYDAPT (midostaurin) labeling:

- **Warnings and Precautions, Section 5.3**
 - The “Warnings and Precautions” section of RYDAPT (midostaurin) labeling was updated to correspond with changes made to the FPI and sections 8.1, 8.2, 8.3 and 17 of labeling.
- **Pregnancy, Section 8.1**
 - The “Pregnancy” section of RYDAPT (midostaurin) labeling was structured in the PLLR format to include the “Risk Summary” and “Data” sections.²⁷
- **Lactation, Section 8.2**
 - The “Lactation” section of RYDAPT (midostaurin) labeling was formatted in the PLLR format to include the “Risk Summary” section.²⁸
- **Females and Males of Reproductive Potential, Section 8.3**
 - The “Females and Males of Reproductive Potential” section of RYDAPT (midostaurin) labeling was formatted in the PLLR format to include the “Pregnancy Testing”, “Contraception” and “Infertility” sections.²⁹
- **Patient Counseling Information, Section 17**
 - The “Patient Counseling Information” section of RYDAPT (midostaurin) labeling was updated to correspond with changes made to sections 5, 8.1, 8.2 and 8.3 of labeling.

LABELING RECOMMENDATIONS

DPMH revised the HPI, sections 5.4, 8.1, 8.2 and 8.3 and 17 of RYDAPT (midostaurin) labeling for compliance with the PLLR (see below). DPMH discussed our labeling recommendations with DHP on 1/26/17. DPMH refers to the final NDA action for final labeling.

²⁷ *Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format*. December 2014. Part IV Specific Subsection A-8.1 Pregnancy, 2-Risk Summary.

²⁸ *Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format*. December 2014. Part IV Specific Subsection, B- 8.2 Lactation, 1- Risk Summary.

²⁹ *Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format*. December 2014. Part IV Specific Subsection C-8.3 Females and Males of Reproductive Potential.

DPMH Proposed RYDAPT (midostaurin) Pregnancy and Lactation Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

WARNING: EMBRYO-FETAL TOXICITY

See full prescribing information for complete boxed warning.

- Midostaurin caused embryo-fetal toxicity, including embryo-fetal death, in animal studies. If midostaurin is used during pregnancy, it can cause birth defects or embryo-fetal death (5.2, 8.1).
- Verify the pregnancy status of females of reproductive potential within 7 days prior to initiating RYDAPT therapy. Advise females of reproductive potential to use effective contraception during treatment and for at least 4 months after last dose (8.3).

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

- Lactation: Advise not to breastfeed. (8.2)

FULL PRESCRIBING INFORMATION

WARNING: EMBRYO-FETAL TOXICITY

Do not use RYDAPT during pregnancy. Midostaurin caused severe embryo-fetal abnormalities and embryo-fetal death. If midostaurin is used during pregnancy, it may cause birth defects or embryo-fetal death. Verify the pregnancy status of females of reproductive potential within 7 days prior to initiating RYDAPT therapy. Advise females of reproductive potential to use effective contraception during and for at least 4 months after RYDAPT therapy [see Warnings and Precautions (5.2), Use in Specific Populations (8.1, 8.3)].

5.2 Embryo-Fetal Toxicity

Based on its mechanism of action and findings from animal reproduction studies, RYDAPT (b) (4) cause fetal harm when administered to pregnant women. In animal (b) (4) studies, (b) (4) midostaurin (b) (4) caused embryo-fetal toxicities, including late embryo-fetal death and reduced fetal birth weight, with delays in fetal growth at doses lower than the recommended human dose. Advise pregnant women of the potential risk to the fetus. Verify the pregnancy status of females of reproductive potential within 7 days prior to initiating RYDAPT therapy. Advise females of reproductive potential to use effective contraception during treatment with RYDAPT and for at least 4 months after the last dose [see Use in Specific Populations (8.1, 8.3) and Clinical Pharmacology (12.1)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on mechanism of action and findings in animal reproduction studies, RYDAPT can cause fetal harm when administered to a pregnant woman [see *Clinical Pharmacology* (12.1)]. There are no available data on RYDAPT use in pregnant women. In animal reproduction studies, oral administration of midostaurin to pregnant rats and rabbits during organogenesis caused embryo-fetal toxicities, including late embryo-fetal death and reduced fetal birth weight, with delays in fetal growth at doses lower than the recommended human dose [see *Data*]. Advise pregnant women of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated population are unknown. (b) (4)

(b) (4) In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

When midostaurin was administered to female rats prior to mating and through the first week of pregnancy at a dose of 60 mg/kg/day (approximately 0.1 (b) (4) times the human exposure at the recommended dose based on AUC), there were increases in pre-implantation loss and post-implantation loss, including total litter loss, resulting in a reduction in the number of live embryos.

During organogenesis, midostaurin administered at oral doses (b) (4) than or equal to 3 mg/kg/day (approximately 0.004 times the human exposure at the recommended dose by AUC) to pregnant female rats caused late embryofetal death (b) (4) (dilated brain ventricles, renal pelvic cavitation, (b) (4) in the absence of maternal toxicity at the highest dose of 30 mg/kg/day (approximately (b) (4) times the human exposure at the recommended dose by AUC). (b) (4) midostaurin (b) (4) administered orally to pregnant rabbits during organogenesis, maternal toxicity (b) (4) some delay in fetal growth (reduced fetal birth weight, (b) (4) at doses greater than or equal to 10 mg/kg/day (approximately (b) (4) times the human exposure at the recommended dose by AUC).

In an oral pre- and postnatal development study in the rat, adverse effects upon maternal performance included dams with signs of dystocia and a lower live litter size at 30 mg/kg/day (approximately (b) (4) times the human exposure at the recommended dose by AUC). For the F1 offspring, lower body weights, accelerated complete eye opening and delayed auricular startle ontogeny were noted at 30 mg/kg/day.

8.2 Lactation

Risk Summary

There are no data on the presence of midostaurin or its active metabolites in human milk, the effect on the breastfed infant, or the effect on milk production. Orally administered midostaurin and its active metabolites pass into the milk of lactating rats. Because of the potential for serious adverse reactions in breastfed infants from RYDAPT (b)(4) advise women not to breastfeed during treatment with RYDAPT and for at least 4 months following the last dose.

8.3 Females and Males of Reproductive Potential

Pregnancy testing

Pregnancy testing is recommended for females of reproductive potential within seven days prior to initiating RYDAPT.

Contraception

Females

RYDAPT can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with RYDAPT and for 4 months after the last dose [see *Use in Specific Populations* (8.1)].

Infertility

Based on findings in animals, RYDAPT may impair fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible [see *Nonclinical Toxicology* (13.1)].

• 17 PATIENT COUNSELING INFORMATION

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

- Embryo-Fetal Toxicity
 - Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with RYDAPT and for at least 4 months after the last dose. Advise females to inform their healthcare provider of a known or suspected pregnancy [see *Warnings and Precaution* (5.3) and *Use in Specific Populations* (8.1, 8.3)].
- Lactation
 - Advise women not to breastfeed during treatment with RYDAPT and for at least 4 months after the last dose [see *Use in Specific Populations* (8.2)].
- Infertility

- Advise females and males of reproductive potential that RYDAPT may impair fertility [see *Use in Specific Populations (8.3) and Nonclinical Toxicology (13.1)*]

APPEARS THIS WAY ON ORIGINAL

Applicant Proposed RYDAPT (midostaurin) Pregnancy and Lactation Labeling

(b) (4)

2 Page(s) of Draft Labeling have been Withheld in Full as
B4 (CCI/TS) immediately following this page

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

/s/

JANE E LIEDTKA
01/27/2017

MIRIAM C DINATALE
01/27/2017

LYNNE P YAO
01/27/2017

CLINICAL OUTCOME ASSESSMENT CONSULT REVIEW

Template version: June 24, 2015

CLINICAL OUTCOME ASSESSMENT (COA)	AT 2016-240
TRACKING NUMBER	
IND/NDA/BLA NUMBER	NDA 207997
LETTER DATE/SUBMISSION NUMBER	August 29, 2016
PDUFA GOAL DATE	November 15, 2016
DATE OF CONSULT REQUEST	September 27, 2016
REVIEW DIVISION	Division of Hematology Products
MEDICAL REVIEWER	Yvette Kasamon
REVIEW DIVISION PM	Kimberly Scott
PRIMARY COA REVIEWER	Wen-Hung Chen
SECONDARY COA REVIEWER	Selena Daniels
ASSOCIATE DIRECTOR, COA STAFF (ACTING)	Elektra Papadopoulos
REVIEW COMPLETION DATE	January 9, 2017
ESTABLISHED NAME	midostaurin
TRADE NAME	Rydapt (PKC412)
SPONSOR/APPLICANT	Novartis
CLINICAL OUTCOME ASSESSMENT TYPE	Patient-reported outcome (PRO)
ENDPOINT(S) CONCEPT(S)	Symptom frequency, severity, and distress
MEASURE(S)	Memorial Symptom Assessment Scale (MSAS)
INDICATION	As single-agent therapy for the treatment of patients with aggressive systemic mastocytosis (ASM) or mast cell leukemia (MCL) (b) (4) (collectively referred to as advanced SM).
INTENDED POPULATION(S)	Patients, aged ≥ 18 years old, with ASM or MCL (b) (4)

A. EXECUTIVE SUMMARY

This Clinical Outcome Assessment review is provided as a response to a request for consultation by the Division of Hematology Products (DHP) regarding NDA 207997 for the treatment of adult patients with advanced systemic mastocytosis.

The applicant used the patient-reported outcome (PRO) assessment, Memorial Symptom Assessment Scale (MSAS; located in Appendix 1), for the measurement of cancer symptoms (frequency, severity, and distress) for use as an exploratory endpoint in their phase 3 clinical trial (Study PKC412D2201). The PRO endpoint was not included in the endpoint hierarchy nor adjusted for multiplicity.

(b)(4)

DHP requested COA Staff to review the validity of the PRO assessment and the interpretability of the results.

This submission did not include an evidence dossier describing the development of the PRO assessment. However, the existing literature indicates that the MSAS was developed for solid tumor cancers and not in the proposed context of use for mastocytosis (Portenoy, 1994). There are some limitations surrounding data interpretability due to the single-arm open label study design. We acknowledge these limitations and defer to the Division (b)(4)

Therefore, the subject of this review focuses on the adequacy of the instrument within the specified population.

The review concludes that the evidence submitted by the applicant is insufficient to demonstrate that the MSAS is adequate to measure the frequency, severity, and distress of cancer symptoms in the proposed context of use.

Our specific comments are as follows:

- Lack of data supporting the development of the MSAS in the specified context of use (i.e., mastocytosis).

Clinical Outcome Assessment Review

Wen-Hung Chen

NDA 207997

midostaurin/Rydapt

MSAS/Symptoms associated with cancer

- MSAS combines both disease related symptoms and treatment related symptoms, which may make interpretation of the scores and results difficult.
- The open label nature of the trial may influence how patients assessed their symptoms. The amount of the influence is unknown.
- The study sample was not enriched to detect symptom improvement as the patients appeared not symptomatic at baseline. The mean and median MSAS total score were 1.0 and 1.0 at baseline indicating that at least half of the study sample rarely experienced the symptoms.
- There was a large amount of incomplete MSAS at baseline (43%) and throughout the study (> 30% excluding early drop-outs). We cannot reliably interpret the findings with this large amount of the missing PRO data.
- PRO hypothesis was not tested within the main statistical hierarchy of the clinical trial (b) (4)

B. CLINICAL OUTCOME ASSESSMENT REVIEW

Materials reviewed:

- Clinical Study Report: “Midostaurin/PKC412, PKC412D2201 - A single arm, Phase II, open-label study to determine the efficacy of 100 mg twice daily oral dosing of midostaurin administered to patients with aggressive systemic mastocytosis or mast cell leukemia +/- an associated hematological clonal non-mast cell lineage disease. Novartis, June, 28, 2016.
- Portenoy RK, Thaler HT, Kornblith AB, et al. (1994). The Memorial Symptom Assessment Scale: an instrument for the evaluation of symptom prevalence, characteristics and distress. *Eur J Cancer*; 30A(9):1326-36.

Mastocytosis is a myeloproliferative neoplasm (MPN), resulting from a clonal, neoplastic proliferation of abnormal mast cells (MC) that accumulate in one or more organs. According to the World Health Organization (WHO) classification system, 4 major variants of systemic mastocytosis (SM) are recognized: indolent systemic mastocytosis (ISM), SM with associated clonal hematological non-mast cell lineage disease (SM-AHNMD), aggressive systemic mastocytosis (ASM), and mast cell leukemia (MCL). SM is characterized by MC proliferation and accumulation in one or more extracutaneous organs, including the bone marrow (BM), gastrointestinal tract, liver and spleen. The clinical severity of SM varies from indolent and asymptomatic to a highly aggressive course (e.g., ASM or MCL). Patients with ASM, SM-AHNMD or MCL have limited treatment options and have generally a poor prognosis with a shortened life expectancy.

1 CONTEXT OF USE (COU)

1.1 Target Study Population and Clinical Setting

Male and female patients, aged ≥ 18 years old, diagnosed with aggressive systemic mastocytosis (ASM) or mast cell leukemia (MCL) with or without an associated clonal hematologic non-mast cell lineage disease (AHNMD) – collectively called advanced systemic mastocytosis (Advanced SM).

Key inclusion criteria:

- Patients ≥ 18 years of age who provided written informed consent, Eastern Cooperative Oncology Group (ECOG) performance status of 0-3 and a life expectancy of >12 weeks, electrocardiogram with a QTcF of ≤ 450 ms, with a diagnosis of SM and sub-variants based on WHO criteria.
- Patients with ASM or MCL were to have one or more measurable clinical findings (termed "C findings") and defined as those attributable to the mast cell disease component and not to AHNMD or any other cause.
- Patients with MCL were to have BM aspirate smears with $\geq 20\%$ immature MCs. Patients with AHNMD were eligible if it was not life-threatening or in an acute stage.

Key exclusion criteria:

- Patients with cardiovascular disease including congestive heart failure class III or IV according to the New York Heart Association classification, left ventricular ejection fraction (LVEF) of $<50\%$, myocardial infarction within the previous 6 months, or poorly controlled hypertension.
- Patients with a heart block of any degree at screening (for Canada only).
- Patients with an AHNMD who required immediate cytoreductive therapy or targeted therapy (other than midostaurin).
- Patients who had demonstrated relapse after 3 or more prior regimens of SM treatment regardless of treatment regimen for supportive care (e.g., symptom-limiting therapies).

1.2 Clinical Trial Design, Protocol, and Analysis Plan

Study PKC412D2201 is a non-randomized, single arm, open-label multi-center study using a Fleming two-stage design to determine the efficacy and safety of twice daily (bid) oral midostaurin in patients with ASM or MCL with or without AHNMD. Midostaurin was administered at a dose of 100 mg bid in continuous cycles of 28 days until disease progression, intolerable toxicity or withdrawal due to any cause, whichever occurred first. The end of study will occur 5 years after last patient first treatment, or when all patients have discontinued the study treatment, whichever occurs first.

The primary objective was to determine the efficacy of midostaurin when administered orally at a dose of 100 mg bid continuously for 6 cycles (of 4 weeks each) in patients with ASM or MCL with or without AHNMD as measured by overall response rate (ORR).

A total of 40 patients eligible for response were planned to be enrolled in the primary efficacy population (PEP) in the Stage I phase of the Study. Enrollment into the Stage II phase was to begin if $\geq 15/40$ responders (confirmed by the SSC adjudication) were observed in the Stage I. Enrollment into the extension phase was to begin as soon as the SSC had identified ≥ 19 responders among the first 40 eligible patients enrolled into the Stage I phase or when ≥ 27 responders among the first 60 eligible patients enrolled into Stage II phase were identified.

A total of 116 patients were treated with midostaurin, and among these 63 patients were enrolled into the Stage I phase and 53 patients were enrolled into the extension phase. Eighty-nine patients were deemed to be eligible for response according to the SSC and were included in the PEP.

The statistical analysis was performed using all data collected in the database for all enrolled patients up to the data cut-off date (01-Dec-2014). The cut-off date was designated to ensure that all patients enrolled in the study and deemed eligible by the SSC had been followed for at least 29 months or had been discontinued from the study.

1.3 Endpoint Positioning

The primary efficacy variable, ORR was defined as the proportion of patients with a best response of (major response (MR) or partial response (PR) that initially occurred in the first 6 cycles of treatment as assessed by the Study Steering Committee (SSC) using modified Valent/Cheson criteria and that was confirmed at least 56 days later.

Secondary efficacy variables were:

- Duration of response (DoR)
- Time to response (TTR)
- Progression-free survival (PFS)
- Overall survival (OS)
- Histopathologic response based on mast cell (MC) infiltration in the bone marrow (BM) and changes in serum tryptase levels as surrogate marker for histopathologic response

PRO as assessed by MSAS was an exploratory efficacy variable.

(b) (4)

2 CONCEPT OF INTEREST (COI) AND CONCEPTUAL FRAMEWORK

The concept of interest are symptoms commonly associated with cancer. Thirty-two items were identified pertaining to symptom assessment and control. Three dimensions were chosen as potentially relevant to symptom evaluation: (1) severity of the symptom; (2) frequency with which it occurs; and (3) the distress it produces.

Among the 32 symptoms, there are two main factors, psychological and physical symptoms, that distinguish three major groups of symptoms, psychological symptoms, high prevalence physical symptoms, and low prevalence physical symptoms. The psychological group can be divided into two subgroups, psychological state and concentration. The high prevalence physical symptoms, has two subgroups, symptoms associated with pain and its treatment and gastrointestinal symptoms.

3 CLINICAL OUTCOME ASSESSMENT (COA) MEASURE(S)

The MSAS questions (Appendix 1) asks patients about their experiences of 32 symptoms during the previous week. Twenty-four symptoms are evaluated in terms of severity, frequency and distress, and eight symptoms are evaluated in terms of severity and distress. A patient may indicate that a symptom was not experienced by checking a column labeled 'did not have.' If a symptom was experienced, the patient describes its severity and frequency, if appropriate, on a 4-point categorical scale; and its associated distress on a 5-point categorical scale.

The values for the severity and frequency measurements are on a scale of 1 to 4, where 1 is 'slight' on the severity scale and 'rarely' on the frequency scales, and 4 is 'very severe' on the severity scale and 'almost constantly' on the frequency scale. For ease of calculation, the values on the distress scale are set to a range that is roughly similar to the other dimensions: 'not at all' is scored as 0.8, 'a little bit' is 1.6, 'somewhat' is 2.4, 'quite a bit' is 3.2, and 'very much' is 4.

The initial step calculates a score for each symptom. If a symptom is not experienced, each dimension is scored as 0, and the score for that symptom is 0. If a symptom is experienced, the score for that symptom is determined as the average of the scores on the severity, frequency and

distress scales, or if appropriate, on the severity and distress scales only. Items that are missing are simply not included in the calculation of this symptom score. If a symptom that is supposed to have all three dimensions completed by the patient actually has two dimensions completed, the score for that symptom is the average of the two items rather than the three items. Only a selected amount of missing data should be allowed before a patient is excluded from the calculation of MSAS scores. The developers of MSAS used missing of 13% of the items as the criterion for excluding patients their study for the development of MSAS.

In calculating the Global Distress Index, only one dimension is used for each symptom, and the score on the single dimension is considered the symptom score. A short form of the MSAS can be developed that similarly used a score on a single dimension as the overall symptom score. The symptom scores are combined into various subscale scores:

- (1) The Psychological (PSYCH) subscale score is the average of the symptom scores for six symptoms: feeling sad, worrying, feeling irritable, feeling nervous, difficulty sleeping and difficulty concentrating;
- (2) The Physical (PHYS) subscale score is the average of the symptom scores for the 12 symptoms identified as high prevalence physical symptoms: lack of appetite, lack of energy, pain, feeling drowsy, constipation, dry mouth, nausea, vomiting, change in taste, weight loss, feeling bloated and dizziness;
- (3) The Global Distress Index is the average of the single dimension scores for 10 symptoms: the frequency scores for feeling sad, worrying, feeling irritable and feeling nervous, and the distress scores for lack of appetite, lack of energy, pain, feeling drowsy, constipation and dry mouth; and
- (4) The total MSAS score is the average of the symptom scores for all 32 symptoms.

If the original MSAS is used, each symptom score is an average of the dimensions; if the short form is used, each symptom score is the score on the single dimension used to assess the symptom. The total MSAS score can provide valid information about symptom distress, but is less meaningful from the clinical perspective than the Global Distress Index.

4 CONTENT VALIDITY

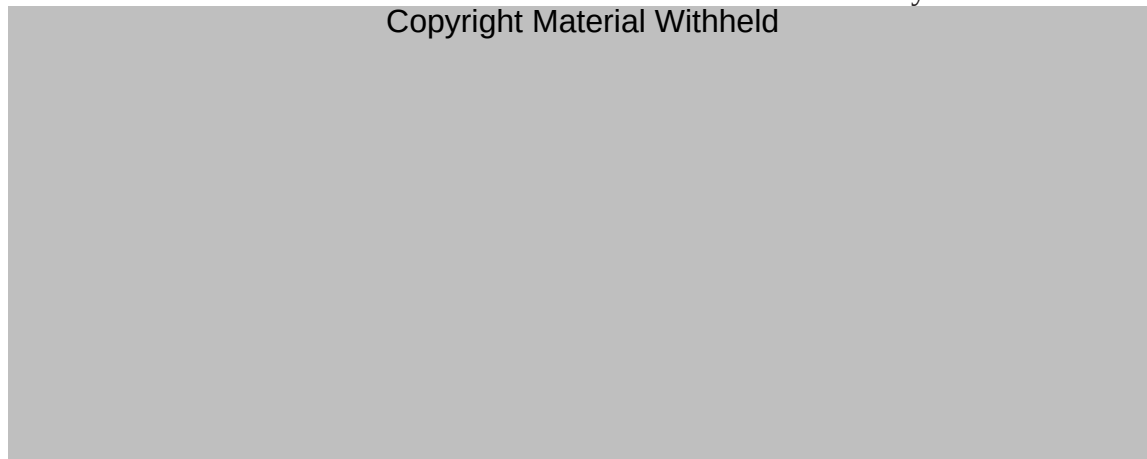
The only support of content validity is the statement in the publication where the developer of the MSAS reported that thirty-three symptoms commonly associated with cancer were selected following a review of the literature pertaining to symptom assessment and control (Portenoy et al, 1994). To the reviewer's best knowledge, no other information on content validity of MSAS is available.

5 OTHER MEASUREMENT PROPERTIES (RELIABILITY, CONSTRUCT VALIDITY, ABILITY TO DETECT CHANGE)

The reliability of MSAS was not reported.

Convergent validity of the MSAS was reported in Portenoy et al, 1994, with correlation with other similar measures (Table 1).

Table 1. Correlations between validation measures and MSAS summary scales and subscales
Copyright Material Withheld

A large rectangular area is completely redacted with a solid gray fill, obscuring the data for Table 1.

Known group validity was reported in Portenoy et al, 1994, by the scoring difference between inpatients and outpatients, and among patients with different extent of disease (Table 2).

Table 2. MSAS scores in inpatients versus outpatients and advanced disease versus early disease
Copyright Material Withheld

A large rectangular area is completely redacted with a solid gray fill, obscuring the data for Table 2.

No other measurement properties were reported.

6 INTERPRETATION OF SCORES

This submission did not include information on interpretation of scores for review.

7 LANGUAGE TRANSLATION AND CULTURAL ADAPTATION

This submission did not include information on language translation or culture adaptation for review.

8 REFORMATTING FOR NEW METHOD OR MODE OF ADMINISTRATION

Not applicable.

9 REVIEW USER MANUAL

This submission did not include a user manual for review.

10 KEY REFERENCES FOR MEASURE

Portenoy RK, Thaler HT, Kornblith AB, et al (1994) The Memorial Symptom Assessment Scale: an instrument for the evaluation of symptom prevalence, characteristics and distress. Eur J Cancer; 30A(9):1326-36.

C. APPENDICES

Appendix 1. Memorial Symptom Assessment Scale (MSAS)

Appendix 1. Memorial Symptom Assessment Scale (MSAS)

MEMORIAL SYMPTOM ASSESSMENT SCALE														
Name										Date				
Section 1														
Instructions: We have listed 24 symptoms below. Read each one carefully. If you have had the symptom during this past week, let us know how <u>OFTEN</u> you had it, how <u>SEVERE</u> it was usually and how much it <u>DISTRESSED</u> or <u>BOTHERED</u> you by circling the appropriate number. If you <u>DID NOT HAVE</u> the symptom, make an "X" in the box marked "<u>DID NOT HAVE</u>."														
<u>DURING THE PAST WEEK</u> Did you have any of the following symptoms?	D I D N O T H A V E	<u>IF YES</u> How <u>OFTEN</u> did you have it?				<u>IF YES</u> How <u>SEVERE</u> was it usually				<u>IF YES</u> How much did it <u>DISTRESS</u> or <u>BOTHER</u> you?				
		Rarely	Occasionally	Frequently	Almost Constantly	Slight	Moderate	Severe	Very Severe	Not at all	A Little Bit	Somewhat	Quite a Bit	Very Much
Difficulty concentrating		1	2	3	4	1	2	3	4	0	1	2	3	4
Pain		1	2	3	4	1	2	3	4	0	1	2	3	4
Lack of energy		1	2	3	4	1	2	3	4	0	1	2	3	4
Cough		1	2	3	4	1	2	3	4	0	1	2	3	4
Feeling nervous		1	2	3	4	1	2	3	4	0	1	2	3	4
Dry mouth		1	2	3	4	1	2	3	4	0	1	2	3	4
Nausea		1	2	3	4	1	2	3	4	0	1	2	3	4
Feeling drowsy		1	2	3	4	1	2	3	4	0	1	2	3	4
Numbness/tingling in hands/feet		1	2	3	4	1	2	3	4	0	1	2	3	4
Difficulty sleeping		1	2	3	4	1	2	3	4	0	1	2	3	4
Feeling bloated		1	2	3	4	1	2	3	4	0	1	2	3	4
Problems with urination		1	2	3	4	1	2	3	4	0	1	2	3	4
Vomiting		1	2	3	4	1	2	3	4	0	1	2	3	4
Shortness of breath		1	2	3	4	1	2	3	4	0	1	2	3	4
Diarrhea		1	2	3	4	1	2	3	4	0	1	2	3	4
Feeling sad		1	2	3	4	1	2	3	4	0	1	2	3	4
Sweats		1	2	3	4	1	2	3	4	0	1	2	3	4
Worrying		1	2	3	4	1	2	3	4	0	1	2	3	4
Problems with sexual interest or activity		1	2	3	4	1	2	3	4	0	1	2	3	4
Itching		1	2	3	4	1	2	3	4	0	1	2	3	4
Lack of appetite		1	2	3	4	1	2	3	4	0	1	2	3	4
Dizziness		1	2	3	4	1	2	3	4	0	1	2	3	4
Difficulty swallowing		1	2	3	4	1	2	3	4	0	1	2	3	4
Feeling irritable		1	2	3	4	1	2	3	4	0	1	2	3	4

Clinical Outcome Assessment Review
Wen-Hung Chen
NDA 207997
midostaurin/Rydapt
MSAS/Symptoms associated with cancer

Section 2										
INSTRUCTIONS: We have listed 8 symptoms below. Read each one carefully. If you have had the symptom during this past week, let us know how SEVERE it was usually and how much it DISTRESSED or BOTHERED you by circling the appropriate number. If you DID NOT HAVE the symptom, make an "X" in the box marked "DID NOT HAVE."										
<u>DURING THE PAST WEEK.</u> Did you have any of the following symptoms?	D I D N O T H A V E	IF YES How SEVERE was it usually?				IF YES How much did it DISTRESS or BOTHER you?				
		Slight	Moderate	Severe	Very Severe	Not at all	A little bit	Somewhat	Quite a bit	Very much
Mouth sores		1	2	3	4	0	1	2	3	4
Change in the way food tastes		1	2	3	4	0	1	2	3	4
Weight loss		1	2	3	4	0	1	2	3	4
Hair loss		1	2	3	4	0	1	2	3	4
Constipation		1	2	3	4	0	1	2	3	4
Swelling of arms or legs		1	2	3	4	0	1	2	3	4
"I don't look like myself"		1	2	3	4	0	1	2	3	4
Changes in skin		1	2	3	4	0	1	2	3	4
IF YOU HAD ANY OTHER SYMPTOMS DURING THE PAST WEEK, PLEASE LIST BELOW AND INDICATE HOW MUCH THE SYMPTOM HAS DISTRESSED OR BOTHERED YOU.										
Other:						0	1	2	3	4
Other:						0	1	2	3	4
Other:						0	1	2	3	4

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

/s/

WEN-HUNG CHEN
01/09/2017

SELENA R DANIELS
01/10/2017

ELEKTRA J PAPADOPOULOS
01/10/2017

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

NDA	NDA 207997
Brand Name	Rydapt
Generic Name	Midostaurin (PKC412)
Sponsor	Novartis Pharmaceuticals Corporation
Indication	Treatment of adult patients with advanced systemic mastocytosis (Advanced SM)
Dosage Form	Capsule
Drug Class	Protein kinase C (PKC) inhibitor
Therapeutic Dosing Regimen	50 mg b.i.d. for acute myeloid leukemia (AML); 100 mg b.i.d. for advanced systemic mastocytosis (AdSM)
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	MTD not defined as no DLT observed. MFD (maximum feasible dose) is 225-300 mg/day based on GI toxicity and max. acceptable number of capsule intake
Submission Number and Date	SDN 002; 29 Aug 2016
Review Division	DHP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No significant QTc prolongation effect of midostaurin (PKC412) (75 mg b.i.d.) was detected in TQT study PKC412A2113. The largest upper bound of the two-sided 90% CI for the mean difference between midostaurin and placebo was below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI for the $\Delta\Delta\text{QTcF}$ for moxifloxacin was 4.5 ms, slightly less than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 3, indicating that assay sensitivity was established.

The major limitation of the TQT study is the dose does not cover the steady state therapeutic exposures of metabolite CGP52421. At steady state, the observed mean C_{max} is 5670 ng/mL following 50 mg b.i.d. dosing (same dosing as proposed for AML indication) in diabetes mellitus patients and mean C_{min} is 2742 ng/mL following 100 mg

b.i.d. dosing in AdSM patients. These CGP52421 concentrations are 5-fold and 2.4-fold of the mean $C_{\max}$ observed in the TQT study.

In this randomized, blinded, 3-arm parallel TQT study, 192 healthy subjects were randomized to receive midostaurin 75 mg b.i.d. on days 1 and 2 and o.d. on day 3, placebo, and a single oral dose of moxifloxacin 400 mg. Overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bound for Midostaurin (75 mg b.i.d.) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Day	Time (hour)	$\Delta\Delta QTcF$ (ms)	90% CI (ms)
Midostaurin (75 mg b.i.d.)	3	24	0.6	(-3.5, 4.7)
Moxifloxacin 400 mg*	3	1	10.7	(4.5, 16.9)

* Multiple endpoint adjustment of 3 time points was applied.

The relationships between $\Delta\Delta QTcF$ and concentrations for midostaurin and metabolites (CGP62221 and CGP52421), investigated by linear mixed-effects modeling, showed no exposure-response relationship for any of these moieties (no statistically significant positive slope).

The 75 mg b.i.d. midostaurin dose in this study exceeds the proposed 50 mg b.i.d. dose for the treatment of acute myeloid leukemia (AML), while it is lower than the proposed 100 mg b.i.d. dose for the treatment of advanced systemic mastocytosis (AdSM). The peak midostaurin concentrations on Day 3 in this study are not higher than those for the expected worst case scenarios of drug interaction with strong CYP3A4 inhibitors, which would result in approximately 1.8-fold increase in midostaurin $C_{\max}$ (while decreasing the $C_{\max}$ for both metabolites to approximately half). Considering the time-dependent pharmacokinetics of midostaurin that leads to progressive decrease in midostaurin concentrations with multiple dosing, the clinical relevance of this interaction of strong CYP3A4 inhibitors on midostaurin exposure may be limited. Based on the summary of cross study comparison of exposures of drug and metabolites with various dosing regimen (Table 2 in the document), the midostaurin and metabolite CGP62221 $C_{\max}$ observed on day 3 at 75 mg b.i.d. in the current TQT study (2203 and 1829 ng/mL respectively) are higher than those observed in patients with diabetes mellitus at 50 mg b.i.d (1160 and 1050 ng/mL respectively) and reasonably cover or are similar to the exposures of these two moieties at steady state (day 28) for 100 mg b.i.d. ($C_{\min}$ of 1206 and 2105 respectively).

To investigate the effect of increased metabolite CGP52421 concentrations on the QTc interval, the data from study PKC412D2201 were analyzed. Study PKC412D2201 was a single arm, Phase II, open-label efficacy study in AdSM patients with administration of midostaurin 100 mg b.i.d. dose in continuous cycles of 28 days in 116 patients. The exposure-response relationship investigated by linear mixed-effects modeling showed no statistically significant relationship between $\Delta QTcF$ and midostaurin, CGP62221 or CGP52421 concentrations. However, 5 subjects (4.3%) had $480 < QTcF \leq 500$ ms and 8 (7.2%) subjects had $\Delta QTcF > 60$ ms. The study protocol involved prophylactic use of anti-emetics (e.g., ganisetron, ondansetron, metoclopramide, methotrimaprazine,

cyclizine, prochlorperazine, tropisetron) for the prevention of nausea and vomiting, to be administered to all patients prior to each dose of midostaurin. Some of these anti-emetics are known to prolong QT interval. Thus the evaluation of QT effect due to midostaurin administration in AdSM patients could be confounded by these anti-emetic medications.

1.2 COMMENTS TO THE DIVISION

It is difficult to determine if the QTc prolongation adverse events observed in clinical studies in patients with AdSM or AML are due to midostaurin administration or the concomitant use of anti-emetic agents that prolong the QTc interval. A summary of QTc outlier data across all clinical studies should be included in either Section 12.2 (as suggested below) or Section 6 of the label.

2 PROPOSED LABEL

The label proposed by the sponsor is as follows:

12.2 Pharmacodynamics

Cardiac Electrophysiology



Reviewer's comment: [redacted] (b)(4)
[redacted] as proposed by the sponsor. The following is QT-IRT's proposed labeling language which is a suggestion only. We defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of RYDAPT on the QTc interval was evaluated in a randomized, placebo and moxifloxacin controlled, multiple-dose, blinded, parallel study [redacted] (b)(4). Multiple dosing with 75 mg b.i.d. for 3 days did not result in clinically significant prolongation of QTc. There was no relationship between changes in QTc and concentrations for midostaurin and its metabolites (CGP62221 and CGP52421). The study duration was not long enough to estimate the QTc prolongation effects of accumulation of the metabolite CGP52421.

In pooled clinical studies [redacted] (b)(4) with advanced systemic mastocytosis, no patient experienced a QTcF value of > 500 ms, 4.7% patients had a post-baseline QTc interval of

> 480 ms and 6.3% patients had an increase of > 60 ms in QTc interval compared to baseline.

In a randomized placebo-controlled study in (b)(4) patients with AML, the proportion of patients with QTc prolongation was (b)(4) higher in the midostaurin vs placebo groups (QTcF >480 ms: 10.1% vs 5.7%; QTcF >500 ms: 6.2% vs 2.6%; >60 ms (b)(4) 18.4% vs 10.7%).

3 BACKGROUND

3.1 PRODUCT INFORMATION

Midostaurin (PKC412; CGP41251; chemical name: N-benzoylstauroporine) is a derivative of staurosporine, a naturally occurring alkaloid. It is a potent kinase inhibitor of Fms-like tyrosine kinase 3 (FLT3), tyrosine-protein kinase Kit (c-KIT), beta-type platelet-derived growth factor (PDGFR- α), vascular endothelial growth factor (VEGFR-2), fibroblast growth factor receptor (FGFR receptors) and protein kinase C. Midostaurin is equally active against internal tandem duplication (ITD), tyrosine kinase domain (TKD) -mutated FLT3 and wildtype FLT3. Midostaurin inhibits FLT3 receptor signaling and induces cell cycle arrest and apoptosis in leukemic cells expressing mutant receptors or overexpressing wild type receptors. Midostaurin has two active metabolites – CGP52421 and CGP62221, which are also the major circulating metabolites in vivo.

Midostaurin is currently being developed for the treatment of adult patients with acute myeloid leukemia (AML) that is FLT3 mutation-positive as detected by an FDA-approved test and advanced systemic mastocytosis (AdSM).

3.2 MARKET APPROVAL STATUS

Midostaurin is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

Midostaurin and its two major human metabolites hydroxy-midostaurin (CGP52421) and desmethyl-midostaurin (CGP62221) were evaluated in vitro in the human ether-a-go-go related gene (hERG) assay for the potential to cause QTc interval prolongation.

Midostaurin did not inhibit hERG channel activity in HEK293 cells up to the limit of solubility of 12 μ M (6.8 μ g/mL). CGP52421 inhibited hERG current by 38.5% at 1.50 μ M, while CGP62221 inhibited hERG current by 11.3% at 1.21 μ M.

Cardiovascular and renal functions were studied in rats by both i.v. and oral routes of administration. In anesthetized rats, midostaurin (dissolved in dimethylsulfoxide (DMSO)) infused intravenously over 30 minutes at doses of 3, 8, and 25 mg/kg caused a significant dose-related decrease in mean arterial pressure (MAP, 31- 47%) and heart rate (HR, 18 – 21%) at 8 and 25 mg/kg compared to pre-dose values. Both effects were of slow onset and long duration. Infusion of 2.5 mg/kg/min in rats induced severe hypotension and respiratory arrest and was lethal after 14 to 21 minutes of infusion, i.e., after total doses of 35-53 mg/kg. By contrast, oral administration of midostaurin as a single dose of 300 mg/kg had no effect on MAP and HR over six hours in conscious rats. Oral administration of midostaurin (30 to 300 mg/kg) increased sodium and chloride

excretion by about 100% and 50% respectively; at doses of 100 and 300 mg/kg with no effects on urine volume or potassium excretion, suggesting weak diuretic effects.

The potential adverse effects of midostaurin on the cardiovascular system were also evaluated in 13- and 52-week oral toxicity studies in dogs. A decrease in HR was seen in individual animals at 10 and 30 mg/kg after 13-weeks of treatment and during the recovery period (30 mg/kg only) in the 13-week study. A physiological prolongation of the P-Q interval was also noted. No associated morphological changes were found in the heart. Slight prolongation of the P-Q interval was also noted in a few animals at 3 mg/kg and 10 mg/kg in weeks 26 or 52 of the 52-week study.

The results of the cardiovascular system assessment indicate that the risk of hERG-associated QT interval prolongation by midostaurin or its metabolites CGP52421 and CGP62221 appears to be low. Based on the findings from preclinical species, midostaurin may have an impact on cardiovascular parameters such as heart rate and blood pressure; however, there have been no midostaurin-related changes in these parameters reported in clinical studies to date.

3.4 PREVIOUS CLINICAL EXPERIENCE

To date, approximately 2100 subjects have been enrolled into the midostaurin clinical program, of which approximately 1500 subjects have received midostaurin. It has been investigated as a single agent and in combination with other anticancer therapies in hematologic and non-hematologic malignancies, and as a single agent in diabetic macular edema.

In AdSM patients (studies D2201 and A2213) QT prolongation-related events were reported 16.2% of patients; the most commonly reported event was ECG QT prolonged (15 patients; 10.6%) and resulted in discontinuation in 3 patients. A further 2 patients discontinued due to events included in the QT prolongation standard MedDRA query; cardiac arrest and ventricular tachycardia. In study D2201, 2 patients died due to cardiac arrest D2201-0200-00005 and D2201-0506-00010, neither death was suspected to be related to study drug and there was no QT prolongation.

No AdSM patient experienced a QTcF value of > 500 ms. Evaluation of the notable QTcF from the pooled dataset demonstrated that 6 patients had a post-baseline QTc interval of > 480 ms and 8 patients had an increase of > 60 ms in QTc interval compared to baseline.

In AML patients in Study A2301, QT prolongation AEs (any grade) were reported in 24.0% vs 21.2% of patients in the midostaurin vs placebo groups, respectively (NNA sites), primarily ECG QT prolonged (19.2% vs 16.8%) and syncope (5.2% vs 4.9%).

In Study A2301, QT prolongation AEs were reported as SAEs for 1.7% vs 3.1% of patients, and led to discontinuation for 1 patient (0.4%) each in the midostaurin and placebo groups. None of the events had a fatal outcome. The incidence of any grade and grade 3/4 events of QT prolongation was similar in the treatment arms overall and in the induction and consolidation phase. In the continuation phase, the occurrence of QT prolongation events was higher in the midostaurin group than in the placebo group, for any events, grade 3/4 events and study drug related events. The clinical impact is thought

to be limited given as only a small proportion of the total events occurred in the continuation phase.

In AML patients (study A2301), the mean QTcF values were generally similar in patients on midostaurin vs patients on placebo with values close to 400 ms with no meaningful trend upwards or downwards during the induction and consolidation phases of the study. The confidence intervals were narrow, and outliers were similar in both treatment groups.

Similar results were observed when QTcF values from patients in the continuation phase were plotted over time. In all phase (induction, consolidation and continuation), few outliers and narrow CIs further confirmed the robustness of the results.

Reviewer's comments: It is difficult to determine if the QTc prolongation adverse events observed in clinical studies in patients with AdSM or AML are due to midostaurin administration or the concomitant use of anti-emetic agents that prolong the QTc interval. The results of the QT study do not suggest a direct effect of midostaurin on the QTc interval over the doses/exposures evaluated; however, the QTc effects of the long-acting metabolite were not assessed due to the short duration of the study (3 days).

3.5 CLINICAL PHARMACOLOGY

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

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The sponsor submitted the TQT study report PKC412A2113 for midostaurin, including electronic datasets and waveforms to the ECG warehouse. The sponsor also submitted proposed labeling and Integrated Summary of Safety (ISS) for midostaurin.

4.2 TQT STUDY

4.2.1 Title

A phase I, randomized, double-blinded, placebo and active controlled three-way parallel group study to investigate the effect of midostaurin on cardiac intervals in healthy subjects.

4.2.2 Protocol Number

CPKC412A2113

4.2.3 Study Dates

31 Mar 2008 – 19 Jul 2008

4.2.4 Objectives

Primary objectives:

- To determine the effect of multiple doses of midostaurin, administered at 75 mg b.i.d. on days 1 and 2 and o.d. on day 3 on the QTcF intervals in healthy adult volunteers.

Secondary objectives:

- To assess the effects of multiple doses of midostaurin on cardiac intervals (QT, QTcB, QTcI, QRS, RR, and PR) and heart rate in healthy adult volunteers.
- To assess the effects of a single dose of moxifloxacin on cardiac intervals (QTcF, QT, QTcB, QTcI, QRS, RR, and PR) and heart rate in healthy adult volunteers.
- To evaluate the safety and tolerability of midostaurin following single and multiple oral doses in healthy adult volunteers.

Exploratory objectives:

- To potentially explore any relationship of QTc and plasma exposure of midostaurin and its metabolites.

4.2.5 Study Description

4.2.5.1 Design

This is a randomized, 3-arm, parallel study.

4.2.5.2 Controls

The sponsor used both placebo and positive (moxifloxacin) controls.

4.2.5.3 Blinding

All treatment arms were administered blinded using a double dummy approach. Moxifloxacin tablets were over-encapsulated.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

There were 3 treatment arms:

- Midostaurin 75 mg b.i.d. on Days 1 and 2 and o.d. on Day 3
- Moxifloxacin 400 mg
- Placebo

Midostaurin or matching placebo was administered orally at 75 mg b.i.d. on days 1 and 2 and o.d. on day 3. Moxifloxacin 400 mg or placebo was administered orally o.d. on day 3. Midostaurin, placebo, and midostaurin matching placebo were capsules, and moxifloxacin tablets were over-encapsulated.

4.2.6.2 Sponsor's Justification for Doses

The dosing regimen being studied represents a fair balance between achieving maximal plasma exposure for QTc evaluation, while minimizing the risks of additional exposure to healthy volunteers.

The maximal tolerated dose (MTD) of midostaurin in advanced cancer patients was defined as 75 mg t.i.d. in a phase I dose escalation study [Study CPCK412A003]. However, a study in patients with diabetes mellitus [Study CPKC412A001] clearly demonstrated a marked increase in frequency of adverse events above the 75 mg b.i.d. dose regimen. Results from this study clearly suggest that a dosage regimen of 75 mg b.i.d. provided a more favorable safety/tolerability profile as compared to 75 mg t.i.d., and would be ethically more justified, especially when used in healthy volunteers.

The dose utilized in this study, 75 mg b.i.d. for 2 days and o.d on day 3, is greater than the 50 mg b.i.d. dose used in the phase III registration study in de novo AML patients, and the peak concentration is appropriate to exceed the trough concentration of 100 mg b.i.d. dose used in the phase II study in Aggressive Systemic Mastocytosis (ASM), Midostaurin demonstrates time-dependent pharmacokinetics in humans. Following multiple oral doses, plasma concentrations of midostaurin and CGP62221 reach the maximal level around day 3, then decline with time until steady state is achieved. Therefore, this study evaluated the change from baseline to day 3, at maximum plasma levels of both midostaurin and CGP62221.

A dose of 75 mg b.i.d for 3 days in healthy volunteers was expected to be tolerable based on the previous experience from a study in patients with diabetes mellitus [Study CPKC412A001], and would allow to reach cumulative C_{max} for both parent compound and CGP62221. A prolonged exposure of midostaurin was not recommended in order to minimize the potential risks, since multiple doses have not yet tested in healthy volunteers, and the long term effect of prolonged suppression of multiple TK are not fully known.

Reviewer's comments: The 75 mg b.i.d dose selected for this study exceeds the proposed 50 mg b.i.d dose for the treatment of acute myeloid leukemia (AML) and it has a more favorable safety profile than the MTD dose of 75 mg t.i.d. in advanced cancer patients. The 75 mg b.i.d dose seems to be ethically justified when used in healthy volunteers. However, there are limitations with such dose selection. The 75 mg b.i.d. dose is lower than the proposed 100 mg b.i.d. dose for the treatment of advanced systemic mastocytosis (AdSM). The peak midostaurin concentrations on Day 3 in this study are not higher than those for the expected worst case scenarios of drug interaction with strong CYP3A4 inhibitors which would result in approximately 2-fold increase in midostaurin exposure.

Table 2 shows a summary of cross study comparison of exposures of drug and metabolites with various dosing regimen ranging from 25 mg b.i.d to 100 mg b.i.d.

Table 2: Cross-study comparison of exposures of midostaurin and its metabolites (concentrations units of ng/mL) with various dosing regimen

		25 mg bid*		50 mg bid*		75 mg bid*		100 mg bid**		75 mg bid***
		Day 1	Day 28	Day 1	Day 28	Day 1	Day 28	Day 1	Day 28	Day 3
Midostaurin	C _{max}	832	1080	1600	1160	1810	1600			2203
	C _{min}		492		467		932		1206	870
CGP62221	C _{max}		1000		1050		1290			1829
	C _{min}		756		825		1298		2105	1460
CGP52421	C _{max}		3290		5670		6120			1137
	C _{min}		2600		3949		4970		2742	1020

*Study in Diabetes Mellitus patients (C-99-PKC412-A001)

**Study in AdSM patients (PKC412D2201)

***TQT study in healthy subjects (PKC412A2113)

Based on the summary above, the midostaurin and CGP62221 C_{max} observed on day 3 at 75 mg b.i.d. in the current TQT study (2203 and 1829 ng/mL respectively) are higher than those observed in patients with diabetes mellitus at 50 mg b.i.d. (1160 and 1050 ng/mL respectively) and reasonably cover or are similar to the exposures of these two moieties at steady state (day 28) for 100 mg b.i.d. (C_{min} of 1206 and 2105 respectively). However, the CGP52421 C_{max} observed on day 3 at 75 mg b.i.d. in the current TQT study (1137 ng/mL) is lower than the observed steady state C_{max} in patients with diabetes mellitus at 50 mg b.i.d. dose level (5670 ng/mL) as well as observed steady state concentrations levels (C_{min} of 2742 ng/mL) in AdSM patients at 100 mg b.i.d. dose. This is expected due to the long half-life of CGP52421. The time dependent decrease in midostaurin and CGP62221 metabolite concentrations with multiple dosing of drug due to induction of metabolic enzymes, and increase in CGP52421 metabolite is evident from PK data in AdSM patients (Study PKC412D2201) as shown in Figure 6.

No increase in exposure to plasma midostaurin in subjects with mild or moderate hepatic impairment compared to subjects with normal hepatic function was observed in the hepatic impairment study. PopPK analysis showed no significant impact of renal function on the exposure of midostaurin.

4.2.6.3 Instructions with Regard to Meals

Morning doses of study medication were taken with 240 mL of water between 08.00 and 09.00 after a ≥ 11 hour fast. A light breakfast was consumed at 10.00. All evening doses were taken at 20.00 after dinner at 17.30.

Reviewer's comments: Acceptable. The rate of absorption (C_{max}) was decreased by 20% (90% CI: 0.64-0.98) for a standard meal (approximately 25% fat of the total 450 caloric content of the meal) and 27% (90% CI: 0.59-0.90) for the high fat meal.

4.2.6.4 ECG and PK Assessments

12-lead digital ECGs were obtained in triplicate at 9 time points over 24 hours at the same relative time (at 0, 0.5, 1, 2, 3, 4, 8, 12, and 24 hours post-dose) during baseline (Day -1) and on study Day 3, and at 2 time points (2 and 3 hours post-dose) on Day 1. PK samples were collected on Day 1 and Day 3 and PK time points were identical to those for ECG assessments.

Reviewer's comments: The timing of ECG and PK assessments is acceptable to evaluate effects near T_{max} for drug and metabolites and any delayed effects.

4.2.6.5 Baseline

The time-matched QT/QTc values on Day -1 were used as baselines.

4.2.7 ECG Collection

Standard 12-Lead ECGs were obtained while subjects were recumbent.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

A total of 192 healthy subjects (136 males and 56 females) were randomized to the study, and 166 eligible subjects completed the study. Of the 166 subjects, 56 subjects were in midostaurin arm, 44 subjects were in moxifloxacin arm, and 66 subjects were in placebo arm. The safety, PK, and ECG analysis sets include 191, 113, and 161 subjects, respectively.

The average age (SD) of the 192 subjects was 29.9 (8.2) years, ranging from 18 to 45 years. One hundred and forty subjects (140/192, 72.9%) were Black, 51 subjects (51/192, 26.6%) were Caucasian, and 1 subject (1/192, 0.5%) was Asian.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

For the midostaurin treatment arm, the upper bounds of 90% CI (equivalent to one-sided 95% upper confidence boundary) for change from time-matched baseline for all the 9 time points on day 3, compared with placebo, were less than 10ms. The maximum mean change from baseline for midostaurin, compared to placebo, occurred at 24 hours post dose on day 3 and was 0.715ms and its upper bound of 90% CI was 4.707ms, which excluded 10ms. Therefore it is concluded that midostaurin demonstrates a lack of QTc prolongation effects.

The sponsor's primary analysis results are displayed in the following Table 3 and Table 4.

**Table 3: Summary of Statistical Analysis for QTcF (Time Matched Effect)
(Sponsor's Results based on ECG Set)**

Treatment	Time point (h)	Test	Placebo	Difference (Test - Placebo)	90 % CI
Midostaurin	0	-3.153	-0.449	-2.704	(-6.696 ; 1.287)
	0.5	-5.233	-3.336	-1.896	(-5.888 ; 2.096)
	1	-6.323	-2.627	-3.695	(-7.687 ; 0.297)
	2	-6.231	-1.151	-5.081	(-9.073 ; -1.089)
	3	-5.216	-1.356	-3.860	(-7.853 ; 0.133)
	4	-6.394	-2.974	-3.419	(-7.414 ; 0.575)
	8	-1.851	-1.174	-0.676	(-4.670 ; 3.318)
	12	-3.100	-2.522	-0.578	(-4.569 ; 3.414)
	24	-3.890	-4.605	0.715	(-3.277 ; 4.707)
Moxifloxacin	0	-1.020	-0.449	-0.572	(-4.831 ; 3.688)
	0.5	2.347	-3.336	5.683	(1.424 ; 9.942)

**Table 4: Summary of Statistical Analysis for QTcF (Time Matched Effect)
(Sponsor's Results based on ECG Set Continue)**

Treatment	Time point (h)	Test	Placebo	Difference (Test - Placebo)	90 % CI
	1	8.031	-2.627	10.659	(6.400 ; 14.918) ¹
	2	7.275	-1.151	8.426	(4.166 ; 12.686)
	3	5.678	-1.356	7.034	(2.775 ; 11.293)
	4	2.565	-2.974	5.539	(1.280 ; 9.798)
	8	5.575	-1.174	6.749	(2.491 ; 11.008)
	12	2.725	-2.522	5.248	(0.989 ; 9.507)
	24	-0.084	-4.605	4.521	(0.262 ; 8.780)

¹ Confidence intervals in this table are not adjusted for multiplicity

Source: The sponsor's clinical study report PKC412A2113, Table 11-3, page 51

Reviewer's comments: Please see the reviewer's analysis in section 5.2.

4.2.8.2.2 Assay Sensitivity

For the moxifloxacin treatment arm, the maximum mean change from baseline, compared to placebo, occurred at 1 hour post-dose on day 3 and was 10.659 ms and its lower bound of 90% CI was 6.400 ms. Without considering the multiple comparison correction, the p value associated with testing that the difference was greater than 5 ms for the time point of 1 hour post dose was 0.015. This p-value was adjusted to 0.073 when the individual p values from the 5 protocol specified post-dose time points, 0.5, 1, 2, 3, 4 hours post dose, were corrected by Simes method.

The sponsor's results for assay sensitivity analysis are displayed the above Table 3 and Table 4.

Reviewer's comments: Please see the reviewer's analysis in section 5.2.

4.2.8.2.3 Categorical Analysis

No subject had a 30-60, >60, new >500 ms or new >480 ms change from baseline for QTcF or QTcI.

Two subjects (2/44, 4.5%) in the moxifloxacin group had new >450 ms change from baseline in QTcF.

4.2.8.3 Safety Analysis

There were no SAEs or deaths during the study.

A total of 61 subjects experienced adverse events while on study drug. Nineteen subjects were discontinued due to adverse events in the midostaurin group, seventeen due to the known toxicity of nausea and vomiting associated with midostaurin. Each adverse event had resolved at the EOS visit.

The adverse events seen in the study were as expected for this population and this class of drug. They were mostly mild and transient, did not seem to be dose-related and gave no indication of target organ toxicity.

Two patients, patient 0501-05149 and 0501-05173, in the midostaurin group experienced tachycardia grade 1 during the placebo run-in period (day -1) and were discontinued prior to treatment with midostaurin. They were both followed until resolution of symptoms. No other cardiac events were reported in any patients.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

The PK results are presented in Table 5 and Table 6 for midostaurin and the metabolites on day 1 and day 3, respectively. The study included only a single dosing regimen of 75 mg b.i.d for 3 days.

Table 5: PK parameters for midostaurin and metabolites on day 1

	T _{max} [h]	C _{max} [ng/mL]	AUC _{0-12h} [h.ng/mL]
midostaurin (N=70)	1 (1-3.12)	2142.1 (690.10)	11662.6 (3723.65)
CGP62221 (N=70)	3.08 (2.08;4.02)	866.3 (169.20)	7848.2 (1579.89)
CGP52421 (N=67)	4 (2.08;4.03)	384.5 (65.12)	3509.2 (609.76)

Values are mean (SD) except for T_{max} which is median (range)

Table 6: PK parameters for midostaurin and metabolites on day 3

	T _{max} [h]	C _{max} [ng/mL]	AUC _{0-24h} [h.ng/mL]
midostaurin (N=54)	1.08 (1.08;3.08)	2273.3 (710.28)	25657.5 (10872.71)
CGP62221 (N=51)	3.08 (0.00;8.08)	1882.0 (432.47)	36486.5 (9769.72)
CGP52421 (N=45)	3.08 (1.08 -8.08)	1248.6 (208.36)	25837.2 (4034.03)

Values are mean (SD) except for T_{max} which is median (range)

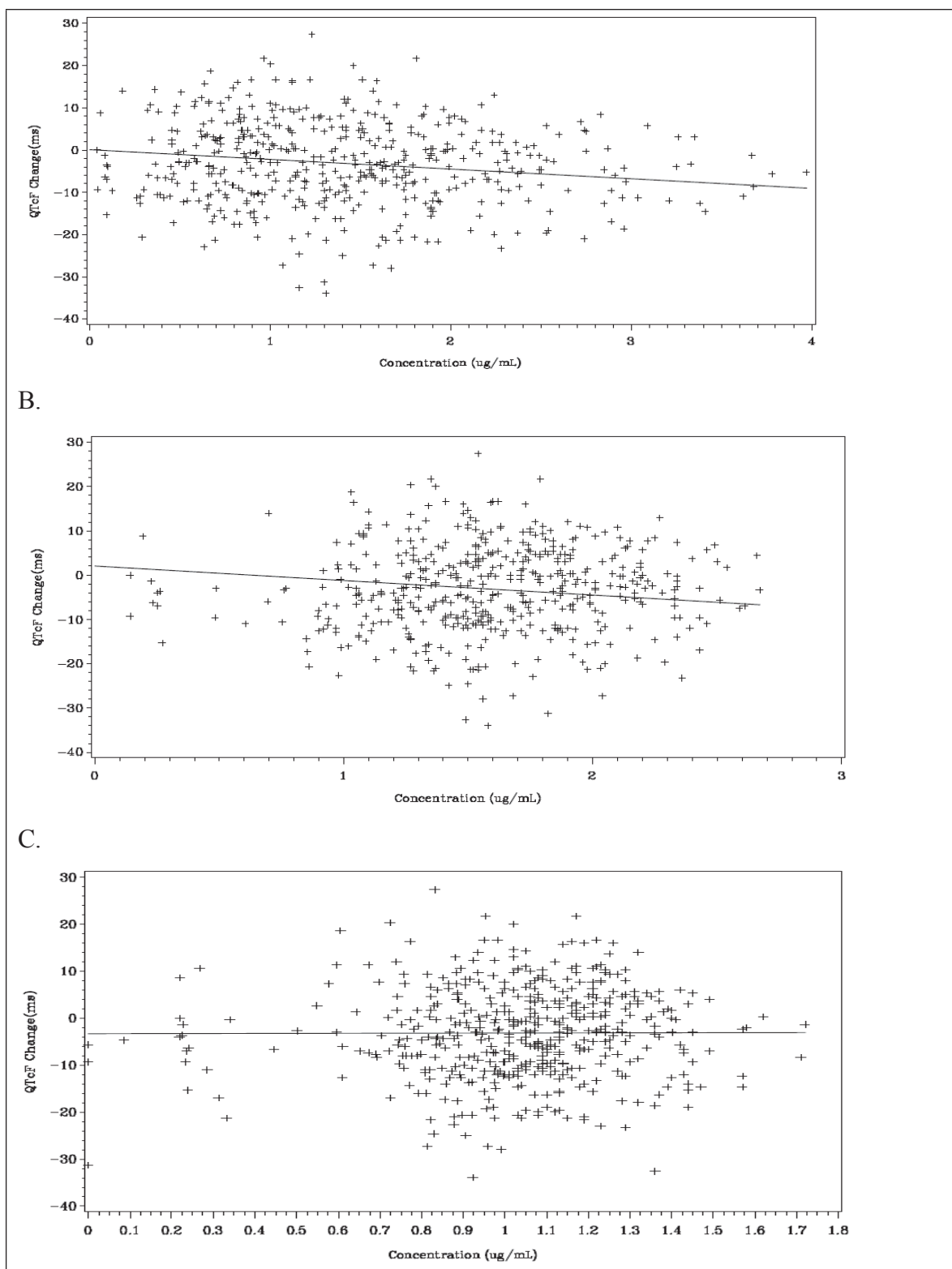
4.2.8.4.2 Exposure-Response Analysis

The sponsor preformed exposure-response analyses and did not identify a significant positive concentration-dependent effect of midostaurin or its metabolites (CGP62221, CGP52421) on QTcF (Figure 1). A significant relationship was identified for moxifloxacin (slope = 3.21 ms per µg/mL).

Figure 1: Plasma concentration versus QTcF change from baseline on day 3 for (A) Midostaurin, (B) metabolite CGP62221 and (C) metabolite CGP52421

A.

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Reviewer's comments: Plots of $\Delta\Delta QTcF$ vs. midostaurin and its metabolites are shown in the reviewer's analysis in Section 5.3 below.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

We evaluated the appropriateness of the correction methods (QTcB, QTcF and QTcI). Baseline values were excluded in the validation. Ideally, a good correction QTc would result in no relationship of QTc and RR intervals.

We used the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based on the results listed in Table 7, it appears that QTcF is the best correction method.

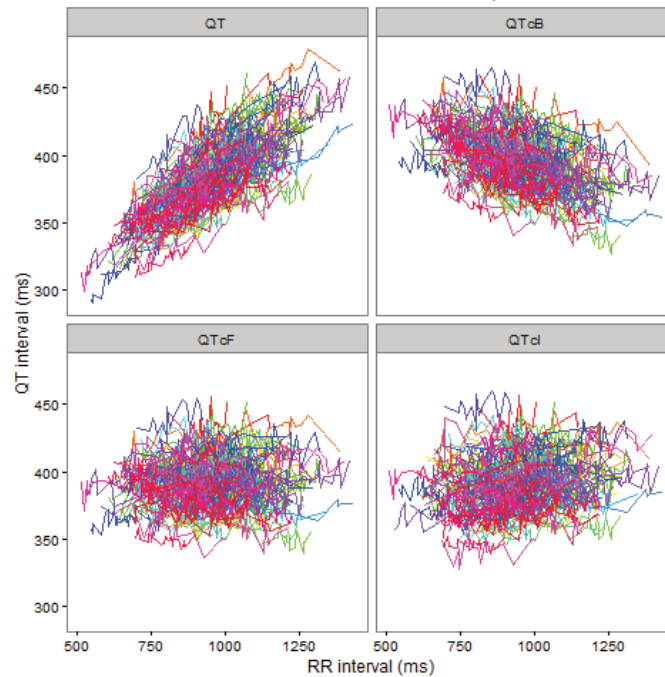
Therefore, QTcF was used for the primary statistical analysis.

Table 7: Average of Sum of Squared Slopes for Different QT-RR Correction Methods

	QTcB		QTcF		QTcI	
Treatment Group	N	MSSS	N	MSSS	N	MSSS
Placebo	161	0.00598	161	0.00127	161	0.00088
Moxifloxacin 400 mg	43	0.00616	43	0.00193	43	0.00229
Midostaurin	54	0.00934	54	0.00177	54	0.00200
All	161	0.00599	161	0.00094	161	0.00106

The relationship between different correction methods and RR is presented in Figure 2.

Figure 2: QT, QTcB, QTcF, and QTcI vs. RR (Each Subject's Data Points are Connected with a Line)



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for Midostaurin

The statistical reviewer used mixed model to analyze the Δ QTcF effect. The model includes treatment, time point, and treatment by time point as fixed effects and subject as a random effect. Baseline values are also included in the model as a covariate. The analysis results are listed in the following tables.

Table 8: Analysis Results of Δ QTcF and $\Delta\Delta$ QTcF for Midostaurin on Day 3

	Δ QTcF (ms) Midostaurin	Δ QTcF (ms) Placebo	$\Delta\Delta$ QTcF (ms) Midostaurin	
Time (hour)	LSmean	LSmean	LSmean	90% CI
0	-2.7	-1.4	-2.8	(-7.0, 1.4)
0.5	-3.2	-2.9	-2.0	(-6.4, 2.4)
1	-6.1	-4.1	-3.8	(-8.2, 0.6)
2	-6.3	-3.0	-5.2	(-9.6, -0.8)
3	-5.0	-3.4	-4.0	(-8.2, 0.2)
4	-3.8	-3.3	-3.6	(-7.6, 0.4)
8	1.7	-0.3	-0.8	(-4.7, 3.0)
12	-0.8	-1.4	-0.7	(-4.7, 3.4)
24	-2.0	-4.5	0.6	(-3.5, 4.7)

The upper bounds of the 2-sided 90% CI for the mean difference between midostaurin and placebo were less than 10 ms at all time points and all of the CIs include 0.

5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 9. The largest unadjusted 90% lower confidence interval was 6.0 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval was 4.5 ms. The slightly less than 5 ms QTcF effect was most likely due to the over-encapsulation of moxifloxacin, thus assay sensitivity is deemed established.

Table 9: Analysis Results of Δ QTcF and $\Delta\Delta$ QTcF for Moxifloxacin

	Δ QTcF (ms) Moxifloxacin 400 mg	Δ QTcF (ms) Placebo	$\Delta\Delta$ QTcF (ms) Moxifloxacin 400 mg		
Time (hour)	LSmean	LSmean	LSmean	90% CI	Adjust 90% CI*
0	-3.4	-1.4	-0.5	(-5.0, 4.0)	(-6.3, 5.3)
0.5	1.9	-2.9	5.7	(1.1, 10.4)	(-0.3, 11.8)
1	5.6	-4.1	10.7	(6.0, 15.5)	(4.5, 16.9)
2	3.8	-3.0	8.5	(3.9, 13.2)	(2.5, 14.6)
3	2.6	-3.4	7.1	(2.6, 11.6)	(1.3, 12.9)
4	1.1	-3.3	5.6	(1.4, 9.8)	(0.1, 11.1)
8	6.9	-0.3	6.7	(2.6, 10.8)	(1.4, 12.1)
12	5.0	-1.4	5.2	(0.9, 9.4)	(-0.4, 10.7)
24	-0.9	-4.5	4.6	(0.2, 9.0)	(-1.1, 10.3)

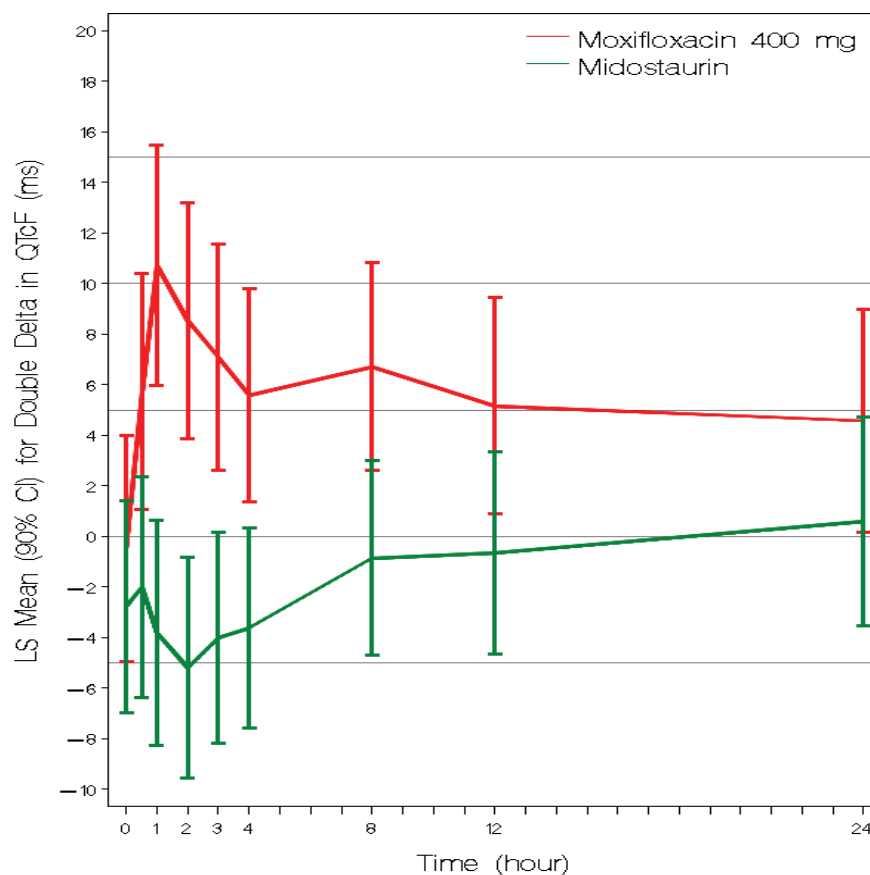
* Bonferroni method was applied to all time points to adjust for multiple endpoint evaluation at 3 time points around moxifloxacin C_{max} .

5.2.1.3 Graph of $\Delta\Delta$ QTcF Over Time

The following figure displays the time profile of $\Delta\Delta$ QTcF for different treatment groups. It should be noted that CIs are all unadjusted, including those for moxifloxacin.

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Figure 3: Mean and 90% CI $\Delta\Delta$ QTcF Timecourse



5.2.1.4 Categorical Analysis

Table 10 lists the number of subjects as well as the number of observations whose QTcF values were ≤ 450 ms and between 450 ms and 480 ms. No subject's QTcF was above 480 ms.

Table 10: Categorical Analysis for QTcF

Treatment Group	Total N		QTcF $\leq$ 450 ms		450<QTcF $\leq$ 480 ms	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Predose	191	191	190 (99.5%)	190 (99.5%)	1 (0.5%)	1 (0.5%)
Placebo	189	2550	188 (99.5%)	2548 (99.9%)	1 (0.5%)	2 (0.1%)
Moxifloxacin 400 mg	44	352	42 (95.5%)	349 (99.1%)	2 (4.5%)	3 (0.9%)
Midostaurin	75	669	75 (100%)	669 (100%)	0 (0.0%)	0 (0.0%)

Table 11 lists the categorical analysis results for ΔQ_{TcF} . No subject's change from baseline in Q_{TcF} was above 60 ms.

Table 11: Categorical Analysis of ΔQ_{TcF}

	Total N		$\Delta Q_{TcF} \leq 30$ ms		$30 < \Delta Q_{TcF} \leq 60$ ms	
Treatment Group	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Placebo	185	1045	185 (100%)	1045 (100%)	0 (0.0%)	0 (0.0%)
Moxifloxacin 400 mg	44	352	43 (97.7%)	351 (99.7%)	1 (2.3%)	1 (0.3%)
Midostaurin	74	668	74 (100%)	668 (100%)	0 (0.0%)	0 (0.0%)

5.2.2 HR Analysis

The same statistical analysis was performed based on HR. The point estimates and the 90% confidence intervals are presented in Table 12. The largest upper limit of 90% CI for the HR mean differences between midostaurin and placebo was 4.9 bpm.

The outlier analysis results for HR are presented in

Table 13.

Table 12: Analysis Results of ΔHR and $\Delta \Delta HR$ for Midostaurin on Day 3

	ΔHR (bpm) Midostaurin	ΔHR (bpm) Placebo	$\Delta \Delta HR$ (bpm) Midostaurin	
Time (hour)	LSmean	LSmean	LSmean	90% CI
0	1.7	0.6	1.8	(-0.8, 4.3)
0.5	2.3	1.9	1.1	(-1.2, 3.5)
1	2.0	2.1	1.0	(-1.5, 3.4)
2	3.4	1.3	2.6	(0.4, 4.9)
3	2.5	0.2	2.4	(-0.1, 4.9)
4	-0.7	-0.8	0.6	(-2.0, 3.3)
8	3.0	2.6	1.0	(-1.7, 3.7)
12	2.3	4.0	-0.3	(-2.9, 2.3)
24	6.1	6.8	0.1	(-2.4, 2.6)

Table 13: Categorical Analysis for HR

	Total N	HR≤100 bpm	HR>100 bpm	HR>45 bpm	HR≤45 bpm
Treatment Group	Subj. #	Subj. #	Subj. #	Subj. #	Subj. #
Predose	191	189 (99.0%)	2 (1.0%)	190 (99.5%)	1 (0.5%)
Placebo	189	186 (98.4%)	3 (1.6%)	182 (96.3%)	7 (3.7%)
Moxifloxacin 400 mg	44	44 (100%)	0 (0.0%)	44 (100%)	0 (0.0%)
Midostaurin	75	73 (97.3%)	2 (2.7%)	74 (98.7%)	1 (1.3%)

5.2.3 PR Analysis

The same statistical analysis was performed based on PR interval. The point estimates and the 90% confidence intervals are presented in Table 14. The largest upper limit of 90% CI for the PR mean differences between midostaurin and placebo was 4.1 ms and all of the CIs include 0.

The outlier analysis results for PR are presented in

Table 15.

Table 14: Analysis Results of Δ PR and $\Delta\Delta$ PR for Midostaurin on Day 3

	ΔPR (ms) Midostaurin	ΔPR (ms) Placebo	$\Delta\Delta$PR (ms) Midostaurin	
Time (hour)	LSmean	LSmean	LSmean	90% CI
0	3.1	2.1	-0.5	(-4.7, 3.6)
0.5	0.2	2.9	-3.5	(-7.5, 0.4)
1	1.7	2.9	-2.0	(-6.1, 2.1)
2	2.1	1.7	-1.5	(-5.4, 2.4)
3	2.8	1.8	-0.7	(-4.8, 3.3)
4	1.6	1.3	-1.7	(-5.5, 2.1)
8	3.3	1.7	-0.7	(-4.5, 3.1)
12	3.9	1.3	0.2	(-3.7, 4.1)
24	-0.9	0.1	-2.1	(-6.0, 1.7)

Table 15: Categorical Analysis for PR

	Total N		PR≤200 ms		PR>200 ms	
Treatment Group	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Predose	191	191	191 (100%)	191 (100%)	0 (0.0%)	0 (0.0%)
Placebo	189	2550	184 (97.4%)	2537 (99.5%)	5 (2.6%)	13 (0.5%)
Moxifloxacin 400 mg	44	352	43 (97.7%)	351 (99.7%)	1 (2.3%)	1 (0.3%)
Midostaurin	75	669	73 (97.3%)	664 (99.3%)	2 (2.7%)	5 (0.7%)

5.2.4 QRS Analysis

The same statistical analysis was performed based on QRS interval. The point estimates and the 90% confidence intervals are presented in Table 16. The largest upper limit of 90% CI for the QRS mean differences between midostaurin and placebo was 2.4 ms and all of the CIs include 0.

The outlier analysis results for QRS are presented in Table 17.

Table 16: Analysis Results of ΔQRS and ΔΔQRS for Midostaurin on Day 3

	ΔQRS (ms) Midostaurin	ΔQRS (ms) Placebo	ΔΔQRS (ms) Midostaurin	
Time (hour)	LSmean	LSmean	LSmean	90% CI
0	-0.6	0.6	-1.1	(-2.9, 0.7)
0.5	-0.1	-0.5	-0.2	(-2.0, 1.6)
1	0.4	-0.4	0.2	(-1.5, 1.9)
2	-0.1	0.9	-0.8	(-2.5, 0.9)
3	0.1	0.0	0.2	(-1.7, 2.0)
4	-0.4	-0.3	-0.0	(-1.8, 1.8)
8	0.6	0.7	0.0	(-1.7, 1.8)
12	0.7	0.4	0.6	(-1.2, 2.4)
24	-0.9	-1.2	-0.3	(-2.0, 1.4)

Table 17: Categorical Analysis for QRS

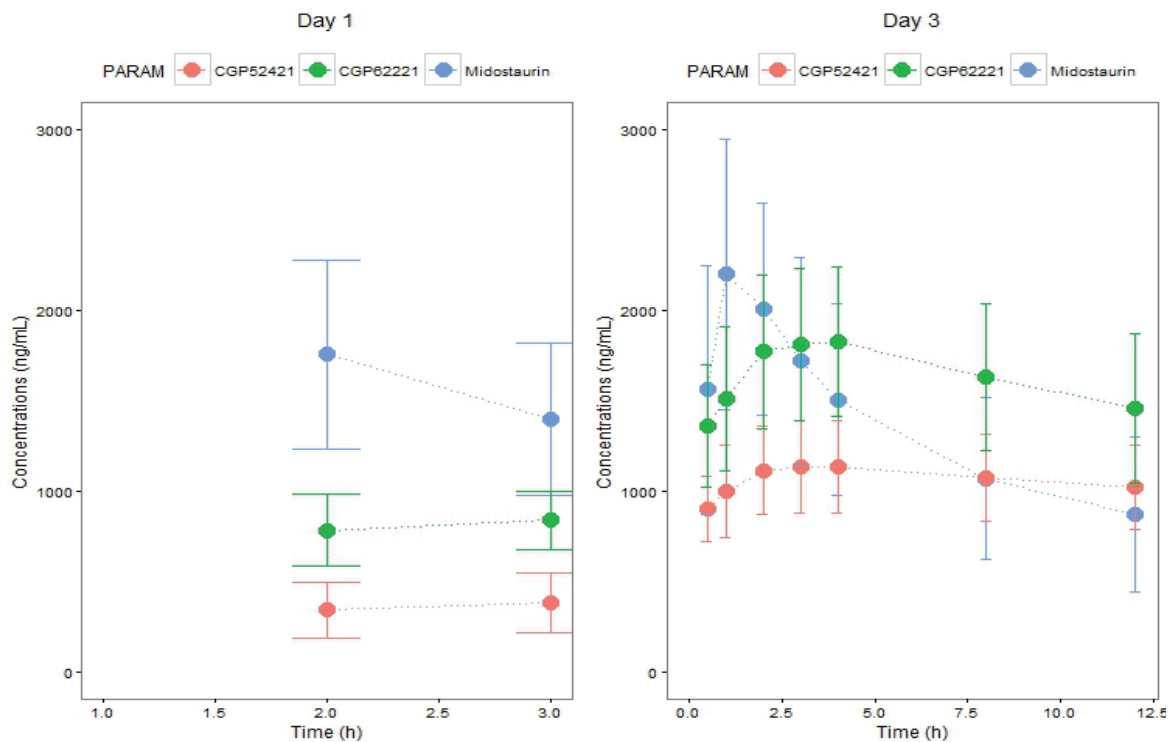
Treatment Group	Total N		QRS≤110 ms		QRS>110 ms	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Predose	191	191	191 (100%)	191 (100%)	0 (0.0%)	0 (0.0%)
Placebo	189	2550	188 (99.5%)	2546 (99.8%)	1 (0.5%)	4 (0.2%)
Moxifloxacin 400 mg	44	352	44 (100%)	352 (100%)	0 (0.0%)	0 (0.0%)
Midostaurin	75	669	75 (100%)	669 (100%)	0 (0.0%)	0 (0.0%)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

TQT Study PKC412A2113

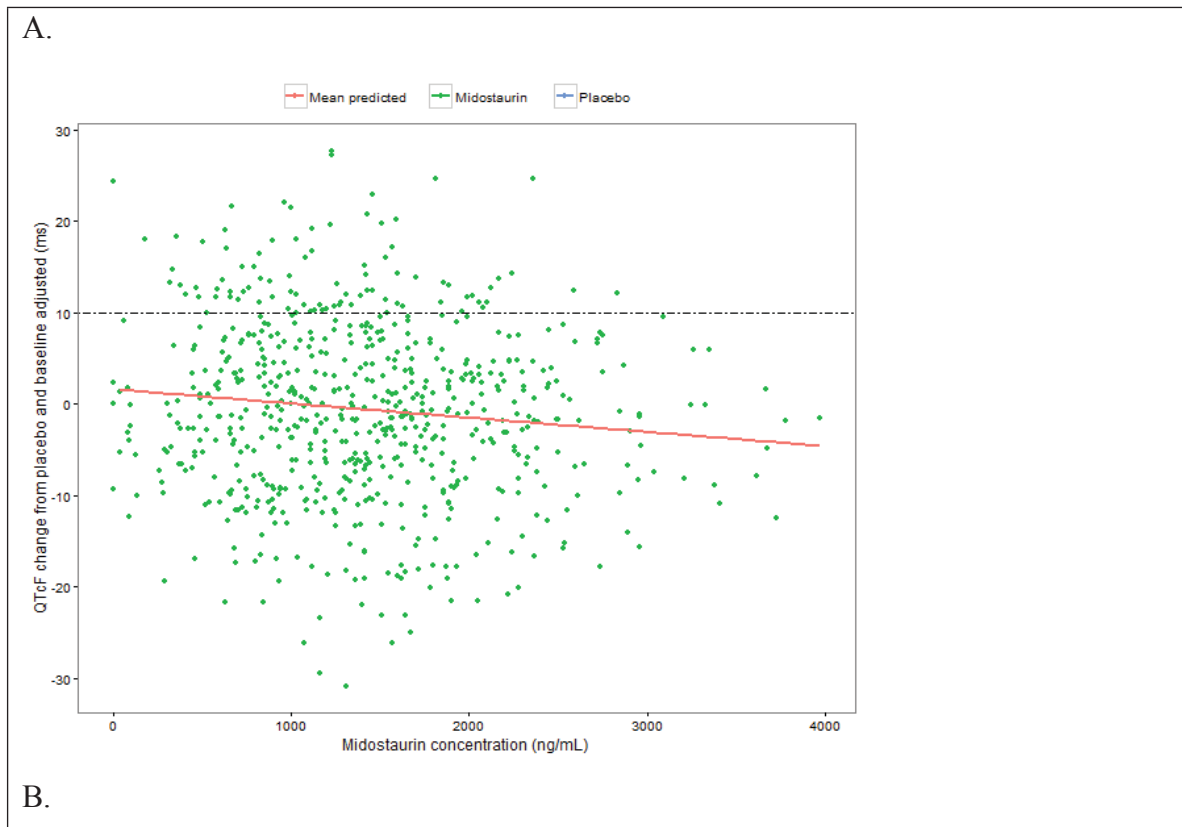
The mean concentration-time profiles for midostaurin, and its metabolites (CGP62221 and CGP52421) are illustrated in Figure 4.

Figure 4: Mean (±SD) Concentration-Time Profiles for Midostaurin, and its Metabolites (CGP62221 and CGP52421) on Day 1 and Day 3 (primary analysis day)

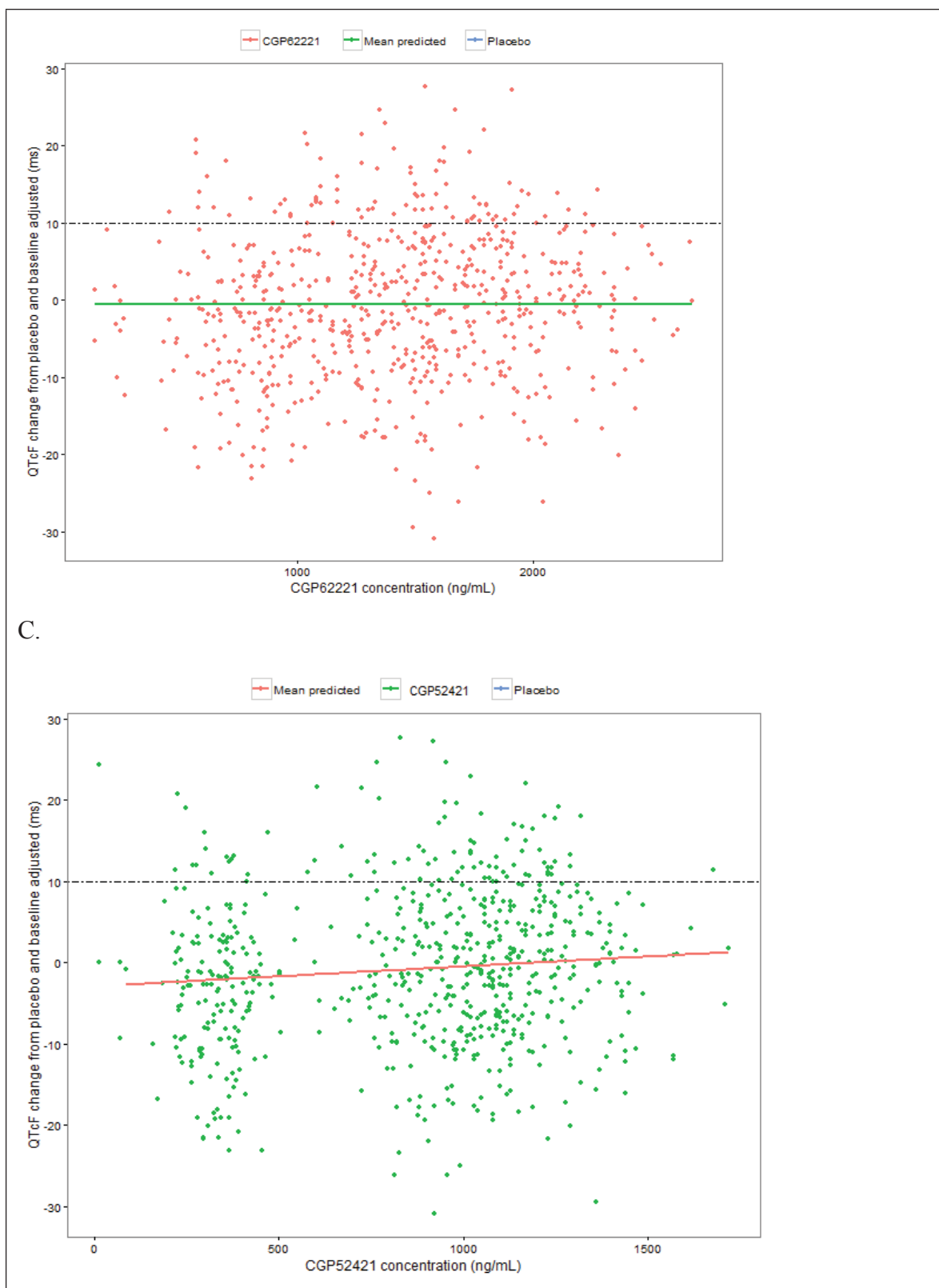


The relationships between $\Delta\Delta\text{QTcF}$ and concentrations for midostaurin, CGP62221 and CGP52421 were investigated by linear mixed-effects modeling. The relationships are visualized in Figure 5. There is no statistically significant positive slope for exposure-response relationship for any of these moieties.

Figure 5: $\Delta\Delta\text{QTcF}$ vs. Concentration for (A) midostaurin, (B) CGP62221 and (C) CGP52421



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Study PKC412D2201 in AdSM patients

A single arm, Phase II, open-label efficacy study PKC412D2201 in AdSM patients involved administration of midostaurin 100 mg b.i.d. dose in continuous cycles of 28 days, which is the proposed therapeutic dose in this population. Midostaurin was administered until disease progression, intolerable toxicity or withdrawal due to any cause, whichever occurred first. A total of 116 patients were treated with midostaurin in this study. 12-Lead ECG assessment was performed at screening, on Day 3 of Cycle 1 and then at pre-dose timepoint at the end of each cycle (day 28). The time matched ECG/PK samples are available for day 3 of cycle 1 (C1D3), and day 28 of cycle 1, 2, 5, 8, 11 (C1D28, C2D28, C5D28, C8D28, C11D28).

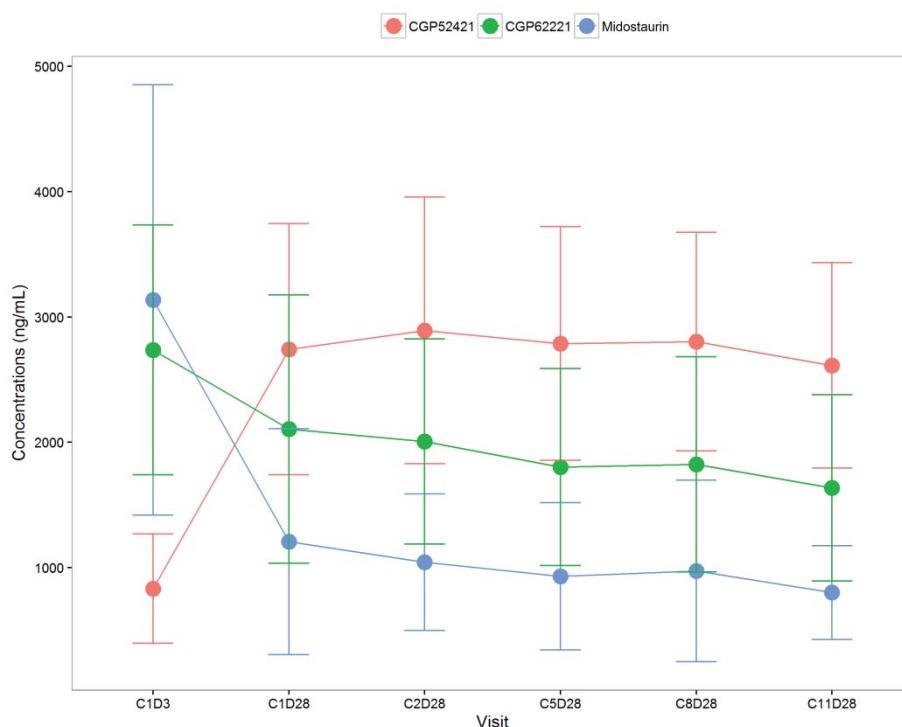
Data from study PKC412D2201 were analyzed for this review for two specific reasons:

1. The dosing in this study (100 mg b.i.d.) was higher than the dosing of 75 mg b.i.d. utilized in the TQT study PKC412A2113.
2. Due to the long half-life of the metabolite CGP52421 (482 hours) and the duration of the TQT study (3 days), the effect of the long-lasting (accumulating) metabolite CGP52421 on QT intervals could not have been determined adequately at Day 3 in TQT study.

The mean concentration-time profiles for midostaurin, and its metabolites (CGP62221 and CGP52421) with multiple dosing in successive cycles are illustrated in Figure 6.

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Figure 6: Mean ($\pm$ SD) Concentration-Time Profiles for Midostaurin, and its Metabolites (CGP62221 and CGP52421) with multiple dosing in successive cycles



In this study, 5 subjects (4.3%) had $480 < QTcF \leq 500$ ms and 25 subjects (21.6%) had $450 < QTcF \leq 480$ ms. Eight (7.2%) subjects had $\Delta QTcF > 60$ ms, and 33 subjects (29.7%) had $\Delta QTcF$ between 30-60 ms.

The relationships between $\Delta QTcF$ and midostaurin, CGP62221, or CGP52421 concentrations are visualized in Figure 7, Figure 8, and Figure 9. The exposure-response relationship investigated by linear mixed-effects modeling showed no statistically significant relationship between $\Delta QTcF$ and midostaurin, CGP62221 or CGP52421 concentrations.

There were multiple factors that limit the interpretation of ECG data from this study:

- The study had just single 12-lead ECG assessments at trough concentrations.
- There was no placebo or positive control in the study.
- The study protocol involved prophylactic use of anti-emetics (e.g., ganisetron, ondansetron, metoclopramide, methotrimaprazine, cyclizine, prochlorperazine, tropisetron) for the prevention of nausea and vomiting, to be administered to all patients prior to each dose of midostaurin. Some of these anti-emetics are known to prolong QT interval. Thus the evaluation of QT effect due to midostaurin administration in AdSM patients is confounded by these anti-emetic con-medications.

Figure 7: Δ QTcF vs. midostaurin concentration

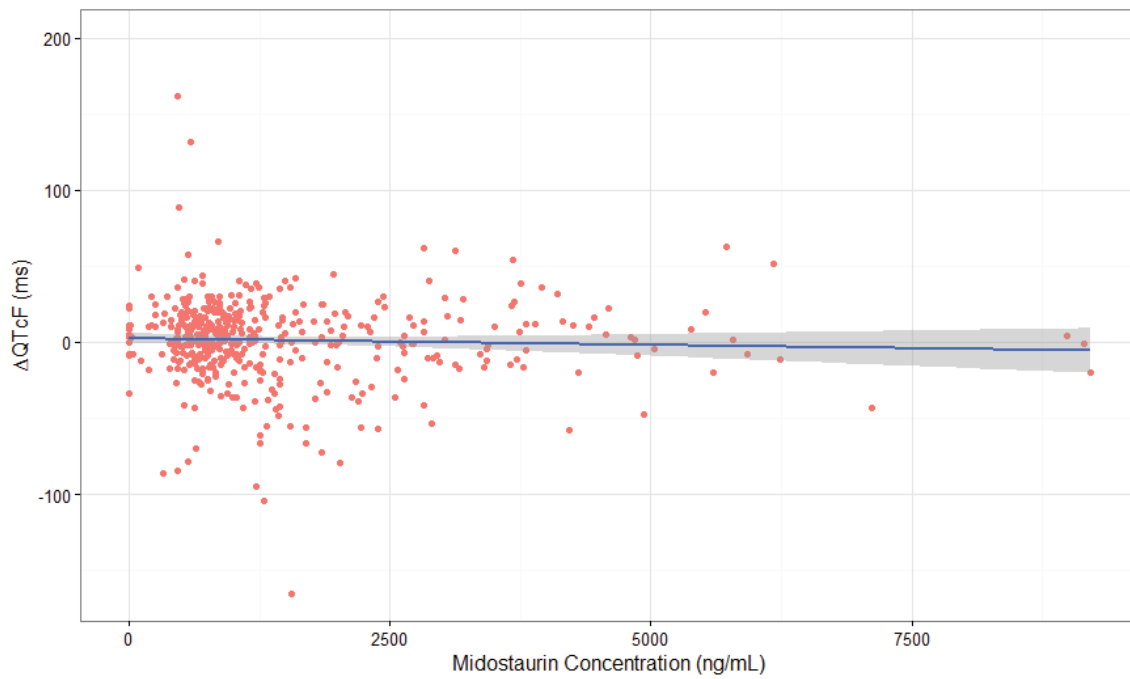


Figure 8: Δ QTcF vs. CGP62221 concentration

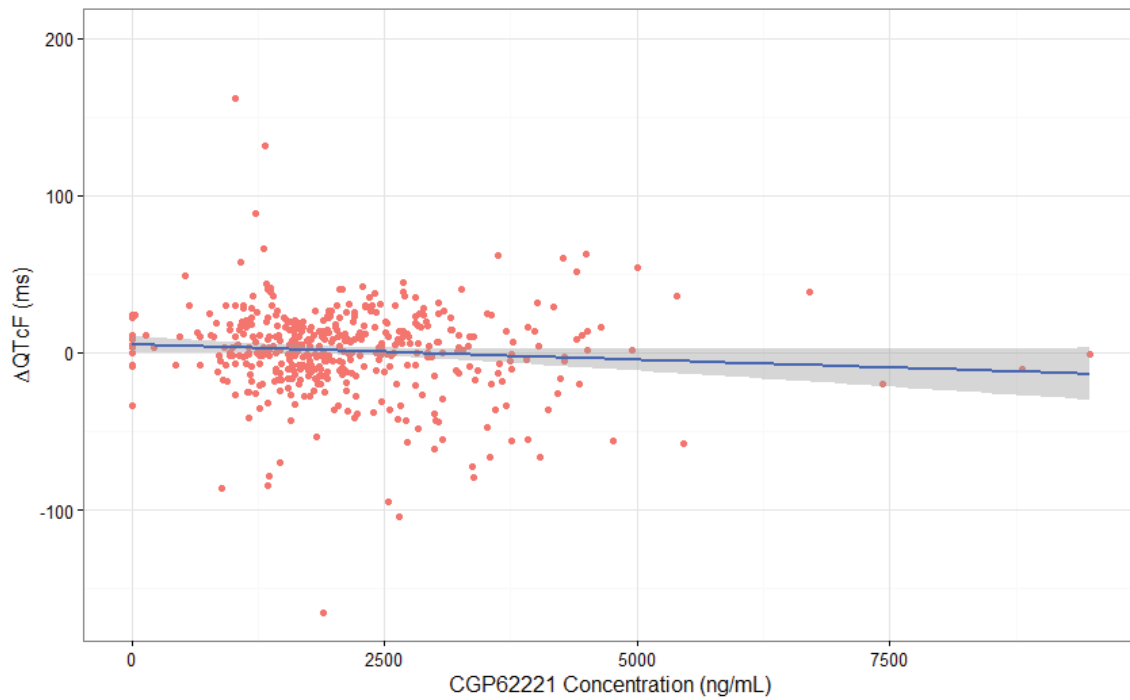
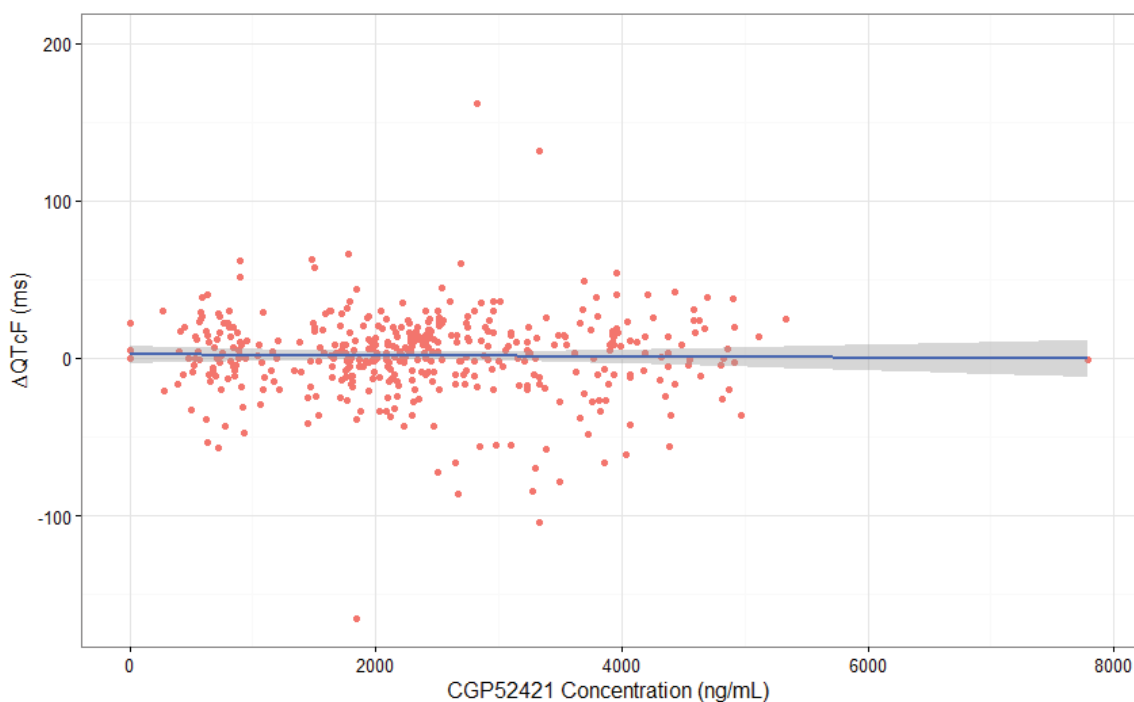


Figure 9: Δ QTcF vs. CGP52421 concentration



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines (i.e., syncope, seizure, significant ventricular arrhythmias or sudden cardiac death) occurred in the TQT study.

5.4.2 ECG assessments

Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 Effects on other ECG Intervals

There were no effects on heart rate, PR and QRS intervals.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	AML: 50 mg bid Advanced SM (AdSM): 100 mg bid
Maximum tolerated dose	The MTD could not be defined by conventional means. However, as GI toxicity caused drop outs at 225-300 mg daily and the maximum number of capsules regarded as acceptable for choice of dosing was 12 (300 mg/day), the MFD (maximum feasible dose) for practical purposes in this population should be

	regarded as 225-300mg/day even though no DLT was observed.	
Principal adverse events	The safety profile of midostaurin is well-characterized, with predictable, primarily gastrointestinal (nausea, vomiting) events and cytopenias that are generally manageable with use of anti-emetic therapy and dose adjustment/temporary interruption. As expected, AML patients receiving midostaurin in combination with intensive chemotherapy (daunorubicin and cytarabine) experienced a higher incidence of liver function test elevations, infections, uncomplicated febrile neutropenia and grade 3 and 4 cytopenias.	
Maximum dose tested	Single Dose	100 mg
	Multiple Dose	300 mg bid (after intra-patient dose escalation CPKC412A2104E2)
Exposures Achieved at Maximum Tested Dose	Single Dose	• Single dose 100mg day 1 (100mg bid , D2201 Geometric mean (%CV) Midostaurin • C_{max}: = 2871.45 ng/ml (32.72) • AUC₀₋₁₂= 21495 h.ng/ml (43.19) • AUC_{inf}= 46375.71 h.ng/ml (79.01) CGP62221 • C_{max}=913.61 ng/ml (34.51) • AUC₀₋₁₂= 7175.54 h.ng/ml (45.18) CGP52421 • C_{max}= 292.68 ng/ml (30.06) • AUC₀₋₁₂= 2357 ng/ml (37.68)
	Multiple Dose	• 300 mg bid (CPKC412A2104E2): no PK data available, so the next available exposures achieved at the maximum tested dose is: multiple dose (day3, 75 mg o.d following a 75 mg bid on Day 1 and day 2 dosing, CPKC412A2213, TQT study) Geometric mean (%CV) Midostaurin • C_{max} = 2104.37ng/ml (53.94) • AUC₀₋₂₄= 23071.5 h.ng/ml (58.38) CGP62221 • C_{max}= 1808.47 ng/ml (34.43) • AUC₀₋₂₄ = 34606.5 h.ng/ml (40.15) CGP52421 • C_{max}=1231.59 ng/ml(16.97) • AUC₀₋₂₄=25504.5 ng/ml (16.79)
Range of	Following single dose administration, exposure to midostaurin and its	

linear PK	metabolites increased in a dose-proportional manner within the dose range of 25 mg to 100 mg. The slope estimates for AUC_{0-12h} were 1.045, 0.944 and 1.101 for midostaurin, CGP62221 and CGP52421 respectively. For C_{max}, the slope estimates were 0.87, 0.861 and 1.036 for midostaurin, CGP62221 and CGP52421, respectively. Upon twice-daily administration, there was no dose-proportional increase in exposure (C_{min}) within the dose range of 50 mg to 200 mg total daily dose
Accumulation at steady state	Within the tested dose range (50 mg bid, 100 mg bid and 75 mg tid), the PK of midostaurin was time-dependent following multiple oral doses, with an initial increase in plasma concentrations during the first week (peak C_{min}) followed by a decline with time to reach steady-state after approximately 28 days. Midostaurin peak C_{min} at 50 mg bid was observed on C1D8 at 2600 ng/mL, and for 100 mg bid on C1D8 at 1840 ng/mL. Steady state concentration after 28 days of dosing for 50 mg bid was 1180 ng/mL, and for 100 mg bid (AdSM) was 1080 ng/mL. The pharmacokinetics of active metabolite CGP62221 showed similar trends as for midostaurin pharmacokinetics also with an initial increase in plasma concentrations during the first week (C1D8 50 mg=2450 ng/ml C1D8 100 mg AdSM=3320 ng/ml) followed by a decline with time to reach steady-state after approximately 28 days (C1D28 50 mg=1220 ng/ml C1D28 100 mg AdSM=2070 ng/ml). Since midostaurin and its active metabolites were shown to have in vitro inducing effects on CYP3A4, the time-dependency of midostaurin and CGP62221 is likely due to CYP3A4 autoinduction, and support the little or no difference in the measured concentrations of midostaurin and CGP62221 at the two doses 50 mg and 100 mg bid at steady-state (Day 28) indicating a lack of dose-proportional change in exposure within this dose range. After bid dosing, active metabolite CGP52421 concentrations do not appear to decline significantly as like midostaurin and CGP62221. Nevertheless, CGP52421 may have also shown a different time-dependent PK, potentially due to auto-induction of enzymes involved in its clearance, such as CYP3A4. Based on the human absorption, distribution, metabolism, and excretion (ADME) data, the geometric mean half-life of CGP52421 (estimated 482 h) was significantly longer than that of midostaurin (19.6 h) or CGP62221 (32.2 h). After one month of treatment, CGP52421 concentrations increased up to 2.5-fold compared to midostaurin in advanced SM patients (D2201 and A2213) receiving 100 mg bid daily, and 9-fold compared to midostaurin in AML patients (2104E1) receiving 50 or 100 mg bid daily continually until at least Cycle 3. In Study A2301 (50 mg bid in combination with chemotherapy), the increase in CGP52421 concentrations was 3-fold as compared to midostaurin during the continuation phase. Given these accumulation factors (2.5 to 9-fold), the accumulation half-life of CGP52421 can be estimated to be 20 h to 70 h, suggesting auto-induction may limit the accumulation of this metabolite.
Metabolites	Two pharmacologically active metabolites: - CGP62221, (O-demethyl metabolite of midostaurin is pharmacologically active: IC₅₀ = 26 nM (FLT3), 71 nM (KIT). - CGP52421, (7-hydroxy metabolite of midostaurin). It is a pool of two epimers: P39.8 epimer 2, P37.7 epimer 1. CGP52421 is also pharmacologically active, the two epimers are equipotent: IC₅₀ = 584 nM (FLT3), 233 nM (KIT).

	- These two major metabolites represent 38% (CGP52421) and 28% (CGP62221) of the dose-related plasma AUC after a single midostaurin dose of 50 mg Other inactive metabolites include P21.2, P22.6B, P28.8B, P29.6B, P33 (formed by O-demethylations followed or preceded by hydroxylation), P33.6, P34.5, P35.3 (formed by oxidation at benzene ring), P6, P6B (formed by amide hydrolysis and conjugation), P22.6, P15.5 (formed by N-demethylation).	
Absorption	Absolute/Relative Bioavailability	Absolute BA in human was not determined. Relative BA of the FMI and the CSF were determined: FMI was higher by 15 % vs. CSF (fasted) and higher by 26% vs. OS (fasted), and CSF higher by 9% vs OS (fasted). Relative BA of the OS and the FMI were similar (fed).
	Tmax	Median (range) Tmax is 1 h [1 – 3] for midostaurin is 3 h [2 – 4] for CGP62221, and is 3 h [2 – 6] for CGP52421.
Distribution	Vd/F or Vd	Geometric mean Vd/F is 95.2 L (geometric mean CV = 30.8%).
	% bound	Midostaurin is highly bound (> 99.9 %) in human.
Elimination	Route	The primary excretion route is via feces (77.6% of the dose within 20 days). Excretion in urine is minor (4% within 168 h).
	Terminal t _{1/2}	Geometric mean T _{1/2} is 19.6 h (CV = 38.8%) for midostaurin, is 32.2 h (CV = 31.1%) for CGP62221, and is 482 h (CV = 24.9%) for CGP52421.
	CL/F or CL	Mean CL/F is 3.79 L/h (CV = 55.1%).
Intrinsic Factors	Age	No impact of age was observed on the exposure midostaurin and the active metabolites.
	Sex	There was a slight decrease in exposure (7 to 22%) in females compared to males for midostaurin and the active metabolites. Since there was little or no association with midostaurin and metabolites with safety parameters, this decrease in exposure for females is deemed not clinically relevant. In the pivotal Study A2301, there was no impact of gender on the exposure of midostaurin, CGP62221 and CGP52421. Furthermore, gender showed no significant effect on the PK of midostaurin or either of its metabolites in the PopPK analyses for AdSM and AML. The anticipated changes in exposure were not deemed to be clinically relevant

	Race	The exposure of midostaurin and its metabolites after single doses was generally similar among Caucasians, Asians and Black healthy subjects
	Hepatic & Renal Impairment	Based on the hepatic impairment study, and subsequent PBPK modelling, an initial decrease in exposure (AUC0-tau) was observed for mild and moderately impaired patients. In patients with moderate hepatic impairment, there is a predicted increase in exposure at steady state. However, in studies in AdSM analyses by hepatic function did not demonstrate any major differences between the proportion of patients with AEs among the normal hepatic function and mild and moderate hepatic impairment subgroups. Additional analysis using popPK modeling showed that mild and moderate hepatic impairment did not have a significant effect on the PK of midostaurin or its metabolites. Therefore, this potential temporal effect of hepatic impairment on exposure in patients with mild and moderate hepatic impairment is considered not clinically relevant. Renal impairment: based on popPK analysis, there was no significant impact of renal function on the PK of midostaurin
Extrinsic Factors	Drug interactions	Midostaurin undergoes extensive metabolism mainly by CYP3A4 enzyme, and two of its metabolites are pharmacologically active (CGP62221 and CGP52421) - Strong CYP3A4 inhibitors: In a pooled analysis across Ad SM and AML patients receiving midostaurin as single-agent therapy (not including patients from A2301), there was maximum of 2.7-fold increase of midostaurin exposure (Cmin) at steady-state upon co-administration with strong CYP3A4 inhibitors. When exposure to the sum of active moieties was compared, the geometric mean Cmin increased by 1.76-fold (76%) upon co-administration with CYP3A4 inhibitors. In Study A2104E2, AML patients who were concomitantly administered the strong CYP3A4 inhibitor Itraconazole (n=7) with midostaurin 50 mg bid had a 2.09-fold increase in midostaurin Cmin at steady state compared to when they received midostaurin 50 mg bid

		alone. A similar finding was confirmed through population PK analysis for AML patients. The above analyses of data at steady state confirmed the potential for drug-drug interaction based on findings from a single dose DDI study in healthy volunteers (A2109) where co-administration of ketoconazole increased midostaurin C_{max} and AUC_{inf} by 1.8 and 10-fold, respectively. However, the observed effect on a single dose of midostaurin would be of limited clinical importance at steady-state given the time-dependent kinetics of midostaurin. Overall, an average of approximately 2-fold increase of midostaurin exposure was observed and this increase was not associated with any significant clinical findings, therefore, no dose adjustment is required when midostaurin is co-administered with CYP3A4 inhibitors - Strong CYP3A4 inducers In healthy subjects, co-administration of the strong CYP3A4 inducer rifampicin (600 mg daily) to steady state with a single dose of midostaurin, increased midostaurin apparent clearance by 16.9-fold, representing notable mean decreases in C_{max} and AUC of 73% and 94%, respectively. Therefore, concomitant administration of medicinal products that are strong inducers of CYP3A4 with midostaurin should be avoided, and alternative therapeutics with a lower CYP3A4 induction potential should be considered - Sensitive CYP3A4 substrates The PK of a single dose of midazolam (sensitive CYP3A4 probe substrate) was not affected in a clinically meaningful manner following four-dosing days (4) of midostaurin administration in healthy subjects (Study A2112). The geomean C_{max} and AUC_{inf} of midazolam decreased by 9% and 5%, respectively. However, it cannot be excluded that midostaurin may be an inducer of CYP3A4, as the dose of midazolam was administered only after four dosing days of midostaurin and not at steady-state. Based on PBPK analysis, the simulated results indicate that midazolam geomean ratio of AUC could be
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		reduced by 25% at steady-state levels of midostaurin, as compared to clinically observed value (Study A2112 on Day 8). This suggests that significant clinical DDI between midazolam and midostaurin would be unlikely at steady-state.
	Food Effects	A food effect was observed on the pharmacokinetics of midostaurin. The extent of absorption (AUC _{inf}) was increased by 22% (90% CI: 0.94-1.60) for a standard meal (approximately 25% fat of the total 450 caloric content of the meal) and by 59% (90% CI: 1.22-2.08) for the high fat meal. The rate of absorption (C _{max}) was decreased by 20% (90% CI: 0.64-0.98) and 27% (90% CI: 0.59-0.90) respectively.
Expected High Clinical Exposure Scenario	Across the clinical development, only C _{trough} levels were collected after multiple doses, therefore, expected fold change of C _{max} and AUC in the worst case scenario cannot be performed. Thus, in the Phase 3 AML pivotal trial (50 mg bid, A2301), up to 62 % patients received concomitant antifungal therapy, including strong CYP3A4 inhibitors, to prevent or treat fungal infections. Because strong inhibitors of CYP3A4 had been observed to have a relatively significant impact on the exposure to midostaurin, an analysis was performed to determine the impact coadministration of strong CYP3A4 inhibitors on drug exposure and total circulating activity compared to all other patients (i.e. those who did not receive strong CYP3A4 inhibitors, but who received other concomitant medications, including mild and moderate CYP3A4 inhibitors). In patients who received concomitant strong CYP3A4 inhibitors, midostaurin concentrations (C _{min}) were 1.44-fold higher compared to all remaining patients in the study, and the overall change in exposure to the sum of active moieties was estimated to be 1.22-fold.	
Preclinical Cardiac Safety	<i>In vitro</i>, no inhibition of hERG in HEK293 cells was shown at a concentration of 12 µM midostaurin (6.8 µg/mL, highest midostaurin soluble concentration). CGP52421 and CGP62221 inhibited hERG current by 38.5% at 1.50 µM and 11.3% at 1.21 µM respectively. midostaurin and the two metabolites are highly protein bound, and the free drug concentration in patients is low relative to the total drug. The highest concentrations of midostaurin, CGP52421 and CGP6221 tested in the minimal or no hERG inhibition are much higher than the free drug concentrations in patients. The risk of hERG-related QTc interval prolongation from midostaurin and the two metabolites at therapeutic exposures is therefore considered low. In dogs, a decrease in heart rate in individual animals and a PQ prolongation was seen after repeated doses of midostaurin. No associated morphological changes in the heart were noticed.	
Clinical Cardiac Safety	In study CPKC421A2113, 75 mg BID midostaurin were administered for 3 days in 70 patients (PK population set). The dose utilized in this study, 75 mg b.i.d. for 3 days, was greater than the 50 mg b.i.d. dose used in the phase III registration study in de novo AML patients. Midostaurin demonstrates time-	

dependent pharmacokinetics in humans. Following multiple oral doses, plasma concentrations of midostaurin and CGP62221 reach the maximal level during the first week and then decline with time until steady state is achieved. This study evaluated the change from baseline to day 3, at maximum plasma levels of both midostaurin and CGP62221.

The PK parameters at day 1 were

	T _{max} [h]	C _{max} [ng/mL]	AUC _{0-12h} [h.ng/mL]
midostaurin (N=70)	1 (1-3.12)	2142.1 (690.10)	11662.6 (3723.65)
CGP62221 (N=70)	3.08 (2.08;4.02)	866.3 (169.20)	7848.2 (1579.89)
CGP52421 (N=67)	4 (2.08;4.03)	384.5 (65.12)	3509.2 (609.76)

Values are mean (SD) except for T_{max} which is median (range)

PK parameters on Day 3 were:

	T _{max} [h]	C _{max} [ng/mL]	AUC _{0-24h} [h.ng/mL]
midostaurin (N=54)	1.08 (1.08;3.08)	2273.3 (710.28)	25657.5 (10872.71)
CGP62221 (N=51)	3.08 (0.00;8.08)	1882.0 (432.47)	36486.5 (9769.72)
CGP52421 (N=45)	3.08 (1.08 -8.08)	1248.6 (208.36)	25837.2 (4034.03)

Values are mean (SD) except for T_{max} which is median (range)

midostaurin did not prolong QTc since the upper bound of the one sided 90% CI (equivalent to one-sided 95% upper confidence boundary) for the largest time matched effect of midostaurin versus placebo excluded 10 ms.

QT Parameter	Estimate of the Concentration Slope (ms per µg/mL)	SD of the Slope (ms per µg/mL)	p-value	Predicted QT parameter at mean C _{max} (ms)	90% CI Lower Bound (ms)	90% CI Upper Bound (ms)
QT	0.9317	0.8793	0.2898	-7.2471	-10.5460	-3.9483
QTcB	-5.1875	0.6907	<.0001	-5.1087	-8.6911	-1.5263
QTcF	-2.2817	0.4962	<.0001	-5.1184	-8.3932	-1.8436
QTcI	-1.5818	0.5190	0.0024	-4.7541	-8.1219	-1.3863

Study No	Study Objective	Population	No. of Subjects/patients	Treatment Duration	Medication (midostaurin) dose and day (n)
Studies in healthy subjects					
Biopharmaceutics (BA/BE/food effect studies)					
CPKC412A21 08	(r)BA study of midostaurin following a single oral dose of 50 mg given as CSF, FMI or oral solution formulations.	Healthy subjects	CSF:18 FMI:18 Oral solution: 18	Single dose	50 mg

CPKC412A21 11	Effect of food on the PK of the FMI capsule, BA of midostaurin FMI and oral solution formulations in fed state	Healthy subjects	FMI fasted:13 FMI standard meal:12 FMI high- fat meal:13 Oral solution standard meal:12	Single dose	50 mg
Pharmacokinetic studies					
CPKC412A00 1	Single-dose PK, dose proportionality safety and tolerability	Healthy subjects	18	Single dose	1 (2pts) , 4 (2pts), 12.5 (5pts) , 25 mg (5 pts) 4 placebo
CPKC412A21 07	Absorption, distribution, metabolism and excretion (Mass Balance)	Healthy subjects	6	Single dose	50 mg ¹⁴ C-midostaurin
Special Safety Studies					
CPKC412A21 13	Dedicated QT study, placebo and active control	Healthy subjects	Midostaurin: 80 Moxifloxacin: 44 Placebo: 68	3 days	Midostaurin or Placebo: 75 mg two times daily on Days 1 and 2 Midostaurin or Placebo: 75 mg once daily on Day 3 Moxifloxacin or Placebo: 400 mg (Avelox®)
Drug-Drug interaction studies					
CPKC412A21 09	Drug-drug interaction study between ketoconazole and single-dose midostaurin	Healthy subjects	47	10 days	50 mg-single dose midostaurin (Day 6) 400 mg once daily ketoconazole or placebo for 10 days

CPKC412A21 10	Drug-drug interaction study between rifampicin and single-dose midostaurin	Healthy subjects	47	14 days	50 mg- single dose midostauri n (Day 9) 600 mg once daily rifampicin or placebo for 14 days
CPKC412A21 12	Drug-drug interaction study between midostaurin and single- dose midazolam	Healthy subjects	20	4 days	100 mg once daily then 50 mg twice daily for 3 days of midostauri n (Day 3 to 6) 4 mg of midazolam (Day 1, Day 3 and Day 8)
Studies in special populations					
CPKC412A21 16	PK, Safety and tolerability of midostaurin in subjects with hepatic impairment, compared to healthy control subjects	Healthy subjects and patients with mild, moderate and severe hepatic impairment	Severe: 0, ongoing Mild: 10 Moderate: 7 HV: 13	7 days	50 mg bid from day 1 to Day 6, 50 mg single dose on Day 7
CPKC412A11 01	Single-dose pharmacokine tics, safety and tolerability of midostaurin in Japanese Subjects	Healthy Japanese subjects	40; 8 subjects at each dose level	Single dose	25 mg, 50 mg, 75 mg, 100 mg, Placebo
CPKC412A21 14	Pediatric PK, safety, tolerability of midostaurin monotherapy	Pediatric AML patients	22	Until unaccepta ble toxicity or progressiv e disease	30 mg/m ² bid (7 patients) 60 mg/m ² bid (15 patients)
Studies in patients					

CPKC412A002	PK, safety and tolerability of midostaurin	Patients with advanced tumors	32	Until unacceptable toxicity or progressive disease	12.5 mg once daily (3 patients), 12.5 mg twice daily (3 patients) 25 mg bid (3 patients) 50 mg bid (3 patients) 75 mg bid (4 patients) 75 mg tid (9 patients) 100 mg tid (7 patients)
C-99-PKC412-001	PK, safety and tolerability of midostaurin	Patients with diabetes mellitus	86	28 days	25 mg bid (13 patients) 50 mg bid (13 patients) 75 mg bid (14 patients) 75 mg tid (15 patients) 100 mg tid (9 patients) Placebo (19 patients)
CPKC412A006	PK, safety and tolerability of midostaurin	Patients with stage III-IV chronic lymphocytic leukemia or non-Hodgkin's lymphoma	21	14 days	25 mg qd (7 patients) 75 mg bid (7 patients) 75 mg tid (7 patients)
Studies in AdSM patients					
CPKC412A2213	PK, safety and tolerability of midostaurin monotherapy	Patients with advanced systemic mastocytosis and MCL	26	Until unacceptable toxicity or progressive disease	100 mg bid
CPKC412D2201	PK, safety and tolerability of midostaurin monotherapy	Patients with advanced systemic mastocytosis	116	Until unacceptable toxicity or progressive disease	100 mg bid
Studies in AML patients					

CPKC412A2104	PK, safety and tolerability of midostaurin monotherapy	Patients with relapsed/refractory or Rx-ineligible AML and MDS with either wild type or mutated FLT3	20	Until unacceptable toxicity or progressive disease	75 mg tid
CPKC412A2104E1	PK, safety and tolerability of midostaurin monotherapy	Patients with relapsed/refractory or Rx-ineligible AML and MDS with either wild type or mutated FLT3	95	Until unacceptable toxicity or progressive disease	50 mg bid (51 patients) and 100 mg bid (44 patients)
CPKC412A2104E2	PK, safety and tolerability of midostaurin monotherapy or combination with itraconazole	Patients with relapsed/refractory or Rx-ineligible AML and MDS with either wild type or mutated FLT3	29	Until unacceptable toxicity or progressive disease	Arm 1: intra-dose escalation up to 300 mg bid (16 patients) Arm 2: midostaurin (100 mg for 2 days followed by 50 mg bid) combination with itraconazole: (13 patients)
CPKC412A2106	PK, safety and tolerability of twice daily oral dosing of midostaurin administered in combination sequentially and concomitantly with daunorubicin and cytarabine for consolidation.	Patients with newly-diagnosed FLT3+ AML	69	Until relapse, or for up to 3 years from the time of diagnosis, in the absence of safety concerns	100 mg bid (29 patients) 50 mg bid (40 patients)

CPKC412A23 01 (CALGB 10603)	Study of induction (daunorubicin /cytarabine) and consolidation (high-dose cytarabine) chemotherapy of + midostaurin or placebo	Newly diagnosed patients <60 years of age with FLT3 mutated AML	717	18 months 50 mg bid
Source: Individual CSRs,				
In AdSM patients (studies D2201 and A2213) QT prolongation-related events were reported 16.2% of patients; the most commonly reported event was ECG QT prolonged (15 patients; 10.6%) and resulted in discontinuation in 3 patients [SCS Appendix 1-Table 5-27.1]. A further 2 patients discontinued due to events included in the QT prolongation standard MedDRA query; cardiac arrest and ventricular tachycardia [SCS Appendix 1-Table 5-27.1]. In study D2201, 2 patients died due to cardiac arrest D2201-0200-00005 and D2201-0506-00010, neither death was suspected to be related to study drug and there was no QT prolongation (these events are also discussed in SCS – Section 5.5.1 and short narratives are provided). No AdSM patient experienced a QTcF value of > 500 ms. Evaluation of the notable QTcF from the pooled dataset demonstrated that 6 patients had a post-baseline QTc interval of > 480 ms and 8 patients had an increase of > 60 ms in QTc interval compared to baseline. (SCS Table 5-12). QTcF analysis by timepoint was presented in [SCS Appendix-Table 5-17.7c]. A linear mixed effects model was used to fit the change from baseline in QTcF as a response variable, with log-transformed concentration (of midostaurin and both metabolites), baseline QTcF and relevant covariates (identified through backwards selection) fitted as fixed effects. A negative effect of concentration was observed on QTcF for all three analytes [SCP Section 3.11.4]. These results are also supported by the dedicated QT study A2113 [SCP Section 2.2.6]. In AML patients in Study A2301, QT prolongation AEs (any grade) were reported in 24.0% vs 21.2% of patients in the midostaurin vs placebo groups, respectively (NNA sites), primarily ECG QT prolonged (19.2% vs 16.8%) and syncope (5.2% vs 4.9%) [Study A2301-Table 14.3.1-5.1]. In Study A2301, QT prolongation AEs were reported as SAEs for 1.7% vs 3.1% of patients, and led to discontinuation for 1 patient (0.4%) each in the midostaurin and placebo groups (note that these are the same patients that are counted as discontinuations in the analysis of arrhythmia AEs in SCS Section 5.5.2) (Table 5-13). None of the events had a fatal outcome. The incidence of any grade and grade 3/4 events of QT prolongation was similar in the treatment arms overall and in the induction and consolidation phase [Study A2301-Table 14.3.1-5.1]. In the continuation phase, the occurrence of QT prolongation events was higher in the midostaurin group than in the placebo group, for any events, grade 3/4 events and study drug related events. The clinical impact is thought to be limited given as only a small proportion of the total events occurred in the				

	continuation phase [Study A2301-Table 14.3.1- 5.1]. In AML patients (study A2301), the mean QTcF values were generally similar in patients on midostaurin vs patients on placebo with values close to 400 ms with no meaningful trend upwards or downwards during the induction and consolidation phases of the study. The confidence intervals were narrow, and outliers were similar in both treatment groups (SCS Figure 5-1). Similar results were observed when QTcF values from patients in the continuation phase were plotted over time. In all phase (induction, consolidation and continuation), few outliers and narrow CIs further confirmed the robustness of the results (SCS Figure 5-1). Overall, based on the currently available data, it is considered that treatment with midostaurin is not associated with QT prolongation effect
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/s/

DHANANJAY D MARATHE

12/28/2016

Xiaofeng Wang was the primary Clin Pharm reviewer.

XIAOFENG WANG

12/28/2016

JANELLE E CHEN

12/29/2016

QIANYU DANG

12/29/2016

MICHAEL Y LI

12/30/2016

CHRISTINE E GARNETT

12/30/2016

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:	08 November 2016
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	NDA 207997
Product Name and Strength:	Rydapt (midostaurin) capsules, 25 mg
Product Type:	Single-Ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Novartis
Submission Date:	5 April 2016, 26 May 2016, 25 July 2016, and 29 August 2016
OSE RCM #:	2016-1821
DMEPA Primary Reviewer:	Leeza Rahimi, Pharm.D.
DMEPA Acting Team Leader:	Hina Mehta, Pharm.D.

1 REASON FOR REVIEW

The Division of Hematology Products (DHP) requested a review of the proposed carton labeling, container labels, sample labels, Prescribing Information (PI), and Patient Information for Rydapt (midostaurin) NDA 207997, submitted on 29 August 2016, 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
Human Factors Study	N/A
ISMP Newsletters	N/A
FDA Adverse Event Reporting System (FAERS)*	N/A
Other	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

Novartis submitted a 505 (b)(1) NDA to obtain marketing approval of Rydapt (midostaurin) capsules. We performed a risk assessment of the proposed labels and labeling for all carton and containers, sample labels, Prescribing Information, and Patient Information to identify deficiencies that may lead to medication error and other areas of improvement.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed labels and labeling can be improved to increase the readability and prominence of important information and promote the safe use of the product and mitigate any confusion.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information (PI)

1. Highlights of Prescribing Information, Dosage and Administration
 - a. Include statement “with food” immediately after the dose so this important information is not overlooked and to maintain consistency with the full prescribing information.
 - b. Add a bullet stating “Capsule should be swallowed whole and not to be opened, crushed, or chewed” so this important information is not overlooked and to maintain consistency with the full prescribing information

2. Dosage And Administration:

Under Section “2.4 (b) (4) Administration (b) (4)”, we recommend rephrasing the following sentences:

a) (b) (4)
We recommend rephrasing the sentence to read, “If a dose is missed (b) (4) take the next (b) (4) dose at the scheduled time”.

(b) (4)
(b) (4) from the sentence to read (b) (4) vomit (b) (4) take the next (b) (4) dose”.

(b) (4)

3. Dosage Forms and Strengths:

- a) We recommend adding the term “gelatin” next to the word “soft” for the description of the capsules.

4. How Supplied/Storage And Handling:

- a) As currently presented the “Content” section states:

“Each carton contains two inner packs, each with 28 capsules (7 blisters with 4 capsules each).” We recommend adding the term “cards” next to the word “blister” to conform with container labels. We suggest revising the sentence to read: “Each carton contains two inner packs, each with 28 capsules (7 blister cards with 4 capsules each).”

- b) See section 3-a.

4.2 RECOMMENDATIONS FOR NOVARTIS

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

A. Carton and Carton Labels:

- 1) We recommend removing the term “soft” from the “soft capsules” appearing next to the quantities on all carton and container labels in order to be consistent with the dosage form description.

B. Sample Carton and Container Labels:

- 2) Please change the font color or/and size for the term “Sample-Not for Sale” to make it more prominent and enhance differentiation from the strength.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Rydapt that Novartis submitted on 29 August 2016.

Table 2. Relevant Product Information for Rydapt	
Initial Approval Date	N/A
Active Ingredient	Midostaurin
Indication	Aggressive systemic mastocytosis (ASM) / mast cell leukemia (MCL) / acute myeloid leukemia (AML)
Route of Administration	Oral
Dosage Form	Capsules
Strength	25 mg
Dose and Frequency	ASM/MCL: 4 capsules (100 mg) twice daily (every 12 hours); AML: 2 capsules (50 mg) twice daily (every 12 hours)
How Supplied	Blister packs
Storage	Room temperature

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On 5 September 2016, we searched the L:drive and AIMS using the terms, Rydapt to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified 2 previous reviews^a.

Information to include in the citation for previous reviews:

^aMistry, M. *Proprietary Name Review for Rydapt (midostaurin) IND 057120. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 OCT 20. RCM No.: OSE 2015-455888*

Baugh, D. *Proprietary Name Review for Rydapt (midostaurin) IND 57120. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2009 JUL 02*

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^a along with postmarket medication error data, we reviewed the following RYDAPT labels and labeling submitted by NOVARTIS on 29 August 2016.

- Container label
- Carton labeling
- Professional Sample Carton Labeling
- Professional Sample Blister cards

G.2 Label and Labeling Images

Container Labels:



^a Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

LEEZA RAHIMI
11/08/2016

HINA S MEHTA
11/08/2016