

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207997Orig1s000

207997Orig2s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 207997

SUPPL #

HFD #

- NDA 207997/Original #1: treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated hematological neoplasm (SM-AHN), or mast cell leukemia (MCL).
- NDA 207997/Original #2: 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.

Trade Name RYDAPT

Generic Name Midostaurin

Applicant Name Novartis Pharmaceuticals Corporation

Approval Date, If Known April 28, 2017

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

c) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

Novartis requests 7 years exclusivity for orphan designation for the following indications:

- NDA 207997/Original #1: treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated hematological neoplasm (SM-AHN), or mast cell leukemia (MCL).
- NDA 207997/Original #2: 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.

d) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.) IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
!
IND # YES ! NO
! Explain:

Investigation #2 !
!
IND # YES ! NO
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
!
YES ! NO
Explain: ! Explain:

Investigation #2 !
!
YES ! NO
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to

have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

Name of person completing form: Kimberly Scott
Title: Regulatory Project Manager
Date: April 28, 2017

Name of Division Director signing form: Ann T. Farrell, MD
Title: Director, Division of Hematology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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
04/28/2017

ANN T FARRELL
04/28/2017

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA #: 207997

Supplement Number:

NDA Supplement Type (e.g. SE5):

Division Name: Hematology Products

PDUFA Goal Date: April 28, 2017

Stamp Date: August 29, 2016

Proprietary Name: RYDAPT®

Established/Generic Name: Midostaurin, PKC412

Dosage Form: Capsules

Applicant: Novartis Pharmaceuticals Corporation

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):

(1) N/A

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 2

(Attach a completed Pediatric Page for each indication in current application.)

Indication: The treatment of adult patients with advanced systemic mastocytosis

Q1: Is this application in response to a PREA PMR?

Yes Continue

No Please proceed to Question 2.

If Yes, NDA/BLA#:

Supplement #:

PMR #:

Does the division agree that this is a complete response to the PMR?

Yes. Please proceed to Section D.

No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW active ingredient(s) (includes new combination); indication(s); dosage form; dosing regimen; or route of administration?*

(b) No. PREA does not apply. **Skip to signature block.**

* **Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

Q3: Does this indication have orphan designation?

Yes. PREA does not apply. **Skip to signature block.**

No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

Yes: (Complete Section A.)

No: Please check all that apply:

Partial Waiver for selected pediatric subpopulations (Complete Sections B)

Deferred for some or all pediatric subpopulations (Complete Sections C)

Completed for some or all pediatric subpopulations (Complete Sections D)

Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)

Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (check, and attach a brief justification for the reason(s) selected)

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed):
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):						
		minimum	maximum		Not feasible [#]	Not meaningful therapeutic benefit*	Ineffective or unsafe [†]	Formulation failed ^Δ
☐	Neonate	wk. mo.	wk. mo.		☐	☐	☐	☐
☐	Other	yr. mo.	yr. mo.		☐	☐	☐	☐
☐	Other	yr. mo.	yr. mo.		☐	☐	☐	☐
☐	Other	yr. mo.	yr. mo.		☐	☐	☐	☐
☐	Other	yr. mo.	yr. mo.		☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (check reason corresponding to the category checked above, and attach a brief justification):

- # Not feasible:
- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed):

* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

 Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	wk. mo.	wk. mo.	☐	☐	☐	☐
☐	Other	yr. mo.	yr. mo.	☐	☐	☐	☐
☐	Other	yr. mo.	yr. mo.	☐	☐	☐	☐
☐	Other	yr. mo.	yr. mo.	☐	☐	☐	☐
☐	Other	yr. mo.	yr. mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
Date studies are due (mm/dd/yy):							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason:

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum		maximum		PeRC Pediatric Assessment form attached?.	
☐	Neonate	wk.	mo.	wk.	mo.	Yes ☐	No ☐
☐	Other	yr.	mo.	yr.	mo.	Yes ☐	No ☐
☐	Other	yr.	mo.	yr.	mo.	Yes ☐	No ☐
☐	Other	yr.	mo.	yr.	mo.	Yes ☐	No ☐
☐	Other	yr.	mo.	yr.	mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.		16 yr. 11 mo.		Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum		maximum	
☐	Neonate	wk.	mo.	wk.	mo.
☐	Other	yr.	mo.	yr.	mo.
☐	Other	yr.	mo.	yr.	mo.
☐	Other	yr.	mo.	yr.	mo.
☐	Other	yr.	mo.	yr.	mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.		16 yr. 11 mo.	

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpms@fda.hhs.gov) OR AT 301-796-0700.

requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:							
Population		minimum		maximum		Extrapolated from:	
						Adult Studies?	Other Pediatric Studies?
☐	Neonate	wk.	mo.	wk.	mo.	☐	☐
☐	Other	yr.	mo.	yr.	mo.	☐	☐
☐	Other	yr.	mo.	yr.	mo.	☐	☐
☐	Other	yr.	mo.	yr.	mo.	☐	☐
☐	Other	yr.	mo.	yr.	mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.		16 yr. 11 mo.		☐	☐

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: The treatment of patients with newly diagnosed FLT3 mutation positive acute myeloid leukemia (AML)**Q1:** Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
- No. Please proceed to the next question.

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
- Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 - Deferred for some or all pediatric subpopulations (Complete Sections C)
 - Completed for some or all pediatric subpopulations (Complete Sections D)
 - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (check, and attach a brief justification for the reason(s) selected)

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed):
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):						
		minimum	maximum		Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
☐	Neonate	wk. mo.	wk. mo.		☐	☐	☐	☐
☐	Other	yr. mo.	yr. mo.		☐	☐	☐	☐
☐	Other	yr. mo.	yr. mo.		☐	☐	☐	☐
☐	Other	yr. mo.	yr. mo.		☐	☐	☐	☐
☐	Other	yr. mo.	yr. mo.		☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed):

* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpms@fda.hhs.gov) OR AT 301-796-0700.

PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for some or all pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
				Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
Population		minimum	maximum				
☐	Neonate	wk. mo.	wk. mo.	☐	☐	☐	☐
☐	Other	yr. mo.	yr. mo.	☐	☐	☐	☐
☐	Other	yr. mo.	yr. mo.	☐	☐	☐	☐
☐	Other	yr. mo.	yr. mo.	☐	☐	☐	☐
☐	Other	yr. mo.	yr. mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
Date studies are due (mm/dd/yy):							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason:

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):							
Population		minimum		maximum		PeRC Pediatric Assessment form attached?	
☐	Neonate	wk.	mo.	wk.	mo.	Yes ☐	No ☐
☐	Other	yr.	mo.	yr.	mo.	Yes ☐	No ☐
☐	Other	yr.	mo.	yr.	mo.	Yes ☐	No ☐
☐	Other	yr.	mo.	yr.	mo.	Yes ☐	No ☐
☐	Other	yr.	mo.	yr.	mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.		16 yr. 11 mo.		Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:					
Population		minimum		maximum	
☐	Neonate	wk.	mo.	wk.	mo.
☐	Other	yr.	mo.	yr.	mo.
☐	Other	yr.	mo.	yr.	mo.
☐	Other	yr.	mo.	yr.	mo.
☐	Other	yr.	mo.	yr.	mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.		16 yr. 11 mo.	

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	wk. mo.	wk. mo.	☐	☐
☐	Other	yr. mo.	yr. mo.	☐	☐
☐	Other	yr. mo.	yr. mo.	☐	☐
☐	Other	yr. mo.	yr. mo.	☐	☐
☐	Other	yr. mo.	yr. mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 6/2008)

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
04/13/2017

Scott, Kimberly

From: Abraham, Abbey <abbey.abraham@novartis.com>
Sent: Friday, April 28, 2017 9:46 AM
To: Scott, Kimberly
Cc: Qiu, Yuhong; Carioti, Theresa
Subject: RE: NDA 207997 Midostaurin: Approval Letter

Sensitivity: Confidential

Hi Kim

Received. Thank you very much.

Abbey Abraham, PharmD
Oncology Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation

Phone +1 862-778-8998
Fax +1 973-781-3473
abbey.abraham@novartis.com
www.novartis.com

From: Scott, Kimberly [<mailto:Kimberly.Scott@fda.hhs.gov>]
Sent: Friday, April 28, 2017 9:43 AM
To: Abraham, Abbey <abbey.abraham@novartis.com>
Cc: Qiu, Yuhong <yuhong.qiu@novartis.com>; Carioti, Theresa <Theresa.Carioti@fda.hhs.gov>
Subject: NDA 207997 Midostaurin: Approval Letter
Importance: High
Sensitivity: Confidential

Good morning Abbey,

Please see the attached Approval letter (courtesy copy) for the New Molecular Entity, NDA 207997, Midostaurin submitted on August 29, 2016. This approval is for the following indications:

- Original #1 – treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated hematological neoplasm (SM-AHN), or mast cell leukemia (MCL).
- Original #2 – 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.

Kindly confirm receipt of this email.

Thank you,
Kim
Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager

Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Rm 3231
Silver Spring, MD 20993
Phone: 240-402-4560
Fax: 301-796-9849
[|Kimberly.scott@fda.hhs.gov](mailto:Kimberly.scott@fda.hhs.gov)

APPEARS THIS WAY ON ORIGINAL

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
04/28/2017

Scott, Kimberly

From: Scott, Kimberly
Sent: Wednesday, April 26, 2017 10:37 AM
To: Abraham, Abbey
Cc: Qiu, Yuhong
Subject: NDA 207997 Midostaurin : FDA edits PI: respond by 11:30am (ET) today
Attachments: NDA 207997 FINAL Midostaurin PI FDA Tracked 4-26-17 Updated.docx

Importance: High
Sensitivity: Confidential

Good morning Abbey,

The Agency has reviewed your proposed edits to the PI for NDA 207997, midostaurin. Please see the attached PI with revisions in track changes and comments. If Novartis agrees, please send the final agreed upon label via email and officially through the gateway.

Please respond by 11:30AM (ET) today, April 26, 2017.

Kindly confirm receipt.

Thank you,

Kim

From: Abraham, Abbey [mailto:abbey.abraham@novartis.com]
Sent: Tuesday, April 25, 2017 5:26 PM
To: Scott, Kimberly
Cc: Qiu, Yuhong
Subject: RE: NDA 207997 Midostaurin : FDA edits PI: send TRACKED version of PI
Sensitivity: Confidential

Hi Kim

We also submitted the tracked version I emailed also via the Gateway. Please advise if the changes are acceptable and if so, if you would like to have clean version submitted as well formally.

Thanks

Abbey

From: Scott, Kimberly [mailto:Kimberly.Scott@fda.hhs.gov]
Sent: Tuesday, April 25, 2017 3:16 PM
To: Abraham, Abbey <abbey.abraham@novartis.com>
Cc: Qiu, Yuhong <yuhong.qiu@novartis.com>
Subject: RE: NDA 207997 Midostaurin : FDA edits PI: send TRACKED version of PI
Sensitivity: Confidential

Thank you.

From: Abraham, Abbey [mailto:abbey.abraham@novartis.com]
Sent: Tuesday, April 25, 2017 3:15 PM
To: Scott, Kimberly
Cc: Qiu, Yuhong

Subject: RE: NDA 207997 Midostaurin : FDA edits PI: send TRACKED version of PI
Sensitivity: Confidential

Hi Kim

Here is the Tracked version, with the Novartis proposals.

Abbey Abraham, PharmD
Oncology Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation

Phone +1 862-778-8998
Fax +1 973-781-3473
abbey.abraham@novartis.com
www.novartis.com

From: Scott, Kimberly [<mailto:Kimberly.Scott@fda.hhs.gov>]
Sent: Tuesday, April 25, 2017 3:13 PM
To: Abraham, Abbey <abbey.abraham@novartis.com>
Cc: Qiu, Yuhong <yuhong.qiu@novartis.com>
Subject: RE: NDA 207997 Midostaurin : FDA edits PI: send TRACKED version of PI
Importance: High
Sensitivity: Confidential

Abbey,

Please send the revised PI with the “tracked” changes Novartis is recommending to the document. The Agency does not want the clean version of the PI unless mutually agreed on all changes in the document.

Kindly confirm receipt.

Thank you,
Kim

From: Abraham, Abbey [<mailto:abbey.abraham@novartis.com>]
Sent: Tuesday, April 25, 2017 2:18 PM
To: Scott, Kimberly
Cc: Qiu, Yuhong
Subject: RE: NDA 207997 Midostaurin : FDA edits PI: minor edit to PI- confirm agreement
Sensitivity: Confidential

Hi Kim

Yes we are in agreement but we note that the following highlighted changes should be also incorporated as this is specific to the partner company’s registered trademark. I took the liberty of including these revisions into the attached clean version but if you need a tracked version, please advise.

Abbey Abraham, PharmD
Oncology Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation

Phone +1 862-778-8998

1. Section 14

14 CLINICAL STUDIES

14.1 Acute Myeloid Leukemia

Study 1

RYDAPT in combination with chemotherapy was investigated in a randomized, double-blind placebo-controlled trial of 717 patients with newly-diagnosed FLT3-mutated AML. In this study, FLT3 mutation status was determined prospectively with a clinical trial assay and verified retrospectively using the companion diagnostic LeukoStrat[®] CDx **FLT3** Mutation Assay*, which is an FDA-approved test for selection of patients with AML for RYDAPT treatment. Patients were stratified by FLT3 mutation status: TKD, ITD with allelic ratio less than 0.7, and ITD with allelic ratio greater than or equal to 0.7. Patients with acute promyelocytic leukemia or therapy-related AML were not eligible. 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 daunorubicin (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. There was no re-randomization at the start of post consolidation therapy. Patients who proceeded to hematopoietic stem cell transplantation (SCT) stopped receiving study treatment.

2. Section 17

17 PATIENT COUNSELING INFORMATION

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

- Pulmonary Adverse Reactions: Inform patients to seek medical attention for new cough, chest discomfort, or shortness of breath [see Warnings and Precautions (5.2)].
- Gastrointestinal Adverse Reactions: Inform patients that RYDAPT can cause nausea, vomiting, and diarrhea. Advise patients to contact their healthcare provider if these symptoms occur or are persisting despite supportive medications [see Adverse Reactions (6.1)].
- 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 Precautions (5.1), Use in Specific Populations (8.1, 8.3)].
 - Advise male patients with female partners of reproductive potential to use effective contraception during treatment with RYDAPT and for 4 months after the last dose [see Use in Specific Populations (8.3)].
- Lactation
 - Advise women not to breastfeed during treatment with RYDAPT and for at least 4 months after the final 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), Nonclinical Toxicology (13.1)].

(b) (4)

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

From: Scott, Kimberly [<mailto:Kimberly.Scott@fda.hhs.gov>]
Sent: Tuesday, April 25, 2017 12:10 PM
To: Abraham, Abbey <abbey.abraham@novartis.com>
Cc: Qiu, Yuhong <yuhong.qiu@novartis.com>
Subject: RE: NDA 207997 Midostaurin : FDA edits PI: minor edit to PI- confirm agreement
Importance: High
Sensitivity: Confidential

Good afternoon Abbey,

Please see the attached PI with the Agency's minor edit in Section 14.1. The "s" in LeukoStrat should be capitalized. Please confirm you agree in making the revision.

Kindly confirm receipt.

Thank you,
Kim

From: Abraham, Abbey [<mailto:abbey.abraham@novartis.com>]
Sent: Tuesday, April 25, 2017 10:44 AM
To: Scott, Kimberly
Cc: Qiu, Yuhong
Subject: RE: NDA 207997 Midostaurin : FDA edits PI: Review by 10:30AM(ET) tomorrow, Tuesday, 4/25
Sensitivity: Confidential

Hi Kim

Please see attached the final US PI. We are in agreement with the proposed agency revision sent yesterday. I will be sending this via the gateway as soon as possible and as I mentioned previously, there are formatting (different font size etc) that seem to keep appearing when these labels are being sent and opened via email so just want to confirm the FDA team will use the version sent via the Gateway as the FINAL version for the action.

Thank you

Abbey Abraham, PharmD
Oncology Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation

Phone +1 862-778-8998
Fax +1 973-781-3473
abbey.abraham@novartis.com
www.novartis.com

From: Scott, Kimberly [<mailto:Kimberly.Scott@fda.hhs.gov>]
Sent: Monday, April 24, 2017 9:41 PM
To: Abraham, Abbey <abbey.abraham@novartis.com>
Cc: Qiu, Yuhong <yuhong.qiu@novartis.com>

Subject: NDA 207997 Midostaurin : FDA edits PI: Review by 10:30AM(ET) tomorrow, Tuesday, 4/25

Importance: High

Sensitivity: Confidential

Good evening Abbey,

The Agency has accepted the proposed edits by Novartis to the PI and PPI for NDA 207997, midostaurin. Please see the attached PI which has additional revisions to include the companion diagnostic name of the Section 14.1 (page 15 of 19).

Please respond by 10:30AM (ET) tomorrow morning, Tuesday, April 25, 2017. If agreed, please send the final agreed upon label officially through the gateway.

Kindly confirm receipt.

Thank you,

Kim

Kimberly Scott, RN, BSN, OCN®

CDR, U.S. Public Health Service

Regulatory Health Project Manager

Division of Hematology Products

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, Bldg. 22, Rm 3231

Silver Spring, MD 20993

Phone: 240-402-4560

Fax: 301-796-9849

[|Kimberly.scott@fda.hhs.gov](mailto:Kimberly.scott@fda.hhs.gov)

21 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/

KIMBERLY L SCOTT
04/26/2017

Scott, Kimberly

From: Scott, Kimberly
Sent: Tuesday, April 25, 2017 11:22 AM
To: 'Abraham, Abbey'
Cc: Qiu, Yuhong
Subject: RE: NDA 207997 Midostaurin : FDA edits PI: Review by 10:30AM(ET) tomorrow, Tuesday, 4/25

Sensitivity: Confidential

Good morning Abbey,

Thank you for confirming you're in agreement with the Agency's proposed revisions to the PI that were sent yesterday evening.

Thank you,
Kim

From: Abraham, Abbey [<mailto:abbey.abraham@novartis.com>]
Sent: Tuesday, April 25, 2017 10:44 AM
To: Scott, Kimberly
Cc: Qiu, Yuhong
Subject: RE: NDA 207997 Midostaurin : FDA edits PI: Review by 10:30AM(ET) tomorrow, Tuesday, 4/25
Sensitivity: Confidential

Hi Kim

Please see attached the final US PI. We are in agreement with the proposed agency revision sent yesterday. I will be sending this via the gateway as soon as possible and as I mentioned previously, there are formatting (different font size etc) that seem to keep appearing when these labels are being sent and opened via email so just want to confirm the FDA team will use the version sent via the Gateway as the FINAL version for the action.

Thank you

Abbey Abraham, PharmD
Oncology Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation

Phone +1 862-778-8998
Fax +1 973-781-3473
abbey.abraham@novartis.com
www.novartis.com

From: Scott, Kimberly [<mailto:Kimberly.Scott@fda.hhs.gov>]
Sent: Monday, April 24, 2017 9:41 PM
To: Abraham, Abbey <abbey.abraham@novartis.com>
Cc: Qiu, Yuhong <yuhong.qiu@novartis.com>
Subject: NDA 207997 Midostaurin : FDA edits PI: Review by 10:30AM(ET) tomorrow, Tuesday, 4/25

Importance: High

Sensitivity: Confidential

Good evening Abbey,

The Agency has accepted the proposed edits by Novartis to the PI and PPI for NDA 207997, midostaurin. Please see the attached PI which has additional revisions to include the companion diagnostic name of the Section 14.1 (page 15 of 19).

Please respond by 10:30AM (ET) tomorrow morning, Tuesday, April 25, 2017. If agreed, please send the final agreed upon label officially through the gateway.

Kindly confirm receipt.

Thank you,

Kim

Kimberly Scott, RN, BSN, OCN®

CDR, U.S. Public Health Service

Regulatory Health Project Manager

Division of Hematology Products

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, Bldg. 22, Rm 3231

Silver Spring, MD 20993

Phone: 240-402-4560

Fax: 301-796-9849

Kimberly.scott@fda.hhs.gov

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
05/01/2017

Scott, Kimberly

From: Scott, Kimberly
Sent: Tuesday, April 25, 2017 12:10 PM
To: Abraham, Abbey
Cc: Qiu, Yuhong
Subject: RE: NDA 207997 Midostaurin : FDA edits PI: minor edit to PI- confirm agreement
Attachments: NDA 207997 FINAL Midostaurin PI NVS Clean 4-25-17.docx

Importance: High
Sensitivity: Confidential

Good afternoon Abbey,

Please see the attached PI with the Agency's minor edit in Section 14.1. The "s" in LeukoStrat should be capitalized. Please confirm you agree in making the revision.

Kindly confirm receipt.

Thank you,
Kim

From: Abraham, Abbey [<mailto:abbey.abraham@novartis.com>]
Sent: Tuesday, April 25, 2017 10:44 AM
To: Scott, Kimberly
Cc: Qiu, Yuhong
Subject: RE: NDA 207997 Midostaurin : FDA edits PI: Review by 10:30AM(ET) tomorrow, Tuesday, 4/25
Sensitivity: Confidential

Hi Kim

Please see attached the final US PI. We are in agreement with the proposed agency revision sent yesterday. I will be sending this via the gateway as soon as possible and as I mentioned previously, there are formatting (different font size etc) that seem to keep appearing when these labels are being sent and opened via email so just want to confirm the FDA team will use the version sent via the Gateway as the FINAL version for the action.

Thank you

Abbey Abraham, PharmD
Oncology Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation

Phone +1 862-778-8998
Fax +1 973-781-3473
abbey.abraham@novartis.com
www.novartis.com

From: Scott, Kimberly [<mailto:Kimberly.Scott@fda.hhs.gov>]
Sent: Monday, April 24, 2017 9:41 PM
To: Abraham, Abbey <abbey.abraham@novartis.com>

Cc: Qiu, Yuhong <yuhong.qiu@novartis.com>

Subject: NDA 207997 Midostaurin : FDA edits PI: Review by 10:30AM(ET) tomorrow, Tuesday, 4/25

Importance: High

Sensitivity: Confidential

Good evening Abbey,

The Agency has accepted the proposed edits by Novartis to the PI and PPI for NDA 207997, midostaurin. Please see the attached PI which has additional revisions to include the companion diagnostic name of the Section 14.1 (page 15 of 19).

Please respond by 10:30AM (ET) tomorrow morning, Tuesday, April 25, 2017. If agreed, please send the final agreed upon label officially through the gateway.

Kindly confirm receipt.

Thank you,

Kim

Kimberly Scott, RN, BSN, OCN®

CDR, U.S. Public Health Service

Regulatory Health Project Manager

Division of Hematology Products

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, Bldg. 22, Rm 3231

Silver Spring, MD 20993

Phone: 240-402-4560

Fax: 301-796-9849

Kimberly.scott@fda.hhs.gov

19 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/

KIMBERLY L SCOTT
04/25/2017

Scott, Kimberly

From: Scott, Kimberly
Sent: Monday, April 24, 2017 9:41 PM
To: Abraham, Abbey
Cc: Qiu, Yuhong
Subject: NDA 207997 Midostaurin : FDA edits PI: Review by 10:30AM(ET) tomorrow, Tuesday, 4/25
Attachments: NDA 207997 Agency Edits PI sent 4 24 17.docx
Importance: High
Sensitivity: Confidential

Good evening Abbey,

The Agency has accepted the proposed edits by Novartis to the PI and PPI for NDA 207997, midostaurin. Please see the attached PI which has additional revisions to include the companion diagnostic name of the Section 14.1 (page 15 of 19).

Please respond by 10:30AM (ET) tomorrow morning, Tuesday, April 25, 2017. If agreed, please send the final agreed upon label officially through the gateway.

Kindly confirm receipt.

Thank you,
Kim
Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Rm 3231
Silver Spring, MD 20993
Phone: 240-402-4560
Fax: 301-796-9849
Kimberly.scott@fda.hhs.gov

19 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/

KIMBERLY L SCOTT
04/24/2017

Scott, Kimberly

From: Scott, Kimberly
Sent: Friday, April 21, 2017 2:55 PM
To: 'Abraham, Abbey'
Cc: Qiu, Yuhong
Subject: RE: NDA 207997 Midostaurin : ASCO Burst

Importance: High
Sensitivity: Confidential

Tracking:	Recipient	Read
	'Abraham, Abbey'	
	Qiu, Yuhong	
	Scott, Kimberly	Read: 4/21/2017 3:13 PM

Good afternoon Abbey,

Thank you for sending the agreed upon PI. I've been in meetings throughout the afternoon, but wanted to respond to your questions. At this time, the Agency is planning on having an ASCO Burst release, and taking Action by the PDUFA V date, April 28, 2017.

Kirsten Goldberg will be contacting you to request Novartis review in the final draft of the ASCO Burst release.

Kindly confirm receipt.

Thank you,
Kim

From: Abraham, Abbey [mailto:abbey.abraham@novartis.com]
Sent: Friday, April 21, 2017 9:03 AM
To: Scott, Kimberly
Cc: Qiu, Yuhong
Subject: RE: NDA 207997 Midostaurin PI and PPI: respond by 9:00AM (ET) tomorrow, April 21st
Sensitivity: Confidential

Hi Kim

Please see attached the final version of the PI. We have accepted the additional edits proposed by the FDA team. We will submitting via the Gateway shortly. Please also let me know if you have some time this morning to discuss timelines the agency is targeting for action and regarding FDA press release.

Thank you

Abbey Abraham, PharmD
Oncology Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation

Phone +1 862-778-8998
Fax +1 973-781-3473

abbey.abraham@novartis.com

www.novartis.com

From: Scott, Kimberly [<mailto:Kimberly.Scott@fda.hhs.gov>]
Sent: Thursday, April 20, 2017 5:20 PM
To: Abraham, Abbey <abbey.abraham@novartis.com>
Cc: Qiu, Yuhong <yuhong.qiu@novartis.com>
Subject: RE: NDA 207997 Midostaurin PI and PPI: respond by 9:00AM (ET) tomorrow, April 21st
Sensitivity: Confidential

If you agree to all the edits/changes then I would consolidate and just submit once with the agreed upon revisions via the gateway tomorrow morning.

Thank you,
Kim

From: Abraham, Abbey [<mailto:abbey.abraham@novartis.com>]
Sent: Thursday, April 20, 2017 5:16 PM
To: Scott, Kimberly
Cc: Qiu, Yuhong
Subject: RE: NDA 207997 Midostaurin PI and PPI: respond by 9:00AM (ET) tomorrow, April 21st
Sensitivity: Confidential

Hi Kim

Just to clarify, we were in the process of sending the version I sent via email at 3:50 today through the Gateway. Do you still want us to submit that version officially via the Gateway and then the final version by tomorrow 9 am or just hold and send one final version?

Thanks
Abbey

From: Scott, Kimberly [<mailto:Kimberly.Scott@fda.hhs.gov>]
Sent: Thursday, April 20, 2017 5:10 PM
To: Abraham, Abbey <abbey.abraham@novartis.com>
Cc: Qiu, Yuhong <yuhong.qiu@novartis.com>
Subject: RE: NDA 207997 Midostaurin PI and PPI: respond by 9:00AM (ET) tomorrow, April 21st
Importance: High
Sensitivity: Confidential

Good afternoon Abbey,

Please see the attached revisions from the Agency in response to your request for clarification. Please review the PI and response by 9:00AM (ET) tomorrow morning, Friday, April 21, 2017. If agreed, please send the final agreed upon label officially through the gateway.

I received your voicemail and will get back with you early tomorrow morning regarding the timing of the Action.

Kindly confirm receipt.

Thank you,
Kim

From: Abraham, Abbey [<mailto:abbey.abraham@novartis.com>]
Sent: Thursday, April 20, 2017 3:58 PM
To: Scott, Kimberly
Cc: Qiu, Yuhong
Subject: RE: NDA 207997 Midostaurin PI and PPI: respond by 3:30PM (ET) Today, April 20, 2017
Sensitivity: Confidential

Hi Kim

Please attached our revised labeling. We have accepted all revision as proposed with one new clarification for table 7 on the confidence interval for the MCL column. Please see attached. We will submit this via the Gateway today if possible. Please note that we seem to be hitting formatting via the versions sent through email as the font sizes and some tables format are not how Novartis had revised. For any additional correspondence maybe we should use the only the version sent via the Gateway to ensure the formatting is kept.

Thanks

Abbey Abraham, PharmD
Oncology Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation

Phone +1 862-778-8998
Fax +1 973-781-3473
abbey.abraham@novartis.com
www.novartis.com

From: Scott, Kimberly [<mailto:Kimberly.Scott@fda.hhs.gov>]
Sent: Thursday, April 20, 2017 12:24 PM
To: Abraham, Abbey <abbey.abraham@novartis.com>
Cc: Qiu, Yuhong <yuhong.qiu@novartis.com>
Subject: NDA 207997 Midostaurin PI and PPI: respond by 3:30PM (ET) Today, April 20, 2017
Importance: High
Sensitivity: Confidential

Good afternoon Abbey,

Please see the attached FDA labeling revisions to the prescribing information (PI) and Patient Packet Information (PPI) for NDA 207997, Midostaurin.

Please review the attached documents with your team with the following:

- **Accepting changes that you agree with**
- **Making any edits that you do not agree with using track-changes only (*do not reject any changes that the FDA proposed and do not delete any of the FDA's comments*)**
- **Enter any comments in "bubble" on the document**

After you have made any necessary changes, please send the *revised tracked changes labeling documents* (PI, and PPI) before you make your official submission electronically.
Any edits you make should be in tracked changes.

Please respond by **3:30PM (ET) today, April 20, 2017**

Kindly confirm receipt.

Thank you,

Kim

Kimberly Scott, RN, BSN, OCN®

CDR, U.S. Public Health Service

Regulatory Health Project Manager

Division of Hematology Products

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, Bldg. 22, Rm 3231

Silver Spring, MD 20993

Phone: 240-402-4560

Fax: 301-796-9849

Kimberly.scott@fda.hhs.gov

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
05/01/2017

Scott, Kimberly

From: Scott, Kimberly
Sent: Thursday, April 20, 2017 5:10 PM
To: Abraham, Abbey
Cc: Qiu, Yuhong
Subject: RE: NDA 207997 Midostaurin PI and PPI: respond by 9:00AM (ET) tomorrow, April 21st
Attachments: NDA 207997 Midostaurin PI WORKING FDA response 4-20-17.docx

Importance: High
Sensitivity: Confidential

Good afternoon Abbey,

Please see the attached revisions from the Agency in response to your request for clarification. Please review the PI and response by 9:00AM (ET) tomorrow morning, Friday, April 21, 2017. If agreed, please send the final agreed upon label officially through the gateway.

I received your voicemail and will get back with you early tomorrow morning regarding the timing of the Action.

Kindly confirm receipt.

Thank you,
Kim

From: Abraham, Abbey [<mailto:abbey.abraham@novartis.com>]
Sent: Thursday, April 20, 2017 3:58 PM
To: Scott, Kimberly
Cc: Qiu, Yuhong
Subject: RE: NDA 207997 Midostaurin PI and PPI: respond by 3:30PM (ET) Today, April 20, 2017
Sensitivity: Confidential

Hi Kim

Please attached our revised labeling. We have accepted all revision as proposed with one new clarification for table 7 on the confidence interval for the MCL column. Please see attached. We will submit this via the Gateway today if possible. Please note that we seem to be hitting formatting via the versions sent through email as the font sizes and some tables format are not how Novartis had revised. For any additional correspondence maybe we should use the only the version sent via the Gateway to ensure the formatting is kept.

Thanks

Abbey Abraham, PharmD
Oncology Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation

Phone +1 862-778-8998
Fax +1 973-781-3473
abbey.abraham@novartis.com
www.novartis.com

From: Scott, Kimberly [<mailto:Kimberly.Scott@fda.hhs.gov>]
Sent: Thursday, April 20, 2017 12:24 PM
To: Abraham, Abbey <abbey.abraham@novartis.com>
Cc: Qiu, Yuhong <yuhong.qiu@novartis.com>
Subject: NDA 207997 Midostaurin PI and PPI: respond by 3:30PM (ET) Today, April 20, 2017
Importance: High
Sensitivity: Confidential

Good afternoon Abbey,

Please see the attached FDA labeling revisions to the prescribing information (PI) and Patient Packet Information (PPI) for NDA 207997, Midostaurin.

Please review the attached documents with your team with the following:

- Accepting changes that you agree with
- Making any edits that you do not agree with using track-changes only (***do not reject any changes that the FDA proposed and do not delete any of the FDA's comments***)
- Enter any comments in "bubble" on the document

After you have made any necessary changes, please send the *revised tracked changes labeling documents* (PI, and PPI) before you make your official submission electronically.

Any edits you make should be in tracked changes.

Please respond by **3:30PM (ET) today, April 20, 2017**

Kindly confirm receipt.

Thank you,
Kim
Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Rm 3231
Silver Spring, MD 20993
Phone: 240-402-4560
Fax: 301-796-9849
Kimberly.scott@fda.hhs.gov

22 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/

KIMBERLY L SCOTT
04/20/2017

Scott, Kimberly

From: Scott, Kimberly
Sent: Thursday, April 20, 2017 12:24 PM
To: 'Abraham, Abbey'
Cc: Qiu, Yuhong (yuhong.qiu@novartis.com)
Subject: NDA 207997 Midostaurin PI and PPI: respond by 3:30PM (ET) Today, April 20, 2017
Attachments: NDA 207997 Midostaurin PI WORKING version 4-19-17.docx; NDA 207997 DMPP-OPDP PPI April-2017 NVS Revision.doc

Importance: High

Good afternoon Abbey,

Please see the attached FDA labeling revisions to the prescribing information (PI) and Patient Packet Information (PPI) for NDA 207997, Midostaurin.

Please review the attached documents with your team with the following:

- Accepting changes that you agree with
- Making any edits that you do not agree with using track-changes only (***do not reject any changes that the FDA proposed and do not delete any of the FDA's comments***)
- Enter any comments in "bubble" on the document

After you have made any necessary changes, please send the *revised tracked changes labeling documents* (PI, and PPI) before you make your official submission electronically.

Any edits you make should be in tracked changes.

Please respond by **3:30PM (ET) today, April 20, 2017**

Kindly confirm receipt.

Thank you,

Kim

Kimberly Scott, RN, BSN, OCN®

CDR, U.S. Public Health Service

Regulatory Health Project Manager

Division of Hematology Products

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, Bldg. 22, Rm 3231

Silver Spring, MD 20993

Phone: 240-402-4560

Fax: 301-796-9849

Kimberly.scott@fda.hhs.gov

24 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/

KIMBERLY L SCOTT
04/20/2017

Scott, Kimberly

From: Scott, Kimberly
Sent: Tuesday, April 18, 2017 2:49 PM
To: 'Abraham, Abbey'
Cc: Qiu, Yuhong
Subject: RE: NDA 207997, Midostaurin: Clinical IR DUE 3PM tomorrow, Wednesday, 4/19

Sensitivity: Confidential

Good afternoon Abbey,

With the clarifications below, this information request has been met.

Kind regards,
Kim

From: Abraham, Abbey [mailto:abbey.abraham@novartis.com]
Sent: Tuesday, April 18, 2017 1:38 PM
To: Scott, Kimberly
Cc: Qiu, Yuhong
Subject: RE: NDA 207997, Midostaurin: Clinical IR DUE 3PM tomorrow, Wednesday, 4/19
Sensitivity: Confidential

Hi Kim

We are working to meet the request but just would like to note the following

1. The note references AADJ.xpt file but it should be the AADJ2.xpt that should be referenced when determining best overall response. In the AADJ2 dataset there is only one time point for each variable for each patient.
2. In ARESPPDIS.xls, there are variables (RESPSSC for study D2201 and RESP2213 for study A2213) describing the following modalities:
 - Major response
 - Partial response
 - "No response or not evaluable" for D2201
 - "No response" for A2213 as there no patients deemed "not evaluable" in A2213.

Please note: The category "No response" is the grouping of "Progressive disease" and "Stable disease" so if needed for D2201, using the variable RESSTA3C in AADJ2.xls, allows for breakdown of the exact values for no response and subsequently the "not evaluable".

Would the agency consider the 2nd point as a viable option to meeting the request to designate subcategories of major, partial and no response/not evaluable?

Abbey Abraham, PharmD
Oncology Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation

Phone +1 862-778-8998
Fax +1 973-781-3473
abbey.abraham@novartis.com
www.novartis.com

From: Scott, Kimberly [<mailto:Kimberly.Scott@fda.hhs.gov>]
Sent: Tuesday, April 18, 2017 10:53 AM
To: Abraham, Abbey <abbey.abraham@novartis.com>
Cc: Qiu, Yuhong <yuhong.qiu@novartis.com>
Subject: RE: NDA 207997, Midostaurin: Clinical IR DUE 3PM tomorrow, Wednesday, 4/19
Importance: High
Sensitivity: Confidential

Good morning Abbey,

Although response subtypes are included in the AADJ.xpt and ARESPAT.xpt files, the multiple response designations for various timepoints make identification of best overall response and response subtype with 6 cycles (D2201) or 2 cycles (A2213) challenging. To facilitate evaluation of efficacy, for studies D2201 and A2213, submit a revised ARESPPDIS.xpt file that:

- Adds a variable that designates the subcategory of response per Valent/modified Valent criteria as follows:
 - Subcategories of major response: CR, incomplete remission, pure clinical response, and unspecified
 - Subcategories of partial response: good PR, minor response, and unspecified.
- Differentiates “no response” from “not evaluable”

Please respond by 3:00pm (ET) tomorrow, Wednesday, April 19, 2017.

Kindly confirm receipt.

Thank you,
Kim

From: Abraham, Abbey [<mailto:abbey.abraham@novartis.com>]
Sent: Tuesday, April 18, 2017 10:00 AM
To: Scott, Kimberly
Cc: Qiu, Yuhong
Subject: RE: NDA 207997, Midostaurin: Clinical IR DUE 330PM today
Sensitivity: Confidential

Hi Kim

For the table 7 of the USPI, these are the variables and datasets that were requested to identified:

-  (b) (4)

Abbey Abraham, PharmD

Oncology Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation

Phone +1 862-778-8998
Fax +1 973-781-3473
abbey.abraham@novartis.com
www.novartis.com

From: Scott, Kimberly [<mailto:Kimberly.Scott@fda.hhs.gov>]
Sent: Tuesday, April 18, 2017 9:08 AM
To: Abraham, Abbey <abbey.abraham@novartis.com>
Subject: RE: NDA 207997, Midostaurin: Clinical IR DUE 330PM today
Sensitivity: Confidential

Thank you.

From: Abraham, Abbey [<mailto:abbey.abraham@novartis.com>]
Sent: Tuesday, April 18, 2017 9:01 AM
To: Scott, Kimberly
Cc: Qiu, Yuhong
Subject: RE: NDA 207997, Midostaurin: Clinical IR DUE 330PM today
Sensitivity: Confidential

Hi Kim

Let me get back to you shortly on this.

Abbey

From: Scott, Kimberly [<mailto:Kimberly.Scott@fda.hhs.gov>]
Sent: Tuesday, April 18, 2017 8:54 AM
To: Abraham, Abbey <abbey.abraham@novartis.com>
Cc: Qiu, Yuhong <yuhong.qiu@novartis.com>
Subject: NDA 207997, Midostaurin: Clinical IR DUE 330PM today
Importance: High
Sensitivity: Confidential

Good morning Abbey,

As per our telephone conversation on Thursday, April 13, the results in D2201 CSR Table 11-9 could not be confirmed due to a missing variable for the modified Valent response subcategories (e.g., CR, ICR, PCR, etc). For the mastocytosis trials D2201 and A2213, please identify the variable in the data files that contains the response subcategories.

Please respond by 3:30PM (ET) today.

Kindly confirm receipt.

Thank you,

Kim

Kimberly Scott, RN, BSN, OCN®

CDR, U.S. Public Health Service

Regulatory Health Project Manager

Division of Hematology Products

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, Bldg. 22, Rm 3231

Silver Spring, MD 20993

Phone: 240-402-4560

Fax: 301-796-9849

Kimberly.scott@fda.hhs.gov

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
04/18/2017

Scott, Kimberly

From: Scott, Kimberly
Sent: Tuesday, April 18, 2017 8:54 AM
To: Abraham, Abbey
Cc: Qiu, Yuhong (yuhong.qiu@novartis.com)
Subject: NDA 207997, Midostaurin: Clinical IR DUE 330PM today

Importance: High

Good morning Abbey,

As per our telephone conversation on Thursday, April 13, the results in D2201 CSR Table 11-9 could not be confirmed due to a missing variable for the modified Valent response subcategories (e.g., CR, ICR, PCR, etc). For the mastocytosis trials D2201 and A2213, please identify the variable in the data files that contains the response subcategories.

Please respond by 3:30PM (ET) today.

Kindly confirm receipt.

Thank you,

Kim

Kimberly Scott, RN, BSN, OCN®

CDR, U.S. Public Health Service

Regulatory Health Project Manager

Division of Hematology Products

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, Bldg. 22, Rm 3231

Silver Spring, MD 20993

Phone: 240-402-4560

Fax: 301-796-9849

Kimberly.scott@fda.hhs.gov

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
04/18/2017

MEMORANDUM OF TELECONFERENCE

Teleconference Date: April 13, 2017
Application Number: NDA 207997
Product Name: Midostaurin
Applicant Name: Novartis Pharmaceuticals

Subject: Novartis requested a teleconference to discuss [REDACTED] (b) (4)
[REDACTED] the Indication/Limitation of Use (LoU) and Dosage/Administration
sections [REDACTED] (b) (4)

FDA Participants :

- Donna Przepiorka, MD, PhD, Clinical Team Leader
- Kimberly Scott, RN, BSN, OCN®. Regulatory Project Manage

Applicant Participants :

Samit Hirawat, Executive VP, Head Oncology Global Development
Gabriela Gruia, Senior Vice President, Global Head Drug Regulatory Affairs, Oncology
Noah Berkowitz, Executive Director, Global Clinical Program Head
Allison Florance, Executive Director, Biostatistics
Karen Habucky, Head, US Clinical Strategy - Leukemia,
Shanthi Ganeshan, Vice President, North America Region Head, Drug Regulatory Affairs
Yuhong Qiu, Senior Director, Drug Regulatory Affairs
Abbey Abraham, Director, Drug Regulatory Affairs

1.0 BACKGROUND:

The sponsor requested a telecon to discuss labeling comments sent by FDA on April 11, 2017.

2.0 DISCUSSION:

1. FDA notified Novartis that the LOA from Invivoscribe has the wrong PMA number, and an LOA for the Invivoscribe PMA was requested. Novartis agreed to submit the LOA.
2. FDA referred to the labeling comment requesting a breakdown of response by modified Valent response subcategory (e.g., CR, ICR, PCR, etc) for the mastocytosis studies. FDA indicated that the results in D2201 CSR Table 11-9 could not be confirmed due to a missing variable. FDA requested that when Novartis sends their response, they should identify the variable in the data set that has the response subcategory so that FDA could verify the results. Novartis agreed to do so.

3. Novartis proposed text for a Limitation of Use for single agent therapy in induction (b) (4)
(b) (4) FDA indicated that approach might be acceptable, (b) (4)

4. Novartis requested clarification as to why (b) (4)
FDA explained (b) (4)
. Novartis requested an explanation of (b) (4). FDA provided the explanation.

(b) (4)

6. Novartis requested additional time to provide a response to the labeling comments, and they proposed to have the response by Monday COB. FDA agreed to extend the deadline for the response.

3.0 ACTION ITEMS:

1. Novartis will submit an LOA from Invivoscribe with the correct PMA number.
2. Novartis will submit the revised PI to the Agency by Monday, April 17, 2017.
3. The response will include identification of the variable in the SM data set that has the modified Valent response subcategory.

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
04/18/2017

Scott, Kimberly

From: Scott, Kimberly
Sent: Thursday, April 13, 2017 4:06 PM
To: 'Abraham, Abbey'
Cc: Qiu, Yuhong
Subject: RE: NDA 207997 Midostaurin PI/PPI/PMR: TCON summary

Importance: High
Sensitivity: Confidential

Good afternoon Abbey,

Thank you for sending your revisions after our teleconference this afternoon discussing the labeling for NDA 207997, Midostaurin sent from the Agency on April 11, 2017.
Per the meeting, Novartis agreed to the following:

- Submit an LOA from Invivoscribe with the correct PMA number.
- Submit the revised PI to the Agency by Monday, April 17, 2017 which will include identification of the variable in the SM data set that has the modified Valent response subcategory.

Please send the names of those who participated in the teleconference this afternoon.

Kindly confirm receipt.

Thank you,
Kim

From: Abraham, Abbey [mailto:abbey.abraham@novartis.com]
Sent: Thursday, April 13, 2017 2:30 PM
To: Scott, Kimberly
Cc: Qiu, Yuhong
Subject: RE: NDA 207997 Midostaurin PI/PPI/PMR: TCON Granted 2PM today
Sensitivity: Confidential

Hi Kim

Thank you for setting the discussion up as it was very helpful and productive. As we discussed, please see below, the text we will be submitting with the rest of the label on Monday.

RYDAPT US PI

INDICATIONS AND USAGE

1.1 Acute Myeloid Leukemia

RYDAPT is indicated, in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation chemotherapy, for the treatment of adult patients with newly diagnosed acute myeloid leukemia (AML) who are FLT3 mutation-positive, as detected by a FDA approved test [see Dosage and Administration (2.1), Clinical Studies (14.1)].

Limitations of Use

RYDAPT is not indicated as a single agent therapy (b)(4) induction for the treatment of patients with AML.

DOSAGE AND ADMINISTRATION

2.2 Recommended Dosage in Acute Myeloid Leukemia

The recommended dose of RYDAPT for patients with acute myeloid leukemia is 50 mg orally twice daily with food on days 8 to 21 of each cycle of induction with cytarabine and daunorubicin and on days 8 to 21 of each cycle of consolidation with high-dose cytarabine [see Clinical Studies (14.1)]. For (b) (4) beyond induction and consolidation, see Clinical Studies (14.1).

Thank you

Abbey Abraham, PharmD
Oncology Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation

Phone +1 862-778-8998
Fax +1 973-781-3473
abbey.abraham@novartis.com
www.novartis.com

Abbey

From: Scott, Kimberly [<mailto:Kimberly.Scott@fda.hhs.gov>]
Sent: Thursday, April 13, 2017 1:31 PM
To: Abraham, Abbey <abbey.abraham@novartis.com>
Cc: Qiu, Yuhong <yuhong.qiu@novartis.com>
Subject: RE: NDA 207997 Midostaurin PI/PPI/PMR: TCON Granted 2PM today
Sensitivity: Confidential

Hi Abbey,

Thank you for sending the information for the meeting.

Kim

From: Abraham, Abbey [<mailto:abbey.abraham@novartis.com>]
Sent: Thursday, April 13, 2017 12:37 PM
To: Scott, Kimberly
Cc: Qiu, Yuhong
Subject: RE: NDA 207997 Midostaurin PI/PPI/PMR: TCON Granted 2PM today
Sensitivity: Confidential

Hi Kim

Please use the following TC info

US/CAN Toll free: (b) (4)
Participant Passcode (b) (4)

Can you also confirm if Dr. Farrell and Dr. Pazdur will be attending?

Thank you

Abbey

From: Scott, Kimberly [<mailto:Kimberly.Scott@fda.hhs.gov>]
Sent: Thursday, April 13, 2017 12:32 PM
To: Abraham, Abbey <abbey.abraham@novartis.com>
Cc: Qiu, Yuhong <yuhong.qiu@novartis.com>
Subject: RE: NDA 207997 Midostaurin PI/PPI/PMR: TCON Granted 2PM today
Importance: High
Sensitivity: Confidential

Good afternoon Abbey,

The Agency would like to request a teleconference for 2:00pm – 2:30pm (ET) today. Please provide a teleconference number for the meeting.

Kindly confirm receipt.

Thank you,
Kim

From: Abraham, Abbey [<mailto:abbey.abraham@novartis.com>]
Sent: Wednesday, April 12, 2017 4:19 PM
To: Scott, Kimberly
Cc: Qiu, Yuhong
Subject: RE: NDA 207997 Midostaurin PI/PPI/PMR: respond by COB, 4/13/17
Sensitivity: Confidential

Hi Kim

After reviewing the agency's current proposed PI for NDA 207997, Novartis still concern related to (b) (4)

The Novartis team is working to address the agency's latest round of comments but given the limited time to PDUFA action date, we request a follow-up TC at the earliest convenience with the review team including Dr. Farrell and Dr. Pazdur. We can provide specific labeling proposals for review in advance of this discussion per the agency's timeline. If possible, Novartis requests the meeting for this week/Monday April 17 and for additional time to send back our response for the label, to either Monday April 17th/Tuesday April 18th.

Thanks

Abbey Abraham, PharmD
Oncology Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation

Phone +1 862-778-8998
Fax +1 973-781-3473
abbey.abraham@novartis.com
www.novartis.com

From: Scott, Kimberly [<mailto:Kimberly.Scott@fda.hhs.gov>]
Sent: Tuesday, April 11, 2017 3:21 PM
To: Abraham, Abbey <abbey.abraham@novartis.com>
Cc: Qiu, Yuhong <yuhong.qiu@novartis.com>; Scott, Kimberly <Kimberly.Scott@fda.hhs.gov>

Subject: NDA 207997 Midostaurin PI/PPI/PMR: respond by COB, 4/13/17

Importance: High

Sensitivity: Confidential

Good afternoon Abbey,

Please see the attached FDA labeling revisions to the prescribing information (PI), Patient Packet Information (PPI), and Post Marketing Requirement (PMR) for NDA 207997, Midostaurin.

Please review the attached documents with your team with the following:

- Accepting changes that you agree with
- Making any edits that you do not agree with using track-changes only (***do not reject any changes that the FDA proposed and do not delete any of the FDA's comments***)
- Enter any comments in "bubble" on the document

After you have made any necessary changes, please send the *revised tracked changes labeling documents* (PI, PPI, and PMR) before you make your official submission electronically.

Any edits you make should be in tracked changes.

Please respond by **COB, Thursday, April 13, 2017.**

Kindly confirm receipt.

Thank you,

Kim

Kimberly Scott, RN, BSN, OCN®

CDR, U.S. Public Health Service

Regulatory Health Project Manager

Division of Hematology Products

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, Bldg. 22, Rm 3231

Silver Spring, MD 20993

Phone: 240-402-4560

Fax: 301-796-9849

Kimberly.scott@fda.hhs.gov

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
04/13/2017

Scott, Kimberly

From: Scott, Kimberly
Sent: Thursday, April 13, 2017 12:32 PM
To: 'Abraham, Abbey'
Cc: Qiu, Yuhong
Subject: RE: NDA 207997 Midostaurin PI/PPI/PMR: TCON Granted 2PM today

Importance: High
Sensitivity: Confidential

Good afternoon Abbey,

The Agency would like to request a teleconference for 2:00pm – 2:30pm (ET) today. Please provide a teleconference number for the meeting.

Kindly confirm receipt.

Thank you,
Kim

From: Abraham, Abbey [<mailto:abbey.abraham@novartis.com>]
Sent: Wednesday, April 12, 2017 4:19 PM
To: Scott, Kimberly
Cc: Qiu, Yuhong
Subject: RE: NDA 207997 Midostaurin PI/PPI/PMR: respond by COB, 4/13/17
Sensitivity: Confidential

Hi Kim

After reviewing the agency's current proposed PI for NDA 207997, Novartis still concern related (b) (4)

 he Novartis team is working to address the agency's latest round of comments but given the limited time to PDUFA action date, we request a follow-up TC at the earliest convenience with the review team including Dr. Farrell and Dr. Pazdur. We can provide specific labeling proposals for review in advance of this discussion per the agency's timeline. If possible, Novartis requests the meeting for this week/Monday April 17 and for additional time to send back our response for the label, to either Monday April 17th/Tuesday April 18th.

Thanks

Abbey Abraham, PharmD
Oncology Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation

Phone +1 862-778-8998
Fax +1 973-781-3473
abbey.abraham@novartis.com
www.novartis.com

From: Scott, Kimberly [<mailto:Kimberly.Scott@fda.hhs.gov>]
Sent: Tuesday, April 11, 2017 3:21 PM

To: Abraham, Abbey <abbey.abraham@novartis.com>

Cc: Qiu, Yuhong <yuhong.qiu@novartis.com>; Scott, Kimberly <Kimberly.Scott@fda.hhs.gov>

Subject: NDA 207997 Midostaurin PI/PPI/PMR: respond by COB, 4/13/17

Importance: High

Sensitivity: Confidential

Good afternoon Abbey,

Please see the attached FDA labeling revisions to the prescribing information (PI), Patient Packet Information (PPI), and Post Marketing Requirement (PMR) for NDA 207997, Midostaurin.

Please review the attached documents with your team with the following:

- Accepting changes that you agree with
- Making any edits that you do not agree with using track-changes only (***do not reject any changes that the FDA proposed and do not delete any of the FDA's comments***)
- Enter any comments in "bubble" on the document

After you have made any necessary changes, please send the *revised tracked changes labeling documents* (PI, PPI, and PMR) before you make your official submission electronically.

Any edits you make should be in tracked changes.

Please respond by **COB, Thursday, April 13, 2017.**

Kindly confirm receipt.

Thank you,

Kim

Kimberly Scott, RN, BSN, OCN[®]

CDR, U.S. Public Health Service

Regulatory Health Project Manager

Division of Hematology Products

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, Bldg. 22, Rm 3231

Silver Spring, MD 20993

Phone: 240-402-4560

Fax: 301-796-9849

[|Kimberly.scott@fda.hhs.gov](mailto:Kimberly.scott@fda.hhs.gov)

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
04/13/2017

Scott, Kimberly

From: Scott, Kimberly
Sent: Tuesday, April 11, 2017 3:21 PM
To: 'Abraham, Abbey'
Cc: Qiu, Yuhong (yuhong.qiu@novartis.com); Scott, Kimberly (Kimberly.Scott@fda.hhs.gov)
Subject: NDA 207997 Midostaurin PI/PPI/PMR: respond by COB, 4/13/17
Attachments: NDA 207997 DMPP-OPDP PPI April-2017 Marked.doc; NDA 207997 Midostaurin PI WORKING version mod 3-23-17.docx; PMR1.docx

Importance: High

Good afternoon Abbey,

Please see the attached FDA labeling revisions to the prescribing information (PI), Patient Packet Information (PPI), and Post Marketing Requirement (PMR) for NDA 207997, Midostaurin.

Please review the attached documents with your team with the following:

- Accepting changes that you agree with
- Making any edits that you do not agree with using track-changes only (*do not reject any changes that the FDA proposed and do not delete any of the FDA's comments*)
- Enter any comments in "bubble" on the document

After you have made any necessary changes, please send the *revised tracked changes labeling documents* (PI, PPI, and PMR) before you make your official submission electronically.
Any edits you make should be in tracked changes.

Please respond by **COB, Thursday, April 13, 2017.**

Kindly confirm receipt.

Thank you,

Kim

Kimberly Scott, RN, BSN, OCN®

CDR, U.S. Public Health Service

Regulatory Health Project Manager

Division of Hematology Products

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, Bldg. 22, Rm 3231

Silver Spring, MD 20993

Phone: 240-402-4560

Fax: 301-796-9849

Kimberly.scott@fda.hhs.gov

29 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/

KIMBERLY L SCOTT
04/11/2017

Scott, Kimberly

From: Scott, Kimberly
Sent: Friday, March 31, 2017 1:00 PM
To: Abraham, Abbey
Cc: Scott, Kimberly; Qiu, Yuhong (yuhong.qiu@novartis.com)
Subject: NDA 207997 Midostaurin: Response due by COB Thursday, April 6th
Attachments: PMR1.docx

Importance: High
Sensitivity: Confidential

Good afternoon Abbey,

The Agency is requesting review of the attached Post Marketing Requirement for NDA 207997, Midostaurin. Please respond with the following information:

- Making any edits that you do not agree with using track-changes only (***do not reject any changes that the FDA proposed***)
- Enter any comments in "bubble" on the attached document.

Please send the *revised tracked changes to the document* before you make your official submission electronically. Any edits you make should be in tracked changes.

Please respond by COB, Thursday, April 6, 2017.

Kindly confirm receipt.

Thank you,

Kim

Kimberly Scott, RN, BSN, OCN®

CDR, U.S. Public Health Service

Regulatory Health Project Manager

Division of Hematology Products

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, Bldg. 22, Rm 3231

Silver Spring, MD 20993

Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

PMR #1

Establish a Pregnancy Registry to collect and analyze information for 10 years on pregnancy complications and birth outcomes in women exposed to midostaurin during pregnancy. Add notice of the pregnancy registry and the telephone contact number to the prescribing information. Submit yearly ^{(b)(4)} reports, ^{(b)(4)} on the cumulative findings and analyses from the Pregnancy Registry.

Draft Protocol Submission: x/x

Final Protocol Submission: x/x

Revised Prescribing Information: x/x

Interim Report #1: x/x

Interim Report #2: x/x

Interim Report #3: x/x

Interim Report #4: x/x

Interim Report #5: x/x

Interim Report #6: x/x

Interim Report #7: x/x

Interim Report #8: x/x

Interim Report #9: x/x

Study Completion: x/x

Final Report Submission: x/x

APPEARS THIS WAY ON ORIGINAL

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
03/31/2017

Scott, Kimberly

From: Scott, Kimberly
Sent: Friday, March 10, 2017 2:22 PM
To: Abraham, Abbey
Cc: Qiu, Yuhong
Subject: RE: NDA 207997, Midostaurin Clinical 1 #13 IR response DUE 1:00PM on March 14th

Importance: High
Sensitivity: Confidential

Good afternoon Abbey,

Novartis' proposed approach to presenting treatment-emergent laboratory abnormalities is not acceptable.

1) Calculation of the denominator

a. Sponsor's proposal: [REDACTED] (b) (4)

FDA response: This is unacceptable. For the all-grades analysis, the denominator is either the total number of patients in the safety population (142, as done by FDA), or the number of patients with least one gradeable post-baseline value of any grade for a given parameter.

b. Sponsor's proposal: [REDACTED] (b) (4)

FDA response: This is unacceptable. The denominator is the same as in FDA's response to 1a. The baseline value does not inform the choice of denominator here.

2) Calculation of the numerator:

a. Sponsor's proposal: [REDACTED] (b) (4)

FDA response: We confirm that patients with a grade ≥ 1 abnormality post-treatment, but unknown baseline grade, should be assumed to be worse than baseline. Therefore, for all-grades analysis, the numerator comprises patients with at least one post-baseline grade worsened from baseline, plus patients with at least one post-baseline grade ≥ 1 but unknown baseline grade.

b. Sponsor's proposal: [REDACTED] (b) (4)

FDA response: This is unacceptable. A patient with a grade 3 laboratory value at baseline that worsens to grade 4 has a treatment-emergent abnormality. As such, the patient must not only be regarded as worse than baseline (as done in the ALRS.xpt file), but also must be included in the numerator for grade ≥ 3 treatment-emergent toxicities.

Kindly confirm receipt.

Thank you,

Kim

Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Rm 3231
Silver Spring, MD 20993
Phone: 240-402-4560 | Kimberly.scott@fda.hhs.gov

From: Abraham, Abbey [mailto:abbey.abraham@novartis.com]
Sent: Friday, March 10, 2017 11:08 AM
To: Scott, Kimberly
Cc: Qiu, Yuhong
Subject: RE: NDA 207997, Midostaurin Clinical #1 IR regarding PI Table 5 DUE COB March 15th
Sensitivity: Confidential

Hi Kim

So in regards to this response, we think it would be a good idea to describe in a bit more detail the approach we had used for calculating the frequencies before we do an actual adjudicating of the values between the Novartis and FDA proposals. If you would please forward the below to the FDA review team as appropriate and advise if the approach is acceptable, then we can submit the Table 5 officially by Wednesday with an accounting of each difference, in particular where the incidence is less than the FDA calculation.

RYDAPT Draft US PI: Table 5- Novartis approach for incidence calculation

(b)(4)

Thanks

Abbey Abraham, PharmD
Oncology Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation

Phone +1 862-778-8998
Fax +1 973-781-3473
abbey.abraham@novartis.com
www.novartis.com

From: Scott, Kimberly [mailto:Kimberly.Scott@fda.hhs.gov]
Sent: Thursday, March 09, 2017 8:08 PM
To: Abraham, Abbey <abbey.abraham@novartis.com>

Subject: RE: NDA 207997, Midostaurin Clinical #1 IR regarding PI Table 5 DUE COB March 15th

Sensitivity: Confidential

Your welcome. 😊

From: Abraham, Abbey [<mailto:abbey.abraham@novartis.com>]

Sent: Thursday, March 09, 2017 8:06 PM

To: Scott, Kimberly

Cc: Qiu, Yuhong

Subject: RE: NDA 207997, Midostaurin Clinical #1 IR regarding PI Table 5 DUE COB March 15th

Sensitivity: Confidential

Thank you Kim

From: Scott, Kimberly [<mailto:Kimberly.Scott@fda.hhs.gov>]

Sent: Thursday, March 09, 2017 5:23 PM

To: Abraham, Abbey <abbey.abraham@novartis.com>

Cc: Qiu, Yuhong <yuhong.qiu@novartis.com>; Scott, Kimberly <Kimberly.Scott@fda.hhs.gov>

Subject: NDA 207997, Midostaurin Clinical #1 IR regarding PI Table 5 DUE COB March 15th

Importance: High

Sensitivity: Confidential

Good afternoon Abbey,

The Agency is requesting the following information from Novartis regarding NDA 207997, Midostaurin:

- Review the attached information request along with the two corresponding .xpt files.

Please respond by **COB, Wednesday, March 15, 2017**

Kindly confirm receipt.

Thank you,

Kimberly Scott, RN, BSN, OCN®

CDR, U.S. Public Health Service

Regulatory Health Project Manager

Division of Hematology Products

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, Bldg. 22, Rm 3231

Silver Spring, MD 20993

Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

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
05/01/2017

Scott, Kimberly

From: Scott, Kimberly
Sent: Thursday, March 09, 2017 5:23 PM
To: Abraham, Abbey
Cc: Qiu, Yuhong (yuhong.qiu@novartis.com); Scott, Kimberly
Subject: NDA 207997, Midostaurin Clinical #1 IR regarding PI Table 5 DUE COB March 15th
Attachments: AdSM IR regarding Table 5, 3-9-17.docx; ALRS2_Hyper.xpt; ALRS2_Hypo.xpt

Importance: High

Good afternoon Abbey,

The Agency is requesting the following information from Novartis regarding NDA 207997, Midostaurin:

- Review the attached information request along with the two corresponding .xpt files.

Please respond by **COB, Wednesday, March 15, 2017**

Kindly confirm receipt.

Thank you,

Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Rm 3231
Silver Spring, MD 20993
Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

Midostaurin information request – 3/9/2017

1) To facilitate safety analysis, for the proposed PI Table 5 (treatment-emergent lab abnormalities in AdSM), clarify whether the denominator for toxicity reporting is the total number of patients in the safety population (142), or the total number of evaluable patients for a given lab parameter (namely, those with a baseline and at least one post-baseline gradeable value). FDA used the former, however either approach is acceptable.

2) FDA has largely confirmed the Sponsor's results for Table 5, although some calculations differ. (b) (4)

In the version below of Table 5, FDA has edited with tracked-changes those calculations that differ from the Sponsor's. To facilitate comparison, FDA has added the number of patients corresponding to each percentage, and has attached the two corresponding .xpt files used to analyze ALRS2.xpt labs that are either worse than baseline or worse than baseline unknown: one .xpt file for post-baseline grades of +1 through +4 and one .xpt file for post-baseline grades of -1 through -4. To facilitate safety analysis, please resolve the discrepant findings in Table 5. (b) (4)

[Redacted]

[Redacted] (b) (4)

(b) (4)

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
03/09/2017

Scott, Kimberly

From: Scott, Kimberly
Sent: Tuesday, February 28, 2017 9:03 PM
To: 'Abraham, Abbey'
Cc: Qiu, Yuhong (yuhong.qiu@novartis.com)
Subject: FW: NDA 207997 Midostaurin USPI: Agency response to Novartis- DUE 1pm today
Attachments: NDA 207997 Response to FDA Labeling Comments and PMCs.docx; Grouped PTs Novartis Annotized.docx; NDA 207997 Midostaurin WORKING version US PI DRAFT with Novartis Response-Comment.docx

Importance: High
Sensitivity: Confidential

Tracking:	Recipient	Read
	'Abraham, Abbey'	
	Qiu, Yuhong (yuhong.qiu@novartis.com)	
	Rahimi, Leeza	Read: 3/1/2017 8:13 AM
	Scott, Kimberly (Kimberly.Scott@fda.hhs.gov)	
	Scott, Kimberly (Kimberly.Scott@fda.hhs.gov)	
	Scott, Kimberly	Read: 3/1/2017 7:37 AM

Good evening Abbey,

After reviewing our records, it appears the attached response from Novartis regarding the US, PI, PPI, Carton/Container Labeling, and grouped PT's were not officially submitted to your Application.

Please be sure to officially submit (as soon as possible) via the gateway.

Kindly confirm receipt.

Thank you,
Kim

From: Abraham, Abbey [mailto:abbey.abraham@novartis.com]
Sent: Thursday, February 16, 2017 1:38 PM
To: Scott, Kimberly
Cc: Qiu, Yuhong
Subject: RE: NDA 207997 Midostaurin USPI: Agency response to Novartis- DUE 1pm today
Sensitivity: Confidential

Hi Kim

Please see a consolidated US PI and PPI with Novartis comments included and where applicable a reference to a section of the second response document, *Response to Labeling Comments and PMCs*, is made. The *Response to Labeling Comments and PMCs* also includes response to labeling carton comments and the proposed PMCs. Lastly the Novartis proposal for the groupings is being resubmitted.

From: Scott, Kimberly [mailto:Kimberly.Scott@fda.hhs.gov]
Sent: Thursday, February 16, 2017 12:38 PM

To: Abraham, Abbey <abbey.abraham@novartis.com>
Cc: Qiu, Yuhong <yuhong.qiu@novartis.com>
Subject: RE: NDA 207997 Midostaurin USPI: Agency response to Novartis- DUE 1pm today
Sensitivity: Confidential

Abbey,

I understand some of your comments are way longer than would fit in a comment bubble, but it's not acceptable to have multiple documents to work off of.

The responses your submitted were not reviewable. Therefore please put comments on the PI word document (comment bubble), and the PMC and Carton comments (if too long) may have a single companion response document for longer comments, but there needs to be an identifier on the word document to point to the exact response in the single companion response document.

Please let me know if have any questions.

Thanks,
Kim

From: Scott, Kimberly
Sent: Thursday, February 16, 2017 10:39 AM

From: Abraham, Abbey [<mailto:abbey.abraham@novartis.com>]
Sent: Thursday, February 16, 2017 12:34 PM
To: Scott, Kimberly
Cc: Qiu, Yuhong
Subject: RE: NDA 207997 Midostaurin USPI: Agency response to Novartis- DUE 1pm today
Sensitivity: Confidential

Hi Kim

I will put our responses from tabular into the label. The PMC document also responses to specific topics which are too extensive to put into the margins as bubbles. Can we retain these responses together with the response to the PMC s and Carton comments or do you want these separated?

Thanks
Abbey

From: Scott, Kimberly [<mailto:Kimberly.Scott@fda.hhs.gov>]
Sent: Thursday, February 16, 2017 12:26 PM
To: Abraham, Abbey <abbey.abraham@novartis.com>
Cc: Qiu, Yuhong <yuhong.qiu@novartis.com>
Subject: RE: NDA 207997 Midostaurin USPI: Agency response to Novartis- DUE 1pm today
Sensitivity: Confidential

Abbey,

Please put the comments on the PI Word document and PMC documents. There needs to be an identified on the PI and PMC documents in order to point the exact response.

Thank you,
Kim

From: Abraham, Abbey [<mailto:abbey.abraham@novartis.com>]
Sent: Thursday, February 16, 2017 11:14 AM
To: Scott, Kimberly
Cc: Qiu, Yuhong
Subject: RE: NDA 207997 Midostaurin USPI: Agency response to Novartis- DUE 1pm today
Sensitivity: Confidential

Hi Kim

We provided the response table to give the team a clean label to see our text revisions and work from but we can put our response comments into one document.

Abbey

From: Scott, Kimberly [<mailto:Kimberly.Scott@fda.hhs.gov>]
Sent: Thursday, February 16, 2017 11:01 AM
To: Abraham, Abbey <abbey.abraham@novartis.com>
Cc: Qiu, Yuhong <yuhong.qiu@novartis.com>
Subject: RE: NDA 207997 Midostaurin USPI: Agency response to Novartis- DUE 1pm today
Importance: High
Sensitivity: Confidential

Good morning Abbey,

After reviewing the labeling and MedGuide, the Agency is requesting Novartis provide labeling comments and responses on both the PI and MG using comment bubbles within the one document. Please complete this by 1:00pm today.

Kindly confirm receipt.

Thank you,
Kim

From: Abraham, Abbey [<mailto:abbey.abraham@novartis.com>]
Sent: Thursday, February 16, 2017 8:46 AM
To: Scott, Kimberly
Cc: Qiu, Yuhong
Subject: RE: NDA 207997 Midostaurin USPI: Agency response to Novartis
Sensitivity: Confidential

Hi Kim

Apologize for the delays in sending this as the team has been working continuously to address the FDA comments. Please see attached the following documents as the response to the agency's comments on the Draft US PI and PPI and proposed PMCs

1. **Revised US PI/PPI:** As per your email, we have accepted tracked changes where we are in agreement and any FDA proposed text that we have counter proposal for has been accepted and then tracked as a deletion. All FDA comments have been preserved in the margin and any new text we are proposing is tracked.
2. **Labeling Comment Response Table:** While this is a relatively large document, it provides a section by section /comment by comment comparison of the FDA proposal and our response. This is essentially the draft US PI in tabular format but it mainly serves to show what the Novartis response to all FDA comments or proposals
3. **Response to Labeling Comments and PMCs:** This document is extension of the Comment-Response table as this provides response on a few select topics that needed additional space and text. This also includes our response to the Carton labeling comments and the PMCs

4. **Grouped PTs Novartis Annotated:** Novartis Rationale for the revisions to the groupings

Please let me know if you have any questions

Abbey Abraham, PharmD

Oncology Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation

Phone +1 862-778-8998
Fax +1 973-781-3473
abbey.abraham@novartis.com
www.novartis.com

From: Abraham, Abbey
Sent: Wednesday, February 15, 2017 4:28 PM
To: 'Kimberly.Scott@fda.hhs.gov' <Kimberly.Scott@fda.hhs.gov>
Cc: Qiu, Yuhong <yuhong.qiu@novartis.com>
Subject: RE: NDA 207997 Midostaurin USPI: Agency response to Novartis
Sensitivity: Confidential

Hi Kim

I hate to say this as we know the team already gave us a couple extensions but due to last minute QC findings for the revised adverse reaction section, we will need to postpone sending the full label by about 12 hours. Will have to you by 8 am tomorrow morning. Hope this is acceptable.

Thanks

Abbey Abraham

Phone +1 862-778-8998

From: Miller, Kelly [<mailto:Kelly.Miller@fda.hhs.gov>]
Sent: Monday, February 13, 2017 7:36 AM
To: Abraham, Abbey <abbey.abraham@novartis.com>; Qiu, Yuhong <yuhong.qiu@novartis.com>
Cc: Scott, Kimberly <Kimberly.Scott@fda.hhs.gov>
Subject: NDA 207997 Midostaurin USPI: Agency response to Novartis
Sensitivity: Confidential

Good Morning Abbey,

I am covering for Kim today. In response to your email below, the team would prefer to have everything at one time. You can submit the whole PI by Wednesday, February 15, 2017 COB. Send the whole PI at one time rather than in parts. If you have any questions, feel free to contact me. Kindly confirm receipt of this email.

Thank you,
Kelly

From: Abraham, Abbey [<mailto:abbey.abraham@novartis.com>]
Sent: Sunday, February 12, 2017 7:09 PM

To: Scott, Kimberly
Cc: Qiu, Yuhong
Subject: RE: NDA 207997 Midostaurin USPI: Agency response to Novartis
Sensitivity: Confidential

Hi Kim

We were able to open and review the file but given the time the team here is needing additional to assess the comments and potential revision to the Adverse section. What we propose is that we will submit the rest of the US PI by Monday morning and then section 6, Adverse Reaction, by Wednesday 8 am, Feb 15th. Please let us know this is acceptable.

Thank you

Abbey Abraham, PharmD
Oncology Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation

Phone +1 862-778-8998
Fax +1 973-781-3473
abbey.abraham@novartis.com
www.novartis.com

Kelly Miller R.Ph.
Regulatory Project Manager
Division of Hematology Products (DHP)
OHOP/OND/CDER
U.S. Food and Drug Administration
Telephone: 240-402-6613
Email: kelly.miller@fda.hhs.gov

61 Page(s) 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/

KIMBERLY L SCOTT

03/03/2017

requesting Applicant officially submit their response regarding label/Carton/Container

MEMORANDUM OF TELECONFERENCE

Teleconference Date: March 2, 2017

Application Number: NDA 207997

Product Name: Midostaurin

Sponsor/Applicant Name: Novartis Pharmaceuticals

Subject: Novartis requested a teleconference to discuss a few of the labeling revisions proposed by the FDA.

FDA Participants : Ann T. Farrell, MD, Division Director

- Donna Przepiorcka, MD, PhD, Clinical Team Leader
- Yvette Kasamon, MD, Clinical Reviewer
- Ashley Ward, MD, Clinical Reviewer
- Virginia Kwitkowski, MS, RN, ACNP-BC
- Kimberly Scott, RN, BSN, OCN[®], Regulatory Project Manager

Applicant Participants :

- Renaud Capdeville, Vice President, Global Program Head
- Noah Berkowitz, Executive Director, Global Clinical Program Head
- Allison Florance, Executive Director, Biostatistics
- Alice Huntsman-Labed, Director, Biostatistics
- Jacqueline Kinyamu-Akunda, Director, Preclinical Safety
- Karen Habucky, Head, US Clinical Strategy - Leukemia,
- Iulian Alecu, Senior Director, Integrated Medical Safety
- Selim Aydin, Brand Safety Leader, Integrated Medical Safety
- Shanthi Ganeshan, Vice President, North America Region Head, Drug Regulatory Affairs
- Yuhong Qiu, Senior Director, Drug Regulatory Affairs
- Abbey Abraham, Director, Drug Regulatory Affairs

1.0 BACKGROUND:

The sponsor requested a telecon to discuss labeling comments sent by FDA on 2/28/2017.

2.0 DISCUSSION:

FDA opened the telecon with an explanation that since there was no material for review prior to the telecon, “agreements” might not be reached immediately, but FDA would give the best advice possible.

1.

(b) (4)

(b) (4)

2. (b) (4)

3. (b) (4)
FDA recommended that the sponsor submit their comments in writing for review.

4. (b) (4)
FDA indicated that this was under discussion internally.

5. (b) (4)

6. (b) (4)

(b) (4)
FDA indicated that the text was still under discussion internally as well.

3.0 ACTION ITEMS: The sponsor requested an extension to provide a response. FDA granted an extension to noon Wednesday, March 8.

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
03/03/2017

Scott, Kimberly

From: Scott, Kimberly
Sent: Wednesday, March 01, 2017 4:25 PM
To: Abraham, Abbey
Cc: Qiu, Yuhong
Subject: RE: NDA 207997 Midostaurin, USPI/PPI/grouped Terms: DUE COB, Monday, 3/6

Importance: High
Sensitivity: Confidential

Good afternoon Abbey,

The Agency has approved a teleconference to discuss the topics (below) for NDA 207997, Midostaurin (labeling and Grouped terms) for tomorrow, Thursday, March 2, 2017 from 11:15am-12:00noon. Please provide a teleconference number for the meeting.

Kindly confirm receipt.

Thank you,
Kim

From: Abraham, Abbey [mailto:abbey.abraham@novartis.com]
Sent: Wednesday, March 01, 2017 12:10 PM
To: Scott, Kimberly
Cc: Qiu, Yuhong
Subject: RE: NDA 207997 Midostaurin, USPI/PPI/grouped Terms: DUE COB, Monday, 3/6
Sensitivity: Confidential

Hi Kim

Please see a list of topics we would like to discuss.

- 1.
- 2.
- 3.
- 4.
- 5.
- 6.

(b) (4)

Thanks

Abbey Abraham, PharmD
Oncology Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation

Phone +1 862-778-8998
Fax +1 973-781-3473
abbey.abraham@novartis.com
www.novartis.com

From: Scott, Kimberly [<mailto:Kimberly.Scott@fda.hhs.gov>]
Sent: Tuesday, February 28, 2017 8:54 PM
To: Abraham, Abbey <abbey.abraham@novartis.com>
Cc: Qiu, Yuhong <yuhong.qiu@novartis.com>
Subject: RE: NDA 207997 Midostaurin, USPI/PPI/grouped Terms: DUE COB, Monday, 3/6
Importance: High
Sensitivity: Confidential

Good evening Abbey,

The Agency is requesting Novartis send the specific text/sections you are requesting to review.

Please send the items you would like to discuss with the Agency.

Kind regards,
Kim

From: Abraham, Abbey [<mailto:abbey.abraham@novartis.com>]
Sent: Tuesday, February 28, 2017 4:00 PM
To: Scott, Kimberly
Cc: Qiu, Yuhong
Subject: RE: NDA 207997 Midostaurin, USPI/PPI/grouped Terms: DUE COB, Monday, 3/6
Sensitivity: Confidential

Hi Kim

Thank you for the revised US PI and groupings document. After review of the agency's feedback, Novartis would like to request a TC to discuss a few of the proposed FDA revisions. (b) (4)

Propose that we will provide a list of the specific text/sections we would like to review with the team in advance of this meeting. Please let me know if the agency will be able to grant our request and can provide the TC information and the list of topics as soon as you need.

Thanks

Abbey Abraham, PharmD
Oncology Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation

Phone +1 862-778-8998
Fax +1 973-781-3473
abbey.abraham@novartis.com
www.novartis.com

From: Scott, Kimberly [<mailto:Kimberly.Scott@fda.hhs.gov>]
Sent: Tuesday, February 28, 2017 12:45 PM
To: Abraham, Abbey <abbey.abraham@novartis.com>
Cc: Qiu, Yuhong <yuhong.qiu@novartis.com>; Scott, Kimberly <Kimberly.Scott@fda.hhs.gov>
Subject: NDA 207997 Midostaurin, USPI/PPI/grouped Terms: DUE COB, Monday, 3/6

Importance: High

Sensitivity: Confidential

Good afternoon Abbey,

Please see the attached FDA labeling revisions to the prescribing information (PI), Patient Packet Information (PPI), and grouped Terms, for NDA 207997, Midostaurin.

Please review the FDA revised labeling revisions with your team by:

- Accepting changes that you agree with
- Making any edits that you do not agree with using track-changes only (***do not reject any changes that the FDA proposed and do not delete any of the FDA's comments***)
- Enter any comments in "bubble" on the document

After you have made any necessary changes, please send the *revised tracked changes labeling documents* (PI, PPI, grouped Terms) before you make your official submission electronically.

Any edits you make should be in tracked changes.

Please respond by COB, Monday, March 6, 2017.

Kindly confirm receipt.

Thank you,

Kim

Kimberly Scott, RN, BSN, OCN®

CDR, U.S. Public Health Service

Regulatory Health Project Manager

Division of Hematology Products

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, Bldg. 22, Rm 3231

Silver Spring, MD 20993

Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

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
03/01/2017

Scott, Kimberly

From: Scott, Kimberly
Sent: Tuesday, February 28, 2017 12:45 PM
To: Abraham, Abbey
Cc: Qiu, Yuhong (yuhong.qiu@novartis.com); Scott, Kimberly
Subject: NDA 207997 Midostaurin, USPI/PPI/grouped Terms: DUE COB, Monday, 3/6
Attachments: Grouped PTs 2017 0228.docx; NDA 207997 Midostaurin WORKING version US PI DRAFT 2-27-17.docx

Importance: High

Good afternoon Abbey,

Please see the attached FDA labeling revisions to the prescribing information (PI), Patient Packet Information (PPI), and grouped Terms, for NDA 207997, Midostaurin.

Please review the FDA revised labeling revisions with your team by:

- Accepting changes that you agree with
- Making any edits that you do not agree with using track-changes only (*do not reject any changes that the FDA proposed and do not delete any of the FDA's comments*)
- Enter any comments in "bubble" on the document

After you have made any necessary changes, please send the *revised tracked changes labeling documents* (PI, PPI, grouped Terms) before you make your official submission electronically.

Any edits you make should be in tracked changes.

Please respond by COB, Monday, March 6, 2017.

Kindly confirm receipt.

Thank you,

Kim

Kimberly Scott, RN, BSN, OCN®

CDR, U.S. Public Health Service

Regulatory Health Project Manager

Division of Hematology Products

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, Bldg. 22, Rm 3231

Silver Spring, MD 20993

Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

36 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/

KIMBERLY L SCOTT
02/28/2017

Scott, Kimberly

From: Scott, Kimberly
Sent: Tuesday, February 28, 2017 12:45 PM
To: Abraham, Abbey
Cc: Qiu, Yuhong (yuhong.qiu@novartis.com); Scott, Kimberly
Subject: NDA 207997 Midostaurin, USPI/PPI/grouped Terms: DUE COB, Monday, 3/6
Attachments: Grouped PTs 2017 0228.docx; NDA 207997 Midostaurin WORKING version US PI DRAFT 2-27-17.docx

Importance: High

Good afternoon Abbey,

Please see the attached FDA labeling revisions to the prescribing information (PI), Patient Packet Information (PPI), and grouped Terms, for NDA 207997, Midostaurin.

Please review the FDA revised labeling revisions with your team by:

- [Accepting changes that you agree with](#)
- [Making any edits that you do not agree with using track-changes only \(*do not reject any changes that the FDA proposed and do not delete any of the FDA's comments*\)](#)
- [Enter any comments in "bubble" on the document](#)

After you have made any necessary changes, please send the *revised tracked changes labeling documents* (PI, PPI, grouped Terms) before you make your official submission electronically.
Any edits you make should be in tracked changes.

Please respond by COB, Monday, March 6, 2017.

Kindly confirm receipt.

Thank you,

Kim

Kimberly Scott, RN, BSN, OCN[®]

CDR, U.S. Public Health Service

Regulatory Health Project Manager

Division of Hematology Products

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, Bldg. 22, Rm 3231

Silver Spring, MD 20993

Phone: 240-402-4560 | Kimberly.scott@fda.hhs.gov

36 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/

KIMBERLY L SCOTT
02/28/2017

Scott, Kimberly

From: Scott, Kimberly
Sent: Tuesday, February 21, 2017 8:56 AM
To: Abraham, Abbey
Cc: Qiu, Yuhong (yuhong.qiu@novartis.com)
Subject: NDA 207997 Midostaurin: PMCs- respond by COB on Thursday, 2/23
Attachments: NDA 207997 PMCs - Novartis 2.21.17.docx

Importance: High

Good morning Abbey,

The Agency is requesting the following information from Novartis regarding NDA 207997, Midostaurin:

- Review the attached PMC's: make edits/comments on the attached document.
- Submit to NDA 207997 a Letter of Authorization from the organization sponsoring the RATIFY trial to allow FDA permission to review information in their IND for the RATIFY trial.

Please respond by COB, Thursday, February 23, 2017.

Kindly confirm receipt.

Thank you,

Kim

Kimberly Scott, RN, BSN, OCN®

CDR, U.S. Public Health Service

Regulatory Health Project Manager

Division of Hematology Products

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, Bldg. 22, Rm 3231

Silver Spring, MD 20993

Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

1 Page has 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/

KIMBERLY L SCOTT
02/21/2017

Scott, Kimberly

From: Scott, Kimberly
Sent: Friday, February 17, 2017 1:34 PM
To: Abraham, Abbey
Cc: Qiu, Yuhong (yuhong.qiu@novartis.com)
Subject: NDA 207997, Midostaurin labeling IR 1: respond by COB, Monday, February 20

Importance: High

Good afternoon Abbey,

The Agency has the following information request for NDA 207997, Midostaurin label:

- Reference is made to the response to 2/7/2017 FDA labeling comments and PMCs. (b) (4)
(b) (4)
efficacy analysis, provide the modified Valent response rates (ORR, MR, PR) in the D2201 PEP overall using the programmed calculations.

Please respond by COB, Monday, February 20, 2017.

Kindly confirm receipt.

Thank you,

Kim

Kimberly Scott, RN, BSN, OCN®

CDR, U.S. Public Health Service

Regulatory Health Project Manager

Division of Hematology Products

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, Bldg. 22, Rm 3231

Silver Spring, MD 20993

Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

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
02/17/2017

Scott, Kimberly

From: Scott, Kimberly
Sent: Thursday, February 16, 2017 2:15 PM
To: Abraham, Abbey
Cc: Qiu, Yuhong (yuhong.qiu@novartis.com)
Subject: NDA 207997 midostaurin for AML (Study A2301) OSI IR: Due COB, February 20th

Importance: High

Good afternoon Abbey,

The Agency is requesting the following information for NDA 207997, Midostaurin:



Please respond by COB on Monday, February 20, 2017.

Kindly confirm receipt.

Thank you,

Kim

Kimberly Scott, RN, BSN, OCN®

CDR, U.S. Public Health Service

Regulatory Health Project Manager

Division of Hematology Products

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, Bldg. 22, Rm 3231

Silver Spring, MD 20993

Phone: 240-402-4560 | Kimberly.scott@fda.hhs.gov

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
02/16/2017

Scott, Kimberly

From: Scott, Kimberly
Sent: Friday, February 10, 2017 5:26 PM
To: Abraham, Abbey
Cc: Qiu, Yuhong
Subject: RE: NDA 207997 Midostaurin USPI: Agency response to Novartis
Attachments: Groups.jmp

Importance: High
Sensitivity: Confidential

Good evening Abbey,

Please see the attached file as well as the comment from the team in response to your request for clarification regarding the adverse section of the draft USPI. Please see the following comments:

(b) (4)

Kindly confirm receipt of this email.

Thank you,
Kim

From: Abraham, Abbey [mailto:abbey.abraham@novartis.com]
Sent: Thursday, February 09, 2017 10:15 PM
To: Scott, Kimberly
Cc: Qiu, Yuhong
Subject: RE: NDA 207997 Midostaurin PUI, MG, and PMC response due COB, Friday, 2/10
Sensitivity: Confidential

Hi Kim

The team here has some follow-up clarification questions regarding the adverse section of the draft US PI.

(b) (4), could
the team please provide some additional clarity on (b) (4)?

We also are raising the following points of concern:

1.

(b) (4)

2.

3.

4.

5.

Appreciate if the FDA team could provide feedback as soon as possible, thank you.

Abbey Abraham, PharmD

Oncology Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation

Phone +1 862-778-8998
Fax +1 973-781-3473
abbey.abraham@novartis.com
www.novartis.com

From: Scott, Kimberly [<mailto:Kimberly.Scott@fda.hhs.gov>]
Sent: Wednesday, February 08, 2017 8:47 PM
To: Abraham, Abbey <abbey.abraham@novartis.com>
Cc: Qiu, Yuhong <yuhong.qiu@novartis.com>
Subject: RE: NDA 207997 Midostaurin PUI, MG, and PMC response due COB, Friday, 2/10
Sensitivity: Confidential

Hi Abbey,

Yes, this is acceptable.

Thank you,
Kim
Kimberly Scott, RN, BSN, OCN®

CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Rm 3231
Silver Spring, MD 20993
Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

From: Abraham, Abbey [<mailto:abbey.abraham@novartis.com>]
Sent: Wednesday, February 08, 2017 5:10 PM
To: Scott, Kimberly
Cc: Qiu, Yuhong
Subject: RE: NDA 207997 Midostaurin PUI, MG, and PMC response due COB, Friday, 2/10
Sensitivity: Confidential

Hello Kim,

Thanks for sending the labeling revisions yesterday. I know you want our response to the labeling and the proposed PMCs by COB of Friday (Feb 10). Given the extensiveness of the revision, we would like to ask for an extension over the weekend and to submit the response by 8 am on Monday Feb 13 so that we can complete the internal review process. Please let me know whether this is acceptable.

Thanks,

Abbey Abraham, PharmD
Oncology Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation

Phone +1 862-778-8998
Fax +1 973-781-3473
abbey.abraham@novartis.com
www.novartis.com

From: Scott, Kimberly [<mailto:Kimberly.Scott@fda.hhs.gov>]
Sent: Tuesday, February 07, 2017 6:00 PM
To: Abraham, Abbey <abbey.abraham@novartis.com>
Subject: RE: NDA 207997 Midostaurin PUI, MG, and PMC response due COB, Friday, 2/10
Sensitivity: Confidential

Thank you

Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Rm 3231
Silver Spring, MD 20993
Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

From: Abraham, Abbey [<mailto:abbey.abraham@novartis.com>]
Sent: Tuesday, February 07, 2017 5:39 PM
To: Scott, Kimberly
Cc: Qiu, Yuhong
Subject: RE: NDA 207997 Midostaurin PUI, MG, and PMC response due COB, Friday, 2/10
Sensitivity: Confidential

Thank you Kim received

From: Scott, Kimberly [<mailto:Kimberly.Scott@fda.hhs.gov>]
Sent: Tuesday, February 07, 2017 4:43 PM
To: Abraham, Abbey <abbey.abraham@novartis.com>
Cc: Qiu, Yuhong <yuhong.qiu@novartis.com>
Subject: NDA 207997 Midostaurin PUI, MG, and PMC response due COB, Friday, 2/10
Importance: High
Sensitivity: Confidential

Good afternoon Abbey,

Please refer to the attached FDA labeling revisions to the prescribing information (PI) with the Grouped PTs Finalized(see attached) and MedGuide for both indications for Midostaurin, NDA 207997.

Please review the FDA revised labeling with your team by:

- [Accepting changes that you agree with](#)
- [Making any edits that you do not agree with using track-changes only \(*do not reject any changes that the FDA proposed and do not delete any of the FDA's comments*\)](#)

After you have made any necessary changes, please send the revised tracked changes labeling documents (PI and MG) before you make your official submission electronically. Any edits you make should be in tracked changes.

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.

In addition, we are also providing you with proposed post marketing studies.

We have determined that the following clinical trials are necessary as post-marketing commitments (PMCs), based on the data available to date. We may have additional PMRs/PMCs later. These brief descriptions are intended to describe the main objective and trial characteristics of interest. Please provide edits and comments in clarifying mutually acceptable descriptions of the key trial elements. It is also necessary for you to provide schedule milestone dates as indicated. Most milestones only require the applicant to provide the month and year for completion of each category. For milestone calculation purposes only, assume that an approval occurs on the PDUFA date.

Upon mutual agreement, we ask you to submit both by email and officially a copy of the PMC studies/trials description to us with a statement that you agree to perform the trials as described and within the timelines that you specify for the trial.

Note, final PMC designation numbers will be assigned later.

Please send your response to both labeling (PI and MG) and proposed PMCs via email by **COB of Friday, February 10, 2017.**

Kindly confirm receipt.

Thank you,

Kim

Kimberly Scott, RN, BSN, OCN®

CDR, U.S. Public Health Service

Regulatory Health Project Manager

Division of Hematology Products

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, Bldg. 22, Rm 3231

Silver Spring, MD 20993

Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

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
02/10/2017

Scott, Kimberly

From: Scott, Kimberly
Sent: Tuesday, February 07, 2017 4:43 PM
To: Abraham, Abbey
Cc: Qiu, Yuhong (yuhong.qiu@novartis.com)
Subject: NDA 207997 Midostaurin PUI, MG, and PMC response due COB, Friday, 2/10
Attachments: N 207997 PMCs.docx; NDA 207997 Midostaurin WORKING version USPI DRAFT - 2-7-17.docx; Grouped PTs.docx

Importance: High

Good afternoon Abbey,

Please refer to the attached FDA labeling revisions to the prescribing information (PI) with the Grouped PTs Finalized(see attached) and MedGuide for both indications for Midostaurin, NDA 207997.

Please review the FDA revised labeling with your team by:

- [Accepting changes that you agree with](#)
- [Making any edits that you do not agree with using track-changes only \(*do not reject any changes that the FDA proposed and do not delete any of the FDA's comments*\)](#)

After you have made any necessary changes, please send the revised tracked changes labeling documents (PI and MG) before you make your official submission electronically. Any edits you make should be in tracked changes.

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.

In addition, we are also providing you with proposed post marketing studies.

We have determined that the following clinical trials are necessary as post-marketing commitments (PMCs), based on the data available to date. We may have additional PMRs/PMCs later. These brief descriptions are intended to describe the main objective and trial characteristics of interest. Please provide edits and comments in clarifying mutually acceptable descriptions of the key trial elements. It is also necessary for you to provide schedule milestone dates as indicated. Most milestones only require the applicant to provide the month and year for completion of each category. For milestone calculation purposes only, assume that an approval occurs on the PDUFA date.

Upon mutual agreement, we ask you to submit both by email and officially a copy of the PMC studies/trials description to us with a statement that you agree to perform the trials as described and within the timelines that you specify for the trial.

Note, final PMC designation numbers will be assigned later.

Please send your response to both labeling (PI and MG) and proposed PMCs via email by **COB of Friday, February 10, 2017.**

Kindly confirm receipt.

Thank you,

Kim

Kimberly Scott, RN, BSN, OCN®

CDR, U.S. Public Health Service

Regulatory Health Project Manager

Division of Hematology Products

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, Bldg. 22, Rm 3231

Silver Spring, MD 20993

Phone: 240-402-4560 | Kimberly.scott@fda.hhs.gov

3 Page(s) have been Withheld in Full as b4 (CCI/TS)
immediately following this page

PMC #1

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 (b)(4) subjects in the RATIFY trial. Submit a data file with results of the full mutational profiling at baseline performed by Alliance and/or Novartis in addition to the full study report.

Desired milestones:

Draft Protocol Submission	xx/xxxx
Final Protocol Submission	xx/xxxx
Study Completion	xx/xxxx
Final Report Submission	04/2018

PMC #2

To demonstrate that the treatment effect of midostaurin is consistent across prognostic subgroups, provide subgroup analyses for (b)(4) subjects 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 LeukemiaNet (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.

Desired milestones:

Draft Protocol Submission	xx/xxxx
Final Protocol Submission	xx/xxxx
Study Completion	xx/xxxx
Final Report Submission	04/2018

40 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/

KIMBERLY L SCOTT
02/08/2017



IND 057120

**GRANT –
BREAKTHROUGH THERAPY DESIGNATION**

Novartis Pharmaceuticals Corporation
Attention: Yuhong Qiu, PhD
Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936

Dear Dr. Qiu:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for PKC412 (midostaurin).

We also refer to your December 11, 2015, request for Breakthrough Therapy designation. We have reviewed your request and have determined that PKC 412 (midostaurin) for 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 meets the criteria for Breakthrough Therapy designation. Therefore, we are granting your request for Breakthrough Therapy designation. Please note that if the clinical development program does not continue to meet the criteria for Breakthrough Therapy designation, we may rescind the designation.

FDA will work closely with you to provide guidance on subsequent development of PKC412 (midostaurin) for the above indication to help you design and conduct a development program as efficiently as possible. For further information regarding Breakthrough Therapy designation and FDA actions to expedite development of a designated product, please refer to section 902 of the Food and Drug Administration Safety and Innovation Act (FDASIA) and the *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics*.¹

When breakthrough therapy designation is granted, sponsors are asked to submit a Type B meeting request for a multidisciplinary comprehensive discussion of the drug development program, including planned clinical trials and plans for expediting the manufacturing development strategy. Please refer to MAPP 6025.6 - *Good Review Practice: Management of Breakthrough Therapy-Designated Drugs and Biologics*, Attachment 1, for potential topics for discussion at this initial breakthrough therapy meeting².

¹ <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

²

<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/Ma>

We note your recent Pre-New Drug Application meeting held on September 2, 2015 for a different indication (treatment of patients with aggressive systemic mastocytosis or mast cell leukemia [REDACTED] (b) (4) At this point in your drug development program, holding this initial breakthrough therapy meeting is not necessary. However, you may request a separate Pre-New Drug Application meeting for the indication that was granted Breakthrough Therapy designation. Please contact the Regulatory Project Manager noted below to determine if any information is required at this time to expedite the review of your breakthrough designated product.

If the breakthrough therapy designation for PKC412 (midostaurin) for 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 is rescinded, submission of portions of the NDA will not be permitted under this program. However, if you have Fast Track designation you will be able to submit portions of your application under the Fast Track program.

If you have any questions, contact Kris Kolibab, Senior Regulatory Project Manager, at (240) 402-0277.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, MD
Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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

/s/

ANN T FARRELL
01/29/2016

Scott, Kimberly

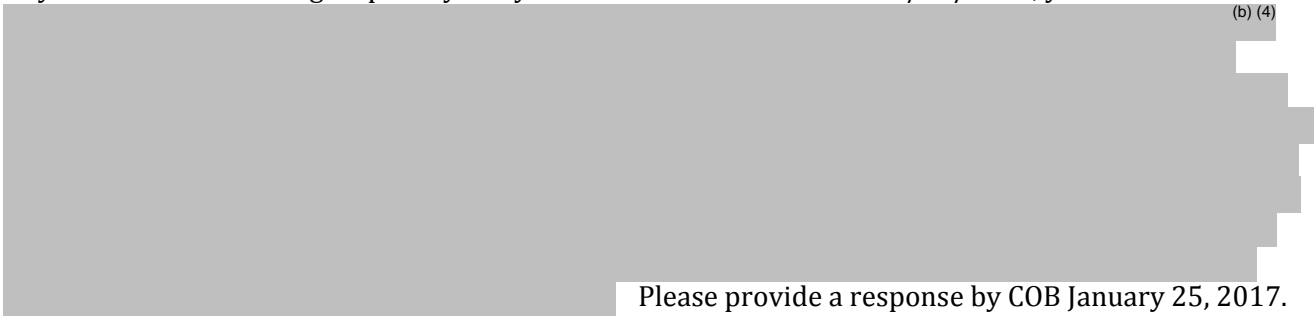
From: Scott, Kimberly
Sent: Saturday, January 21, 2017 2:09 PM
To: Abraham, Abbey
Cc: Qiu, Yuhong (yuhong.qiu@novartis.com)
Subject: NDA 207997, Midostaurin: Original 2 IR # 3 DUE COB January 25th

Importance: High

Good morning Abbey

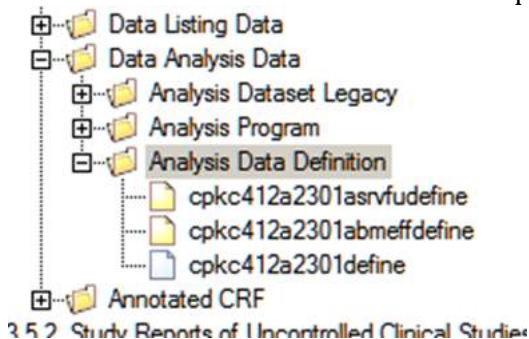
The Agency has the following information request for NDA 207997, Midostaurin:

1. In your RATIFY trial subgroup analysis by NPM1 mutation submitted 11/30/2016, you conclude that (b) (4)



Please provide a response by COB January 25, 2017.

2. There were 717 subjects accrued to RATIFY, but acmd.xpt includes concomitant medications for only 665 subjects. Please identify the reasons why concomitant medications are not included for the other 52 subjects. Please provide a response by COB January 25, 2017.
3. Page 30 of the CRF for RATIFY includes the karyotype description. Please identify the data file and variable that has the karyotype description. If you have not submitted this data, please do so. Please provide a response by COB January 25, 2017.
4. For RATIFY, please clarify whether you have a derived variable for cytogenetic/molecular prognostic category. If so, please identify the data file and variable that has the cytogenetic/molecular prognostic category. Please provide a response by COB January 25, 2017.
5. The current version of the PKC412A2301 Analysis Data Definition folder includes 3 define files, one of which is an amendment and one of which is an appendix.



As per our correspondence 9/30/2016, there should be a single define.pdf file for each data set. A define file does not have separate amendments or appendices. Replace the PKC412A2301 Analysis Data define file with an updated version that accounts for all xpt files in the Analysis Dataset. Please replace the incomplete define.pdf file by COB January 25, 2017.

Kindly confirm receipt of this email.

Thank you,

Kim

Kimberly Scott, RN, BSN, OCN®

CDR, U.S. Public Health Service

Regulatory Health Project Manager

Division of Hematology Products

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, Bldg. 22, Rm 3231

Silver Spring, MD 20993

Phone: 240-402-4560 | Kimberly.scott@fda.hhs.gov

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
05/01/2017

Scott, Kimberly

From: Scott, Kimberly
Sent: Wednesday, January 18, 2017 3:23 PM
To: Abraham, Abbey
Cc: Miller, Kelly; Qiu, Yuhong (yuhong.qiu@novartis.com)
Subject: NDA 207997 Midostaurin Original 1 # 11 IR: response due 2 pm EST, Thursday January 19

Importance: High

Good afternoon Abbey,

The Agency has the following information request for NDA 207997, Midostaurin:

- Time to response in AdSM: Reference is made to your response to the 16 Jan 2017 IR, (b) (4)
 (b) (4)
To
facilitate efficacy analysis, for the D2201 PEP, for all patients who achieved MR or PR (modified Valent criteria) by 6 cycles as adjudicated by the SSC, please submit an .xpt file with the unique subject ID, the date of first response as adjudicated by the SSC, and the category of initial response (MR, PR).

Please respond to by 2:00pm (ET) tomorrow, Thursday, January 19, 2017.

Kindly confirm receipt.

Thank you,

Kim

Kimberly Scott, RN, BSN, OCN®

CDR, U.S. Public Health Service

Regulatory Health Project Manager

Division of Hematology Products

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, Bldg. 22, Rm 3231

Silver Spring, MD 20993

Phone: 240-402-4560 | Kimberly.scott@fda.hhs.gov

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
01/18/2017

Scott, Kimberly

From: Scott, Kimberly
Sent: Monday, January 16, 2017 8:19 PM
To: 'Abraham, Abbey'
Cc: Qiu, Yuhong (yuhong.qiu@novartis.com); Miller, Kelly
Subject: NDA 207997 Midostaurin Original 1 IR # 10: DUE COB 1/17/17

Importance: High

Good evening Abbey,

The Agency has the following information request for NDA 207997, Midostaurin:

- Time to response in AdSM: (b) (4)
 For
efficacy analysis, clarify how this is possible.

Please respond by COB tomorrow, Tuesday, January 17, 2017.

Kindly confirm receipt.

Thank you,

Kim

Kimberly Scott, RN, BSN, OCN®

CDR, U.S. Public Health Service

Regulatory Health Project Manager

Division of Hematology Products

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, Bldg. 22, Rm 3231

Silver Spring, MD 20993

Phone: 240-402-4560 | Kimberly.scott@fda.hhs.gov

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
01/31/2017

Scott, Kimberly

From: Carioti, Theresa
Sent: Thursday, January 12, 2017 1:19 PM
To: abbey.abraham@novartis.com
Cc: yuhong.qiu@novartis.com; Scott, Kimberly; Carioti, Theresa
Subject: NDA 207997 Midostaurin: Clinical Information request - Due 10AM Tuesday, January 17, 2017

Good Afternoon Abbey,
I am sending this email on behalf of Kimberly Scott.

Please refer to NDA 207997, Midostaurin, Original 1 (AML). We have the following clinical information request. Please respond via email by 10AM Tuesday, January 17, 2017, and also follow with a formal submission to the NDA file.

Clinical Information request:

With AE reporting, you did not capture grade 5 events in the AdSM studies. We note that multiple fatal events, such as cardiac arrest, myocardial infarction, CHF, and sepsis, were coded as grade <5 in the study-specific and/or integrated AAEV.xpt, AAEVIN1.xpt, and AAERISK.xpt files, including a case of fatal pneumonia that was designated grade 3 (CPKC412D2201_0180_00007). For safety review, clarify whether all fatal AEs are included but designated a grade less than 5 in the AAEV, AAERISK, and ADLB2 .xpt files. If they are not, then

- a) Submit an .xpt file, with one fatal event per patient and row, that indicates the unique subject ID (STYSID1A), study ID (STY1A), date of AE, date of death, and preferred term (PT_TXT) for every on-treatment death on Studies A2213 and D2201 reported as of the Day 120 safety update.
- b) If some but not all fatal AEs are included in the above .xpt files, specify which cases were previously included but at a lower designated grade and which are new, in order to avoid overlap.

Please kindly confirm receipt.

Thank you,
Theresa

Theresa A. Carioti, MPH
Chief, Project Management Staff
Division of Hematology Products, OHOP, CDER, FDA
email: Theresa.Carioti@fda.hhs.gov
phone: 301-796-2848

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
01/12/2017

Scott, Kimberly

From: Scott, Kimberly
Sent: Thursday, January 05, 2017 10:53 AM
To: Abraham, Abbey
Cc: Qiu, Yuhong
Subject: RE: NDA 207997 Midostaurin, Original 1: Clinical #8- information requests -Due 12:00pm Friday, January 6, 2017

Importance: High
Sensitivity: Confidential

Good morning Abbey,

The Agency has the following information request in response to your January 3, 2017 response:

- “We have found differences between OS1_1N and OS_2N in 5 patients that belong to the study D2201 primary efficacy population, as shown in the table below. Please provide clarifications to these discrepancies.



Please respond to by 2:00pm(ET) tomorrow, January 6, 2017.

Kindly confirm receipt.

Thank you,

Kim

Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Rm 3231
Silver Spring, MD 20993
Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

From: Abraham, Abbey [<mailto:abbey.abraham@novartis.com>]
Sent: Tuesday, January 03, 2017 11:11 PM
To: Scott, Kimberly
Cc: Qiu, Yuhong
Subject: RE: NDA 207997 Midostaurin, Original 1: Clinical #7- information requests -Due COB Tuesday, January 3, 2017
Sensitivity: Confidential

Hi Kim

Please see attached the response for the below IR. This will be also submitted via the Gateway with the respective dataset. Please let me know if you have any comments or questions

Thank you

Abbey Abraham, PharmD
Oncology Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation

Phone +1 862-778-8998
Fax +1 973-781-3473
abbey.abraham@novartis.com
www.novartis.com

From: Scott, Kimberly [<mailto:Kimberly.Scott@fda.hhs.gov>]
Sent: Tuesday, January 03, 2017 8:39 AM
To: Abraham, Abbey <abbey.abraham@novartis.com>
Cc: Qiu, Yuhong <yuhong.qiu@novartis.com>
Subject: NDA 207997 Midostaurin, Original 1: Clinical #7- information requests -Due COB Tuesday, January 3, 2017
Importance: High
Sensitivity: Confidential

Good evening Abbey,

The Agency has the following Clinical information request for NDA 207997, Midostaurin:

Information requests

- 1) In the define file for study D2201, AIDENT.xpt, the variable OS1_E10 is defined as the "Cutoff date, if FUPSRV1C not equal zero and death date greater than cutoff +15." However, there is no definition of FUPSRV1C. For efficacy analysis,
 - a. Define the FUPSRV1C variable.
 - b. For OS reporting in survivors, justify using the study cutoff date, rather than the actual last contact date.
- 2) For the study D2201 PEP, the median OS differs if one uses the "OS1_1N" variable from AIDENT.xpt or ATTE.xpt (median 630 days) or the "OS_2N" variable from the ISE AHCOMP.xpt file (median 672 days). For efficacy analysis, confirm that "OS1_1N" from AIDENT.xpt is an estimate, whereas "OS_2N" provides actual survival time measured from treatment initiation to either death date or last actual contact date and is thus more conservative.
- 3) In AHCOMP.xpt, the duration of follow up (variable FOLLOW), defined as [last contact date - (diagnosis date + 1)] is much longer than the overall survival variable OS_1N, which is likewise measured from (diagnosis date + 1). For efficacy analysis, explain how follow up duration can be longer than overall survival duration.

- 4) OS, as defined in the D2201 protocol and analysis plan, should be the time from treatment to death or last contact up to the data cut-off. In the proposed PI section 12, (b) (4)

(b) (4)

Please respond by COB Tuesday, January 3, 2017.

Kindly confirm receipt.

Thank you,

Kim

Kimberly Scott, RN, BSN, OCN®

CDR, U.S. Public Health Service

Regulatory Health Project Manager

Division of Hematology Products

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, Bldg. 22, Rm 3231

Silver Spring, MD 20993

Phone: 240-402-4560 | Kimberly.scott@fda.hhs.gov

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
01/05/2017

Scott, Kimberly

From: Scott, Kimberly
Sent: Tuesday, January 03, 2017 11:37 AM
To: Abraham, Abbey
Cc: Qiu, Yuhong (yuhong.qiu@novartis.com)
Subject: NDA 207997 Midostaurin Clin Pharm IR #5 DUE 2pm Wednesday, 1/4/17

Importance: High

Good morning Abbey,

The Agency has the following Clinical Pharmacology information request for NDA 207997, Midostaurin:

- 1. Reanalyze Tables HAQ33-6.1 (Dose interruptions due to adverse events) and HAQ33-6.2 (Dose reductions due to adverse events), originally reported in your December 1, 2016 response (Module 1.11.3, SDN 46), by estimating time to dose interruption (DI)/dose reduction (DR) using only patients who were involved in DI/DR, and duration from DI/DR to re-escalation to 200 mg daily dose using only patients who were involved in dose reescalation.*
- 2. How many patients in total and patients involved in PK sampling used CRF version 3 versus CRF versions 1 and 2, and how many patients who used CRF versions 1, 2 or 3 did not have start/end dates for administration of study drug (midostaurin or placebo) in Trial A2301 (RATIFY)? In your December 14, 2016 response (Module 1.11.3, SDN 53) to the Agency's information request, you mentioned that there are 3 versions of midostaurin exposures in A2301: CRF versions 1, 2, and 3.*

Please respond by 2:00PM (ET) tomorrow, Wednesday, January 4, 2017.

Kindly confirm receipt.

Thank you,

Kim

Kimberly Scott, RN, BSN, OCN®

CDR, U.S. Public Health Service

Regulatory Health Project Manager

Division of Hematology Products

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, Bldg. 22, Rm 3231

Silver Spring, MD 20993

Phone: 240-402-4560 | Kimberly.scott@fda.hhs.gov

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
01/03/2017

Scott, Kimberly

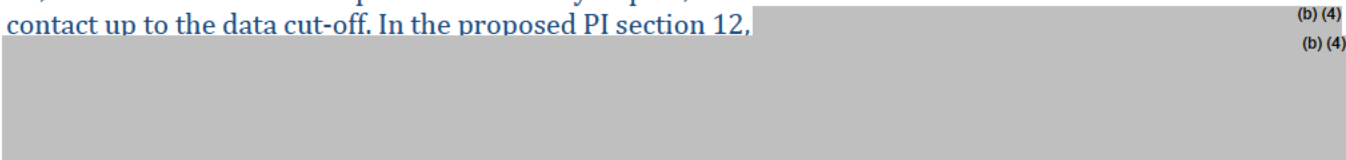
From: Scott, Kimberly
Sent: Tuesday, January 03, 2017 8:39 AM
To: Abraham, Abbey
Cc: Qiu, Yuhong (yuhong.qiu@novartis.com)
Subject: NDA 207997 Midostaurin, Original 1: Clinical #7- information requests -Due COB Tuesday, January 3, 2017

Importance: High

Good evening Abbey,

The Agency has the following Clinical information request for NDA 207997, Midostaurin:

Information requests

- 1) In the define file for study D2201, AIDENT.xpt, the variable OS1_E10 is defined as the "Cutoff date, if FUPSRV1C not equal zero and death date greater than cutoff +15." However, there is no definition of FUPSRV1C. For efficacy analysis,
 - a. Define the FUPSRV1C variable.
 - b. For OS reporting in survivors, justify using the study cutoff date, rather than the actual last contact date.
- 2) For the study D2201 PEP, the median OS differs if one uses the "OS1_1N" variable from AIDENT.xpt or ATTE.xpt (median 630 days) or the "OS_2N" variable from the ISE AHCOMP.xpt file (median 672 days). For efficacy analysis, confirm that "OS1_1N" from AIDENT.xpt is an estimate, whereas "OS_2N" provides actual survival time measured from treatment initiation to either death date or last actual contact date and is thus more conservative.
- 3) In AHCOMP.xpt, the duration of follow up (variable FOLLOW), defined as [last contact date - (diagnosis date + 1)] is much longer than the overall survival variable OS_1N, which is likewise measured from (diagnosis date + 1). For efficacy analysis, explain how follow up duration can be longer than overall survival duration.
- 4) OS, as defined in the D2201 protocol and analysis plan, should be the time from treatment to death or last contact up to the data cut-off. In the proposed PI section 12, (b) (4)
 (b) (4)

Please respond by COB Tuesday, January 3, 2017.

Kindly confirm receipt.

Thank you,

Kim

Kimberly Scott, RN, BSN, OCN®

CDR, U.S. Public Health Service

Regulatory Health Project Manager

Division of Hematology Products

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Rm 3231
Silver Spring, MD 20993
Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

APPEARS THIS WAY ON ORIGINAL

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
01/03/2017

Scott, Kimberly

From: Scott, Kimberly
Sent: Thursday, December 29, 2016 2:22 PM
To: Abraham, Abbey
Cc: Qiu, Yuhong (yuhong.qiu@novartis.com)
Subject: NDA 207997, Midostaurin Clinical 1 #7 Information request-response due January 2

Importance: High

Good afternoon Abbey,

The Agency has the following information request for NDA 207997, Midostaurin:

- 1) Reference is made to your response to the 12/14/16 information request regarding justification for the Warning and Precaution of pulmonary toxicity. The information requested stated to “include the subject IDs in your justification, and include data from all trials including AML.” In your response, no specific information or subject IDs were provided. Provide the subject IDs and corresponding summary of each pulmonary toxicity that justifies the proposed Warning and Precaution.
- 2) Reference is made to your response to the 12/14/16 information request regarding justification for the (b)(4). The information request stated to “*Include the subject IDs in your justification, and include data from all trials, including AML.*” However (b)(4)
[REDACTED]
- 3) Per the Day 120 ISS update, 3 additional patients on Study D2201 died: 2 due to disease progression and 1 due to multi organ failure. However, a new death narrative is identified only for the case of multiorgan failure (presumably D2201-0150-00014), no subject IDs or narratives are referenced for the two deaths attributed to disease progression, and the timing (on-treatment or off-treatment) of the latter two deaths is not mentioned.

For safety review, provide the unique subject ID and, if applicable, the corresponding Argus IDs for the 2 new deaths on Study D2201 that were attributed to disease progression, specify if they occurred on or off treatment, and provide narratives or link to the narratives.
- 4) Reference is made to your response to the 12/14/16 information request regarding infection and neutropenia, and the corresponding new dataset “AAEVINF1” .xpt. Although events occurring after the cut-off date of 1-December-2014 were included, the on-treatment death A2213-0003-00004 (sepsis complicated by multiorgan failure) was not, and the death narrative does not mention neutrophil count. For safety review, clarify if the sepsis was accompanied by neutropenia.

Please respond by COB, Monday, January 2, 2017.

Kindly confirm receipt.

Happy New Year,
Kim
Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager

Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Rm 3231
Silver Spring, MD 20993
Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

APPEARS THIS WAY ON ORIGINAL

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
12/29/2016

Scott, Kimberly

From: Scott, Kimberly
Sent: Thursday, December 29, 2016 2:32 PM
To: Abraham, Abbey
Cc: Qiu, Yuhong (yuhong.qiu@novartis.com)
Subject: NDA 207997 (midostaurin) Clin Pharm IR #4, response DUE COB 1/3/17

Importance: High

Good afternoon Abbey,

The Agency has the following clinical Pharmacology information request for NDA 207997, Midostaurin:

1. *Identify the study from which patient samples were used to cross check reproducibility of midostaurin and CGPG62221 in bioanalytical report DMPK-R1000620 and CGP52421 in bioanalytical report DMPK-R1300007-02.*
2. *What is the difference between Methods DMPK-R1400935 (which passed) and DMPK-R1000620 (which failed) for CGP54241?*
3. *How does Method DMPK-R1400935 compare with Methods DMPK-R130007 & DMPK-R9000346a for the measurement of CGP52421 in human plasma?*
4. *Provide bioanalytical reports for the measurement of midostaurin, CGPG62221 and CGP52421 in plasma for Studies A2104E1 and A2104E2. These reports are missing.*
5. *Explain the following discrepancy: We noticed that the PopPK for ASM includes CGP52421 data from A2213? The long-term stability was validated for 3.7 years for CGP52421, however majority of the samples in Study A2213 were stored for >3.7 years (study samples analyzed in July-Aug, 2011, while they were collected between 2005-2010). The bioanalytical report DMPK-PKC412A2213a-01 and SCP states that CGP52421 concentration data from study A2213 "should be considered as informative only".*
6. *Provide the complete SAS concentration dataset (*.xpt format) for Study A2104. The SAS concentration data (apkconc.xpt) for the study (Module 5.3.5.2 in SDN 2 and 17) do not appear to include all midostaurin, CGPG62221 and CGP52421 data. For example, the concentration data of selected samples from Study A2104 provided in bioanalytical report DMPK-R1000605 (Tables 11.1 to 11.3), and all the concentration data in bioanalytical reports RCPK412A2104a (Tables 8.1 & 8.2) and RCPK412A2104c (Table 8.1) are not included in the SAS dataset*

Please respond by COB on Tuesday, January 3, 2017.

Kindly confirm receipt.

Thank you,

Kim

Kimberly Scott, RN, BSN, OCN®

CDR, U.S. Public Health Service

Regulatory Health Project Manager

Division of Hematology Products

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, Bldg. 22, Rm 3231

Silver Spring, MD 20993

Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

APPEARS THIS WAY ON ORIGINAL

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
12/29/2016

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Thursday, December 22, 2016 1:50 PM
To: abbey.abraham@novartis.com
Cc: Qiu, Yuhong; Scott, Kimberly
Subject: NDA 207997/Clinical IR/Due December 23

Importance: High

Hello Abbey,

Please refer to NDA 207997. Per the request of the clinical review team please provide a response by **11 am (EST) Friday December 23, 2016** to the following information requests by email to **me and Kim Scott and officially submit to the NDA.**

Clinical Information Requests:

In the "ahcomp" .xpt file for the AdSM ISE, we note that:

- the overall survival censoring flag, OS_CS1F, has 37 missing values.
- the define file does not explain the sensitivity analysis that differentiates the variable "OS-CS1F" from the sensitivity survival censoring flag "OS_CS2F", which has no missing values.

To facilitate evaluation of efficacy,

- a. As all AdSM patients are evaluable for overall survival, explain the missing values for "OS_CS1F".
- b. Explain the sensitivity analysis and derivation for the "OS-CS2F" variable.

Please confirm receipt of this message via e-mail.

Regards,

Kris Kolibab, PhD
Senior Regulatory Health Project Manager
Division of Hematology Products
OHOP/OND/CDER/FDA

Phone: 240-402-0277

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

/s/

KRISTOPHER KOLIBAB
12/22/2016

Scott, Kimberly

From: Scott, Kimberly
Sent: Tuesday, December 20, 2016 4:37 PM
To: Abraham, Abbey
Cc: Qiu, Yuhong (yuhong.qiu@novartis.com); Scott, Kimberly; Kolibab, Kristopher
Subject: NDA 207997, Midostaurin: Clin Pharm DUE 12pm tomorrow

Importance: High

Good evening Abbey,

The Agency has the following clinical pharmacology information request for NDA 207997, Midostaurin:

Please further clarify if the PK sampling dates/times and individual dosing dates/times for midostaurin, and the start and stop dates for the administration of CYP3A4 modulators were accurately recorded for all clinical studies (besides A2301) included in your PopPK analyses, for both AML and AdSM.

Please respond by 12noon (ET) tomorrow, Dec 21, 2016.

Thank you,

Kim

Kimberly Scott, RN, BSN, OCN®

CDR, U.S. Public Health Service

Regulatory Health Project Manager

Division of Hematology Products

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, Bldg. 22, Rm 3231

Silver Spring, MD 20993

Phone: 240-402-4560 | Kimberly.scott@fda.hhs.gov

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
05/01/2017

Scott, Kimberly

From: Scott, Kimberly
Sent: Friday, December 16, 2016 9:39 AM
To: Abraham, Abbey
Cc: Qiu, Yuhong (yuhong.qiu@novartis.com)
Subject: NDA 207997, Midostaurin: Mid-Cycle Communication
Attachments: NDA 207997 Mid Cycle Communication.pdf

Importance: High

Good morning Abbey,

Please see the attached Mid-Cycle Communication from the teleconference with the Agency on December 13, 2016 for NDA 207997, Midostaurin.

Kindly confirm receipt.

Thank you,

Kim

Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Rm 3231
Silver Spring, MD 20993
Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

7 Pages Have Been Withheld As A Duplicate Copy Of The "Mid-Cycle Communication" dated December 13, 2016 Which Is Located In This Administrative Correspondance Section Of This NDA Approval Package.

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
12/16/2016

Scott, Kimberly

From: Scott, Kimberly
Sent: Wednesday, December 14, 2016 9:38 PM
To: Abraham, Abbey
Cc: Qiu, Yuhong (yuhong.qiu@novartis.com)
Subject: NDA 207997, Midostaurin: Clinical #1 IR DUE COB, 12/27/16

Importance: High

Good evening Abbey,

The Agency is requesting information for NDA 207997, Midostaurin by COB, Tuesday, December 27, 2016.

1. Although you concluded that treatment with midostaurin was not associated with QT prolongation, QT prolongation was reported commonly in patients with AML and AdSM, including as an adverse event, and was among the reasons for dose modification or treatment discontinuation. To enable review of safety, for each patient on Study D2201, A2213, and A2301 who had EKG QT prolongation reported as an adverse event, reason for dose modification (interruption or reduction), or reason for treatment discontinuation, submit a table or .xpt file with one row per each occurrence (AE, dose modification, treatment discontinuation) that includes at minimum:

- **Unique subject ID**
- **Study**
- **Treatment start date**
- **QTcF at baseline**
- **Embedded or cross-referenced baseline EKG**
- **Date of QT prolongation associated with the AE/treatment modification/discontinuation**
- **AE flag**
- **QTcF interval at time of AE/treatment modification/treatment discontinuation**
- **Embedded or cross-referenced EKG with QT prolongation**
- **Grade of QT prolongation**
- **Concomitant medications at the time QT prolongation was noted that have the potential for QT prolongation; if none, so state**
- **Other potential contributors to QT prolongation (e.g., hypocalcemia, hypomagnesemia); if none, so state**
- **Actions taken regarding study drug**

2. In patients with AdSM, gastrointestinal events were a leading cause of adverse reactions and dose modifications. For patients in study D2201 and A2213, to inform safety and supportive care, characterize the common and severe AEs, including nausea, vomiting, diarrhea, and grade ≥ 3 infection, with regard to incidence, time to onset, duration and mitigation strategy.

3. (b) (4) In AdSM trials, two grade 5 cases of CHF occurred: one was in the setting of severe valvular dysfunction and pneumonia (D2201-0150-00023) and one was right-sided CHF (D2201-0101-00003). Other cardiac failure AEs (grouped term) included three grade 2 events and two grade 3 events. Include the subject IDs in your justification, and include data from all trials, including AML.

4. Based on review in progress and your analysis of adverse events of special interest in the ISS, safety signals of pneumonitis are not apparent in the AdSM trials. To inform labeling,
 - a. Explain why pulmonary toxicity is a proposed warning and precaution. Include the subject IDs in your justification, and include data from all trials including AML.
 - b. Explain the “grade 4 lung disorder” accompanied by cardiac arrest in subject D2201-0200-00005.

5. (b) (4) We note that:

- SAE and death narratives involving grade ≥ 3 infection do not consistently mention whether the patient had grade ≥ 3 neutropenia.
- Several deaths attributed in the ISS and CSRs to PD or other non-infectious causes had infection as a leading cause of death:
 - 4 from infection with untreated PD (D2201-0180-00001, D2201-0152-00001, D2201 0180_00007, and in ARGUS, D2201 0180_00007, who died not of progressive lung malignancy, but of pneumonia in setting of progressive SM)
 - 1 from infection + hepatic failure from suspected (untreated) PD (D2201-0515-00008)
 - 2 cardiac deaths that were accompanied by grade ≥ 3 pneumonia (D2201-0150-00023, D2201-0506-00010)).

To inform safety review and labeling, for each patient on Study D2201 and A2213 who had an infection-related SAE or grade ≥ 3 infection, submit a table or .xpt file with one row per each occurrence that includes the following minimum information. Include the 7 deaths noted above and the additional deaths reported in ARGUS after the data lock:

- **Unique subject ID**
- **Study**
- **Treatment start date**
- **Date of infection-related SAE or grade ≥ 3 infection**
- **Timing of infection, in days from treatment start**
- **Type of infection (e.g. bacterial sepsis, pneumonia)**
- **Grade of infection**
- **Grade of neutropenia at time infection occurred**

Please confirm receipt of this email.

Kind regards,

Kim

Kimberly Scott, RN, BSN, OCN®

CDR, U.S. Public Health Service

Regulatory Health Project Manager

Division of Hematology Products

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, Bldg. 22, Rm 3231

Silver Spring, MD 20993

Phone: 240-402-4560 | Kimberly.scott@fda.hhs.gov

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
12/14/2016



NDA 207997

MID-CYCLE COMMUNICATION

Novartis Pharmaceuticals Corporation
Attention: Abbey Abraham, PharmD
Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Mr. Abraham:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for RYDAPT (midostaurin) capsules 25 mg.

We also refer to the teleconference between representatives of your firm and the FDA on December 13, 2016. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, please call Kimberly Scott, Regulatory Project Manager at (240) 402-4560.

Sincerely,

{See appended electronic signature page}

Donna Przepiorka, MD, PhD
Cross Discipline Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: Tuesday, December 13, 2016, 2:00 – 3:00 PM ET

Application Number: NDA 207997

Product Name: Midostaurin

Indication:

Original 1: Treatment of adult patients with advanced systemic mastocytosis.

Original 2: 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.

Applicant Name: Novartis Pharmaceuticals Corporation

Meeting Chair: Donna Przepiorka, MD, PhD

Meeting Recorder: Kimberly Scott, BSN, RN, OCN®

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP)/Division of Hematology Products

Ann Farrell, MD, Division Director
Albert B. Deisseroth, MD, PhD, Clinical Team Leader
Donna Przepiorka, MD, PhD, Acting Clinical Team Leader
Yvette Kasamon, MD, Medical Officer
Ashley Ward, MD, Medical Officer
Theresa Carioti, MPH, Chief, Project Management Staff
Kimberly Scott, BSN, RN, OCN®, Regulatory Health Project Manager
Kelly Miller, PharmD, Regulatory Project Manager
Wan Lee, PharmD, Regulatory Project Manager
Diane Leaman, BS, Safety Regulatory Project Manager

OHOP/Division of Hematology, Oncology, Toxicology (DHOT)

Christopher Sheth, PhD, Supervisory Pharmacologist/Toxicologist
Natalie Simpson, PhD, Pharmacologist/Toxicologist Reviewer

Office of Biostatistics, Division of Biometrics V

Lei Nie, PhD, Statistics Team Leader
Chia-Wen Ko, PhD, Statistics Reviewer

Office of Translational Sciences (OTS)/Office of Clinical Pharmacology (OCP)/Division of Clinical Pharmacology V

Stacy Shord, PharmD, Acting, Team Lead
Sriram Subramaniam, Pharm D, Clinical Pharmacology Reviewer

Office of Surveillance and Epidemiology (OSE), Office of Medication Error Prevention and Risk Management (OMEPRM), Division of Medication Error Prevention and Analysis (DMEPA)

Hina Mehta, PharmD, Team Lead
Leeza Rahimi, PharmD, Safety Evaluator

Division of Molecular Genetics and Pathology/Office of In Vitro Diagnostics and Radiological Health

Allen Williams, PhD, Scientific Reviewer

Office of Pharmaceutical Quality/Office of New Drug Product/Division of New Drug Product I

Anamitro Banerjee, PhD, Acting Branch Chief
Sherita McLamore-Hines, PhD, Acting Quality Assessment Lead
Nina Ni, PhD, CMC Reviewer

Office of Pharmaceutical Quality/Office of Process and Facilities/Division of Process Assessment I

Bogdan Kurtyka, PhD, Acting Quality Assessment Lead

APPLICANT ATTENDEES

Renaud Capdeville, MD, Global Program Head
Lisa Rojkjaer, MD, Global Clinical Program Head
Iulian Alecu, MD, Brand Safety Leader,
Taoufik Ouatas, PhD, Site Head, Clinical Pharmacology
Alice Huntsman Labeled, PhD, Program Statistician, Biostatistics
Kannan Natarajan, PhD, Global Head, Biometrics
Shanthi Ganeshan, PhD, North America Region Head, Drug Regulatory Affair
Yuhong Qiu, PhD, Global Program Regulatory Director, Drug Regulatory Affairs
Abbey Abraham, PharmD, Global Program Regulatory Manager, Drug Regulatory Affairs
Gaetano Bonifacio, MD, Sr. Medical Director, US Oncology
Peggy Carter, PhD, US Head, CDx Diagnostic Regulatory

1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response,

and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

2.0 SIGNIFICANT ISSUES

Clinical (Original 1):

1. There is insufficient justification for the 100 mg BID starting dose of midostaurin for treatment of advanced systemic mastocytosis. Based on the pharmacokinetic data provided, by 28 days of midostaurin dosed at 100 mg BID versus 50 mg BID, steady-state levels are notably quite similar. Further, over 50% of patients with advanced systemic mastocytosis required dose modification due to toxicity. Given that steady-state levels of 100 mg BID were similar to those with 50 mg BID, that there were frequent dose modifications due to toxicity for patients who started with 100 mg BID, and that the active metabolite CPG6525421 has a very long $t_{1/2\beta}$ (>400 hours), the proposed recommended starting dose of 100 mg BID may not be appropriate.

Clinical (Original 2):

2. You have evidence of lack of efficacy of midostaurin as monotherapy for treatment of relapsed or refractory FLT3-mutated AML. This may warrant a limitation of use statement in the prescribing information.
3. You have evidence for lack of efficacy of midostaurin as monotherapy for treatment of FLT3-mutated AML, and no data from a proper randomized maintenance study (b) (4)
 (b) (4)
4. You state that midostaurin is a multikinase inhibitor, with activity including inhibition of other kinases known to be active in AML, but you are pursuing an indication for treatment of patients with FLT3-mutated AML specifically. Since AML cells may have more than one kinase mutation, and you have not provided subgroup analyses of efficacy outcomes in Study A2301 (RATIFY) by genetic mutation at diagnosis, it is not clear that you have targeted the correct AML molecular subgroup for your indication.
5.  (b) (4)
We do not agree with this approach. For patients who did not have a CR documented by Day 60, the date of treatment failure should be assigned as Day 1.

Clinical Pharmacology:

6. The tolerability of midostaurin at a dose of 50 mg twice daily when coadministered with a strong cytochrome P450 3A4 inhibitor cannot be assessed with the available data collected from patients with AML. (b) (4)

We do not agree with this approach, as midostaurin shows time-dependent pharmacokinetics with the maximal concentration observed on C1D15 (i.e., 8 days after consecutive dosing) and steady-state achieved by 28 days after consecutive dosing. Additionally, strong CYP3A4 inhibitors may only be given for a portion of each treatment phase (e.g., induction, consolidation). The start and stop dates of the adverse events were also not recorded. The available data from the dedicated drug interaction studies suggests that midostaurin exposure increases 10-fold following a single dose and about 2-fold following multiple doses, suggesting that strong inhibitors may adversely affect the tolerability of midostaurin.

3.0 INFORMATION REQUESTS

Clinical (Original 2):

1. Provide post-hoc analyses of OS and EFS for A2301 in:
 - a. the subset of subjects who did not undergo transplantation
 - b. the subset of subjects who underwent transplantation at any time (not just in CR1)
 - c. all subjects, censored at time of transplantation (not just transplantation in CR1)
2. Provide a post-hoc analysis of EFS for A2301 from the start of therapy using Day 1 as the date of treatment failure for subjects who did not achieve a CR by Day 60.

Please provide a response to #1 and #2 by close of business Wednesday, December 21, 2016.

Clinical Pharmacology:

3. You provided responses to information requests on two occasions; however, the provided responses are unclear in regards to the documentation of the timing of the pharmacokinetic samples, adverse events and dosing of strong CYP3A inhibitors, and the inclusion of the relevant timing of the pharmacokinetic samples in the analyses of drug interactions and adverse reactions. A teleconference occurred on December 13, 2016 to address these remaining concerns. We provided a document listing the specific queries before the scheduled teleconference. You stated you would provide detailed written responses to the queries by 12 noon on December 14, 2016.

Product Quality:

4. We remind your response to our CMC Information Request sent December 13, 2016 is due December 16, 2016, and your response to our CMC Information Request sent December 8, 2016 is due January 6, 2017.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT –

There are no additional major safety concerns identified at this time, and there is currently no need for REMS.

5.0 ADVISORY COMMITTEE MEETING

There are no plans for an AC meeting at this time.

6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

The Late-Cycle meeting with the Applicant is scheduled for January 10, 2017, 2:00 – 3:00 PM. We intend to send the briefing package to you approximately 2 days in advance of the meeting. FDA comments on proposed labeling will be sent to Novartis by February 14, 2017. The PDUVA V goal date is April 28, 2017.

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

/s/

DONNA PRZEPIORKA
12/16/2016

MEMORANDUM OF TELECONFERENCE

Teleconference Date: December 13, 2016

Application Number: NDA 207997

Product Name: **Midostaurin**

Applicant Name: **Novartis Pharmaceuticals Corporation**

Subject: Clinical Pharmacology PK data

FDA Participants :

- Donna Przepiorka, MD, PhD Acting, Clinical Team Leader
- Theresa Carioti, MPH, Chief, CPMS
- Kimberly Scott, RN, BSN, OCN®. Regulatory Project Manager
- Stacy Shord, PharmD
- Sriram Submariam, PharmD
- Lain Ma, PharmD
- Nitin Mehrotra, PharmD

Applicant Participants

Renaud Capdeville, Vice President, Global Program Head
Taoufik Ouatas, Site Head, Oncology Clinical Pharmacology
Vincent Duva, Senior Fellow, Oncology Clinical Pharmacology
Iulian Alecu, Senior Director, Integrated Medical Safety
Allison Florance, Executive Director, Biostatistics
Alice Huntsman-Labed, Director, Biostatistics
Karen Sinclair, Senior Statistician Clinical Pharmacology Biostatistics
Handan He, Director, Nonclinical Drug Metabolism and Pharmacokinetics
Imad Hanna, Director, Nonclinical Drug Metabolism and Pharmacokinetics
Helen Gu, Senior Investigator II, Nonclinical Drug Metabolism and Pharmacokinetics
Shanthi Ganeshan, Vice President, North America Region Head, Drug Regulatory Affairs
Yuhong Qiu, Senior Director, Drug Regulatory Affairs
Abbey Abraham, Director, Drug Regulatory Affairs

1.0 BACKGROUND:

Clinical Pharmacology requested a teleconference with Novartis to discuss the specific information in regards to Midostaurin PK data and dosing/times of CYP3A modulators in trial A2301.

2.0 DISCUSSION:

Agenda for the 12/13/2016 Teleconference

On October 28, 2016, we requested information (Request 1) on the time of dosing of strong CYP3A modulators and pharmacokinetic (PK) sampling in Trial A2301. Following review of your October 31, 2016 response, we requested further clarification on the dosing of strong CYP3A modulators relative to the collection of PK samples on November 23, 2016. We find that your response dated November 28, 2016 regarding the time of the PK sampling and dosing of strong CYP3A inhibitors remains unclear. Consequently, we request that you resolve the following questions during the scheduled teleconference on December 13, 2016:

- 1) Were the dates and times of midostaurin doses recorded in Trial A2301?

Applicants Response: No.

- 2) Were the dates and times of PK samples recorded in Trial A2301? If NOT, what information was recorded for each PK sample collection and how was the date and time of each PK sample collection inferred (i.e., how was a PK sample attributed to a specific cycle and to a specific sampling time in the cycle) for the various PK assessments (e.g., PK characterization, evaluation of extrinsic or intrinsic factors on exposure and safety)?
 - a. In your November 28, 2016 response you state “nominal date and time of PK samples was assigned to the same PK collection number”. What does the statement mean? Were the PK sampling dates and times based on their scheduled dates and times?
- 3) In your response October 31, 2016, you stated that “*the exact start and stop dates were not collected for the administration of CYP3A4 modulators*”. However, in your November 28, 2016 response you stated “*the dosing information of the strong CYP3A4 inhibitors was provided at the cycle level*” and “*was identified according to its start and/or end dates*”.
 - a. Were the start and end dates recorded for the modulators?
 - b. How were the start and end dates inferred for the assessment of the effect of a modulator on safety, activity and exposure, if start and end dates of a CYP3A4 modulator were NOT recorded?
 - c. How would the effect of a CYP3A modulator be assessed on safety and exposure for each phase (i.e., induction, consolidation or maintenance) for a specific patient if the only the start date was known? For example, if only start date of a strong CYP3A inhibitor is available for a patient in the Consolidation phase, and it precedes C1D8 PK sampling, how would the other PK sampling times (i.e., C1D21, C4D8, CD21) in the phase for that patient be treated with regards to the effect of the CYP3A modulator (would they be considered as “Yes” or “No”)?
- 4) In your October 31, 2016, you stated that the exact start and stop dates were not collected for adverse events. How were the dates and times of adverse events inferred?

Novartis stated they cannot provide the start/end dates for the Adverse Events. In addition, they clarified they only have the data covering the period of which the events occurred.

3.0 ACTION ITEMS:

Novartis agreed to provide the Agency a response to the requested PK data for Question #3 by 12:00noon, Wednesday, December 14, 2016.

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
12/13/2016

Scott, Kimberly

From: Scott, Kimberly
Sent: Monday, December 12, 2016 11:39 AM
To: Abraham, Abbey
Cc: Qiu, Yuhong (yuhong.qiu@novartis.com)
Subject: NDA 207997, Midostaurin: Additional Teleconference- Clinical Pharm

Importance: High

Good morning Abbey,

The Clinical Pharmacology reviewers would like to request a teleconference with Novartis prior to the Mid-Cycle Meeting. The Agency is requesting a teleconference for tomorrow, December 13, 2016 from 11:00am-11:30am (ET) with the Agency's clinical pharmacology reviewers and Clinical Team Leader. Please provide a teleconference number for the meeting.

Please acknowledge receipt of this email.

Kind regards,

Kim

Kimberly Scott, RN, BSN, OCN®

CDR, U.S. Public Health Service

Regulatory Health Project Manager

Division of Hematology Products

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, Bldg. 22, Rm 3231

Silver Spring, MD 20993

Phone: 240-402-4560 | Kimberly.scott@fda.hhs.gov

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
12/12/2016

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Friday, December 02, 2016 11:29 AM
To: abbey.abraham@novartis.com
Cc: 'yuhong.qiu@novartis.com'; Scott, Kimberly
Subject: NDA 207997/Clinical IR/Due December 12

Importance: High

Hello Abbey,

Please refer to NDA 207997. Per the request of the clinical review team please provide a response by **2pm (EST) Monday December 12, 2016** to the following information requests by email to me and Kim Scott and officially submit to the NDA.

Clinical Information Requests:

1. On evaluation of efficacy in AdSM, we have noted the following:

- a. There are no derived .xpt files that consolidate date of first objective response and date of best response per modified Valent or IWG criteria.
- b. In tables summarizing the number of relapses to prior SM therapy (SCE Table 14.1-4.4 and corresponding tables in Section 14.1 of the D2201 and A2213 CSRs),
 - The breakdown of number of prior relapses to SM therapy does not account for all patients, and the corresponding percentages are erroneous. For the D2201 PEP (N=89), for example, " (b) (4)
 - These data also appear inconsistent with the number of prior SM regimens. For example, in A2213, " (b) (4)

To facilitate review of efficacy, please submit an .xpt file that provides the following information:

<i>Variable</i>	<i>Data element</i>	<i>Comment</i>
Unique subject ID (STYS1DIA)		
Study Unique subject ID ((STY1A)		
Date of first objective response (MR or PR), per modified Valent criteria (SSC)		• For D2201 PEP
Date of best overall response (MR or PR), modified Valent (SSC)		• For D2201 PEP
Date of last continued response, modified Valent (SSC)		• For D2201 PEP
Date of first objective response (CR or PR), per IWG criteria (12 week confirmation)		• For D2201 FAS
Date of best response, IWG		• For D2201 FAS
Date of last continued response, IWG		• For D2201 FAS
Number of relapses or progressions to prior SM therapy	• 0, 1, 2, etc • Missing	• For D2201 and A2213 FAS • % should sum to 100

2. [REDACTED] (b) (4) D2201
CSR Table 14.2-1.9.1, summarizing best overall response (modified Valent) according to WHO subtypes, is noted. To facilitate confirmation of efficacy,
- a. For the D2201 PEP, submit a table [REDACTED] (b) (4) that summarizes response duration (median, 95% CI) per SSC, according to the centrally confirmed WHO diagnosis (ARESPDIS.xpt variable "DISSSC"): ASM, SM-AHN, MCL, and all confirmed SM subtypes (N=89). Please include the duration of follow up for response (median, range), measured from the date of first objective response.
 - b. For the D2201 FAS, submit a table, [REDACTED] (b) (4), that summarizes best overall response and response duration (median, 95% CI) per IWG criteria (12 week confirmation), according to centrally confirmed WHO diagnosis: ASM, SM-AHN, MCL, and all confirmed SM subtypes (109 non-missing). Include the duration of follow up for response (median, range), measured from the date of first objective response.

3. [REDACTED] (b) (4)
[REDACTED] (b) (4)
[REDACTED] (b) (4) please explain this discrepancy [REDACTED] (b) (4)
[REDACTED] (b) (4) ?

Please confirm receipt of this message via e-mail.

Regards,

Kris Kolibab, PhD
Senior Regulatory Health Project Manager
Division of Hematology Products
OHOP/OND/CDER/FDA

Phone: 240-402-0277

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

/s/

KRISTOPHER KOLIBAB
12/02/2016



NDA 207997

INFORMATION REQUEST

Novartis Pharmaceuticals Corporation
Attention: Elizabeth Purdy
Senior Manager, Regulatory Affairs Global Drug Development
One Health Plaza; Bldg. 339-Room 1256
East Hanover, NJ 07936-1080

Dear Ms. Purdy:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rydapt (Midostaurin) Capsule 25mg.

We also refer to your August 29, 2016 submission, containing your new drug application.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Drug Product:

1. There are two components in your proposed drug product: one is the drug product formulation, the other is the soft capsule shell. In your provided drug product composition table, you have not separated ingredients used in your drug product formulation from the ingredients used in capsule shell. Please provide the drug product composition table which separates the formulation composition and soft capsule shell composition along with its corresponding theoretical weight as well as the total theoretical capsule weight which includes both components.
2. Provide risk assessment and controls for elemental impurities for drug product. Elemental impurities need to be assessed and if necessary controlled as per ICH Q3 (D) for your drug product.
3. Provide a representative copy of the manufacture's COA for your selected primary packaging component of blister for the drug product capsules.

4. Provide statement of compliance to pertinent CFR regulations (b) (4)
for all components used in the blister packaging.

5. On page 11 of your provided pharmaceutical development, you indicated that: (b)(4)

(c)(4)
[Redacted]

Please clarify.

6. [Redacted] (b)(4)

Alternatively, provide justification for lack of data.

7. [Redacted] (b)(4)

8.

[Redacted]

(b)(4) Provide data to justify or revise the acceptance criterion accordingly.

If you have any questions, please contact me, at (240) 402-6153. Please respond by COB
December 9, 2016.

Sincerely,

Rabiya Laiq, Pharm.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Rabiya Laiq -S

Digitally signed by Rabiya Laiq -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Rabiya Laiq -S,
0.9.2342.19200300.100.1.1-2001555007
Date: 2016.12.01 15:59:48 -05'00'



NDA 207997

INFORMATION REQUEST

Novartis Pharmaceuticals Corporation
Attention: Elizabeth Purdy
Senior Manager, Regulatory Affairs Global Drug Development
One Health Plaza; Bldg. 339-Room 1256
East Hanover, NJ 07936-1080

Dear Ms. Purdy:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rydapt (Midostaurin) Capsule 25mg.

We also refer to your August 29, 2016 submission, containing your new drug application.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Drug Substance:

[Redacted content]

(b)(4)

If you have any questions, please contact me, at (240) 402-6153. Please respond ASAP.

Sincerely,

Rabiya Laiq, Pharm.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Rabiya Laiq -

S

Digitally signed by Rabiya Laiq -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Rabiya Laiq -S,
0.9.2342.19200300.100.1.1=2001555007
Date: 2016.11.29 18:33:51 -05'00'

Scott, Kimberly

From: Scott, Kimberly
Sent: Wednesday, November 23, 2016 3:55 PM
To: Abraham, Abbey
Cc: Qiu, Yuhong (yuhong.qiu@novartis.com); Scott, Kimberly
Subject: NDA 207997 Midostaurin: Clin Pharm#2 IR DUE 9AM on Monday, 11/28

Importance: High

Good afternoon Abbey,

The Agency has the following Clinical Pharmacology requested for NDA 207997, Midostaurin:

1. In Section 3.8.3 of the Summary of Clinical Pharmacology (Module 2.7.2, SDN 17) you stated that “For study A2301, since specific PK sampling dates were not available, the criteria for identifying patients who received strong CYP3A4 inhibitors were whether they received the medication at any time (within the cycle of interest) before the end of midostaurin treatment.” Also, your response dated October 31, 2016 (SDN 25, Module 1.11.2) states that “For study A2301, the exact start and stop dates were not collected for the administration of CYP3A4 modulators, for adverse events, or the exact time and date of the PK sample collection. For the analysis in Section 3.8.3 of Module 2.7.2, we considered only a cycle level administration of strong CYP3A4 inhibitor to match the PK sample collected within the same cycle.” Also, Section 11.3.2.1 of the clinical study report for A2301 (Module 5.3.5.1, SDN 3) states that “some *pre-dose* time points may actually correspond to post-dose.”
 - a. Explain how the pharmacokinetic (PK) sample collection dates and times were inferred in Trial A2301 to permit assessment of the effect of CYP3A modulators, as well as other covariates (such as organ impairment) on PK parameters.
 - b. Explain how the effect of strong CYP3A inhibitors on trough concentrations at the various visits within treatment cycles, reported in Tables 5-2a, 5-6a, and 5.8a (Post-text Tables and Figures for Dose-Exposure Analyses, Module 5.3.3.2, SDN 17), were derived for Trial A2301, as the sampling times for the PK samples do not appear to be available.
2. In Post-text Tables and Figures for Dose-Exposure Analyses (Module 5.3.3.2, SDN 17):
 - a. Clarify whether the category identified as “None” in Tables 5-2a, 5-6a, and 5.8a refers to patients who did not take CYP3A modulators in Trial A2301.
 - b. Provide the summary of CGP62221 trough concentrations for the effect of strong CYP3A inhibitors at each visit in Trial A2301. Table 5-6a only provides the summary of the metabolite to parent ratio of CGP62221 trough concentrations at each visit in Trial A2301.
3. Identify patients grouped in the “No Strong CYP3A Inhibitor” category (Table 3-12 of Section 3.8.3 in SCP) who were concomitantly administered mild or moderate CYP3A inhibitors, CYP3A inducers, or no CYP3A modulators in Trial A2301 (RATIFY: AML).
 - a. Reanalyze Table 3-12 (Section 3.8.3 in SCP) by comparing patients who took strong CYP3A inhibitors against patients who did not take CYP3A modulators.

- b. Compare the C_{min} ratio for patients who took moderate and weak CYP3A inhibitors independently against patients who did not take CYP3A modulators.
 - c. Provide a tabular summary of the safety (including grade 3 or 4 adverse events, serious adverse events, adverse events leading to treatment discontinuation, adverse events leading to dose modification and deaths) for patients taking strong, moderate or weak CYP3A inhibitors.
4. Provide a tabular summary of efficacy in patients with mild hepatic impairment, moderate hepatic impairment, and normal hepatic function in advanced SM population. Also, provide a list of AdSM patients (with IDs) with mild, moderate and severe hepatic impairment, and normal hepatic function.
5. Provide a tabular summary of the safety (including grade 3 or 4 adverse events, serious adverse events, adverse events leading to treatment discontinuation, adverse events leading to dose modification and deaths) and efficacy in patients with mild, moderate and severe hepatic impairment and normal hepatic function in AML population. Also, provide a list of AML patients (with IDs) with mild, moderate and severe hepatic impairment, and normal hepatic function.
6. Provide a tabular summary of patients with advanced SM who required a dose modification including the adverse events leading to the dose modification, the time to first dose interruption, the duration of the dose interruption, the alternative dose, and the time to re-escalate the dose to 100 mg BID, and subsequent dose modifications or discontinuations following re-escalation to 100 mg BID. Provide the summary of these events for different adverse event categories, such as treatment emergent adverse events, serious adverse events and grade 3 or 4 events, if feasible.
7. Identify the analytical methods and hyperlink the method validation and bioanalytical study reports for measurement of midostaurin, CGP62221 and CGP54241 in the clinical studies for AML and AdSM populations.

Please respond by **9:00AM (ET) on Monday, November 28, 2016.**

Kindly confirm receipt.

Happy Thanksgiving!

Kim

Kimberly Scott, RN, BSN, OCN®

CDR, U.S. Public Health Service

Regulatory Health Project Manager

Division of Hematology Products

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, Bldg. 22, Rm 3231

Silver Spring, MD 20993

Phone: 240-402-4560 | Kimberly.scott@fda.hhs.gov

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
11/23/2016



NDA 207997

INFORMATION REQUEST

Novartis Pharmaceuticals Corporation
Attention: Elizabeth Purdy
Senior Manager, Regulatory Affairs Global Drug Development
One Health Plaza; Bldg. 339-Room 1256
East Hanover, NJ 07936-1080

Dear Ms. Purdy:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rydapt (Midostaurin) Capsule 25mg.

We also refer to your August 29, 2016 submission, containing your new drug application.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Drug Substance:



(b)(4)



If you have any questions, please contact me, at (240) 402-6153. Please respond by December 6, 2016.

Sincerely,

Rabiya Laiq, Pharm.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Rabiya Laiq -S

Digitally signed by Rabiya Laiq -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Rabiya Laiq -S,
0.9.2342.19200300.100.1.1=2001555007
Date: 2016.11.22 16:06:56 -05'00'

Scott, Kimberly

From: Scott, Kimberly
Sent: Monday, November 21, 2016 9:05 AM
To: Abraham, Abbey
Cc: Qiu, Yuhong (yuhong.qiu@novartis.com)
Subject: NDA 207997, Midostaurin Clinical IR #5 DUE 11am, Tuesday, 11/22

Importance: High

Good morning Abbey,

Please see the following information request from the clinical team for NDA 207997, Midostaurin:

1. In the proposed PI, Section 6.1 Table 3, multiple common adverse events ([redacted] (b) (4)) are not listed [redacted] (b) (4) .
[redacted] Please provide your rationale for excluding these adverse events from Table 3.
2. Based on the AAEV dataset from Study A2301, The NA+NNA safety population appears to include 345 patients who received midostaurin and 335 who received placebo (using the TRTC variable, since according to Section 9.7.2 of the CSR, the two patients randomized to placebo who actually got midostaurin were counted in the midostaurin group for all safety analyses). Please explain why, in Table 3 of the proposed PI, the denominator for the RYDAPT+chemo arm of the Grade 3/4 AE column has n= [redacted] (b) (4) instead of n=345.
3. [redacted] (b) (4) Table 1, below, shows FDA analysis of common ARs (based on aev.xpt for the AdSM pool) [redacted] (b) (4) .
[redacted] (b) (4)

Table 1: Common (≥10%) AR's in AdSM safety population [redacted] (b) (4) (FDA analysis)

System Organ Class and Ungrouped PT	AdSM pool (N = 142)		Any grade		Grade 3-4	
	n	%	n	%	n	%
Gastrointestinal disorders						
Abdominal pain	37	26%	5	4%		
Ascites ^a	14	10%	4	3%		
Musculoskeletal and connective tissue disorders						
Arthralgia	27	19%	3	2%		
Back pain	27	19%	2	1%		

Table 1: Common (≥10%) AR's in AdSM safety population (b) (4)

(FDA analysis)

AdSM pool (N = 142) System Organ Class and Ungrouped PT	Any grade		Grade 3-4	
	n	%	n	%
Musculoskeletal pain	18	13%	1	< 1%
Infection and infestations				
Nasopharyngitis	19	13%	0	0%
Investigations				
Electrocardiogram QT prolonged	15	11%	1	< 1%
Psychiatric disorders				
Insomnia	15	11%	0	0%
Depression	14	10%	0	0%
Skin and Subcutaneous Disorders				
Pruritus	29	20%	4	3%

Represents ARs regardless of causality.

(b) (4)

(b) (4)

^a 9.9% any grade, rounds to 10%

4. In the alrs2.xpt files for the AdSM ISS pool, after selecting for Phase 1C=2 in order to evaluate post-treatment laboratory results, thousands of rows still have a baseline flag (BLFLG1C=Y). To inform safety analysis,
 - a. Explain why baseline values remain after selecting for the treatment phase (Phase 1C=2).
 - b. Clarify how to isolate the laboratory values used to populate the pre-treatment baseline value (BLVAL_1A) and baseline CTC grade (B_CTC_1C).

5. For alrs3.xpt for study A2213, explain why the baseline mast cell value (PARNAM1C=MST, BLFLG_1C = B) is 0 for all patients, both for “BLVAL_1N” and “LABRSL1A”, as shown in the screenshot. To inform response assessment, explain what derived .xpt file and what variables contain the selected baseline mast cell percentage in the bone marrow for study A2213.

6. In AIDENT.xpt for the AdSM pool, explain why the hepatic impairment category (HEPFG1N) is missing for 3 patients from study D2201:

CPKC412D2201_0150_00018

CPKC412D2201_0150_00021

CPKC412D2201_0151_00004

Please respond by 11AM (ET) tomorrow, Tuesday, November 22, 2016.

Kindly confirm receipt.

Thank you,

Kim

Kimberly Scott, RN, BSN, OCN®

CDR, U.S. Public Health Service

Regulatory Health Project Manager

Division of Hematology Products

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, Bldg. 22, Rm 3231

Silver Spring, MD 20993

Phone: 240-402-4560 | Kimberly.scott@fda.hhs.gov

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
11/22/2016

Scott, Kimberly

From: Scott, Kimberly
Sent: Tuesday, November 15, 2016 1:18 PM
To: Abraham, Abbey
Cc: Qiu, Yuhong (yuhong.qiu@novartis.com)
Subject: NDA 207997 midostaurin: Nonclinical IR DUE COB Monday, November 21st

Importance: High

Good afternoon Abbey,

The non-clinical reviewers have the following information requests for NDA 207997, Midostaurin:

Nonclinical IR:

- In reference to your rat EFD study (Study No. 936241) and rabbit EFD study (Study No. 936243).

Rat EFD Study:

- Historical control data for the following visceral malformations/variations that have greater incidence in high dose (HD) rat litters and fetuses compared to concurrent controls: thyroid reduced, lateral ventricles dilated, and ovary and uterus positioned low in abdomen uterine horn adhered together.
- Historical control data for the following skeletal variations that have greater incidence in HD rat litters and fetuses compared to concurrent controls: occipital incompletely ossified, occipital bifid, widened anterior fontanelle, vertebral arch incompletely ossified, vertebral arch not ossified, centra not ossified, centra - bifid (including asymmetrically), sternebra incompletely ossified, sternebra dumb-bell (including asymmetrically), metatarsal incompletely ossified, and metatarsal not ossified.
- Mean late and early resorption data.

Rabbit EFD Study:

- Historical control data for the following external variations that have greater incidence in HD rabbits compared to concurrent controls: pale placenta, placenta reduced in size, placental remains divided and adhered to uterine wall.
- Historical control data for the following visceral variations that have greater incidence in HD rabbit litters and fetuses compared to concurrent controls: caudate lobe of liver adhered to small intestine.
- Historical control data for the following skeletal variations that have greater incidence in HD rabbit litters and fetuses compared to concurrent controls: mandible(s) incompletely ossified, extra lumbar vertebra, metacarpal(s) not ossified, median phalanges (fore limbs) incompletely ossified, median phalanges (hind limbs) incompletely ossified, astragalus incompletely ossified.

Please respond by COB Monday November 21, 2016.

Kindly confirm receipt.

Thank you,

Kim

Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration

10903 New Hampshire Avenue, Bldg. 22, Rm 3231
Silver Spring, MD 20993
Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

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
11/15/2016

Scott, Kimberly

From: Scott, Kimberly
Sent: Thursday, November 10, 2016 11:45 AM
To: Abraham, Abbey
Cc: Qiu, Yuhong (yuhong.qiu@novartis.com)
Subject: NDA 207997, Midostaurin Clinical IR #5 DUE 330PM Today

Importance: High

Follow Up Flag: Follow up

Flag Status: Flagged

Good afternoon Abbey,

The Clinical team has the following information request for NDA 207997, Midostaurin:

1. In the ADAR.xpt for the AdSM pool, the DOSRED and DOSINT variables designated dose reduction and dose interruption, respectively. The "RSNDOS" variable denotes the reason for dose modification, however it is unclear whether this denotes the reason for dose reduction or the reason for dose interruption. As such, it does not appear to be possible, based on the existing dataset structure, to evaluate the reason for dose modifications. To inform safety review,
 - a. Clarify which variable, and in which .xpt file, define the reason for dose reduction, and which defines the reason for dose interruption.
 - b. For the "RSNDOS" codes under "DOSRSNF", 1 = as per protocol and 2 = AE. Since the only protocol-specified dose reductions would be for AE's, clarify the difference between a code of 1 and a code of 2; i.e., would both signify dose modification due to AE's?
2. In the ADAR.xpt file for the AdSM, among patients with dose reduction (DOSRED=1), reference is made to the "DOSREG1A" variable specifying the reason for modification. This includes cases in which it appears only one dose was missed, and hence would appear to be dose interruption rather than dose reduction. For example:

(b)(4)



To inform safety review, clarify why such cases are counted as dose reductions, and clarify which .xpt file and which variables denote actual (lasting) reductions in dosing.

3. For AdSM, clarify which .xpt file and which variable contains the date of diagnosis of SM.

Please respond by 3:30pm today.

Kindly confirm receipt.

Thank you,

Kim

Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service

Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Rm 3231
Silver Spring, MD 20993
Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

APPEARS THIS WAY ON ORIGINAL

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
03/17/2017

Scott, Kimberly

From: Scott, Kimberly
Sent: Wednesday, November 09, 2016 2:27 PM
To: Abraham, Abbey
Cc: Qiu, Yuhong
Subject: RE: NDA 207997, Midostaurin 120 Safety Day response

Importance: High
Sensitivity: Confidential

Hi Abbey,

Your proposal to amend the CSR for Study A2301 to include the additional AEs and SAEs that you became aware of post database lock and submit it at the time of the 120 day safety update is acceptable, as is your proposal to update Table 3 in the proposed label based on the CSR amendment. However, you should also submit revised AAEV.xpt and AAERISK.xpt files for Study A2301 and update the affected tables in a revised ISS. Please submit these additional revised files as early as possible and no later than the time of the 120 day safety update."

Kindly confirm receipt.

Thank you,
Kim
Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Rm 3231
Silver Spring, MD 20993
Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

From: Abraham, Abbey [<mailto:abbey.abraham@novartis.com>]
Sent: Wednesday, November 09, 2016 1:25 PM
To: Scott, Kimberly
Cc: Qiu, Yuhong
Subject: RE: NDA 207997, Midostaurin
Sensitivity: Confidential

Hi Kim

Just wanted to see if the team has any feedback on the proposal for the below.

Thanks
Abbey

From: Scott, Kimberly [<mailto:Kimberly.Scott@fda.hhs.gov>]
Sent: Monday, November 07, 2016 3:30 PM
To: Abraham, Abbey <abbey.abraham@novartis.com>
Cc: Qiu, Yuhong <yuhong.qiu@novartis.com>

Subject: RE: NDA 207997, Midostaurin

Sensitivity: Confidential

Hi Abbey,

I've forwarded your proposal to the reviewers and will get back with you.

Kind regards,

Kim

Kimberly Scott, RN, BSN, OCN®

CDR, U.S. Public Health Service

Regulatory Health Project Manager

Division of Hematology Products

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, Bldg. 22, Rm 3231

Silver Spring, MD 20993

Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

From: Abraham, Abbey [<mailto:abbey.abraham@novartis.com>]

Sent: Monday, November 07, 2016 1:58 PM

To: Scott, Kimberly

Cc: Qiu, Yuhong

Subject: RE: NDA 207997, Midostaurin

Sensitivity: Confidential

Hi Kim

Following up with the last communication, we would like to seek further alignment with the Agency regarding the best way to report the additional AEs/SAEs we became aware of post database lock of study A2301 discussed below.

Enclosed please find two tables, Table 14.3.1-1.1 (AE regardless of causality) and Table 14.3.1-2.1 (SAE regardless of causality) in track change mode, comparing the output from a recent data transfer (Oct 28, 2016) from the Alliance with the output in the Clinical Study Report (CSR) submitted in the NDA. Although this is not the final transfer, we understand the final output will be very similar to this one. From these two track change tables, one can see that the change in overall frequency of these events compared to what we reported previously is small and does not impact any of the safety conclusions.

Based on this, we propose to generate a CSR amendment to include the following:

- In-text table 12-4 (AE regardless of causality) with track change
- In-text table 12-11 (SAE regardless of causality) with track change
- Post-text table 14.3.1-1.1 AE regardless causality by treatment phase, overall, by PT and maximal CTC grade
- Post-text table 14.3.1-2.1 SAE (reconciled) regardless causality by treatment phase, overall, by PT and maximal CTC grade
- Listing 14.3.2-2.1 Reconciled SAE
- Listing 16.2.7-1.1 AEs

The CSR amendment will be submitted together with 120 day safety update. Table 3 in the proposed label will be updated based on the CSR amendment.

Does the Agency agree with above proposal?

From: Scott, Kimberly [<mailto:Kimberly.Scott@fda.hhs.gov>]

Sent: Tuesday, October 18, 2016 4:07 PM

To: Abraham, Abbey <abbey.abraham@novartis.com>

Cc: Qiu, Yuhong <yuhong.qiu@novartis.com>

Subject: RE: NDA 207997, Midostaurin

Importance: High

Sensitivity: Confidential

Good afternoon Abbey,

The Agency has found your proposal acceptable, and do not need a tcon to discuss as this time.

Kindly confirm receipt.

Thank you,

Kim

Kimberly Scott, RN, BSN, OCN[®]

CDR, U.S. Public Health Service

Regulatory Health Project Manager

Division of Hematology Products

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, Bldg. 22, Rm 2222

Silver Spring, MD 20993

Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

From: Abraham, Abbey [<mailto:abbey.abraham@novartis.com>]

Sent: Monday, October 17, 2016 5:59 PM

To: Scott, Kimberly

Cc: Qiu, Yuhong

Subject: NDA 207997, Midostaurin

Sensitivity: Confidential

Hi Kim

Please see attached a courtesy copy of a letter I will be sending via the Gateway officially to the NDA tomorrow. This is regarding a limited number of additional SAEs and AEs from a few of the study A2301 clinical sites that has come to our awareness recently. Data assessment and adjudication is ongoing but as the NDA is being assessed, we wanted to sure the agency was made aware in a timely manner. As I mentioned, the data assessment is still ongoing and we do have a proposal regarding the submission of the information but are proposing a TC to seek alignment with the review team. Please let us the feedback from the team.

Thank you

Abbey Abraham, PharmD

Oncology Drug Regulatory Affairs

Novartis Pharmaceuticals Corporation

Phone +1 862-778-8998

Fax +1 973-781-3473

abbey.abraham@novartis.com

www.novartis.com

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
11/09/2016

Scott, Kimberly

From: Scott, Kimberly
Sent: Tuesday, November 08, 2016 6:08 PM
To: 'Abraham, Abbey'
Cc: Qiu, Yuhong (yuhong.qiu@novartis.com); Scott, Kimberly (Kimberly.Scott@fda.hhs.gov)
Subject: NDA 207997 Midostaurin: statistician Information Request: Due COB 11/14/16

Importance: High

Tracking:	Recipient	Read
	'Abraham, Abbey'	
	Qiu, Yuhong (yuhong.qiu@novartis.com)	
	Scott, Kimberly (Kimberly.Scott@fda.hhs.gov)	
	Scott, Kimberly	Read: 11/8/2016 6:37 PM

Hi Abbey,

Please see the following information request from the statisticians:

- For Study D2201 in patients with ASM or MCL, please clarify the purpose and sample size determination for the extension phase.

Please respond by COB on Monday, November 14, 2016;

Kindly confirm receipt.

Thank you,

Kim

Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Rm 3231
Silver Spring, MD 20993
Phone: 240-402-4560 | Kimberly.scott@fda.hhs.gov

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
11/09/2016

Scott, Kimberly

From: Scott, Kimberly
Sent: Monday, November 07, 2016 8:59 AM
To: Abraham, Abbey
Cc: Qiu, Yuhong (yuhong.qiu@novartis.com)
Subject: NDA 207997, Midostaurin IR: SM diagnosis - response due 11:30AM on Nov 8

Importance: High

Good morning Abbey,

Per the World Health Organization criteria, ASM, MCL, and SM with AHNMD are distinct diagnostic categories. However, we are unable to ascertain the actual diagnoses for subjects in D2201 and A2213. We have identified the following issues:

- Diagnosis tables in the CSR (e.g. D2201 CSR Table 11-3) have no category for ASM, and "SM with AHNMD" appears to include ASM and MCL cases.
- The ADGP2.xpt files have no ASM flag.
- In the proposed PI, [REDACTED] (b)(4)

To enable determination of efficacy,

1. Submit one .xpt file, with one row per patient in Studies D2201 and A2213 combined to identify the diagnosis. Include at minimum the following variables:

Variable	Data element	Comment
Unique subject ID (STYS1DIA)		
Study (STY1A)		
Safety flag (SAFETY)	Y/N	
PEP flag (PEP)	Y/N	
Diagnosis per investigator	• MCL • ASM (by definition, exclude AHNMD) • SM with AHNMD (exclude MCL) • SM subtype unknown	• The diagnostic categories are mutually exclusive, and should sum to the total number of subjects in the study
Confirmed diagnosis per central histopathology review	• MCL • ASM (by definition, exclude AHNMD) • SM with AHNMD (exclude MCL) • SM subtype not confirmed	• The diagnostic categories are mutually exclusive, and should sum to the total number of subjects
Best overall response by 6 cycles, per SSC, according to modified Valent + Cheson criteria	• Major response • Partial response • No response	• For D2201 PEP
Best overall response by 6 cycles, per SSC, according to 2013 IWG-MRT and ECNM consensus response criteria (12 weeks confirmation)	• Complete remission • Partial remission • Clinical improvement • Stable disease • Progressive disease	• For D2201 PEP

Overall response with first 2 cycles, according to Valent criteria

- Major response
- Partial response
- No response

• For A2213 FAS

2. In the proposed PI,  (b)(4)
3. Submit a table for the D2201 PEP, summarizing SSC-assessed efficacy outcomes, per the above diagnostic categories (MCL, ASM without AHNMD, SM with AHNMD, unknown) according to central histopathology review.
4. For the D2201 PEP, for each patient in which the diagnosis was not centrally confirmed, submit a narrative explaining the reason for including the patient in the efficacy analysis.

Please respond by 11:30AM (ET), Tuesday, November 8, 2016.

Kindly confirm receipt.

Thank you,

Kim

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
11/07/2016

Scott, Kimberly

From: Scott, Kimberly
Sent: Tuesday, November 01, 2016 10:35 AM
To: Abraham, Abbey
Cc: Qiu, Yuhong (yuhong.qiu@novartis.com)
Subject: NDA 207997, Midostaurin Clinical IR Y#3, Due Today

Importance: High

Good morning Abbey,

The Clinical team has an information request for NDA 207997, Midostaurin:

- For the ISS datasets, it is unacceptable [REDACTED] (b) (4)

(b) (4)

Please respond by this afternoon.

Kindly confirm receipt.

Thank you,

Kim

Kimberly Scott, RN, BSN, OCN®

CDR, U.S. Public Health Service

Regulatory Health Project Manager

Division of Hematology Products

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, Bldg. 22, Rm 3231

Silver Spring, MD 20993

Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

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
11/01/2016

Scott, Kimberly

From: Scott, Kimberly
Sent: Friday, October 28, 2016 3:42 PM
To: Abraham, Abbey
Cc: Boehmer, Jessica; Qiu, Yuhong (yuhong.qiu@novartis.com)
Subject: NDA 207997, Midostaurin Clinical IR Y#2 DUE COB , Monday, 10/31/16

Importance: High

Good afternoon Abbey,

Please see the information request from the Clinical Reviewers for NDA 207997, Midostaurin:

1. In your response to 27-Oct-2016 IR # 1b regarding missing SAE flags in the iss safety pool, you stated that the "AEVSER1C" flag only concerns the patients in RATIFY trial. However, both ASM studies (D2201, A2213) have a fully populated SAE flag, "AEVSER1C" in aaev.xpt and aaerisk.xpt. files. Furthermore, in the ISS Section 10, the numerous tabular summaries of AE's of special interest include SAE's for all patient groups (healthy volunteers, AML/MDS/ALL monotherapy, AML combination, ASM, diabetes mellitus, and advanced cancers). Therefore, for comprehensive analysis of safety, for the ISS overall safety pool, submit revised aaev.xpt and aaerisk.xpt files with a populated "AEVSER1C" flag for all studies in which SAE data was collected.
2. In your response to 27-Oct-2016 IR # 3 regarding key laboratory abnormalities, you stated (b) (4)
 (b) (4)
(b) (4). Resolve the inconsistency in your response.

Please respond by **COB Monday October 31, 2016**.

Kindly confirm receipt.

Thank you,

Kim

Kimberly Scott, RN, BSN, OCN®

CDR, U.S. Public Health Service

Regulatory Health Project Manager

Division of Hematology Products

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, Bldg. 22, Rm 3231

Silver Spring, MD 20993

Phone: 240-402-4560 | Kimberly.scott@fda.hhs.gov

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
10/28/2016

Scott, Kimberly

From: Scott, Kimberly
Sent: Friday, October 28, 2016 1:07 PM
To: 'Abraham, Abbey'
Cc: Boehmer, Jessica; Qiu, Yuhong (yuhong.qiu@novartis.com); Scott, Kimberly (Kimberly.Scott@fda.hhs.gov)
Subject: NDA 207997, Midostaurin: Clinical Information Request DUE 1:00PM on Monday, 10/31/16

Importance: High

Tracking:	Recipient	Read
	'Abraham, Abbey'	
	Boehmer, Jessica	Read: 10/28/2016 1:15 PM
	Qiu, Yuhong (yuhong.qiu@novartis.com)	
	Scott, Kimberly (Kimberly.Scott@fda.hhs.gov)	
	Scott, Kimberly	Read: 10/28/2016 1:08 PM

Good afternoon Abbey,

Please see the following Clinical Information Request from the Agency regarding NDA 207997, Midostaurin:

- Grade 5 adverse events:** The "aaev.xpt" and "aaerisk.xpt" files for the ASM studies (D2201, A2213) and the ISS overall safety pool are missing multiple grade 5 adverse events:
 - In the aaerisk.xpt and aaev.xpt file for the ASM pool, study D2201 and study A2213, the variable "AEVGRD1C" identifies no grade 5 events. Yet, per ISS Section 4.3.1.1 there were 26 on-treatment deaths in the ASM pool, of which 16 occurred for reasons other than the study indication; and per your response to 18-Oct-2016 Information Request 1a, Table 2-1, 10 were related to adverse events of special interest (and thus would be expected to be included in aaerisk.xpt).
 - Similarly, in the ISS overall safety pool, after selecting patients in the safety population (safety = 1), who had treatment-emergent events (teae=1) while on-treatment (phase 1C=2),
 - the "AEVGRD1C" variable in aaev.xpt identifies 19 grade 5 events, but these are on study A2301 only.
 - the "AEVGRD1C" variable in aaerisk.xpt identifies 14 grade 5 events, but these are on study A2301 only.

For comprehensive review of safety and confirmation of findings,

- Explain why grade 5 adverse events are missing from the adverse event .xpt files above. Include an explanation for why Study A2301 is the only study to have grade 5 events in these files.
 - For all patients in the ISS safety pool, including patients with ASM, explain what derived .xpt files and what variables identify a) grade 5 adverse events and b) grade 5 adverse events of special interest.
- TEAE flags:** For verification of safety findings,
 - In the "aaev.xpt" and "aaerisk.xpt" files, explain why a TEAE flag is available for the ISS overall safety pool, including for ASM patients, but not for the study-specific files for D2201 and A2213.
 - In the proposed PI [REDACTED] (b) (4)

Please respond by 1:30pm on Monday, October 31, 2016.

I will be out of the office on Monday, October 31st, and returning on Tuesday, November 1, 2016. Please send your response to this information request to the Regulatory Project Manager covering for me, Jessica Boehmer (cc'd on this correspondence) as well as myself.

Kindly confirm receipt.

Thank you,

Kim

Kimberly Scott, RN, BSN, OCN®

CDR, U.S. Public Health Service

Regulatory Health Project Manager

Division of Hematology Products

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, Bldg. 22, Rm 3231

Silver Spring, MD 20993

Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

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
10/28/2016

Scott, Kimberly

From: Scott, Kimberly
Sent: Friday, October 28, 2016 12:07 PM
To: 'Abraham, Abbey'
Cc: Qiu, Yuhong (yuhong.qiu@novartis.com)
Subject: NDA 207997, Midostaurin Clin Pharm IR DUE COB 10/31/16

Importance: High

Good morning Abbey,

The Agency has the following clinical pharmacology information requests:

1. Provide the SAS data sets (*.xpt) for the concentration and pharmacokinetic parameters data sets used to evaluate the impact of strong CYP3A inhibitors and inducers on dose exposure, described in Section 3.8.3 of Module 2.7.2 (i.e., Trial A2301, and Pooled analysis of Trials D2201, A2213 & A2104E1). Include the name and dose of the CYP3A inhibitors and inducers and the time of the dosing of the CYP3A inhibitors and inducers relative to the pharmacokinetic sampling and the development of serious adverse events and grade 3 or 4 adverse events, if any, for each individual patient. Conduct comparative analysis of exposure before and after starting strong CYP3A modulators for individual patients if adequate PK data is available to explore the effect of the CYP3A modulators on exposure. Also, analyze the adverse events by treatment period.
2. Please provide analysis datasets, codes, and define files for your exposure-response analyses. If already submitted, please point us to the correct location.

Please respond by COB, Monday, October 31, 2016.

Kindly confirm receipt.

Thank you,

Kim

Kimberly Scott, RN, BSN, OCN®

CDR, U.S. Public Health Service

Regulatory Health Project Manager

Division of Hematology Products

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, Bldg. 22, Rm 3231

Silver Spring, MD 20993

Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

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
10/28/2016



NDA 207997 – Original 1
NDA 207997 – Original 2

**FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED**

Novartis Pharmaceuticals Corporation
Attention: Abbey Abraham, PharmD
Regulatory Affairs, Therapeutic Area Director
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Abraham:

Please refer to your New Drug Application (NDA) dated August 29, 2016, received August 29, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for RYDAPT[®], midostaurin, capsule 25 mg.

We also refer to your amendments dated September 14, 15, 23, and 28; and October 5, 11, 13(2), 18(2), 19, 20, 21, and 25(3), and 2016.

We have administratively split your application into Original 1 and Original 2 which provides for the following indications:

- Original 1: Treatment of adult patients with advanced systemic mastocytosis (ASM)
- Original 2: 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

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR: 314.101(a) this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is April 28, 2017. This application is also subject to the provisions of “the Program” under the Prescription Drug User Fee Act (PDUFA) V (refer to: <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>).

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance

are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by February 7, 2017.

In addition, the planned date for our internal mid-cycle review meeting is November 30, 2016. We are not currently planning to hold an advisory committee meeting to discuss this application.

During our filing review of your application, we identified the following potential review issues:

Clinical (Original 1):

1. In study A2213, you did not collect C-findings on the CRF, and investigator-based responses were not adjudicated independently. You indicated that Novartis' post-hoc review of each subject's clinical course and designated response did not identify inconsistencies in response determination, but that "there was no effort to formally corroborate the best overall response analysis" (reply to 9/20/2016 Information Request #4). Despite conducting a post-hoc analysis, you have not submitted any data files that include the Sponsor-assessed baseline and post-treatment C-findings at each response time point in study A2213; in the reply to IR #4, you instead cite only Sponsor efficacy narratives as support for the response designation. These efficacy narratives in the A2213 CSR alone are not sufficient for review. C-findings are the fundamental basis of response assessment in ASM. Without the additional structured data for review, the information to establish that study A2213 supports the efficacy of midostaurin is inadequate.
2. There is insufficient justification for the 100 mg BID starting dose of midostaurin for treatment of ASM. Based on the pharmacokinetic data provided, by 28 days of midostaurin dosed at 100 mg BID versus 50 mg BID, steady-state levels are notably quite similar. Further, over 50% of ASM patients required dose modification due to toxicity. Given that steady-state levels were similar to those with 50 mg BID, that there were frequent dose modifications due to toxicity, and that the active metabolite CPG6525421 has a very long $t_{1/2\beta}$ (>400 hour), the proposed recommended starting dose of 100 mg BID may not be appropriate.

Clinical (Original 2):

1. You have evidence of lack of efficacy of midostaurin monotherapy for treatment of FLT3-mutated AML. This may warrant a limitation of use statement in the prescribing information.
2. You have evidence for lack of efficacy of midostaurin monotherapy for treatment of FLT3-mutated AML, and no data from a proper randomized maintenance study (b) (4)



3. You have evidence for lack of efficacy of midostaurin monotherapy for treatment of FLT3-mutated AML, but you are pursuing an indication for treatment of patients with FLT3-mutated AML. You state that midostaurin is a multikinase inhibitor, with activity including inhibition of other kinases known to be active in AML. It is not clear that you have targeted the correct AML molecular subgroup for treatment with midostaurin.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

We request that you submit the following information:

Clinical (Original 2):

1. We remind you of your commitment to send a complete dataset for study PKC412A0006 by November 30, 2016.

Clinical Pharmacology:

1. Provide the SAS data sets (*.xpt) for the concentration and pharmacokinetic parameters data sets used to evaluate the impact of strong CYP3A inhibitors and inducers on dose exposure, described in Section 3.8.3 of Module 2.7.2 (i.e., Trial A2301, and Pooled analysis of Trials D2201, A2213 & A2104E1). Include the name and dose of the CYP3A inhibitors and inducers and the time of the dosing of the CYP3A inhibitors and inducers relative to the pharmacokinetic sampling and the development of serious adverse events and grade 3 or 4 adverse events, if any, for each individual patient. Conduct comparative analysis of exposure before and after starting strong CYP3A modulators for individual patients if adequate PK data is available to explore the effect of the CYP3A modulators on exposure. Also, analyze the adverse events by treatment period.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances, and
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), Medication Guide, and patient PI. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft “*Guidance for Industry*” (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), Medication Guide, and patient PI, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

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

Because the drug for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, please call Kimberly Scott, Regulatory Project Manager, at (240) 402-4560.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, MD
Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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

/s/

ANN T FARRELL
10/28/2016

Scott, Kimberly

From: Scott, Kimberly
Sent: Thursday, October 27, 2016 9:53 AM
To: Abraham, Abbey
Cc: Qiu, Yuhong (yuhong.qiu@novartis.com)
Subject: NDA 207997, Midostaurin: Stats IR DUE COB 11/2/16

Importance: High

Good morning Abbey,

The Agency is requesting the following information as a follow –up from the Application Orientation Meeting:

For Study A2301 (AML indication)

1. The overall survival (OS) analysis was not conducted according to the initial plan.
Please explain how you determined the alpha level for the OS primary analysis.
2. With the OS curves reaching plateau around the 36 month time-point, the reported median OS estimates did not appear to be reliable.
Please explore alternative methods, for example the restricted mean survival time, to provide a better time-estimate of midostaurin treatment effect.
3. Provide explanation to the different patterns between treatment arms with regard to stem cell transplantation (SCT).
While most subjects had SCT in the midostaurin arm had allogeneic related SCT, a majority of subjects in the placebo arm had allogeneic unrelated SCT.
In addition, please provide a sensitivity analysis of OS, censoring SCT by type of transplantation.

For Studies D2201 and A2213 (ASM indication)

1. You proposed that “OS data from the two studies will be pooled and compared with historical data from an independent registry”.
Please present the data and results.

Please respond by COB Wednesday, November 2, 2016.

Kindly confirm receipt.

Thank you,

Kim

Kimberly Scott, RN, BSN, OCN®

CDR, U.S. Public Health Service

Regulatory Health Project Manager

Division of Hematology Products

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, Bldg. 22, Rm 2222

APPEARS THIS WAY ON ORIGINAL

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
10/27/2016

Scott, Kimberly

From: Scott, Kimberly
Sent: Thursday, October 27, 2016 6:15 PM
To: Abraham, Abbey
Cc: Qiu, Yuhong (yuhong.qiu@novartis.com)
Subject: NDA 207997, Midostaurin Clinical IR/Y: DUE 1:30pm tomorrow, 10/28

Importance: High

(b)(4)

Good evening Abbey,

The Agency has the following review issues for NDA 207997, Midostaurin:

1. In the AAEV.xpt file for the ISS safety pool, after selecting for patients in the safety population (SAFETY=1) with TEAE=1 and Phase 1C = 2,

- a. MedDRA terms are missing, but the verbatim term (AEVNAM1A) is available, for 8 adverse events as shown. For comprehensive safety review, explain why the MedDRA terms are missing, and submit an .xpt file with the STYSID1A and terms for the full MedDRA hierarchy for these events:
- b. Explain why the SAE flag "AEVSER1C" is missing for 14, 389 of the 27,265 rows (53%).

2. [REDACTED] (b) (4)

For confirmation of your safety findings, clarify whether any preferred terms were grouped and provide a table defining all grouped terms. For example, did "cough" include "cough productive", did "dyspnea" include "dyspnea exertional," and did "upper respiratory tract infection" include nasopharyngitis, pharyngitis, rhinitis, and sinusitis?

3. [REDACTED] (b) (4) explain how post-baseline laboratory abnormalities with known grade but unknown worsening from baseline were handled. In order to verify the calculations, clarify whether such laboratory abnormalities were excluded from analysis, or were presumed to be treatment-emergent.

4. In the cpkc412.scspooldefine file, for description of ADAR .xpt , the “format” hyperlinks for the 3 “reason for dose” variables RSNDOS, RSNDOS1C, and RSNDOS2C (format hyperlinks “DOSRSNF, RSND11_ and RSND21_ respectively) are erroneous, taking one back to page 1 of the define file. These formats are not defined in Section 1.15 “Analysis Data Formats”, thus the variable definitions are not available. Provide explanations for DOSRSNF, RSND11_ and RSND21 for this ADAR.xpt file.

Please respond by 1:30pm (ET), Friday, October 28, 2016.

Kindly confirm receipt.

Thank you,

Kim

Kimberly Scott, RN, BSN, OCN®

CDR, U.S. Public Health Service

Regulatory Health Project Manager

Division of Hematology Products

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, Bldg. 22, Rm 2222

Silver Spring, MD 20993

Phone: 240-402-4560 | Kimberly.scott@fda.hhs.gov

APPEARS THIS WAY ON ORIGINAL

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
10/28/2016

Scott, Kimberly

From: Scott, Kimberly
Sent: Tuesday, October 25, 2016 10:27 AM
To: 'Abraham, Abbey'
Cc: Qiu, Yuhong (yuhong.qiu@novartis.com)
Subject: NDA 207997, Midostaurin: Clinical IR 10/25/16

Importance: High

Good morning Abbey,

The Agency has the following information request in regards to NDA 207997, Midostaurin:

Reference is made to the response received 10/24/2016 to 10/18/2016 IR, item 4, regarding the definition of "key" laboratory abnormalities. You stated that key laboratory abnormalities consisted of related, grade 3/4 changes.

- a. Confirm that key laboratory abnormalities for AML and ASM, as represented in the ISS (e.g., Table 8-2 for ASM, Table 8-4 for AML study A2301) [REDACTED] (b) (4), are restricted to treatment-related findings.
- b. If this is the case, in order to confirm these data, explain how to reproduce these tables from the provided datasets, given that the "alrs2".xpt files for A2301 and D2201 and the "alrs3".xpt file for A2213 do not have an attribution flag.
- c. If key laboratory abnormalities are restricted to treatment-related findings, please submit revised tables listed in point a above, reporting grade 3 and 4 treatment-emergent laboratory abnormalities regardless of causality.

Please respond by 12noon on **Wednesday, October 26, 2016.**

Kindly confirm receipt.

Thank you,

Kim

Kimberly Scott, RN, BSN, OCN®

CDR, U.S. Public Health Service

Regulatory Health Project Manager

Division of Hematology Products

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, Bldg. 22, Rm 2222

Silver Spring, MD 20993

Phone: 240-402-4560 | Kimberly.scott@fda.hhs.gov

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
10/25/2016

Scott, Kimberly

From: Scott, Kimberly
Sent: Tuesday, October 25, 2016 2:00 PM
To: 'Abraham, Abbey'
Cc: Qiu, Yuhong
Subject: RE: NDA 207997, Midostaurin Clinical IR DUE 10/25/16

Sensitivity: Confidential

Hi Abbey,

Our screen shot showed the results for all available views. Our eSub team was involved in the initial review of your NDA submission, and if the plan implemented by Novartis this afternoon is not successful, we will ask the eSub team to contact you directly in order to determine if there is a technical issue that can be identified. In case that should be needed, please clarify whom at Novartis should be contacted by the eSub team regarding your NDA application.

Thanks,

Kim

Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Rm 2222
Silver Spring, MD 20993
Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

From: Abraham, Abbey [mailto:abbey.abraham@novartis.com]
Sent: Tuesday, October 25, 2016 10:56 AM
To: Scott, Kimberly
Cc: Qiu, Yuhong
Subject: RE: NDA 207997, Midostaurin Clinical IR DUE 10/25/16
Sensitivity: Confidential

Hi Kim

Based on the agency's agreement with the use of subfolders to separate the ISS and AdSM pools, Novartis will move forward and will submit the revised folders this afternoon. We will also will update the leaf titles to help differentiate as proposed.

We want to ensure the review team's comments on the ISS folder are addressed satisfactorily and so in regards to the team's comment that the advanced SM pool was not visible, it would seem the view that was shown was the study folder view and we are wondering if there was another view(s) such as the folder view, that could be leveraged within the application? If the view does not address the team's comment, could a consult with the Office of Business Informatics be a next step to help us in regards to this topic?

Thanks

Abbey Abraham, PharmD
Oncology Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation

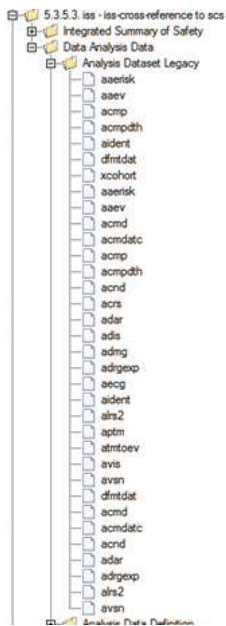
Phone +1 862-778-8998
Fax +1 973-781-3473
abbey.abraham@novartis.com
www.novartis.com

From: Scott, Kimberly [<mailto:Kimberly.Scott@fda.hhs.gov>]
Sent: Monday, October 24, 2016 6:17 PM
To: Abraham, Abbey <abbey.abraham@novartis.com>
Cc: Qiu, Yuhong <yuhong.qiu@novartis.com>
Subject: NDA 207997, Midostaurin Clinical IR DUE 10/25/16
Sensitivity: Confidential

Good evening Abbey,

The Agency has the following comments regarding NDA 207997, Midostaurin:

We cannot confirm the presence of a folder titled “advanced-sm-pool.” Our folder view is below. We very much agree with your proposal to enter the iss main dataset and the advanced sm pool into separate subfolders of the iss analysis data folder.



Kindly confirm receipt of this email.
Thank you,
Kim

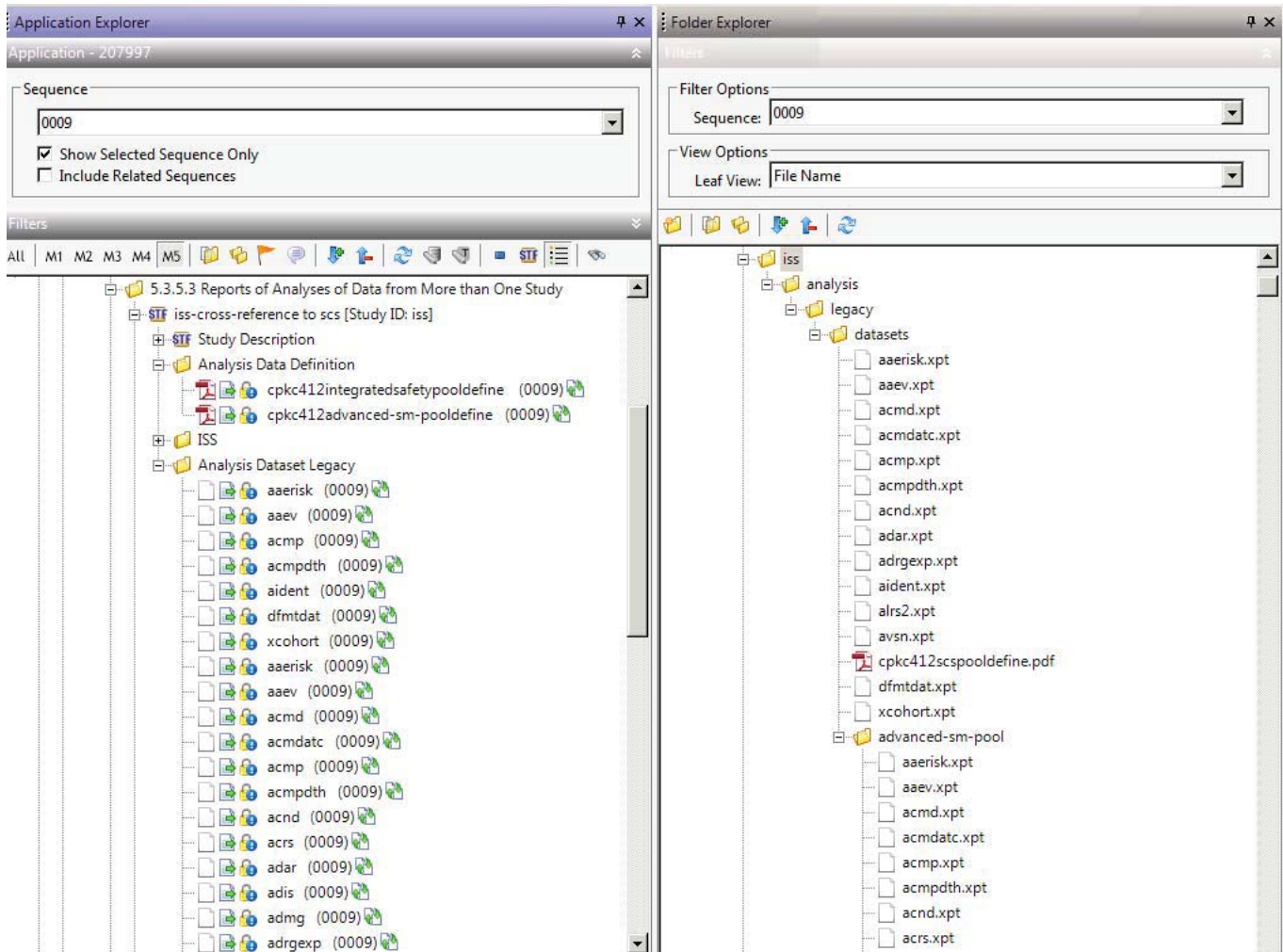
Cc: Abraham, Abbey
Subject: RE: NDA 207997, Midostaurin Clinical IR DUE 10/25/16
Sensitivity: Confidential

Hi Kim,

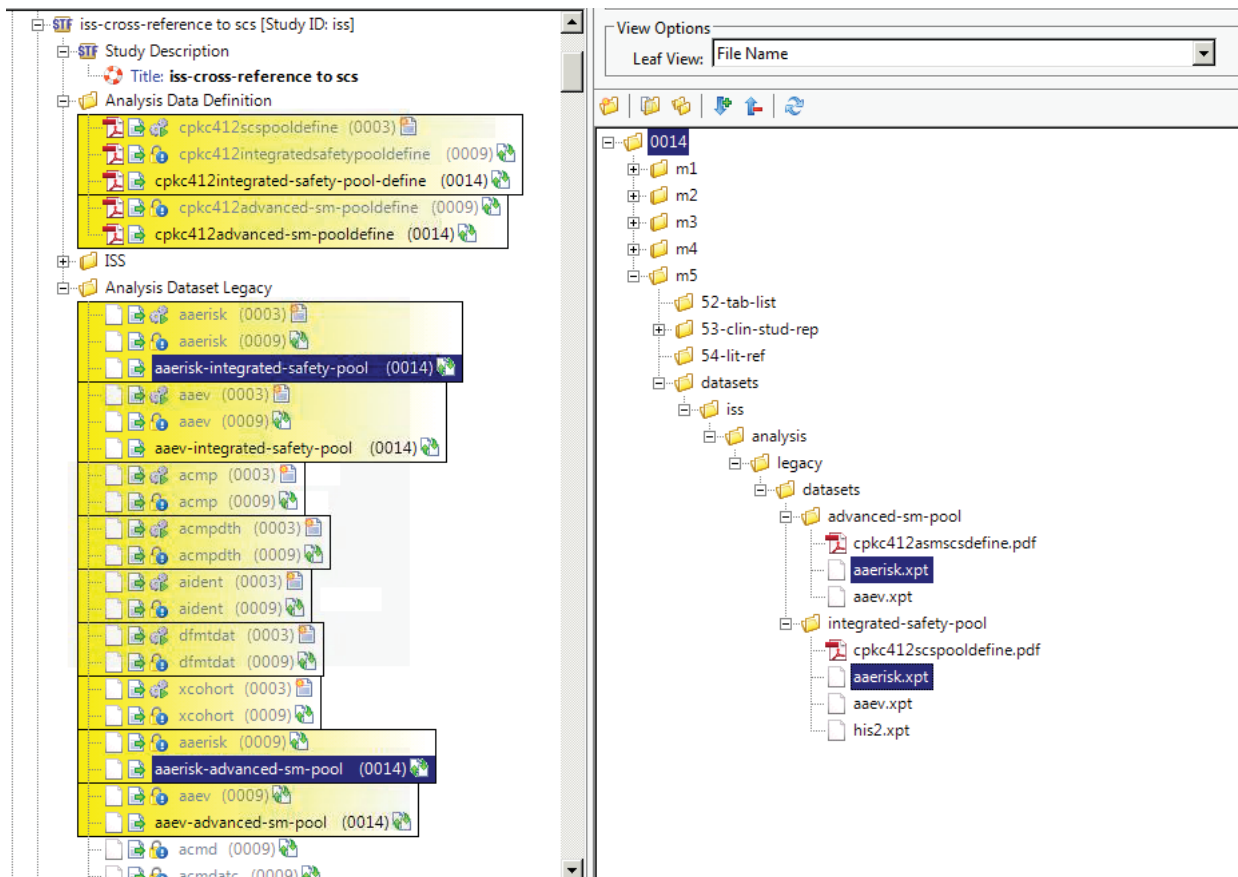
Thank you very much for the mail.

For point 1, we need Agency's guidance on how to proceed.

Please refer to the screen shot below capturing both the study view as well as the folder view (window explorer view) specific to sequence no. 0009. Within the right hand panel (the folder view), the ASM datasets exist in a subfolder within the datasets folder as stated in response to 7g. Since as advised by the Agency, there is only one ISS folder in 5.3.5.3, both the ASM datasets as well as the overall pool datasets are appropriately tagged with ISS study tagging files (STF), and will therefore appear under the same Analysis Dataset folder within the study view (please refer to left hand panel). eCTD structure folders in the study view are driven by the study tags. As a result, the ASM and the ISS pool datasets will appear in the same folder within the study view (left hand panel) irrespective of added folder layers.



As an added measure, Novartis proposes to incorporate more descriptive leaf titles for each file to help distinguish files from different datasets and to facilitate navigation, as illustrated by the blue highlighted files in the screen shot blow. Please note that in the study view, files from both datasets will still appear in the same Analysis Dataset folder. Would the Agency want us to proceed with this approach?



Thanks,

Yuhong

From: Scott, Kimberly [<mailto:Kimberly.Scott@fda.hhs.gov>]
Sent: Saturday, October 22, 2016 11:17 AM
To: Abraham, Abbey
Cc: Qiu, Yuhong
Subject: NDA 207997, Midostaurin Clinical IR DUE 10/25/16
Importance: High
Sensitivity: Confidential

Good morning Abbey,

The Agency has the following comments to Novartis in regards to NDA 207997, Midostaurin:

1. In response to Request 7g, you indicate that you “placed the ASM datasets and define file in a subfolder under the Analysis Dataset folder” but in fact there is no such subfolder, and as you state there are two datasets mixed in one subfolder. As indicated in our correspondence sent 10/11/2016, when you have multiple datasets in one submission, each dataset must be in separate subfolders to identify their provenance. We reiterate that each dataset must be in its own folder with a single define file. Revise the ISS Data Analysis Data Folder to have one subfolder for the main ISS dataset and one subfolder for the asm-pool dataset. This must be completed by COB Tuesday, October 25, 2016.
2. We accept your rationale for not submitting complete datasets for studies C99-PKC412A001 and PKC412A0002. Please submit the complete dataset for study PKC412A0006 by November 30, 2016.

Kindly confirm receipt.

Thank you,

Kim

Kimberly Scott, RN, BSN, OCN®

CDR, U.S. Public Health Service

Regulatory Health Project Manager

Division of Hematology Products

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, Bldg. 22, Rm 2222

Silver Spring, MD 20993

Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

APPEARS THIS WAY ON ORIGINAL

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
10/27/2016



NDA 207997

INFORMATION REQUEST

Novartis Pharmaceuticals Corporation
Attention: Elizabeth Purdy
Senior Manager, Regulatory Affairs Global Drug Development
One Health Plaza; Bldg. 339-Room 1256
East Hanover, NJ 07936-1080

Dear Ms. Purdy:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rydapt (Midostaurin) Capsule 25mg.

We also refer to your August 29, 2016 submission, containing your new drug application.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Drug Process:

1. Adjust the amount of API based on the actual drug substance assay results.
2. Add (b)(4) with acceptance criteria.



1 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

If you have any questions, please contact me, at (240) 402-6153. Please respond by November 14, 2016.

Sincerely,

Rabiya Laiq, Pharm.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Rabiya Laiq -S

Digitally signed by Rabiya Laiq -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Rabiya Laiq -S,
0.9.2342.19200300.100.1.1=2001555007
Date: 2016.10.25 22:46:59 -04'00'

Scott, Kimberly

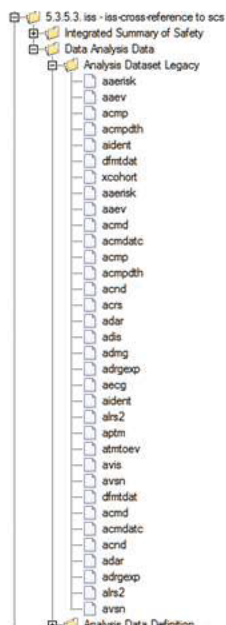
From: Scott, Kimberly
Sent: Monday, October 24, 2016 6:17 PM
To: Abraham, Abbey
Cc: Qiu, Yuhong (yuhong.qiu@novartis.com)
Subject: NDA 207997, Midostaurin Clinical IR DUE 10/25/16

Sensitivity: Confidential

Good evening Abbey,

The Agency has the following comments regarding NDA 207997, Midostaurin:

We cannot confirm the presence of a folder titled "advanced-sm-pool." Our folder view is below. We very much agree with your proposal to enter the iss main dataset and the advanced sm pool into separate subfolders of the iss analysis data folder.



Kindly confirm receipt of this email.

Thank you,
Kim

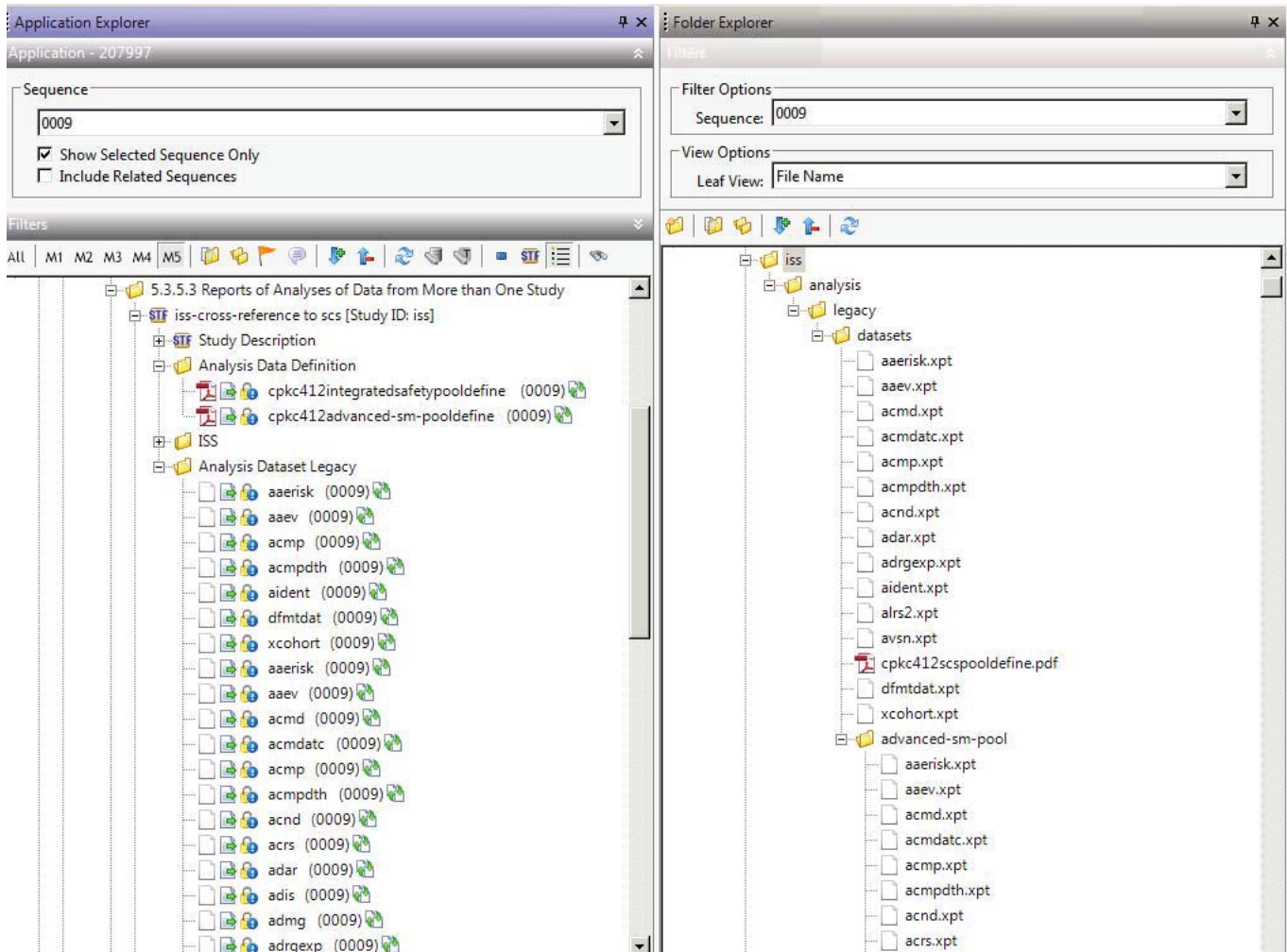
Cc: Abraham, Abbey
Subject: RE: NDA 207997, Midostaurin Clinical IR DUE 10/25/16
Sensitivity: Confidential

Hi Kim,

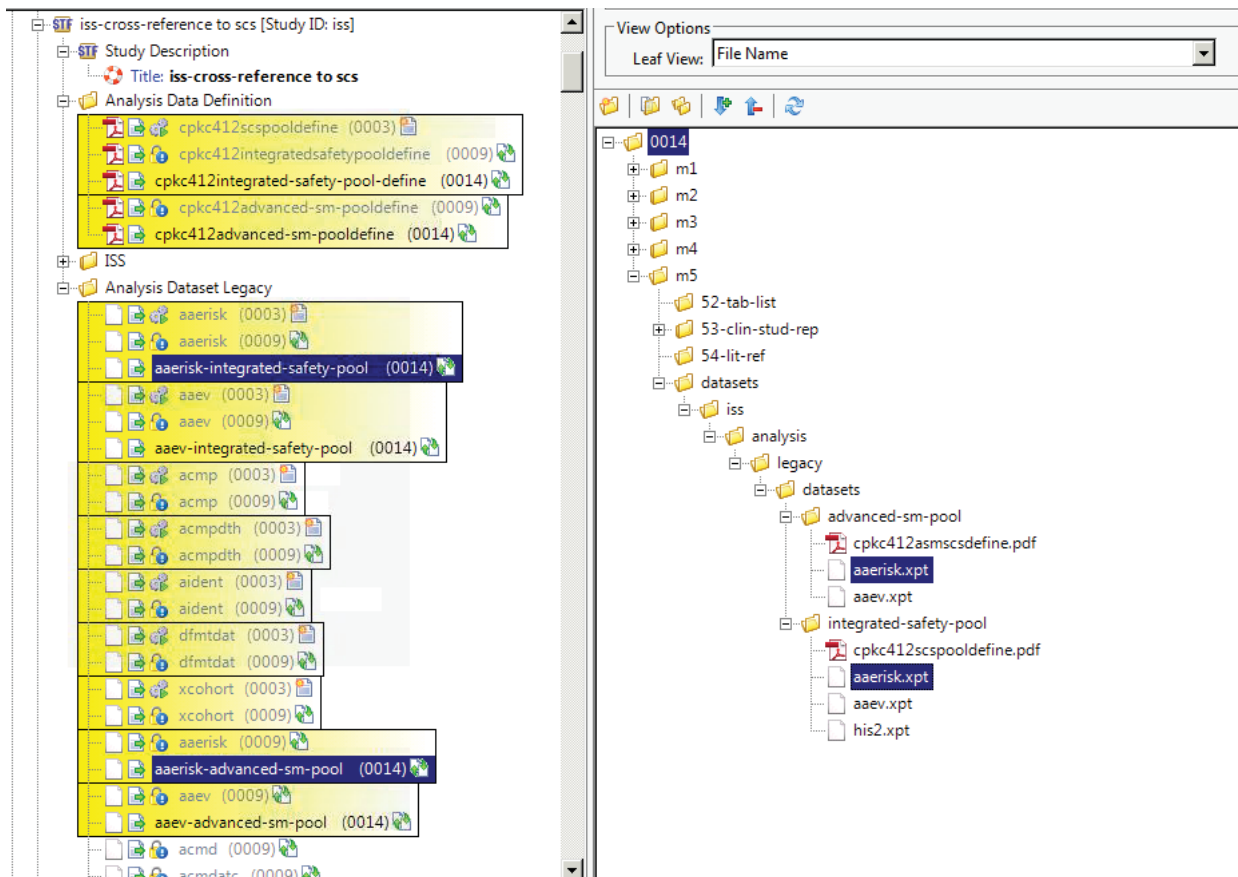
Thank you very much for the mail.

For point 1, we need Agency's guidance on how to proceed.

Please refer to the screen shot below capturing both the study view as well as the folder view (window explorer view) specific to sequence no. 0009. Within the right hand panel (the folder view), the ASM datasets exist in a subfolder within the datasets folder as stated in response to 7g. Since as advised by the Agency, there is only one ISS folder in 5.3.5.3, both the ASM datasets as well as the overall pool datasets are appropriately tagged with ISS study tagging files (STF), and will therefore appear under the same Analysis Dataset folder within the study view (please refer to left hand panel). eCTD structure folders in the study view are driven by the study tags. As a result, the ASM and the ISS pool datasets will appear in the same folder within the study view (left hand panel) irrespective of added folder layers.



As an added measure, Novartis proposes to incorporate more descriptive leaf titles for each file to help distinguish files from different datasets and to facilitate navigation, as illustrated by the blue highlighted files in the screen shot blow. Please note that in the study view, files from both datasets will still appear in the same Analysis Dataset folder. Would the Agency want us to proceed with this approach?



Thanks,

Yuhong

From: Scott, Kimberly [<mailto:Kimberly.Scott@fda.hhs.gov>]
Sent: Saturday, October 22, 2016 11:17 AM
To: Abraham, Abbey
Cc: Qiu, Yuhong
Subject: NDA 207997, Midostaurin Clinical IR DUE 10/25/16
Importance: High
Sensitivity: Confidential

Good morning Abbey,

The Agency has the following comments to Novartis in regards to NDA 207997, Midostaurin:

1. In response to Request 7g, you indicate that you “placed the ASM datasets and define file in a subfolder under the Analysis Dataset folder” but in fact there is no such subfolder, and as you state there are two datasets mixed in one subfolder. As indicated in our correspondence sent 10/11/2016, when you have multiple datasets in one submission, each dataset must be in separate subfolders to identify their provenance. We reiterate that each dataset must be in its own folder with a single define file. Revise the ISS Data Analysis Data Folder to have one subfolder for the main ISS dataset and one subfolder for the asm-pool dataset. This must be completed by COB Tuesday, October 25, 2016.
2. We accept your rationale for not submitting complete datasets for studies C99-PKC412A001 and PKC412A0002. Please submit the complete dataset for study PKC412A0006 by November 30, 2016.

Kindly confirm receipt.

Thank you,

Kim

Kimberly Scott, RN, BSN, OCN®

CDR, U.S. Public Health Service

Regulatory Health Project Manager

Division of Hematology Products

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, Bldg. 22, Rm 2222

Silver Spring, MD 20993

Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

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
10/25/2016

Scott, Kimberly

From: Scott, Kimberly
Sent: Saturday, October 22, 2016 11:17 AM
To: Abraham, Abbey
Cc: Qiu, Yuhong (yuhong.qiu@novartis.com)
Subject: NDA 207997, Midostaurin Clinical IR DUE 10/25/16

Importance: High

Good morning Abbey,

The Agency has the following comments to Novartis in regards to NDA 207997, Midostaurin:

1. In response to Request 7g, you indicate that you “placed the ASM datasets and define file in a subfolder under the Analysis Dataset folder” but in fact there is no such subfolder, and as you state there are two datasets mixed in one subfolder. As indicated in our correspondence sent 10/11/2016, when you have multiple datasets in one submission, each dataset must be in separate subfolders to identify their provenance. We reiterate that each dataset must be in its own folder with a single define file. Revise the ISS Data Analysis Data Folder to have one subfolder for the main ISS dataset and one subfolder for the asm-pool dataset. This must be completed by COB Tuesday, October 25, 2016.
2. We accept your rationale for not submitting complete datasets for studies C99-PKC412A001 and PKC412A0002. Please submit the complete dataset for study PKC412A0006 by November 30, 2016.

Kindly confirm receipt.

Thank you,

Kim

Kimberly Scott, RN, BSN, OCN®

CDR, U.S. Public Health Service

Regulatory Health Project Manager

Division of Hematology Products

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, Bldg. 22, Rm 2222

Silver Spring, MD 20993

Phone: 240-402-4560 | Kimberly.scott@fda.hhs.gov

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
05/01/2017

Scott, Kimberly

From: Scott, Kimberly
Sent: Wednesday, October 19, 2016 5:56 PM
To: Abraham, Abbey
Cc: Qiu, Yuhong (yuhong.qiu@novartis.com)
Subject: NDA 207997, Midostaurin: Y Clinical IR DUE 10/24 and 11/4

Importance: High

Good evening Abbey,

The Agency has additional Information Requests for NDA 207997, Midostaurin. Please note, the following requests have two different due dates:

Due by 10:00am on Monday, October 24, 2016:

1. **ISS special safety topics:**
For pooled safety analyses in the ISS, the tabular summaries of AE's of special interest (ISS Section 10) are missing Grade 5 events. For accurate presentation of safety outcomes,
 - a. Submit the following revised tables for the ISS, in each case adding a row for grade 5 AE's: ISS Tables 10-1 through 10-29 inclusive, with the exception of Tables 10-17 (QTF values in ASM pool), Table 10-22 (treatment-emergent LFTs in A2301) and Table 10-23 (narratives)
 - b. For ISS Table 10-10 (bleeding events in ASM pool), for consistency of presentation, include all events, rather than restricting to events occurring in 2 or more patients.
 - c. Clarify whether "AE's leading to discontinuation" include treatment discontinuation due to death.
2. **ASM events after CSR data cut-offs (ISS 4.3.1.2 and ARGUS listings in SCE Appendix 2):**
For studies D2201 and A2213, information on new on-study deaths and SAE's is inadequate for safety review because of missing subject ID's. Unique subject ID's are missing from death narratives (ISS Section 4.3.1.2), and the ARGUS reports (SCE Appendix 2) are listed by case number with inconsistent mention of unique subject ID.
For studies D2201 and A2213, submit a table that associates the ARGUS case # in SCE appendix 2 with the unique subject ID.
3. **Disposition of ASM patients:**
Per the SCS, 23 / 142 ASM patients (16%) discontinued study treatment for reasons other than PD, death, or AE. In SCS Appendix 1, Table 5-1, the other causes are not delineated. For studies D2201 and A2213, to facilitate review of safety and tolerability, clarify which derived .xpt files and variables contain information on all reasons for study treatment discontinuation.
4. **Safety:**
The criteria for "key laboratory abnormalities" (e.g., ISS Table 8-2) are not specified. To facilitate safety review, define "key" laboratory parameters.
5. **Leukemic transformation of ASM:**
Per the ISS Section 7.3.1, leukemic transformation occurred in 15 / 116 patients (13%) in D2201. To facilitate review of efficacy and safety,

- a. Explain which derived .xpt file and what variables identify patients with leukemic transformation, the date of transformation, and the histologic type of transformation.
- b. If this information was not provided, submit an .xpt file for all cases of leukemic transformation of ASM, containing at minimum the following variables:
 - Study
 - Unique Subject ID
 - Diagnosis (ASM with or without AHNMD)
 - Diagnosis date
 - Midostaurin start and stop dates
 - Date of leukemic transformation
 - Type of leukemia
 - Intervening therapy between midostaurin and the date of leukemic transformation
- c. Clarify whether the D2201 criteria for “progressive disease” distinguished between leukemic transformation and non-leukemic progression of ASM.

Due by COB, Friday, November 4, 2016:

1. ASM response criteria for D2201:

Although D2201 response analysis was based on modified Valent and Cheson criteria, the D2201 protocol (Section 7.4, Efficacy) does not clearly differentiate the modified criteria from the originally published Valent criteria (2003). To facilitate review of response, submit a table that summarizes the differences between the modified and originally published Valent criteria.

2. ASM response assessment:

To facilitate evaluation of efficacy, present a sensitivity analysis for the D2201 primary efficacy population, wherein best response by 6 cycles is summarized according to the 2013 IWG-MRT and ECNM consensus response criteria (Gotlib et al, Blood 2013). Please describe the relevance of response assessment based on modified 2003 Valent criteria, if newer international consensus response criteria have been published.

Kindly confirm receipt of this email.

Thank you,

Kim

Kimberly Scott, RN, BSN, OCN®

CDR, U.S. Public Health Service

Regulatory Health Project Manager

Division of Hematology Products

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, Bldg. 22, Rm 2222

Silver Spring, MD 20993

Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

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
05/01/2017

Scott, Kimberly

From: Scott, Kimberly
Sent: Tuesday, October 18, 2016 9:14 AM
To: Abraham, Abbey
Cc: Qiu, Yuhong (yuhong.qiu@novartis.com)
Subject: NDA 207997 Midostaurin: Clinical Information Request DUE COB 11/14/16

Importance: High

Good morning Abbey,

The Agency has the following information request for NDA 207997, Midostaurin:

1. We have the following questions regarding the multikinase inhibition profile of midostaurin with regard to efficacy for treatment of AML:
 - a. Based on the concentrations of midostaurin and its active metabolites achieved at Cmax and Ctrough using the 50 mg BID dosing regimen in humans, and the results of your in vitro testing of kinase inhibition (e.g., the InVitrogen SelectScreen), identify the wild type and mutant kinases that would be expected to be inhibited in vivo. Show the data that support your selection.
 - b. Provide any pharmacodynamic data in humans to confirm the kinases are inhibited in vivo using the proposed dose and schedule of midostaurin for treatment of patients with AML.
 - c. Provide a summary tabulation of data addressing whether AML cell lines or cells from patients with AML are lysed or growth-inhibited by midostaurin at concentrations relevant to those achieved in vivo at Cmax and Ctrough using the 50 mg BID dosing regimen in humans. Include in the table which kinases were overexpressed or mutated in the individual cell lines tested. Clarify also which assays used PKC412 specifically vs a commercial source of midostaurin.
 - d. In Module 2.7.3 Summary of Clinical Efficacy Section 1.1.2, you state that “Synergistic antiproliferative activity of midostaurin in combination with daunorubicin and cytarabine was observed in AML patient cell lines.” Please show the data that demonstrate the synergistic activity. Include in the table which kinases were overexpressed or mutated in the individual cell lines tested. Clarify also whether PKC412 specifically or midostaurin from a commercial source was used in these experiments.
2. Using all available data, please comment on the efficacy of midostaurin as monotherapy for relapsed or refractory AML that is FLT3-ITD positive vs FLT3-TKD mutation positive vs FLT3-wild type. Submit summary tabulations that address this issue (response, OS, EFS, DFS), such as those presented for Q2 and Q9 during the Application Orientation Meeting. (b) (4)

3. Provide an explanation for the midostaurin dose selected for AML maintenance vs treatment of ASM, especially why the doses differ. Using all available data, provide the results of analyses (including summary tables or figures) showing that the activity of midostaurin for treatment of AML is or is not dose-dependent or exposure-dependent in vivo in humans. For the purposes of exploring dose-

dependency and exposure-dependency, activity could include any level of response for monotherapy, and CR and PFS or OS for combination therapy.

4. Provide a side-by-side comparative table of the observed CR, OS, EFS, transplantation in CR1 and follow-up time for A2301, A2016 and ADE02T. Identify and explain any substantial between-study differences in the observed CR, OS or EFS.
5. Please clarify whether you have any data on minimal residual disease at any time point for subjects in the RATIFY study.
6. You are seeking an indication for treatment of adults with newly diagnosed AML having a FLT3 mutation using combination therapy.
 - a. Please compare the biology of AML with FLT3 mutations in adults <60 years old to those >60 years old, and comment on whether the efficacy results of A2301 can be extrapolated to adults >60 years old who have AML with FLT3 mutations.
 - b. FLT3 mutations occur in patients with AML across the entire age range for adult and pediatric patients. As requested at the pre-NDA meeting May 24, 2016, please also provide data about the biology of AML that can support or refute extrapolation of efficacy for combination therapy from the adult population to the pediatric population for treatment of AML with FLT3 mutation. If efficacy could be extrapolated to only some of the pediatric patients with newly diagnosed AML having a FLT3 mutation, clarify the age range or diagnostic criteria for which the extrapolation would apply.
 - c.  (b)(4)
 - d. For the subjects in the RATIFY trial, please submit a data file (.xpt) with results of the full mutational profiling at baseline performed by Alliance and/or Novartis. Provide subgroup analyses for CR, OS and EFS by prognostic mutations that occurred concurrently with FLT3. Please also clarify whether you are performing additional testing for all subjects on trial, and if so, when the results will be available.

Please respond by COB Monday, November 14, 2016.

Kindly confirm receipt.

Thank you,

Kim

Kimberly Scott, RN, BSN, OCN®

CDR, U.S. Public Health Service

Regulatory Health Project Manager

Division of Hematology Products

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, Bldg. 22, Rm 2222

APPEARS THIS WAY ON ORIGINAL

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
10/18/2016

Scott, Kimberly

From: Scott, Kimberly
Sent: Tuesday, October 18, 2016 4:07 PM
To: 'Abraham, Abbey'
Cc: Qiu, Yuhong
Subject: RE: NDA 207997, Midostaurin

Importance: High
Sensitivity: Confidential

Good afternoon Abbey,

The Agency has found your proposal acceptable, and do not need a tcon to discuss as this time.

Kindly confirm receipt.

Thank you,

Kim

Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Rm 2222
Silver Spring, MD 20993
Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

From: Abraham, Abbey [<mailto:abbey.abraham@novartis.com>]
Sent: Monday, October 17, 2016 5:59 PM
To: Scott, Kimberly
Cc: Qiu, Yuhong
Subject: NDA 207997, Midostaurin
Sensitivity: Confidential

Hi Kim

Please see attached a courtesy copy of a letter I will be sending via the Gateway officially to the NDA tomorrow. This is regarding a limited number of additional SAEs and AEs from a few of the study A2301 clinical sites that has come to our awareness recently. Data assessment and adjudication is ongoing but as the NDA is being assessed, we wanted to sure the agency was made aware in a timely manner. As I mentioned, the data assessment is still ongoing and we do have a proposal regarding the submission of the information but are proposing a TC to seek alignment with the review team. Please let us the feedback from the team.

Thank you

Abbey Abraham, PharmD
Oncology Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation

Phone +1 862-778-8998
Fax +1 973-781-3473
abbey.abraham@novartis.com
www.novartis.com

APPEARS THIS WAY ON ORIGINAL

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
10/18/2016

Scott, Kimberly

From: Scott, Kimberly
Sent: Monday, October 17, 2016 12:10 PM
To: Abraham, Abbey
Cc: Qiu, Yuhong (yuhong.qiu@novartis.com)
Subject: RE: NDA 207997, Midostaurin Information Request

Importance: High

Hi Abbey,

Please note, for 4b the third subgroup should be greater than or equal to 65 years old.

Kindly confirm receipt.

Thank you,
Kim

From: Scott, Kimberly
Sent: Monday, October 17, 2016 9:38 AM
To: Abraham, Abbey
Cc: Qiu, Yuhong (yuhong.qiu@novartis.com)
Subject: NDA 207997, Midostaurin Information Request
Importance: High

Good morning Abbey,

The Agency has the following comments for NDA 207997, Midostaurin:

1. There are discrepancies in the stated molecular weight and in the stated chemical name for midostaurin given in Figure 1-1 of Module 2.4 Nonclinical Overview vs Table 1-2 of Module 2.7.1 Summary of Biopharmaceutical Studies. Please identify the correct molecular weight of and the correct chemical name for midostaurin.
2. Regarding the pharmacological activity of midostaurin, we have the following questions:
 - a. Please provide the predicted total and free concentrations of midostaurin and its active metabolites at C_{max} and C_{trough} for the 50 mg BID dosing regimen and for the 100 mg BID dosing regimen in humans.
 - b. Based on the concentrations of midostaurin and its active metabolites as stated in your response to 2(a), and the results of your in vitro testing of kinase inhibition (e.g., the InVitrogen SelectScreen), identify the wild type and mutant kinases that would be expected to be inhibited at C_{max} and at C_{trough} for the 50 mg BID dosing regimen and for the 100 mg BID dosing regimen.
 - c. Based on the wild type kinases expected to be inhibited by midostaurin and its active metabolites in vivo as indicated in your response to 2(b), please identify the clinical toxicities that might result from the multikinase inhibition profile of midostaurin (i.e., hypertension from VEGFR inhibition, etc.).
3. There are a number of statements, tables or figures in Module 2.6.2 that are not clear. We have the following comments:

- a. On page 12 of Module 2.6.2 you state that “Values of (b) (4) inhibition were observed for (b) (4) kinases with 1 μM midostaurin.” Please identify the (b) (4) kinases to which you refer.
- b. There are substantial discrepancies between the results of your calculation for IC50 in Module 2.6.2 Table 2-1 and published information such as the data you cite in Module 2.6.2 Table 2-2 for several of the kinases (e.g., PKC-alpha, SYK). Please explain the reason for the discrepancies.
- c. In Module 2.6.2 Table 2-4, you indicate in the title and footnote that the IC50 was calculated. Please clarify which column in this table lists the IC50.
- d. For Module 2.6.2 Figure 2-7 (Dose-Effect curve and Combination Index plot), please identify the units for the x-axes for each graph and for the y-axes labeled “Effect.”
- e. Module 2.6.2 Table 2-5 (Summary of cytotoxic interactions) is not interpretable, since the table includes symbols that are not explained in the footnote. Please provide a revised table that can be interpreted. Please also identify the source of the data used to construct the table.

Please provide a response to Comments #1-3 by November 11, 2016.

4. We have not been able to fully characterize the safety population for the overall midostaurin clinical development program from the information submitted in the NDA. We are seeking additional information regarding all studies of midostaurin sponsored by Novartis/CG, but NOT investigator-initiated studies nor compassionate use under investigator INDs/applications. We have identified the following studies of interest:

- All 21 studies listed in Table 1-1 of the ISS
- Study A2120
- Study 002 (Protocol 41251 01 001)
- All 7 studies listed in Table 1-2 of the ISS
- Study (b) (4)
- All Novartis/CG-sponsored compassionate use from Table 1-4 of the ISS

Please provide summary tabulations of the demographics of the study subjects by protocol and regimen for each dose/arm/cohort/portion (including the placebo arms). The rows of each table should include the protocol identifier, whether midostaurin was given alone or in combination with other agents, the midostaurin dose (or placebo), the total enrolled and the total treated. Provide only the numbers of subjects (not percentage) A partial example is below:

Study	Regimen	Dose	Total	Total	Treated Population		
			Enrolled	Treated	Demo #1	Demo #2	Demo #3...
D2201	Mono	100 bid	116	116	n	n	n...
D2301	Combo	50 bid	360	355			
D2301	Combo	Placebo	357	354			
D2301	Maint	50 bid	-	120			
D2301	Maint	Placebo	-	85			
⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮

Please submit summary tables (5) using the following demographic subgroups for columns:

Table by Diagnosis Subgroups: de novo AML, relapsed/refractory AML, ASM, other malignancy, other nonmalignancy (e.g., diabetes), volunteers (i.e., healthy volunteers and organ-impaired subjects on PK/PD studies).

- a. Table by Age Subgroups: <17 years old, 17 to <65 years old, >65 years old, unknown
- b. Table by Gender Subgroups: Male, Female, unknown
- c. Table by Race Subgroups: Caucasian, Black, Asian, other, unknown
- d. Table by Ethnicity Subgroups: Hispanic, non-Hispanic, unknown

Please provide a response to Comment #4 by October 21, 2016.

Kindly confirm receipt.

Thank you,

Kim

Kimberly Scott, RN, BSN, OCN®

CDR, U.S. Public Health Service

Regulatory Health Project Manager

Division of Hematology Products

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, Bldg. 22, Rm 2222

Silver Spring, MD 20993

Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

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

04/28/2017

correspondence from 10/17/16

Scott, Kimberly

From: Scott, Kimberly
Sent: Monday, October 17, 2016 9:38 AM
To: Abraham, Abbey
Cc: Qiu, Yuhong (yuhong.qiu@novartis.com)
Subject: NDA 207997, Midostaurin Information Request

Importance: High

Good morning Abbey,

The Agency has the following comments for NDA 207997, Midostaurin:

1. There are discrepancies in the stated molecular weight and in the stated chemical name for midostaurin given in Figure 1-1 of Module 2.4 Nonclinical Overview vs Table 1-2 of Module 2.7.1 Summary of Biopharmaceutical Studies. Please identify the correct molecular weight of and the correct chemical name for midostaurin.
2. Regarding the pharmacological activity of midostaurin, we have the following questions:
 - a. Please provide the predicted total and free concentrations of midostaurin and its active metabolites at C_{max} and C_{trough} for the 50 mg BID dosing regimen and for the 100 mg BID dosing regimen in humans.
 - b. Based on the concentrations of midostaurin and its active metabolites as stated in your response to 2(a), and the results of your in vitro testing of kinase inhibition (e.g., the InVitrogen SelectScreen), identify the wild type and mutant kinases that would be expected to be inhibited at C_{max} and at C_{trough} for the 50 mg BID dosing regimen and for the 100 mg BID dosing regimen.
 - c. Based on the wild type kinases expected to be inhibited by midostaurin and its active metabolites in vivo as indicated in your response to 2(b), please identify the clinical toxicities that might result from the multikinase inhibition profile of midostaurin (i.e., hypertension from VEGFR inhibition, etc.).
3. There are a number of statements, tables or figures in Module 2.6.2 that are not clear. We have the following comments:
 - a. On page 12 of Module 2.6.2 you state that "Values of (b) (4) inhibition were observed for (b) (4) kinases with 1 µM midostaurin." Please identify the (b) (4) kinases to which you refer.
 - b. There are substantial discrepancies between the results of your calculation for IC₅₀ in Module 2.6.2 Table 2-1 and published information such as the data you cite in Module 2.6.2 Table 2-2 for several of the kinases (e.g., PKC-alpha, SYK). Please explain the reason for the discrepancies.
 - c. In Module 2.6.2 Table 2-4, you indicate in the title and footnote that the IC₅₀ was calculated. Please clarify which column in this table lists the IC₅₀.
 - d. For Module 2.6.2 Figure 2-7 (Dose-Effect curve and Combination Index plot), please identify the units for the x-axes for each graph and for the y-axes labeled "Effect."

- e. Module 2.6.2 Table 2-5 (Summary of cytotoxic interactions) is not interpretable, since the table includes symbols that are not explained in the footnote. Please provide a revised table that can be interpreted. Please also identify the source of the data used to construct the table.

Please provide a response to Comments #1-3 by November 11, 2016.

4. We have not been able to fully characterize the safety population for the overall midostaurin clinical development program from the information submitted in the NDA. We are seeking additional information regarding all studies of midostaurin sponsored by Novartis/CG, but NOT investigator-initiated studies nor compassionate use under investigator INDs/applications. We have identified the following studies of interest:

- All 21 studies listed in Table 1-1 of the ISS
- Study A2120
- Study 002 (Protocol 41251 01 001)
- All 7 studies listed in Table 1-2 of the ISS
- Study (b)(4)
- All Novartis/CG-sponsored compassionate use from Table 1-4 of the ISS

Please provide summary tabulations of the demographics of the study subjects by protocol and regimen for each dose/arm/cohort/portion (including the placebo arms). The rows of each table should include the protocol identifier, whether midostaurin was given alone or in combination with other agents, the midostaurin dose (or placebo), the total enrolled and the total treated. Provide only the numbers of subjects (not percentage) A partial example is below:

Study	Regimen	Dose	Total	Total	Treated Population		
			Enrolled	Treated	Demo #1	Demo #2	Demo #3...
D2201	Mono	100 bid	116	116	n	n	n...
D2301	Combo	50 bid	360	355			
D2301	Combo	Placebo	357	354			
D2301	Maint	50 bid	-	120			
D2301	Maint	Placebo	-	85			
⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮

Please submit summary tables (5) using the following demographic subgroups for columns:

Table by Diagnosis Subgroups: de novo AML, relapsed/refractory AML, ASM, other malignancy, other nonmalignancy (e.g., diabetes), volunteers (i.e., healthy volunteers and organ-impaired subjects on PK/PD studies).

- a. Table by Age Subgroups: <17 years old, 17 to <65 years old, >65 years old, unknown
- b. Table by Gender Subgroups: Male, Female, unknown
- c. Table by Race Subgroups: Caucasian, Black, Asian, other, unknown
- d. Table by Ethnicity Subgroups: Hispanic, non-Hispanic, unknown

Please provide a response to Comment #4 by October 21, 2016.

Kindly confirm receipt.

Thank you,

Kim

Kimberly Scott, RN, BSN, OCN[®]

CDR, U.S. Public Health Service

Regulatory Health Project Manager

Division of Hematology Products

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, Bldg. 22, Rm 2222

Silver Spring, MD 20993

Phone: 240-402-4560 | Kimberly.scott@fda.hhs.gov

APPEARS THIS WAY ON ORIGINAL

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
10/17/2016



NDA 207997

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080

ATTENTION: Abbey Abraham, PharmD
Regulatory Affairs – Therapeutic Area Director

Dear Dr. Abraham:

Please refer to your New Drug Application (NDA) dated and received August 29, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Midostaurin Capsules, 25 mg.

We also refer to your correspondence, dated and received July 25, 2016, requesting review of your proposed proprietary name, Rydapt.

We have completed our review of the proposed proprietary name, Rydapt and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your July 25, 2016 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Neil Vora, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-4845. For any other information regarding this application, contact Kimberly Scott, Regulatory Project Manager, in the Office of New Drugs at (240) 402-4560.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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

/s/

LUBNA A MERCHANT on behalf of TODD D BRIDGES
10/15/2016

Scott, Kimberly

From: Scott, Kimberly
Sent: Tuesday, October 11, 2016 11:22 AM
To: Abraham, Abbey
Cc: Qiu, Yuhong
Subject: RE: NDA 207997, Midostaurin: Information Request for Filing Issues: Agency response for clarification

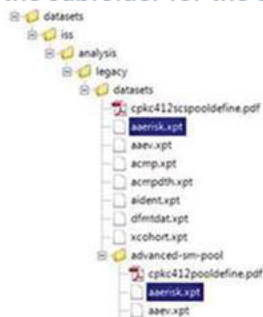
Importance: High
Sensitivity: Confidential

Good morning Abbey,

The Agency has the following response to your request for clarification regarding NDA 207997, Midostaurin:

For question 1: The proposed list of laboratory parameters is reasonable, but please also add direct bilirubin and absolute blasts.

For question 2: If you choose to use a single ISS data file subfolder, then you will need to rename each of the data files from the asm-pool to identify them uniquely, and there should be one define file for all the data files (main ISS plus asm-pool). However, we advised that as an alternative, if you have constructed a special subset for the asm-pool alone, the folder with that data set should be named as such (e.g., "advanced-sm-pool") and moved as a subfolder (data files and define file) into the ISS Analysis Dataset folder as you show in the file explorer figure. We recommend that the define files have more specific names (e.g., mainissdefine, asmpooldefine), and the define file for the asm-pool can remain in the subfolder for the asm-pool.



Using a standardized data format (such as CDSIC), when you have multiple data sets in one submission (such as with multiple clinical study reports) you will always have multiple data files with the same name, but they must be in separate subfolders to identify their provenance.

Thinking ahead to life cycle maintenance (such as with the 120-day update or later NDA supplements), we would anticipate that you replace only the data files and define file for the main ISS data set with updated revisions.

Kindly confirm receipt,

Thank you,

Kim

Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products

From: Abraham, Abbey [mailto:abbey.abraham@novartis.com]
Sent: Monday, October 10, 2016 5:13 PM
To: Scott, Kimberly
Cc: Qiu, Yuhong; Boehmer, Jessica
Subject: RE: NDA 207997, Midostaurin: Information Request for Filing Issues: response DUE 10am, 10/20/16
Sensitivity: Confidential

Hi Kim

As we are preparing for the response on the filing topics, we had two clarifications that need to be addressed. Would you please share with the team and let us know the response for each? Thank you

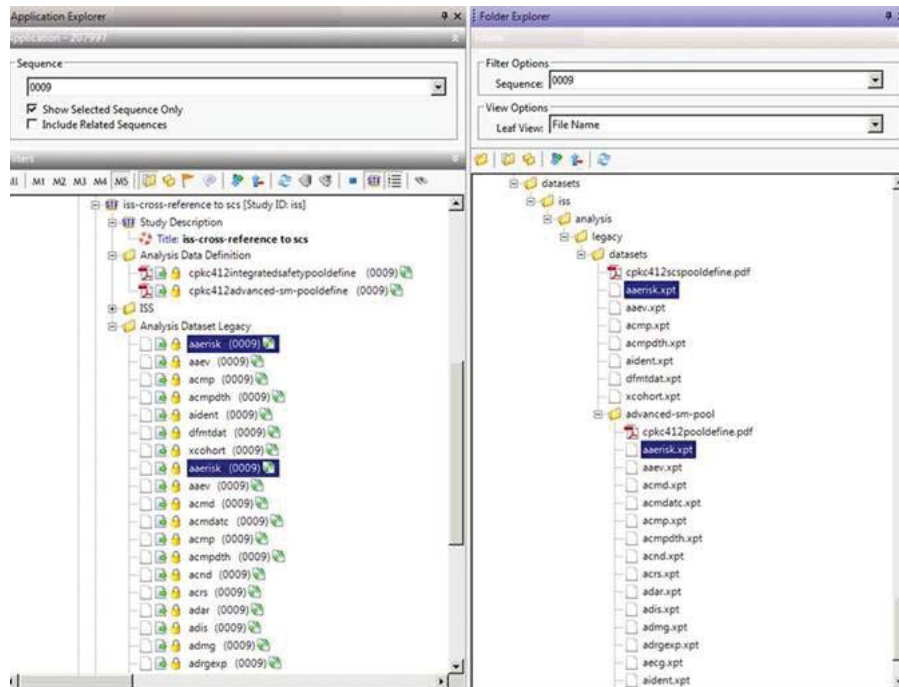
1. Request 4b – ISS pool

Novartis is preparing the ISS dataset to include the additional parameters as requested by the Agency. For the laboratory test results, since different studies collected different parameters and only some of the parameters CTC grade can be derived. The 28 parameters below, which were collected in the majority of the trials and have CTC grading, are proposed to be included for the pooled lab datasets to be submitted by Oct 20. Novartis believes that these lab parameters would allow robust assessment of safety data for the disease states being studied. Does the Agency agree?

LAB Parameter		LAB Parameter	
ABSLYM	Abs. Lymphocytes	LIPASE	Lipase
ABSNEU	Abs. Neutrophils	MAG	Magnesium
ALB	Albumin	PHOS	Phosphatase
ALKPHS	Alk. Phosphatase	POT	Potassium
AMY	Amylase	PTINR (or INR)	Prothrombin Time INR
BIC	Bicarbonate	PTT (or APTT)	Partial Thromboplastin Time
CALC	Calcium	SGOT	SGOT(AST)
CK	Creatine kinase	SGPT	SGPT(ALT)
CREA (or SCREAT)	Creatinine	SOD	Sodium
DPLCNT (or PLAT2)	Platelets	TBIL	Total Bilirubin
FIB	Fibrinogen	TCHOL	Total Cholesterol
GGT	Gamma Glutamyltransferase	TRIGLY	Triglycerides
GLUC	Glucose	UACID	Uric acid
HGB	Hemoglobin	WBC	WBC

2. Request 7g – ISS dataset folder

Novartis simulated the submission to place the ASM datasets and define file in a subfolder under Analysis Dataset folder (right panel). When viewed in the combined STF + cumulative view (left panel), there are two define files in the Analysis Data Definition folder and two sets of files with the same names in the Analysis Dataset folder. Would the team please confirm this view is what is expected based on the Agency’s response.



Abbey Abraham, PharmD
Oncology Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation

Phone +1 862-778-8998
Fax +1 973-781-3473
abbey.abraham@novartis.com
www.novartis.com

From: Scott, Kimberly [<mailto:Kimberly.Scott@fda.hhs.gov>]
Sent: Thursday, October 06, 2016 10:05 AM
To: Abraham, Abbey
Cc: Qiu, Yuhong
Subject: NDA 207997, Midostaurin: Information Request for Filing Issues: response DUE 10am, 10/20/16
Importance: High
Sensitivity: Confidential

Good morning Abbey,

The Agency has reviewed your responses submitted 10/5/2016 to our Information Request for filing issues sent 9/30/2016 for NDA 207997, Midostaurin. We have the following comments:

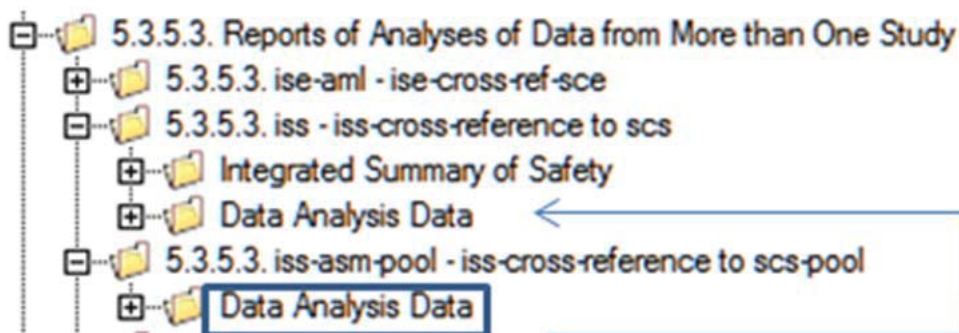
1. Regarding your response to Comment 4a about missing study data sets, we have the following comments:
 - a. Based on the information that you provided, we will not expect you to submit the data sets for the following protocols: PKC412A2120, PKC412A0003, PKC412ADE02T, PKC412A001.
 - b. Based on your commitment made during the teleconference on 10/5/2016, we will expect the data sets by 10/20/2016 for the following protocols: PKC412A2104E2 and PKC412A2114.
 - c. You will still need to submit the study data sets for C99-PKC412A001, PKC412A0002, and PKC412a0006. If you will not be able to submit these by 10/20/2016, please propose an alternate date for submission. Please note that the proposed date will need to allow sufficient time for assessment and

review of the data within the review cycle, and a very late submission may be considered a major amendment.

2. Regarding your response to Comment 7c about the placement of the SCP appendices in Module 5.3.5.3 AML section (Reports of Analyses of Data from More than One Study), move the following elements of SCP Appendix 1 and Appendix 2 currently in Module 5.3.5.3 as follows:
 - a. Move the post-text tables and figures, and datasets and define files corresponding to SCP Sections 3.8.2 to 3.8.7 (Module 2.7.2) to Module 5.3.3 (Reports of Human Pharmacokinetic Studies), and rename them appropriately.
 - b. Move the post-text tables and figures, and datasets and define files corresponding to SCP Section 3.9 (Module 2.7.2) to Module 5.3.3.5 (Population PK Study Reports), and rename them appropriately.
 - c. Move the post-text tables and figures, and datasets and define files corresponding to SCP Section 3.11 (Module 2.7.2) to the corresponding AdSM or AML Sections of Module 5.3.5.3 (Reports of Analyses of Data from More than One Study), and rename them appropriately.
 - d. The Pooling Plan and Statistical Methodology report in SCP Appendix 2, should be split and relocated along with its corresponding post-text tables and figures, and datasets described in Items (a) to (c) above. The reports should be named appropriately.

Also, in addition to the datasets mentioned in FDA Request 13, provide PK parameter data sets for dose exposure after multiple doses described in Section 3.8.3 of Module 2.7.2. In addition to midostaurin and its active metabolites, provide the concentration and PK (if applicable) datasets for potency adjusted exposure to the sum of active moieties.

3. Regarding your response to Comment 7g, we reiterate that there should be one folder in 5.3.5.3 for the ISS in this submission. That folder should contain a subfolder for the ISS pdf and additional documents, and one subfolder for the Analysis Dataset. Ideally, there should be one Analysis Dataset, but if you have constructed a special subset for ASM alone, the folder with that dataset should be named as such and moved as a subfolder in the Analysis Dataset subfolder.



**Rename and move to a single subfolder
for all ISS datasets**

4. Your planned response to Comment 8 is not acceptable. Each document should be identifiable in the CTD structure. Either submit the CSR for A2301 as a single pdf with bookmarks, submit the CSR in granular format by section/appendix according to ICH E3, or submit parts with file names identifying which sections/appendices (according to ICH E3) are in the part. Do not split appendices across sections. For additional information about the appendices of a Clinical Study Report, see <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073113.pdf>.

5. The remainder of your responses in your 10/5/2016 submission are considered incomplete, since you only provide a plan and have not actually resolved the filing issues. You will need to submit a point by point response when you revise your NDA to address the filing issues that were identified in the Information Request sent 9/30/2016.

We strongly recommend that you review the current version of the comprehensive CTD table of contents to familiarize yourself with the expected granularity and placement of documents in the submission so that the reviewers will be able to find information quickly. As indicated in some of our comments, grouping multiple reports/documents into one pdf with a nondescriptive name is not acceptable; each individual report should go in its own folder with the associated documents and data files. For additional information, see: <http://www.fda.gov/downloads/drugs/developmentapprovalprocess/formsubmissionrequirements/electronic submissions/ucm163175.pdf>.

Please respond to the Agency's request by **10:00am (ET) on Thursday, October 20, 2016**.

Kindly confirm receipt.

Regards,

Kim

Kimberly Scott, RN, BSN, OCN®

CDR, U.S. Public Health Service

Regulatory Health Project Manager

Division of Hematology Products

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, Bldg. 22, Rm 2222

Silver Spring, MD 20993

Phone: 240-402-4560 | Kimberly.scott@fda.hhs.gov

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
03/03/2017

Boehmer, Jessica

From: Boehmer, Jessica
Sent: Friday, October 07, 2016 1:04 PM
To: abbey.abraham@novartis.com
Cc: Scott, Kimberly; Boehmer, Jessica
Subject: Response Required: Information Request: NDA 207997

Importance: High

Dear Abbey,

Please refer to NDA 207797. Please respond to the following information requests to Kimberly Scott via email by the due dates indicated. You will also need to formally submit the information to your NDA.

Response due 10/11/2016:

1. Adverse Event datasets: To facilitate evaluation of safety, clarify the relationship between the events in the “aev.xpt” and “aerisk.xpt” files for studies D2201 and A2213. Are all AE’s in “aev.xpt” included in “aerisk.xpt”?
2. GRDDIR1C (test direction based on CTC_1C): For the D2201 “alrs2.xpt” and A2213 “alrs3.xpt” files, the explanation of the GRDDIR1C variable in the define files (d2201alrs2define.pdf, a2213.alrs3define.pdf) is difficult to interpret. The define files state “if a parameter is two directional and CTC grade is negative and positive, then GRDDIR1C = both.” To facilitate review of laboratory findings and safety, please explain what parameters would fit this scenario. For example, why might GRDDIR1C might be “hyper”, “hypo”, or “both” when the B_CTC_1C and CTC_1C are both 0?
3. D2201 PEP population: We note that “aadj2.xpt” file includes 2 patients (0152_00005 with MR, and 0180_0001 with SD) not in the PEP, and that patients not in the PEP comprise:
 - a. 23 of 3006 rows in “aadj.xpt”
 - b. 394 of 1519 rows in “aadjinv.xpt”
 - c. 27 of 116 rows in “aadjinv2.xpt”

To facilitate response assessment, please explain why patients not in the PEP were included in the above .xpt files and whether they contributed to the reported ORR.

Response due 10/20/2016:

4. Financial disclosures: In the 9/22/2016 response to 9/20/2016 Question 3, you noted that some A2213 and D2201 investigators were incorrectly designated as having missing disclosures. Clarify whether the A2213 and D2201 Clinical Investigator Financial Disclosure forms and “clinsit2.xpt” files submitted 9/15/2016 contain the correct disclosure information. If they do not, submitted corrected forms and .xpt files.
5. D2201 response variables (AADJ2, AADJ .xpt files). To facilitate response assessment,
 - a. Clarify the variable RESPRG1D - “Event lead to initiat. of res/prg (date)”
 - b. Clarify the variable EVTRES1D - “Event lead to response assessment”
 - c. Clarify which variable designates the date of best response. Does the “RESPRG1S” variable represent the date of any response, date of best response, or another date?

- d. Clarify which variable, and in which derived dataset, designates the date of first objective response, which is not necessarily the date of best response.
6. Missing laboratory data (D2201 alrs2 and A2213 alrs3): We note the many blank entries under “B_CTC_1C” and “WRSCTC1C” for post-baseline laboratory results. With the available variables and data, it is unclear how to differentiate treatment-emergent laboratory abnormalities from post-treatment laboratory abnormalities where worsening from baseline is unknown. Based on your explanation, if one selects only the baseline flag (BLFLG_1C) of “N”, would all 53,710 missing entries under “WRSCTC1C” be because worsening from baseline was unknown?

If not, then to facilitate review of laboratory abnormalities, submit a revised D2201 alrs2.xpt file, A2213 alrs3.xpt file, and corresponding pooled .xpt files such that “WRSCTC1C” is interpretable for all post-baseline laboratory results. Codify all cases where information to assess change from baseline is missing (e.g., missing baseline value, lab normal range, lab units, CTC grade) or is otherwise not applicable.

7. Missing laboratory data (D2201 alrs2.xpt): To facilitate review of laboratory abnormalities,
 - a. After selecting only the rows with a baseline flag (BLFLG_1C) of “N”, explain why “CTC_1C” is missing for >50,000 rows in the D2201 alrs2.xpt file. Please also explain why missing CTC_1C values occur or tend to occur in the rows having missing “B_CTC_1C” values, and why labs for unscheduled visits variably either have or do not have a corresponding grade.
 - b. After selecting only the rows with a baseline flag (BLFLG_1C) of “N”, explain the 772 blank entries under “Phase_1C” in the D2201 alrs2.xpt file.
 - c. For D2201 .alrs2.xpt, explain the difference between a post-baseline laboratory assessments designated as PSTBL_1C=”Y”, a baseline flag (BLFLG_1C) of “N”, and a “Phase_1C” other than 1 (“run-in”).
8. C findings: In the “adis.xpt” files for D2201 and A2213, C findings at pre-study baseline are incompletely characterized, and it is not possible to confirm response analyses. You will need to address the following:
 - a. Under the C-finding categories (e.g., ENTCR IDC, ENTCRI EC, ENTCRI FC, ENTCRI GC, ENTCRI HC), there are numerous blank entries. Per the format, however, (“YNO11_”), all patients with absent C findings are to be codified. As such, it is unclear whether blank entries represent absent C findings, missing data, not evaluable, or some other category. Provide the codification of each C finding to clearly differentiate between these, such that there are no blank entries.
 - b. “YNO11” for C findings has overlapping codes for “No” (0) and “No symptoms” (7). Eliminate the overlapping category or define the distinction.
 - c. In ADIS, C findings of cytopenias from bone marrow dysfunction (ENTCR IDC) are for patients with ASM-AHNMD, yet should only pertain to cases without known non-MC hematopoietic malignancy. Explain this discrepancy, and clarify whether “ENTCR IDC” distinguished cytopenias attributed to bone marrow dysfunction versus to hypersplenism.
 - d. To clarify “ENTCR IDC”, provide an additional column(s) that categorize the presence or absence of each cytopenia (ANC < 1000, , hemoglobin <10, platelets <100)
 - e. Designate whether the hemoglobin and platelet parameters are transfusion dependent or transfusion independent at baseline
 - f. Define transfusion dependence.
 - g. Clarify whether ENTCRI EC, defined as “hepatomegaly with impaired liver function” also includes ascites and/or portal hypertension.

To expedite evaluation of treatment response, we recommend that you submit revised ADIS .xpt files for D2201 and A2213 and define files to clarify C findings at baseline as requested above rather than a separate data file with partial information.

9. Prior ASM therapies: To enable characterization of the patient population and the activity of midostaurin, address the following issues with the “adis.xpt” files for D2201 and A2213:
- D2201, “RCULPLP6C” coding and “TNORLP1C” coding appear erroneous, as they indicates that of the 116 patients, (b) (4) had no prior relapse and no prior therapies, whereas according to Table 11-7 of the D2201 legacy CSR, (b) (4) of the 116 patients had no prior anti-neoplastic regimens.
 - Explain in which derived dataset to find the correct total number of prior therapies, or the minimum number of prior therapies if the total number is unknown. We find coding (b) (4) () unacceptable, because according to the define file, the total number of prior therapies is set to “0” if the number is unknown. Given this and the issues with “RCULPLP6C” coding, how can one differentiate which patients were treated in the front-line setting versus beyond?
 It is also unclear why some patients (in D0002, subjects 0192_00004 and 0503_00003) would have missing values under , rather than 0, per this definition. Even if the total number of prior therapies is unknown, however, you should specify the minimum number of prior therapies (e.g., 2 or more), knowledge of which would be required to confirm that the patient was eligible for D2201. In Table 11-7 of the D2201 legacy CSR, no missing values are mentioned when prior regimens are grouped by 1 vs 2 vs 3 or more.
 - For D2201 “adis.xpt”, explain why “TNORLP1N” is variably either blank or, in two cases, 0 (for patients 0150_00004 and 0515_00003) when the TNORLP1C is 0:

STAGE	SID1A	TNORLP1C	TNORLP1N
2	0142_00005	0	.
1	0150_00003	0	.
1	0150_00004	0	0
1	0150_00006	0	.
1	0150_00007	0	.
1	0150_00009	0	.
1	0150_00011	0	.
1	0150_00012	0	.
1	0150_00013	0	.
1	0150_00014	0	.
2	0150_00015	0	.
2	0150_00016	0	.
2	0150_00017	0	.
2	0150_00018	0	.

- Clarify whether this number of prior therapies includes therapies directed only at the ASM, or includes therapies directed at the associated hematologic neoplasm.
- Clarify if RCULPLP6C, defined as “Patient relapsed to prior SM therapies”, encompasses progressive/refractory disease in addition to relapse.
- In the adis.xpt files for D2201 and A2213, include best response to last treatment per investigator, and define the distinction between relapsed and refractory disease.

Response Due 10/25/2016:

10. ASM response assessments in D2201 and A2213: To facilitate response assessment,
- In patients with AHNMD, describe how response to midostaurin was assessed in subjects with AHNMD who were receiving other treatment for the AHNMD.
 - Describe how steroid use was factored into response assessment. Identify the duration of steroid use and the dose of steroids that rendered a patient potentially inevaluable for response in each trial.
 - For studies D2201 and A2213, identify the variable and derived data file that codifies when and how steroid use was factored into the response assessment. If there is no such variable, submit a data file with this information.

11. D2201 response assessment (aadj2.xpt file). To facilitate response assessment,
 - a. Clarify COM1A for SBJIN 16, considered unevaluable for response: “THE MAJORITY OF THE SSC VOTED THAT RESPONSE COULD BE ADJUDICATED IN THIS PATIENT AT THE LOWER DOSES OF STEROIDS FROM CYCLE 7 FORWARD ALSO BECAUSE THE INVESTIGATOR ADMINISTERED STEROIDS FOR PR. THE”
 - b. Explain why receipt of transfusions in cycle 1 would render a patient unevaluable for ultimate best response (SBJIN = 3), and why transfusions unrelated to SM would render a patient unevaluable for best response. (“SUBJECT RECEIVED RBC TRANSFUSIONS C1D15 AND D17. THE SSC FELT THE TRANSFUSIONS ARE NOT RELATED TO SM AND THEREFORE THE RESPONSE IS NOT EVALUABLE”)

12. ASM therapies: To facilitate evaluation of the patient population,
 - a. In Table 11-7 of the D2201 legacy CSR, clarify why 6 patients had ≥ 3 prior therapies, if the study excluded patients with relapse to 3 or more prior regimens of SM.
 - b. For D2201 and A2213, clarify in which data files information on prior and any subsequent allogeneic HSCT is provided.

13. MedDRA versions: The stated MedDRA versions appear inconsistent. The ADRG for A2213 states MedDRA v17.0 was used, whereas the define file for the ASM pool (cpkc412pooldefine.pdf dated 11 Aug 2016), Section 1.2 (AAERISK) states “Derivations are based on CPKC412D2201 and CPKC412A2213 analysis datasets A_AEV with the updated MedDRA version 18.1.” To facilitate safety review, clarify the MedDRA versions used for the A2213 study-specific datasets and for the pooled ASM datasets.

14. D2201 protocol deviations (aviopto.xpt file): We note that 27 patients in D2201 had “Disease diagnosis for ASM/MCL not met as per SSC adjudication.” To inform review of efficacy in ASM,
 - a. Explain why 23% of patients were entered onto a disease-specific study with the wrong diagnosis, and what variable has the flag to identify these patients in the derived datasets.
 - b. Submit all of the data used by the SSC for adjudication of diagnosis, or clarify where these are located.

Please confirm receipt.

Kind regards,

Jessica

Jessica Boehmer, MBA

Senior Regulatory Project Manager

Division of Hematology Products (DHP)

OHOP/OND/CDER

U.S. Food and Drug Administration

Tel: 301-796-5357

jessica.boehmer@fda.hhs.gov



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

/s/

JESSICA L BOEHMER
10/07/2016

Scott, Kimberly

From: Scott, Kimberly
Sent: Thursday, October 06, 2016 10:14 AM
To: 'Abraham, Abbey'
Cc: Qiu, Yuhong (yuhong.qiu@novartis.com)
Subject: NDA 207997, Midostaurin: Information Request for Filing Issues: response DUE 10am, 10/20/16

Importance: High

Good morning Abbey,

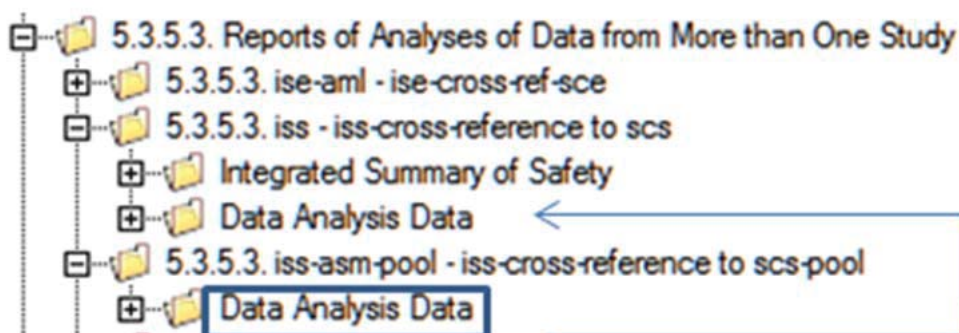
The Agency has reviewed your responses submitted 10/5/2016 to our Information Request for filing issues sent 9/30/0216 for NDA 207997, Midostaurin. We have the following comments:

1. Regarding your response to Comment 4a about missing study data sets, we have the following comments:
 - a. Based on the information that you provided, we will not expect you to submit the data sets for the following protocols: PKC412A2120, PKC412A0003, PKC412ADE02T, PKC412A001.
 - b. Based on your commitment made during the teleconference on 10/5/2016, we will expect the data sets by 10/20/2016 for the following protocols: PKC412A2104E2 and PKC412A2114.
 - c. You will still need to submit the study data sets for C99-PKC412A001, PKC412A0002, and PKC412a0006. If you will not be able to submit these by 10/20/2016, please propose an alternate date for submission. Please note that the proposed date will need to allow sufficient time for assessment and review of the data within the review cycle, and a very late submission may be considered a major amendment.
2. Regarding your response to Comment 7c about the placement of the SCP appendices in Module 5.3.5.3 AML section (Reports of Analyses of Data from More than One Study), move the following elements of SCP Appendix 1 and Appendix 2 currently in Module 5.3.5.3 as follows:
 - a. Move the post-text tables and figures, and datasets and define files corresponding to SCP Sections 3.8.2 to 3.8.7 (Module 2.7.2) to Module 5.3.3 (Reports of Human Pharmacokinetic Studies), and rename them appropriately.
 - b. Move the post-text tables and figures, and datasets and define files corresponding to SCP Section 3.9 (Module 2.7.2) to Module 5.3.3.5 (Population PK Study Reports), and rename them appropriately.
 - c. Move the post-text tables and figures, and datasets and define files corresponding to SCP Section 3.11 (Module 2.7.2) to the corresponding AdSM or AML Sections of Module 5.3.5.3 (Reports of Analyses of Data from More than One Study), and rename them appropriately.
 - d. The Pooling Plan and Statistical Methodology report in SCP Appendix 2, should be split and relocated along with its corresponding post-text tables and figures, and datasets described in Items (a) to (c) above. The reports should be named appropriately.

Also, in addition to the datasets mentioned in FDA Request 13, provide PK parameter data sets for dose exposure after multiple doses described in Section 3.8.3 of Module 2.7.2. In

addition to midostaurin and its active metabolites, provide the concentration and PK (if applicable) datasets for potency adjusted exposure to the sum of active moieties.

3. Regarding your response to Comment 7g, we reiterate that there should be one folder in 5.3.5.3 for the ISS in this submission. That folder should contain a subfolder for the ISS pdf and additional documents, and one subfolder for the Analysis Dataset. Ideally, there should be one Analysis Dataset, but if you have constructed a special subset for ASM alone, the folder with that dataset should be named as such and moved as a subfolder in the Analysis Dataset subfolder.



**Rename and move to a single subfolder
for all ISS datasets**

4. Your planned response to Comment 8 is not acceptable. Each document should be identifiable in the CTD structure. Either submit the CSR for A2301 as a single pdf with bookmarks, submit the CSR in granular format by section/appendix according to ICH E3, or submit parts with file names identifying which sections/appendices (according to ICH E3) are in the part. Do not split appendices across sections. For additional information about the appendices of a Clinical Study Report, see <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073113.pdf>.
5. The remainder of your responses in your 10/5/2016 submission are considered incomplete, since you only provide a plan and have not actually resolved the filing issues. You will need to submit a point by point response when you revise your NDA to address the filing issues that were identified in the Information Request sent 9/30/2016.

We strongly recommend that you review the current version of the comprehensive CTD table of contents to familiarize yourself with the expected granularity and placement of documents in the submission so that the reviewers will be able to find information quickly. As indicated in some of our comments, grouping multiple reports/documents into one pdf with a nondescriptive name is not acceptable; each individual report should go in its own folder with the associated documents and data files. For additional information, see: <http://www.fda.gov/downloads/drugs/developmentapprovalprocess/formsubmissionrequirements/electronic submissions/ucm163175.pdf>.

Please respond to the Agency's request by **10:00am (ET) on Thursday, October 20, 2016**.

Kindly confirm receipt.

Regards,

Kim

Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products

Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Rm 2222
Silver Spring, MD 20993
Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

APPEARS THIS WAY ON ORIGINAL

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
10/06/2016

Scott, Kimberly

From: Scott, Kimberly
Sent: Thursday, October 06, 2016 12:40 PM
To: Abraham, Abbey
Cc: Qiu, Yuhong (yuhong.qiu@novartis.com)
Subject: NDA 207997, Midostaurin: DPMH Information Request: DUE 10/28/16

Importance: High

Hi Abbey,

The Agency has the following information request for NDA 207997, Midostaurin:

- *In the A2301 study, there was one patient that became pregnant and underwent an elective abortion. Can you please provide more details about this pregnancy, including gestational age at the time of exposure, gestational age at the time of abortion, and any fetal malformations that were present? In addition, were there any other reports of pregnancy that have occurred with midostaurin use? If so, please provide the following information about any additional pregnancies, including gestational age at the time of exposure, pregnancy outcomes (gestational age at type of birth, type of delivery, spontaneous abortion, stillbirth, etc) and fetal outcomes (fetal malformations, small-for-gestational age, etc.).*

Please provide a response by 11:00AM on **Friday, October 28, 2016**.

Kindly confirm receipt.

Thanks,

Kim

Kimberly Scott, RN, BSN, OCN®

CDR, U.S. Public Health Service

Regulatory Health Project Manager

Division of Hematology Products

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, Bldg. 22, Rm 2222

Silver Spring, MD 20993

Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

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
05/01/2017

Scott, Kimberly

From: Scott, Kimberly
Sent: Thursday, October 06, 2016 10:05 AM
To: Abraham, Abbey
Cc: Qiu, Yuhong (yuhong.qiu@novartis.com)
Subject: NDA 207997, Midostaurin: Information Request for Filing Issues: response DUE 10am, 10/20/16

Importance: High

Good morning Abbey,

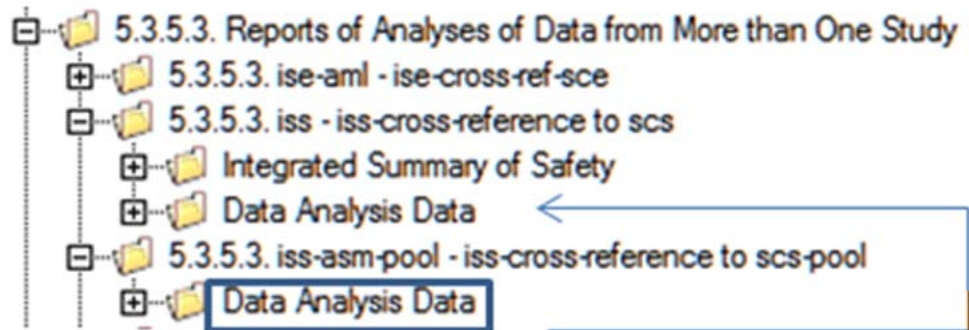
The Agency has reviewed your responses submitted 10/5/2016 to our Information Request for filing issues sent 9/30/0216 for NDA 207997, Midostaurin. We have the following comments:

1. Regarding your response to Comment 4a about missing study data sets, we have the following comments:
 - a. Based on the information that you provided, we will not expect you to submit the data sets for the following protocols: PKC412A2120, PKC412A0003, PKC412ADE02T, PKC412A001.
 - b. Based on your commitment made during the teleconference on 10/5/2016, we will expect the data sets by 10/20/2016 for the following protocols: PKC412A2104E2 and PKC412A2114.
 - c. You will still need to submit the study data sets for C99-PKC412A001, PKC412A0002, and PKC412a0006. If you will not be able to submit these by 10/20/2016, please propose an alternate date for submission. Please note that the proposed date will need to allow sufficient time for assessment and review of the data within the review cycle, and a very late submission may be considered a major amendment.
2. Regarding your response to Comment 7c about the placement of the SCP appendices in Module 5.3.5.3 AML section (Reports of Analyses of Data from More than One Study), move the following elements of SCP Appendix 1 and Appendix 2 currently in Module 5.3.5.3 as follows:
 - a. Move the post-text tables and figures, and datasets and define files corresponding to SCP Sections 3.8.2 to 3.8.7 (Module 2.7.2) to Module 5.3.3 (Reports of Human Pharmacokinetic Studies), and rename them appropriately.
 - b. Move the post-text tables and figures, and datasets and define files corresponding to SCP Section 3.9 (Module 2.7.2) to Module 5.3.3.5 (Population PK Study Reports), and rename them appropriately.
 - c. Move the post-text tables and figures, and datasets and define files corresponding to SCP Section 3.11 (Module 2.7.2) to the corresponding AdSM or AML Sections of Module 5.3.5.3 (Reports of Analyses of Data from More than One Study), and rename them appropriately.
 - d. The Pooling Plan and Statistical Methodology report in SCP Appendix 2, should be split and relocated along with its corresponding post-text tables and figures, and datasets described in Items (a) to (c) above. The reports should be named appropriately.

Also, in addition to the datasets mentioned in FDA Request 13, provide PK parameter data sets for dose exposure after multiple doses described in Section 3.8.3 of Module 2.7.2. In

addition to midostaurin and its active metabolites, provide the concentration and PK (if applicable) datasets for potency adjusted exposure to the sum of active moieties.

3. Regarding your response to Comment 7g, we reiterate that there should be one folder in 5.3.5.3 for the ISS in this submission. That folder should contain a subfolder for the ISS pdf and additional documents, and one subfolder for the Analysis Dataset. Ideally, there should be one Analysis Dataset, but if you have constructed a special subset for ASM alone, the folder with that dataset should be named as such and moved as a subfolder in the Analysis Dataset subfolder.



**Rename and move to a single subfolder
for all ISS datasets**

4. Your planned response to Comment 8 is not acceptable. Each document should be identifiable in the CTD structure. Either submit the CSR for A2301 as a single pdf with bookmarks, submit the CSR in granular format by section/appendix according to ICH E3, or submit parts with file names identifying which sections/appendices (according to ICH E3) are in the part. Do not split appendices across sections. For additional information about the appendices of a Clinical Study Report, see <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073113.pdf>.
5. The remainder of your responses in your 10/5/2016 submission are considered incomplete, since you only provide a plan and have not actually resolved the filing issues. You will need to submit a point by point response when you revise your NDA to address the filing issues that were identified in the Information Request sent 9/30/2016.

We strongly recommend that you review the current version of the comprehensive CTD table of contents to familiarize yourself with the expected granularity and placement of documents in the submission so that the reviewers will be able to find information quickly. As indicated in some of our comments, grouping multiple reports/documents into one pdf with a nondescriptive name is not acceptable; each individual report should go in its own folder with the associated documents and data files. For additional information, see: <http://www.fda.gov/downloads/drugs/developmentapprovalprocess/formsubmissionrequirements/electronic submissions/ucm163175.pdf>.

Please respond to the Agency's request by **10:00am (ET) on Thursday, October 20, 2016**.

Kindly confirm receipt.

Regards,

Kim

Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products

Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Rm 2222
Silver Spring, MD 20993
Phone: 240-402-4560 | Kimberly.scott@fda.hhs.gov

APPEARS THIS WAY ON ORIGINAL

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
05/01/2017



NDA 207997

**PROPRIETARY NAME
ACKNOWLEDGEMENT**

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080

ATTENTION: Abbey Abraham, PharmD
Regulatory Affairs – Therapeutic Area Director

Dear Dr. Abraham:

Please refer to your New Drug Application (NDA) dated and received July 25, 2016 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Midostaurin Capsules, 25 mg.

We acknowledge receipt of your correspondence, dated and received July 25, 2016, requesting a review of your proposed proprietary name, Rydapt.

If the application is filed, the user fee goal date is October 23, 2016.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Neil Vora, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-4845. For any other information regarding this application, contact Kimberly Scott, Regulatory Project Manager, in the Office of New Drugs at (240) 402-4560.

Sincerely,

{See appended electronic signature page}

Neil Vora, Pharm.D., MBA
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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

/s/

NEIL VORA
10/04/2016

MEMORANDUM OF TELECONFERENCE

Teleconference Date: September 30, 2016
Application Number: NDA 207997
Product Name: Midostaurin
Applicant Name: Novartis Pharmaceuticals

Subject:

The Agency requested a teleconference with Novartis to discuss the filing issues identified in the information request sent this afternoon for NDA 207997.

FDA Participants (CDER):

- Ann T. Farrell, MD, Division Director
- Donna Przepiorka, MD, PhD, Cross Discipline Team Leader
- Yvette Kasamon, MD, Clinical Reviewer
- Theresa Carioti, MPH, Chief, CPMS
- Ashley Ward, MD, Clinical Reviewer
- Kelly Norsworthy, MD, Clinical Reviewer
- Karen Boyd MS, PMP, Acting Regulatory Scientist, OHOP-IO
- Kimberly Scott, RN, BSN, OCN®, Regulatory Project Manager

Applicant Participants :

- Shanthi Ganeshan, PhD
- Yuhong Qiu, PhD
- Abbey Abraham PharmD
- Catherine Dutreix, PhD
- Alice Huntsman-Labed, PhD
- YinMiao Chen, PhD
- Luis Cunha

1.0 BACKGROUND:

NDA 207997, Midostaurin was submitted under rolling review by Novartis on August 29, 2016 for the following:

- Original 1: The treatment of patients with advanced systemic mastocytosis (ASM).
- Original 2: The treatment of patients with newly diagnosed FLT3 mutation positive acute myeloid leukemia (AML).

The Agency requested a teleconference with Novartis to discuss the filing issues identified in the information request for NDA 207997, sent on September 30, 2016, (see attached information request). The Agency's filing date is October 28, 2016.

2.0 DISCUSSION:

The Agency discussed the filing concerns as outlined in the Information Request sent on September 30, 2016. The Agency reminded Novartis that resolution of these issues was needed by October 20, 2016, to allow for completion of review for filing. The Agency offered to allow the NDA to resume rolling submissions if the Applicant did not think that the filing issues could be resolved by October 20, 2016.

The Agency requested a follow-up teleconference to discuss whether the Applicant would be able to resolve the filing deficiencies by the requested date.

3.0 ACTION ITEMS:

Novartis agreed to provide a timeline to address the Agency's concerns with the filing deficiencies at a follow-up teleconference on Wednesday, October 5, 2016.

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
03/03/2017

Scott, Kimberly

From: Scott, Kimberly
Sent: Friday, September 30, 2016 12:13 PM
To: 'Abraham, Abbey'
Cc: Qiu, Yuhong (yuhong.qiu@novartis.com)
Subject: NDA 207997, Midostaurin: Information Request for filing Issues DUE 10/20/16
Attachments: NDA 207997 IR for Filing Issues_20160930.pdf

Importance: High

Good morning Abbey,

Please see the attached information request for your August 29, 2016 submission for NDA 207997, Midostaurin. The Agency is requesting a follow up teleconference with Novartis this afternoon at 4:00pm – 4:30pm (ET). Please provide a teleconference number, and have your team available.

The deficiencies (attached) must be resolved by Thursday, October 20, 2016, in order for us to complete this initial review and determine whether your Application can be filed.

Kindly confirm receipt.

Thank you,
Kim

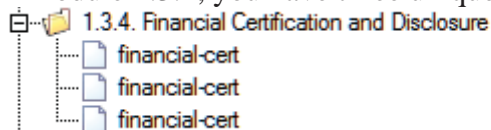
Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Rm 2222
Silver Spring, MD 20993
Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

We have initiated review of NDA 207997, and we note that all required information has not been submitted, and that the organization of the application does not comply with eCTD. The following deficiencies must be resolved by October 20, 2016, in order for us to complete this initial review and determine whether your application can be filed.

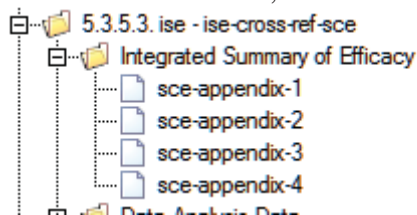
Clinical

1. Files do not have unique names or names that identify the content. For example:

a. In Module 1.3.4, you have three unique files, all titled “financial-cert”.

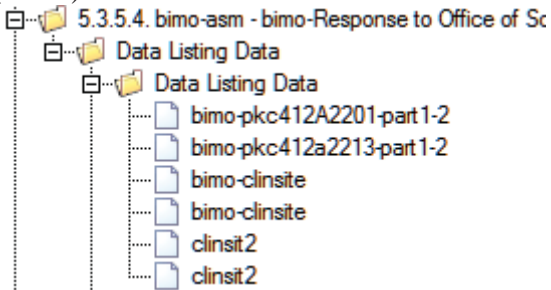


b. There are 4 appendices in the ISE folder in Module 5.3.5.3 AML section (Reports of Analyses of Data from More than One Study), but these appendices are not listed in the SCE table of contents, and the names of the files don't indicate what the files contain.



c. Similarly, there are 6 appendices in the Module 5.3.5.3 AML section (Reports of Analyses of Data from More than One Study) ISS folder, but these appendices are not listed in the content of the ISS, and the files names do not identify their contents.

d. There are two sets of duplicate files in the Data Listing dataset in the Module 5.3.5.4 (ASM) bimo folder



Revise your application to resolve duplicate or unclear names.

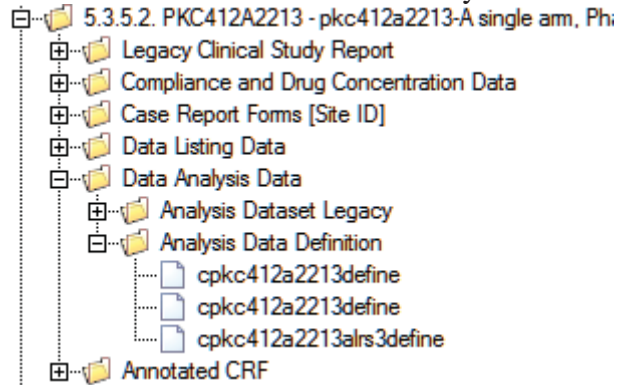
2. You have submitted revised documents or files as additions rather than replacements. For example, in the cover letter for the submission 9/15/2016, you state: “Please note that the new files do not replace the previously submitted versions and include the number “2” to indicate the more current version (e.g. clinsit2.xpt).”

This approach to submission of revised files is not acceptable. Revised documents or files must be submitted as a replacement of the prior version rather than as an additional document or file in the same folder. Review all of your submissions to identify revised documents or revised files submitted as additions and correct these to be replacements.

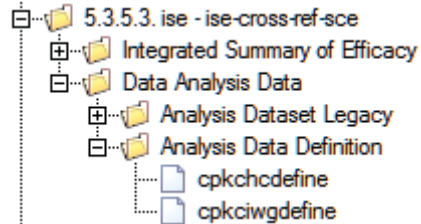
3. Each dataset (i.e., Data Listing Dataset, Analysis Dataset, etc) should have one define file. If a define file needs to be updated or revised, the corrected version of the define file must be submitted as a replacement to the original. Example of problems include:

a. There is no define file for the Data Listing dataset for PKC412A2213

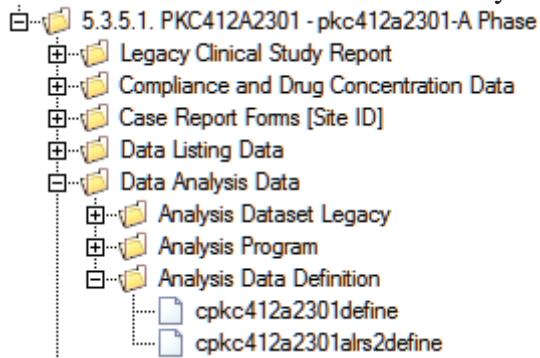
- b. There are 3 define files for the Analysis Data dataset for PKC412A2213



- c. There are 2 define files for the Module 5.3.5.3 AML ISE Analysis Data dataset



- d. There are 2 define files for the PKC412A2301 Analysis Data dataset, the PKC412A2104E1 Analysis Data dataset, and the PKC412A2106 Analysis Data dataset. The tree for the PKC412A2104E1 Analysis Data dataset is shown below as an example.



Review all of your datasets to ensure that each has only one define file.

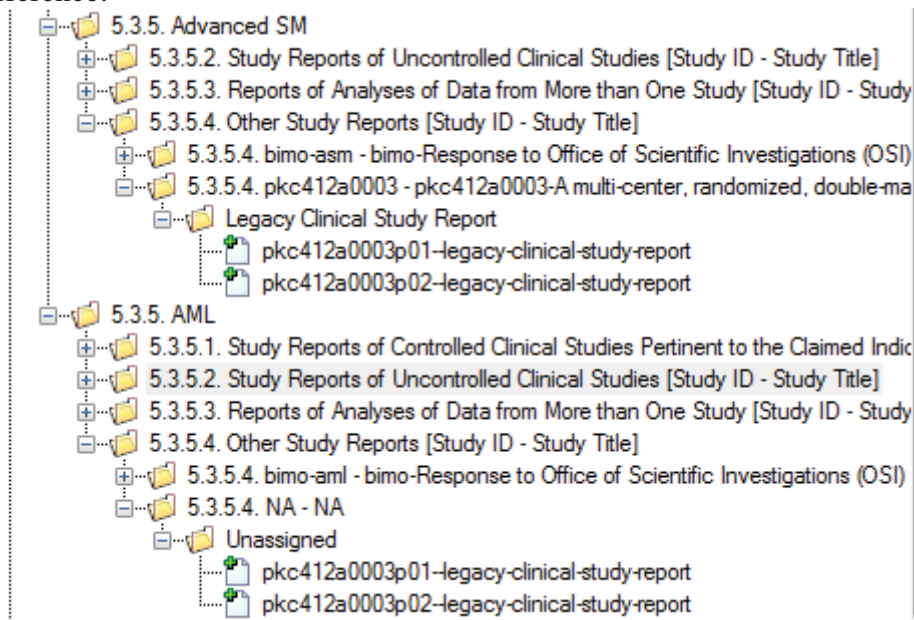
4. There are numerous data files that are missing.

- a. Submit complete datasets for the following clinical studies:
 - i. PKC412A2120 (Bioavailability in healthy volunteers – no data submitted)
 - ii. PKC412A0003 (Phase II in diabetic macular edema – no data submitted)
 - iii. PKC412ADE02T (Phase II after HSCT – no data submitted)
 - iv. PKC412A001 (SAD in healthy volunteers – only PK data submitted)
 - v. C99-PKC412A001 (Dose escalation in diabetic patients –only PK data submitted)
 - vi. PKC412A0002 (Dose escalation in advanced cancer – only PK data submitted)
 - vii. PKC412a0006 (Phase II in CLL/NHL – only PK data submitted)
 - viii. PKC412A2104E2 (Phase II in AML – only PK data submitted)
 - ix. PKC412A2114 (Phase I/II in pediatric leukemia – only PK data submitted)
- b. The ISS dataset is incomplete. Submit the ISS files for medical history, concomitant medications, exposure, laboratory test results and vital signs.

5. The key for many of the variables listed in the define files is incomplete, so the data files are not reviewable. As one example, in the Data Analysis Dataset for study A2301, AAEV.XPT:
 - a. ETH2C variable is coded as 0 or -1 for some subjects; codes missing from key
 - b. AEDISC variable and AEVSER1C variable are supposed to be coded as 0 (no) or 1 (yes) but all subjects are actually coded as 1 or [missing] for these variables
 - c. AEVREL1C variable is coded as -2 and 7 for some subjects; codes missing from key
 - d. AEVREL2C variable is coded as -2, 2, 10, and 19 for some subjects; codes missing from key
 - e. AEVREL4 variable is coded as -2 and 4 for some subjects; codes missing from key
 - f. AEVSMR1C variable is coded as -1, 0 and 9 for some subjects; codes missing from key

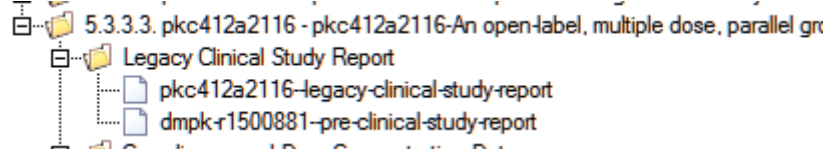
Review the define files for all key clinical studies and submit revised versions with complete keys to decode the values listed in the datasets for each of the variables.

6. We are unable to use the ISS data file aident.xpt to confirm the findings in your analyses, since the file is missing a variable for subject's diagnosis. Revise aident.xpt to include a variable for diagnosis. The data element should specify the actual diagnosis (i.e, healthy volunteer, AML, etc) rather than an arbitrary grouping of diagnoses. Additionally, the variable DISCAT1C is blank for the majority of subjects. If this is the variable used to categorize patients for pools in your analyses in the ISS, the revised file should include the DISCAT1C for each subject in the file.
7. There are numerous documents that have been placed in the wrong file or misnamed.
 - a. DMPKR1500887-01 ((b) (4) DDI study): Currently in Module 5.3.5 under both indications. This is not an efficacy or safety study and should be moved out of Module 5.3.5.
 - b. PKC412A0003 (Phase II in diabetic macular edema): Currently in Module 5.3.5 under both indications, but for AML indication, the folder title should refer to the study and not be "NA-NA" then "unassigned". See screenshot below for an illustration of the difference:



- c. Summary of Clinical Pharmacology (addendum to SCP in 2.7.2): Currently in Module 5.3.5 AML section. This is not an efficacy or safety study and should be moved to Module 2.7.2.

- d. PKC412ADE02T (Phase II in AML after HSCT): Currently in Module 5.3.5.3 AML section (Reports of Analyses of Data from More than One Study). This study report discusses only one study and should be moved to 5.3.5.4 in its own folder.
- e. The steering committee report for PKC412D2201 in Module 5.3.5.3 AML section (Reports of Analyses of Data from More than One Study) is a protocol-related document and should be moved to the protocol information for PKC412D2201
- f. The study report for dmpk-r 1500881 is in the Module 5.3.3.3 folder for PKC412A2116, but dmpk-r 1500881 doesn't appear to be related to PKC412A2116. dmpk-r 1500881 should be moved to the correct folder.



- g. There are two ISS files in Module 5.3.5.3 AML section (Reports of Analyses of Data from More than One Study). All of the ISS files should be in one folder labeled ISS.
- h. Appendix 6 in Module 5.3.5.3 AML section (Reports of Analyses of Data from More than One Study) appears to be safety narratives for PKC412A2301. The CSR for this protocol should contain all narrative rather than having narrative split across eCTD sections. Move this document to the CSR folder.

Revise the submission so that the files are in the proper folders.

8. You have written CSRs in granular format but submitted them as “Legacy Clinical Study Reports” in multiple unidentifiable parts. “Legacy Clinical Study Reports” must be submitted as a single PDF with bookmarks to allow for navigation. Please see guidance for more details at http://www.fda.gov/RegulatoryInformation/Guidances/ucm126959.htm#_Toc111368408. The following CSRs should be reformatted and resubmitted either as a single pdf file, or if that is too large, in granular format:
 - a. PKC412A0003
 - b. PKC412A2301
9. You submitted an appendage to the CSR for PKC412A2106. Given the extent of the corrections made to the CSR for PKC412A2106 (submitted as an original with an addendum that contains over 1000 pages worth of changes), it is not reviewable in its current format. Delete the appendage and submit a complete revised CSR as a replacement to the original CSR. The revision should contain a section that briefly describes the nature of the changes made from the original, along with rationale.
10. The clinical study synopses are missing in Module 2.7.6. Submit the synopses for all of the clinical studies. The synopses may be submitted as individual pdfs in Module 2.7.6 or as a single pdf containing all of the synopses bookmarked by protocol (and preferably in the same order is in the table).
11. The Summary of Clinical Efficacy (SCE) for AML does not include all required elements for an Integrated Summary of Efficacy (ISE), and therefore the ISE for AML is missing from your submission. Since the Clinical Summary already exceeds the 400 page limit, you cannot simply revise and lengthen the SCE. You will need to submit an ISE for AML to Module 5.3.5.3.

Clinical Pharmacology

12. Provide the SAS data sets (*.xpt) for the pharmacokinetic parameters for the following studies: A0006, A2104, A2104E1, A2109, A2112, and A2301.

13. Provide separate SAS data sets (*.xpt) for pharmacokinetic parameter data sets for the parent drug midostaurin and its active metabolites used to estimate the:
 - dose exposure after single dose by food state and dose, described in Section 3.8.2 of Module 2.7.2.
 - steady state and accumulation ratio described in Section 3.8.4 of Module 2.7.2.
 - dose proportionality described in Section 3.8.5 of Module 2.7.2.
 - inter- and intra-patient variability described in Section 3.8.5 of Module 2.7.2.
14. Provide all NONMEM control stream/R code files along with the NONMEM dataset for the population PK analyses reported in pkc412a-modeling-report-aml and pkc214a-modeling-report-asm. Furthermore, all NONMEM control stream/R code files along with the NONMEM dataset for the population PK analysis and simulations used for the report pkc214a-poppk. Provide all SAS program files along with source data for the analyses reported in SCP Appendix 1 and SCP Appendix 2.
15. Provide a separate study report for the exposure-response analyses where the analysis results are organized for relevant topics and discussed in detail for each indication and place in appropriate section of Module 5.
16. Provide model files used to generate final PBPK simulations in both the PBPK reports (Study 1500881 and Study 1500887) (e.g. drug model files, population files, and workspace files, .cmp, .lbr, and .wks). The files should be executable by the FDA reviewers using (b)(4). Provide software specific excel files such as parameter estimation data files and simulation outputs as MS Excel files.

If you need technical advice to resolve the issues identified above in eCTD, please contact the eSub team at esub@fda.hhs.gov

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
09/30/2016

Scott, Kimberly

From: Scott, Kimberly
Sent: Thursday, September 22, 2016 3:40 PM
To: Abraham, Abbey
Cc: Qiu, Yuhong (yuhong.qiu@novartis.com)
Subject: FW: NDA 207997, Midostaurin Non Clinical IR: clarification and reports- FDA response

Importance: High
Sensitivity: Confidential

Follow Up Flag: Follow up
Flag Status: Flagged

Hi Abbey,

Please see the non-clinical teams response to your questions below (in red)

Yes, "-" means not tested for that parameter. We are looking into the feasibility of submitting the reports by Nov 17 but just wanted to clarify.

1. You wanted formal reports for both the kinase panel and the secondary pharmacology data or just the latter?

FDA Response to Question 1: Just the latter.

2. Are there specific off target pharmacology data the team is interested in?

FDA Response to Question 2: It is very early in the review process to comment, but having a complete understanding of methods used and secondary targets assessed will expedite the review process if concerns arise regarding specific off target pharmacology data.

Kindly confirm receipt.

Thank you,
Kim

From: Scott, Kimberly
Sent: Thursday, September 22, 2016 12:31 PM
To: Simpson, Natalie
Cc: Sheth, Christopher
Subject: FW: NDA 207997, Midostaurin Non Clinical IR: clarification and reports
Sensitivity: Confidential

Hi Natalie,

Novartis is requesting feedback for the following questions:

Yes, "-" means not tested for that parameter. We are looking into the feasibility of submitting the reports by Nov 17 but just wanted to clarify.

1. You wanted formal reports for both the kinase panel and the secondary pharmacology data or just the latter?
2. Are there specific off target pharmacology data the team is interested in?

Thank you,
Kim

From: Abraham, Abbey [<mailto:abbey.abraham@novartis.com>]
Sent: Thursday, September 22, 2016 10:34 AM
To: Scott, Kimberly
Cc: Qiu, Yuhong
Subject: RE: NDA 207997, Midostaurin Non Clinical IR: clarification and reports
Sensitivity: Confidential

Hi Kim

Yes, “-“ means not tested for that parameter. We are looking into the feasibility of submitting the reports by Nov 17 but just wanted to clarify.

1. You wanted formal reports for both the kinase panel and the secondary pharmacology data or just the latter?
2. Are there specific off target pharmacology data the team is interested in?

Thanks

Abbey Abraham
Phone +1 862-778-8998

From: Scott, Kimberly [<mailto:Kimberly.Scott@fda.hhs.gov>]
Sent: Wednesday, September 21, 2016 2:02 PM
To: Abraham, Abbey
Cc: Qiu, Yuhong
Subject: NDA 207997, Midostaurin Non Clinical IR: clarification and reports
Importance: High
Sensitivity: Confidential

Hi Abbey,

The reviewers are requesting confirmation with Novartis regarding the following information:

- Please clarify what “-“ means in the second attached file labeled PSP_NVP-BVN113-Cardinal_PKC412 (e.g., does is designate that they did not evaluate a particular target/parameter).

If feasible, please submit the formal reports with methods by **Thursday, November 17, 2016**.

Kindly confirm receipt.

Thanks,
Kim

From: Abraham, Abbey [<mailto:abbey.abraham@novartis.com>]
Sent: Tuesday, September 20, 2016 11:26 PM
To: Scott, Kimberly
Cc: Qiu, Yuhong
Subject: RE: NDA 207997, Midostaurin Non Clinical IR: Due 9/21
Sensitivity: Confidential

Hi Kim

Please see attached the Kinase screen data (Midostaurin ProteinKinaseProfile....pdf) which is being sent as a lab notebook due to the fact a formal report on all the full panel was not completed and will not be possible in the timetable requested by the agency. The secondary pharmacology data for receptors, ion channels, and transporters is also

attached (PSP NVP-BVN113...pdf) but again as this was not published into a formal report, the data is only immediately available in this format. Please advise if these are acceptable.

Thank you

Abbey Abraham

Phone +1 862-778-8998

From: Scott, Kimberly [<mailto:Kimberly.Scott@fda.hhs.gov>]
Sent: Monday, September 19, 2016 11:50 AM
To: Abraham, Abbey
Cc: Qiu, Yuhong
Subject: RE: NDA 207997, Midostaurin Non Clinical IR: Due 9/21
Sensitivity: Confidential

Hi Abbey,

The Agency would like to see the percent inhibition for all the kinases that they tested, not just those with inhibition (b) (4). So we would like additional information to that provided in Table 3-1 of Report RD-2008-01357.

Please confirm receipt.

Thanks,

Kim

Kimberly Scott, RN, BSN, OCN □
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Rm 2222
Silver Spring, MD 20993
Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

From: Abraham, Abbey [<mailto:abbey.abraham@novartis.com>]
Sent: Monday, September 19, 2016 11:04 AM
To: Scott, Kimberly
Cc: Qiu, Yuhong
Subject: RE: NDA 207997, Midostaurin Non Clinical IR: Due 9/21
Sensitivity: Confidential

Hi Kim

Had one clarification regarding the first part of the information request. From the pharmacology written summary, there is a link under table 2-1 to report RD-2008-01357 titled "Biological profile of PKC412 and two metabolites". Section 3.1 of this report provides the Kinase inhibition information, including the list of kinases with greater than 80% inhibition (Table 3-1). Was the team requesting additional information or was this the report that was being requested?

Thanks

Abbey Abraham, PharmD

Oncology Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation

Phone +1 862-778-8998
Fax +1 973-781-3473
abbey.abraham@novartis.com
www.novartis.com

From: Scott, Kimberly [<mailto:Kimberly.Scott@fda.hhs.gov>]
Sent: Monday, September 19, 2016 9:30 AM
To: Abraham, Abbey
Cc: Qiu, Yuhong
Subject: NDA 207997, Midostaurin Non Clinical IR: Due 9/21
Importance: High
Sensitivity: Confidential

Good morning Abbey,

The Agency would like to request the following non-clinical information for NDA207997, Midostaurin:

- Submit the study report(s) for the kinase screen data described in the pharmacology written summary, in which you screened CGP41251 (PKC412) at a concentration of 1 μ M in replicate against ^{(b) (4)} purified kinases; and, if conducted (in house or contracted), secondary pharmacology data for receptors, ion channels, and transporters by COB 9/22/2016.

Please submit your response by 2:00pm on Wednesday, September 21, 2016.

Please acknowledge receipt of this email.

Kind regards,

Kim

Kimberly Scott, RN, BSN, OCN [□]
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Rm 2222
Silver Spring, MD 20993
Phone: 240-402-4560 | Kimberly.scott@fda.hhs.gov

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
05/01/2017

Scott, Kimberly

From: Scott, Kimberly
Sent: Tuesday, September 20, 2016 12:40 PM
To: 'Abraham, Abbey'
Cc: Qiu, Yuhong (yuhong.qiu@novartis.com)
Subject: NDA 207997, Midostaurin: IR- respond ASAP
Attachments: Highlights_ClinPharm_and_Cardiac_Safety.doc

Importance: High

Good afternoon Abbey,

The Agency is requesting Novartis to complete the attached ClinPham and Cardiac Safety Table for NDA 207997, Midostaurin and return it as soon as possible.

Please confirm receipt of this email.

Kind regards,

Kim

Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Rm 2222
Silver Spring, MD 20993
Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

Table 1. Highlights of Clinical Pharmacology and Cardiac Safety

Therapeutic dose and exposure	Include maximum proposed clinical dosing regimen Mean (%CV) C_{max} and AUC at the single maximum proposed clinical dose Mean (%CV) C_{max} and AUC at the steady state with the maximum proposed clinical dosing regimen	
Maximum tolerated dose	Include if studied or NOAEL dose	
Principal adverse events	Include most common adverse events; dose limiting adverse events	
Maximum dose tested	Single Dose	Specify dose
	Multiple Dose	Specify dosing interval and duration
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV) C _{max} and AUC
	Multiple Dose	Mean (%CV) C _{max} and AUC
Range of linear PK	Specify dosing regimen	
Accumulation at steady state	Mean (%CV); specify dosing regimen	
Metabolites	Include listing of all metabolites and activity	
Absorption	Absolute/Relative Bioavailability	Mean (%CV)
	T _{max}	• Median (range) for parent • Median (range) for metabolites
Distribution	V _d /F or V _d	Mean (%CV)
	% bound	Mean (%CV)
Elimination	Route	• Primary route; percent dose eliminated • Other routes
	Terminal t _{1/2}	• Mean (%CV) for parent • Mean (%CV) for metabolites
	CL/F or CL	Mean (%CV)
Intrinsic Factors	Age	Specify mean changes in C _{max} and AUC
	Sex	Specify mean changes in C _{max} and AUC
	Race	Specify mean changes in C _{max} and AUC
	Hepatic & Renal Impairment	Specify mean changes in C _{max} and AUC
Extrinsic Factors	Drug interactions	Include listing of studied DDI studies with mean changes in C _{max} and AUC
	Food Effects	Specify mean changes in C _{max} and AUC and meal type (i.e., high-fat, standard, low-fat)
Expected High Clinical Exposure Scenario	Describe worst case scenario and expected fold-change in C_{max} and AUC. The increase in exposure should be covered by the supra-therapeutic dose.	
Preclinical Cardiac Safety	Summarize <i>in vitro</i> and <i>in vivo</i> results per S7B guidance.	
Clinical Cardiac Safety	Describe total number of clinical trials and number of subjects at different drug exposure levels. Summarize cardiac safety events per ICH E14 guidance (e.g., QT prolongation, syncope, seizures, ventricular arrhythmias, ventricular tachycardia, ventricular fibrillation, flutter, torsade de pointes, or sudden deaths).	

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
09/20/2016

Scott, Kimberly

From: Scott, Kimberly
Sent: Tuesday, September 20, 2016 8:53 AM
To: Abraham, Abbey
Cc: Qiu, Yuhong (yuhong.qiu@novartis.com)
Subject: NDA 207997, Midostaurin: IR Due COB September 21st

Importance: High

Good morning Abbey,

The Agency is requesting the following information for NDA 207997, Midostaurin:

1. For study A2301, we note that the site ID listed in the PDF list of investigators' financial disclosure information (Module 1.3.4) is different from that used in the rest of the submission (bimo-clin-site.xpt file, data analysis and data listing .xpt files, and in the file tree for the case report forms). In addition, the Hospital ID # listed in the CRFs themselves does not match either of the aforementioned site ID numbers – does that refer to the patient's hospital medical record number? If so, is there a field on the CRF itself that gives the Site ID number? Please explain these discrepancies, and provide a table in Module 1.3.4 that lists the site IDs used in the PDF list of investigators, along with a key to the site number for each site used in the rest of the submission as per the example below:

Site Name/Address if needed to distinguish	Financial Disclosure PDF Site #	Rest of Submission Site #
		(b) (6)

2. In the "bimo-clin-site" .xpt file for D2201, clarify whether the response rate a) is for all evaluated patients or is limited to patients in the primary efficacy population, and b) is per the investigator or per the Steering Committee.
3. Per the "financial-cert" forms in module 1.3.4, some investigators in D2201, A2213, A2301, A2104, A2104E1 and A2106 had missing financial disclosure forms. Please list the investigators, and describe the reasons for the missing information in each case and what steps were undertaken in effort to obtain the missing information. Please also revise the FDA 3454 forms to certify that due diligence was exercised in attempting to obtain this information.
4. For A2213, as responses were per investigator only, explain what measures you took to evaluate the accuracy of the response assessment and duration, and describe the outcomes.
5. Cutoff dates: For D2201 and A2213, clarify the data cutoff dates for both safety and efficacy, other than those used for the ASM historical comparison, and resolve the inconsistencies throughout the submission.

For example, SCS Section 1.4.7 states that the ARGUS reporting period for A2213 ended 30 April 2016, whereas Section 3.1 of the "cpkc412scspooldefine" file in Module 5.3.5.3 instead states:

The following cutoff dates will be applied for studies for the SCS.

Study	Cutoff date
CPKC412A2301	01APR2015
CPKC412D2201	01-DEC-2014
CPKC412A2213	03-DEC-2012

On the other hand, the A2213 CSR sites a data cut-off date of 03 Dec 2012 at which point 7 patients remained on midostaurin. Confirm that safety, exposure and survival outcomes were updated for these patients as requested at the pre-BLA meeting, and that the SCS, ISS, and corresponding datasets (including exposure) reflect the April 2016 cut-off date.

Revise all associated define files for ASM studies to have the corrected data cutoff dates.

If datasets for an individual study have different cut off dates, please include a table that lists, by study, the name of the analysis legacy dataset and corresponding cut-off date for those datasets that include time-dependent variables. Ensure consistency with the revised define files.

6. A number of key analyses are missing and/or are insufficiently described in your SCE for AML. Further IRs may be forthcoming, but for now, at the application orientation meeting, please show a table of efficacy results from all studies that involved AML patients to allow comparison of the results across studies. You should include a column or row for each study, and indicate the population (untreated or r/r, age cutoff, diagnostic +/-unselected, etc), the treatment, comparator arm (for A2301), response rates in total and broken down by depth of response, DOR, EFS and OS (the latter two for A2301 only).
7. As a reminder, updated OS data for Study A2301 are required as part of the 120-day safety update.
8. For the D2201 alrs2 .xpt file and A2213 alrs3 .xpt file,
 - a. Please explain why many entries under “B_CTC_1C” are blank for post-baseline laboratory results.
 - b. Clarify why many entries appear to have a missing worse-from-baseline flag (WRSCTC1C), including for post-baseline labs that have a baseline available.
 - c. Please explain how to identify which laboratory values were SAE’s. Refer to the IND 57120 advice letter from 13 June 2016 that requested inclusion of an SAE flag in derived laboratory datasets. If an SAE flag was not included, revise these .xpt files to include this information or explain why this is not possible.
9. For the safety pool: Please explain why the pooled datasets for D2201 and A2213 are submitted under the AML module 5.3.5

Please respond to the request by COB tomorrow, September 21, 2016.

Please confirm receipt of this email.

Thank you,

Kim

Kimberly Scott, RN, BSN, OCN®

CDR, U.S. Public Health Service

Regulatory Health Project Manager

Division of Hematology Products

Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Rm 2222
Silver Spring, MD 20993
Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

APPEARS THIS WAY ON ORIGINAL

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
09/20/2016

Scott, Kimberly

From: Scott, Kimberly
Sent: Monday, September 19, 2016 9:30 AM
To: Abraham, Abbey
Cc: Qiu, Yuhong (yuhong.qiu@novartis.com)
Subject: NDA 207997, Midostaurin Non Clinical IR: Due 9/21

Importance: High

Good morning Abbey,

The Agency would like to request the following non-clinical information for NDA207997, Midostaurin:

- Submit the study report(s) for the kinase screen data described in the pharmacology written summary, in which you screened CGP41251 (PKC412) at a concentration of 1 μ M in replicate against ^{(b) (4)} purified kinases; and, if conducted (in house or contracted), secondary pharmacology data for receptors, ion channels, and transporters by COB 9/22/2016.

Please submit your response by 2:00pm on Wednesday, September 21, 2016.

Please acknowledge receipt of this email.

Kind regards,

Kim

Kimberly Scott, RN, BSN, OCN[®]

CDR, U.S. Public Health Service

Regulatory Health Project Manager

Division of Hematology Products

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, Bldg. 22, Rm 2222

Silver Spring, MD 20993

Phone: 240-402-4560 | Kimberly.scott@fda.hhs.gov

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
09/19/2016

Scott, Kimberly

From: Scott, Kimberly
Sent: Friday, September 16, 2016 10:09 AM
To: Abraham, Abbey
Cc: Qiu, Yuhong (yuhong.qiu@novartis.com)
Subject: NDA 297997 Midostaurin: Clinical Inspection data: IR Due 2pm today

Importance: High

Good morning Abbey,

Please respond to the following information request for NDA 207997, Midostaurin for the site inspection data listing by 2:00pm today:

- *Submit the protocol deviation/violation study subject data listing information as separate pdf files for the following requested clinical study sites:*
 - *Site 180 Dr. J-C Nelemans (Protocol D2201);*
 - *Site 150 Dr. Andreas Reiter (Protocol D2201);*
 - *Site 2937 Dr. Harmut Doehner (Protocol A2301);*
 - *Site 2941 Dr. Arnold Ganser (Protocol A2301), and*
 - *U.S. Site 0177/0234 Dr. Jonathan Koltz (Protocol A2301).*

Please acknowledge receipt of this email.

Kind regards,

Kim

Kimberly Scott, RN, BSN, OCN®

CDR, U.S. Public Health Service

Regulatory Health Project Manager

Division of Hematology Products

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, Bldg. 22, Rm 2222

Silver Spring, MD 20993

Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

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
09/16/2016

Scott, Kimberly

From: Scott, Kimberly
Sent: Friday, September 16, 2016 4:21 PM
To: 'Abraham, Abbey'
Cc: Qiu, Yuhong (yuhong.qiu@novartis.com)
Subject: NDA 207997: Follow-up on Applicant Orientation Meeting; needs foreign visitor clearance

Importance: High
Sensitivity: Confidential

Good afternoon Abbey,

In regards to the foreign visitor forms you sent, I had a few problems.

A few things with this request (it's almost all about Alice):

1. You have a document with Alice label of Renaud Capdeville, but it has a duplicate of Alice Labeled's form. So, Renaud's is missing.
2. Alice Labeled's passport expired on (b) (6). Unless it is renewed, I can't let her in... I can't have a document that says it's renewed. I need the renewed passport.
3. Alice's name in the email is Alice Labeled-Huntsman. If that is what is on her passport, then I need to know...once it's renewed.

Here's the list of those attending:

- Lisa Rojkjaer, MD, Global Clinical Program Head, OGD
- Renaud Capdeville, MD, Global Program Head, Oncology Global Development (OGD)
- Catherine Dutreix, PhD, Senior Fellow, Clinical Pharmacology
- Alice Labeled-Huntsman, PhD, Program Statistician, Biostatistics, OGD
- Abhramoy Mandal, PhD, Senior Programmer, Biostatistics and Data Management
- Iulian Alecu, MD, Brand Safety Leader, OGD

I won't proceed until I hear back from you. However, this needs to be processed asap or I might not be able to get it processed in time.

Please confirm receipt of this email.

Thanks,

Kim

Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Rm 2222
Silver Spring, MD 20993
Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

APPEARS THIS WAY ON ORIGINAL

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
09/19/2016

Scott, Kimberly

From: Scott, Kimberly
Sent: Thursday, September 15, 2016 11:36 AM
To: Abraham, Abbey
Cc: Qiu, Yuhong
Subject: NDA 207997 midostaurin: Information Request BIMO Database: DUE 2:00PM tomorrow
Attachments: Novartis response BIMO Clinsite.pdf
Importance: High
Sensitivity: Confidential

Good afternoon Abbey,

The Agency has reviewed your response and is requesting additional information regarding the BIMO Database:

- We are unable to identify SBJALV1C variable in your AEFF dataset for Study PKC412A2301.
- Please include this variable and resubmit the efficacy dataset.

Please submit the requested information by **2:00PM (ET) tomorrow, Friday, September 16, 2016.**

Please confirm receipt of this email.

Thank you,

Kim

Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Rm 2222
Silver Spring, MD 20993
Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

From: Abraham, Abbey [<mailto:abbey.abraham@novartis.com>]
Sent: Wednesday, September 07, 2016 4:15 PM
To: Scott, Kimberly
Cc: Qiu, Yuhong
Subject: RE: NDA 207997 midostaurin Information Request: Due COB today
Sensitivity: Confidential

Hi Kim

Please see the Novartis response to the Information Request below. We will file this to the IND by early next week. I will be out of the office until Monday Sept 12th so request that Yuhong please be copied on any emails

Thank you
Abbey Abraham
Phone +1 862-778-8998

Novartis Response

(b) (4)

From: Scott, Kimberly [<mailto:Kimberly.Scott@fda.hhs.gov>]
Sent: Wednesday, September 07, 2016 9:50 AM
To: Abraham, Abbey
Subject: NDA 207997 midostaurin Information Request: Due COB today
Importance: High
Sensitivity: Confidential

Good morning Abbey,

The Agency is requesting the following information:

In review of BIMO CLINSITE dataset submitted on 8/29/16, we are unable to complete QC process for CDER's Clinical Investigator Site Selection Tool, which loaded with data you provided in the clinsite.xpt for Study PKC412A2301. Please explain further how the TRTEFFE variable was calculated for each site by treatment arm.

Please acknowledge receipt of this email, and respond by COB today.

Thank you,
Kim
Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Rm 2222
Silver Spring, MD 20993

Appears this way on original



Abbey Abraham, Pharm.D.
Director
Drug Regulatory Affairs
Oncology Global Development

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080
Tel: 862-778-8998
Fax: 973-781-5217
Email: abbey.abraham@novartis.com

Ann Farrell, M.D.
Division Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Hematology Products
Office of Oncology Drug Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

NDA No.: 207997

**RYDAPT® (midostaurin, PKC412)
25 mg capsules**

Other: Response to Information Request

Dear Dr. Farrell:

Reference is made to NDA 207997 which was completed submission on August 29, 2016. An information Request was received from FDA via email on September 7 as follows:

In review of BIMO CLINSITE dataset submitted on 8/29/16, we are unable to complete QC process for CDER's Clinical Investigator Site Selection Tool, which loaded with data you provided in the clinsite.xpt for Study PKC412A2301. Please explain further how the TRTEFFE variable was calculated for each site by treatment arm.

Novartis provided the following response by email to FDA project manager Kimberly Scott on September 7 and hereby submits the response formally to NDA 207997.

Novartis Response



(b) (4)

Should you have any comments or questions regarding this submission, please do not hesitate to contact me directly at (862) 778-8998, or by email at abbey.abraham@novartis.com. In my absence, please contact Dr. Yuhong Qiu at (862) 778-3753 or Dr. Shanthi Ganeshan at (862) 778-2673.

Sincerely,

Abbey Abraham, PharmD.
Director
Drug Regulatory Affairs
Oncology Global Development

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
05/01/2017

Scott, Kimberly

From: Scott, Kimberly
Sent: Tuesday, September 13, 2016 3:12 PM
To: 'Abraham, Abbey'
Cc: Qiu, Yuhong (yuhong.qiu@novartis.com)
Subject: NDA 207997 Midostaurin: Information Request with attached picture
Attachments: 7-25-16 submission snapshot.docx

Importance: High

Tracking:	Recipient	Read
	'Abraham, Abbey'	
	Qiu, Yuhong (yuhong.qiu@novartis.com)	
	Scott, Kimberly	Read: 9/13/2016 3:13 PM

Good afternoon Abbey,

The Agency has the following information requests for NDA 207997, Midostaurin.

- Explain the content and location of the ASM analysis legacy datasets submitted in 7/25/2016 module 5.3.5.3. Refer to the attached snapshot of the submission. Attachment 1 to the cover letter does not mention these datasets. The associated define files (cpkciwgdefine, cpkchcdefine) with one exception do not describe to which ASM study the analysis legacy data belong, and the context is unclear. Most of these datasets are specific to D2201, others (Adiagns) are specific to A2213, and others (e.g., Ahcomp) have both.
- Please explain what is in each data file in the Analysis Dataset Legacy folder in the snapshot attached. Please also explain why datasets specific to one study are submitted under “reports of analysis of data from more than one study”, and why there are two define files for one data folder.

Please respond by COB Wednesday September 14, 2016.

Please acknowledge receipt of my email.

Kind regards,

Kim

Kimberly Scott, RN, BSN, OCN®

CDR, U.S. Public Health Service

Regulatory Health Project Manager

Division of Hematology Products

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, Bldg. 22, Rm 2222

Silver Spring, MD 20993

Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

Hi Kim, Donna has approved the IR below. There is a picture associated with it, attached. Thus, at day's end, I have 2 IR's due by COB tomorrow, and the BIMO IR due Friday. Please confirm – thanks (Phew!)

Explain the content and location of the ASM analysis legacy datasets submitted in 7/25/2016 module 5.3.5.3. Refer to the attached snapshot of the submission. Attachment 1 to the cover letter does not mention these datasets. The associated define files (cpkciwgdefine, cpkchcdefine) with one exception do not describe to which ASM study the analysis legacy data belong, and the context is unclear. Most of these datasets are specific to D2201, others (Adiagns) are specific to A2213, and others (e.g., Ahcomp) have both.

Please explain what is in each data file in the Analysis Dataset Legacy folder in the snapshot attached. Please also explain why datasets specific to one study are submitted under “reports of analysis of data from more than one study”, and why there are two define files for one data folder. [Respond by COB Wednesday September 14, 2016.](#)



Sequence

- 0003 (4) 08/29/2016 ORIG-1 /Multiple Categories/Subcategories
 - 0002 (3) 07/25/2016 ORIG-1 /Multiple Categories/Subcategories
 - 1. Regional
 - 2. Common Technical Document Summaries
 - 5. Clinical Study Reports
 - 5.2. Tabular Listing of all Clinical Studies
 - 5.3.2. Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials
 - 5.3.3. Reports of Human Pharmacokinetic (PK) Studies
 - 5.3.5. Reports of Efficacy and Safety Studies [Indication]
 - 5.3.5. Advanced SM
 - 5.3.5.2. Study Reports of Uncontrolled Clinical Studies [Study ID - Study Title]
 - 5.3.5.2. PKC412D2201 - pkc412d2201-A single am, Phase II, open-label study to determine the efficacy of 100 mg twice da
 - Legacy Clinical Study Report
 - Compliance and Drug Concentration Data
 - Case Report Forms [Site ID]
 - Data Listing Data
 - Data Analysis Data
 - Annotated CRF
 - 5.3.5.3. Reports of Analyses of Data from More than One Study [Study ID - Study Title]
 - 5.3.5.3. ise - ise-cross-ref-sce
 - Integrated Summary of Efficacy
 - Data Analysis Data
 - Analysis Dataset Legacy
 - adiagns
 - ahcomp
 - allivfab
 - alspleno
 - applall
 - applanc
 - applane
 - applasc
 - applhypo
 - applmci
 - applthro
 - appltry
 - areg
 - Analysis Data Definition
 - cpkchdefine
 - cpkciwdefine
 - 5.3.5.3. steering-committee-minutes - steering-committee-minutes (PKC412D2201)
 - 5.3.5. AML
 - 5.4. Literature References
- 0001 (2) 05/26/2016 ORIG-1 /Multiple Categories/Subcategories
- 0000 (1) 04/05/2016 ORIG-1 /Multiple Categories/Subcategories



Life Cycle

Current

Regulatory Activity

Sequence

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
09/13/2016

Scott, Kimberly

From: Scott, Kimberly
Sent: Tuesday, September 13, 2016 9:28 AM
To: 'Abraham, Abbey'
Cc: 'Qiu, Yuhong'
Subject: RE: NDA 207997 midostaurin Information Request: response

Importance: High
Sensitivity: Confidential

Good morning Abbey,

We are unable to identify SBJALV1C variable in your AEFf dataset for Study PKC412A2301. Please include this variable and resubmit the efficacy dataset.

Please acknowledge receipt of this email.

Kind regards,
Kim

Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Rm 2222
Silver Spring, MD 20993
Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

From: Scott, Kimberly
Sent: Wednesday, September 07, 2016 5:10 PM
To: 'Abraham, Abbey'
Cc: Qiu, Yuhong
Subject: RE: NDA 207997 midostaurin Information Request: Due COB today
Sensitivity: Confidential

Thank you.

Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Rm 2222
Silver Spring, MD 20993
Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

From: Abraham, Abbey [<mailto:abbey.abraham@novartis.com>]
Sent: Wednesday, September 07, 2016 4:33 PM
To: Scott, Kimberly
Cc: Qiu, Yuhong
Subject: RE: NDA 207997 midostaurin Information Request: Due COB today
Sensitivity: Confidential

Thank you and I meant we will file to the NDA 207997. Also there was a small typo in the last sentence of the response. Should be as highlighted.

“...variables ‘DEATH’ and ‘CENSOR’ respectively.”

Abbey Abraham
Phone +1 862-778-8998

From: Scott, Kimberly [<mailto:Kimberly.Scott@fda.hhs.gov>]
Sent: Wednesday, September 07, 2016 4:19 PM
To: Abraham, Abbey
Cc: Qiu, Yuhong
Subject: RE: NDA 207997 midostaurin Information Request: Due COB today
Sensitivity: Confidential

Good afternoon Abbey,

Thank you for your response to the request. Yuhong, sorry I didn't mean to exclude you from the previous email. I will be sure to copy you on all emails.

Thanks,
Kim

From: Abraham, Abbey [<mailto:abbey.abraham@novartis.com>]
Sent: Wednesday, September 07, 2016 4:15 PM
To: Scott, Kimberly
Cc: Qiu, Yuhong
Subject: RE: NDA 207997 midostaurin Information Request: Due COB today
Sensitivity: Confidential

Hi Kim

Please see the Novartis response to the Information Request below. We will file this to the IND by early next week. I will be out of the office until Monday Sept 12th so request that Yuhong please be copied on any emails

Thank you
Abbey Abraham
Phone +1 862-778-8998

Novartis Response

[Redacted content]

(b) (4)

From: Scott, Kimberly [<mailto:Kimberly.Scott@fda.hhs.gov>]
Sent: Wednesday, September 07, 2016 9:50 AM
To: Abraham, Abbey
Subject: NDA 207997 midostaurin Information Request: Due COB today
Importance: High
Sensitivity: Confidential

Good morning Abbey,

The Agency is requesting the following information:

In review of BIMO CLINSITE dataset submitted on 8/29/16, we are unable to complete QC process for CDER's Clinical Investigator Site Selection Tool, which loaded with data you provided in the clinsite.xpt for Study PKC412A2301. Please explain further how the TRTEFFE variable was calculated for each site by treatment arm.

Please acknowledge receipt of this email, and respond by COB today.

Thank you,

Kim

Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Rm 2222
Silver Spring, MD 20993
Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

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
09/13/2016

Scott, Kimberly

From: Scott, Kimberly
Sent: Tuesday, September 13, 2016 11:35 AM
To: 'Abraham, Abbey'
Cc: Qiu, Yuhong (yuhong.qiu@novartis.com)
Subject: NDA 207997 Midostaurin - BIMO site information IR Due COB Thursday, 9/15
Attachments: Clinical Investigator Financial Disclosure, modified - ASM.doc

Importance: High

Good morning Abbey,

The Agency is requesting information for NDA 207997, Midostaurin.

- For trials D2201 and A2213: revise the "bimo-clinsite" .xpt files submitted in 8/29/2016 module 5.3.5.4 to add the number of investigators per site, number of missing disclosures, and number of investigators with a disclosed potential conflict.
- In addition, for each of these trials, please fill out the provided Clinical Investigator Financial Disclosure form.

Please respond by COB, Thursday, September 15, 2016.

Please acknowledge receipt of this email.

Kind regards,

Kim

Kimberly Scott, RN, BSN, OCN®

CDR, U.S. Public Health Service

Regulatory Health Project Manager

Division of Hematology Products

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, Bldg. 22, Rm 2222

Silver Spring, MD 20993

Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

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
09/13/2016

Scott, Kimberly

From: Scott, Kimberly
Sent: Monday, September 12, 2016 4:20 PM
To: Abraham, Abbey
Cc: Qiu, Yuhong
Subject: RE: NDA 207997, Midostaurin: Information Request DUE 9/14

Importance: High
Sensitivity: Confidential

Hi Abbey,

Yes, the Agency's requesting the information from the request sent this morning. In particular, the response to item #2 should be formatted as described.

Please confirm receipt of this email.

Thanks,

Kim

Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Rm 2222
Silver Spring, MD 20993
Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

From: Scott, Kimberly
Sent: Monday, September 12, 2016 4:01 PM
To: 'Abraham, Abbey'
Cc: Qiu, Yuhong
Subject: RE: NDA 207997, Midostaurin: Information Request DUE 9/14
Sensitivity: Confidential

Hi Abbey,

I just received your email and will discuss with the team.

Thanks,

Kim +

Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Rm 2222

From: Abraham, Abbey [<mailto:abbey.abraham@novartis.com>]
Sent: Monday, September 12, 2016 3:17 PM
To: Scott, Kimberly
Cc: Qiu, Yuhong
Subject: RE: NDA 207997, Midostaurin: Information Request DUE 9/14
Sensitivity: Confidential

Hi Kim

We are looking into the request the team made but just want to double check, since we provided the BIMOs for both study 2201 and 2301 in the NDA, was there anything additional the team was looking for? The information requested below should be found in the respective BIMO parts 1-2 (module 5.3.5.2 for 2201 and module 5.3.5.1 for 2301 in the NDA) but let me know if there is anything additional the team is looking from what has been submitted. Since it will take a fair bit of time to pull and reformat this into pdfs as requested, could the team confirm by the end of today?

Thanks

Abbey Abraham
Phone +1 862-778-8998

From: Scott, Kimberly [<mailto:Kimberly.Scott@fda.hhs.gov>]
Sent: Monday, September 12, 2016 11:35 AM
To: Abraham, Abbey; Qiu, Yuhong
Subject: NDA 207997, Midostaurin: Information Request DUE 9/14
Importance: High
Sensitivity: Confidential

Good morning Abbey,

The Agency is requesting information for NDA 207997, Midostaurin. Please refer to your NDA submitted under section 505b1 of the Public Health Service Act for midostaurin. Your NDA is currently under review and we have the following requests for information:

1. For Protocols D2201 and A2301, identify the address and contact information for where the Sponsor's study documents and data are located.
2. Submit the following study subject data listing information as grouped pdf files, sorted separately by the following requested clinical study sites, for Site 180 Dr. J-C Nelemans (Protocol D2201); Site 150 Dr. Andreas Reiter (Protocol D2201); Site 2937 Dr. Harmut Doehner (Protocol A2301); Site 2041 Dr. Arnold Ganser (Protocol A2301), and U.S. Site 0177/0234 Dr. Jonathan Kolitz (Protocol A2301).
 - a. Subject discontinuations (If applicable per treatment group: site, subject number, screening visit date, randomization date (if applicable), date of first dose/last dose, date of discontinuation, reason for discontinuation).
 - b. Subject assignment per treatment arm (as applicable).
 - c. Study efficacy endpoint raw data (treatment response including lab results for Study D2201, and survival raw data for Study A2301, as applicable).
 - d. Concomitant medication list (i.e., non-study medications).
 - e. All adverse events, both during treatment or post-treatment AEs, as submitted to the NDA (If applicable, per treatment group: preferred term/investigator entry, date start/stopped, severity/resolution, serious adverse event (SAE [yes/no], death [yes/no])).

We request a response by 10:00AM on September 14, 2016, via e-mail. Please also follow up with an official response under the NDA.

Please acknowledge receipt of this email.

Kind regards,

Kim

Kimberly Scott, RN, BSN, OCN®

CDR, U.S. Public Health Service

Regulatory Health Project Manager

Division of Hematology Products

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, Bldg. 22, Rm 2222

Silver Spring, MD 20993

Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

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
09/12/2016

Scott, Kimberly

From: Scott, Kimberly
Sent: Monday, September 12, 2016 4:01 PM
To: 'Abraham, Abbey'; Qiu, Yuhong (yuhong.qiu@novartis.com)
Subject: NDA 207997 Midostaurin: AOM

Importance: High

Good afternoon Abbey,

The intent of the Application Orientation Meeting is not a detailed review of all of the information in the application. Instead, it should highlight unusual aspects of any module in the application and provide only a high-level overview of critical information for the individual review disciplines.

In addition, please also address the following (no more than one slide each):

1. Safety and efficacy of midostaurin for treatment of AML in children.
2. Efficacy of midostaurin in FLT3-ITD vs FLT3-TKD vs FLT3-wild type AML.
3. For study A2301
 - a. The OS analysis was not conducted according to the protocol pre-specified plan. Please explain what is the appropriate alpha level for this OS analysis adjusted for interim analyses. In your presentation, please use 2-sided p-values rather than 1-sided p-values that were used in your study report.
 - b. OS curve plateaued before median OS in the treatment arm, thus median OS cannot be reliably estimated. Please explore whether there are some alternative methods to better describe treatment effect in addition to the hazard ratio.
 - c. Provide rationale that placebo is a reasonable comparator in the continuation therapy stage (maintenance stage), given no treatment benefit were observed prior to the continuation therapy stage.
 - d. Provide explanation of the different patterns in two arms with regard to SCT. While most subjects had SCT in the treatment arm had allogeneic related SCT, a majority of subjects in the placebo arm had allogeneic unrelated SCT.
4. For study D2201 and D2213, present the exploratory comparison of the pooled OS data from the two studies and Germany registry data from an independent registry.
5. Provide an explanation for dose selection for AML vs ASM, especially why the doses differ.
6. Clarify the pooling strategy used in the integrated summary of safety. How much safety data is there for maintenance after transplantation for AML?
7. For Study A2301, provide an overview of the most common TEAE during induction, during consolidation, and during maintenance.
8. Provide an update on the status of your interactions with Invivoscribe regarding the IVD.

Please confirm receipt of this email.

Kind regards,

Kim

Kimberly Scott, RN, BSN, OCN®

CDR, U.S. Public Health Service

Regulatory Health Project Manager

Division of Hematology Products

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Rm 2222
Silver Spring, MD 20993
Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

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
09/12/2016

Scott, Kimberly

From: Scott, Kimberly
Sent: Monday, September 12, 2016 11:35 AM
To: Abraham, Abbey; Qiu, Yuhong (yuhong.qiu@novartis.com)
Subject: NDA 207997, Midostaurin: Information Request DUE 9/14

Importance: High

Good morning Abbey,

The Agency is requesting information for NDA 207997, Midostaurin. Please refer to your NDA submitted under section 505b1 of the Public Health Service Act for midostaurin. Your NDA is currently under review and we have the following requests for information:

1. For Protocols D2201 and A2301, identify the address and contact information for where the Sponsor's study documents and data are located.
2. Submit the following study subject data listing information as grouped pdf files, sorted separately by the following requested clinical study sites, for Site 180 Dr. J-C Nelemans (Protocol D2201); Site 150 Dr. Andreas Reiter (Protocol D2201); Site 2937 Dr. Harmut Doehner (Protocol A2301); Site 2041 Dr. Arnold Ganser (Protocol A2301), and U.S. Site 0177/0234 Dr. Jonathan Kolitz (Protocol A2301).
 - a. Subject discontinuations (If applicable per treatment group: site, subject number, screening visit date, randomization date (if applicable), date of first dose/last dose, date of discontinuation, reason for discontinuation).
 - b. Subject assignment per treatment arm (as applicable).
 - c. Study efficacy endpoint raw data (treatment response including lab results for Study D2201, and survival raw data for Study A2301, as applicable).
 - d. Concomitant medication list (i.e., non-study medications).
 - e. All adverse events, both during treatment or post-treatment AEs, as submitted to the NDA (If applicable, per treatment group: preferred term/investigator entry, date start/stopped, severity/resolution, serious adverse event (SAE [yes/no], death [yes/no])).

We request a response by 10:00AM on September 14, 2016, via e-mail. Please also follow up with an official response under the NDA.

Please acknowledge receipt of this email.

Kind regards,

Kim

Kimberly Scott, RN, BSN, OCN®

CDR, U.S. Public Health Service

Regulatory Health Project Manager

Division of Hematology Products

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, Bldg. 22, Rm 2222

Silver Spring, MD 20993

Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

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
09/12/2016

Scott, Kimberly

From: Scott, Kimberly
Sent: Wednesday, September 07, 2016 9:50 AM
To: 'Abraham, Abbey'
Subject: NDA 207997 midostaurin Information Request: Due COB today

Importance: High

Good morning Abbey,

The Agency is requesting the following information:

In review of BIMO CLINSITE dataset submitted on 8/29/16, we are unable to complete QC process for CDER's Clinical Investigator Site Selection Tool, which loaded with data you provided in the clinsite.xpt for Study PKC412A2301. Please explain further how the TRTEFFE variable was calculated for each site by treatment arm.

Please acknowledge receipt of this email, and respond by COB today.

Thank you,

Kim

Kimberly Scott, RN, BSN, OCN®

CDR, U.S. Public Health Service

Regulatory Health Project Manager

Division of Hematology Products

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, Bldg. 22, Rm 2222

Silver Spring, MD 20993

Phone: 240-402-4560 | Kimberly.scott@fda.hhs.gov

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
09/07/2016

Scott, Kimberly

From: Scott, Kimberly
Sent: Wednesday, August 10, 2016 10:43 PM
To: 'Abraham, Abbey'
Cc: Qiu, Yuhong
Subject: RE: NDA 207997 Midostaurin:
Attachments: Foreign Visitor Data Request Form.doc

Importance: High
Sensitivity: Confidential

Good evening Abbey,

The Agency has agreed to a face-to-face meeting with Novartis on Monday, September 26, 2016 at 1:00pm – 2:00pm(ET) to meet the statisticians to discuss the datasets for NDA 207997, Midostaurin. Please see the attached foreign visitor data request form that needs to be submitted at least two weeks prior to the meeting date.

Please confirm Novartis is able to attend the requested meeting date. Also, please send any meeting materials for the team to review prior to meeting.

Please confirm receipt of this email.

Kind regards,

Kim

Kimberly Scott, RN, BSN, OCN®
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Bldg. 22, Rm 2222
Silver Spring, MD 20993
Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

From: Abraham, Abbey [mailto:abbey.abraham@novartis.com]
Sent: Wednesday, August 10, 2016 4:40 PM
To: Scott, Kimberly
Cc: Qiu, Yuhong
Subject: RE: NDA 207997 Midostaurin:
Sensitivity: Confidential

Hi Kim

Any luck with scheduling for a face to face?

Thanks

Abbey Abraham
Phone +1 862-778-8998

From: Abraham, Abbey
Sent: Wednesday, August 03, 2016 4:57 PM
To: 'Kimberly.Scott@fda.hhs.gov'
Cc: Qiu, Yuhong
Subject: RE: NDA 207997 Midostaurin:
Sensitivity: Confidential

Hi Kim

Well the Novartis stats team was proposing to walk thru the datasets and related items so we think a f2f would be the most effective way to do this. Is there a chance we could have this f2f in the mid-September timeframe?

Abbey Abraham
Phone +1 862-778-8998

From: Scott, Kimberly [<mailto:Kimberly.Scott@fda.hhs.gov>]
Sent: Wednesday, August 03, 2016 4:14 PM
To: Abraham, Abbey
Cc: Qiu, Yuhong
Subject: RE: NDA 207997 Midostaurin:
Sensitivity: Confidential

Hi Abbey,

I'm in the process of trying to schedule a meeting mid-September. Is the team able to discuss via teleconference?

Thanks,
Kim

From: Abraham, Abbey [<mailto:abbey.abraham@novartis.com>]
Sent: Wednesday, August 03, 2016 4:06 PM
To: Scott, Kimberly
Cc: Qiu, Yuhong
Subject: RE: NDA 207997 Midostaurin:
Sensitivity: Confidential

Hi Kim

Just wanted to check if the team has proposed any dates/times for this meeting.

Thanks by the way for keeping me and Yuhong copied on all emails. I actually will be out of the office tomorrow and Friday without email access so Yuhong will get back to you with a confirmation for any dates.

Thanks again.

Abbey Abraham
Phone +1 862-778-8998

From: Scott, Kimberly [<mailto:Kimberly.Scott@fda.hhs.gov>]
Sent: Friday, July 29, 2016 4:20 PM
To: Abraham, Abbey
Cc: Qiu, Yuhong
Subject: RE: NDA 207997 Midostaurin:
Sensitivity: Confidential

Good afternoon Abbey,

I forwarded your request for a meeting with the stats team from the Agency, and they have agreed to meet with your team. I'm in the process of scheduling, and will get back with you early next week with the date and time.

Thank you,

Kim

Kimberly Scott, RN, BSN, OCN®

CDR, U.S. Public Health Service

Regulatory Health Project Manager

Division of Hematology Products

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, Bldg. 22, Rm 2222

Silver Spring, MD 20993

Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

From: Abraham, Abbey [<mailto:abbey.abraham@novartis.com>]

Sent: Thursday, July 28, 2016 4:27 PM

To: Scott, Kimberly

Cc: Qiu, Yuhong

Subject: RE: NDA 207997 Midostaurin:

Sensitivity: Confidential

Hi Kim

Just one more additional note regarding the review session proposed between the stats/programming team from Novartis and the agency. We got word that some of the team will need 3-4 weeks lead time to secure visa's into the US so if the agency team was in agreement with a mid-Aug to mid-September as Yuhong mentioned, we would need to start the visa process asap. Any direction from the review team on this would be really helpful to this end.

Thanks again.

From: Qiu, Yuhong

Sent: Thursday, July 21, 2016 9:28 AM

To: 'Kimberly.Scott@fda.hhs.gov'

Cc: Abraham, Abbey

Subject: RE: NDA 207997 Midostaurin:

Sensitivity: Confidential

Hello Kim,

To follow up with Abbey's mail below, after the wave 3 submission which is targeted for next Monday July 25, all datasets, except those for SCS/ISS, would have been submitted. The last sets of the datasets will be included in the last wave which is targeted for end of August.

We believe a meeting between Novartis statistician/programmer and Agency statistical reviewers would facilitate the review. Given our submission timeline and the fact our programmer needs some time to procure travel documents, we propose a meeting between mid-Aug to mid-Sept. It would be greatly appreciated if you could let us know Agency's thought on this and the potential meeting dates.

Thank you very much,

Yuhong

From: Abraham, Abbey
Sent: Wednesday, July 20, 2016 4:52 PM
To: Kimberly.Scott@fda.hhs.gov
Cc: Qiu, Yuhong
Subject: NDA 207997 Midostaurin:
Sensitivity: Confidential

Hi Kim

Just wanted to give you a heads up regarding the submission for the rolling NDA 207997. We are targeting Monday July 25th for the third part to be submitted and this will include module 2 nonclinical and clinical efficacy summaries, clinical study reports for pivotal studies A2301 and D2201 and some additional module 1 elements. I will of course outline this again in my cover memo for the July 25 submission but all BIMOs, remaining module 2 documents (Clinical overviews, Summary of Clinical Safety etc) and labeling will be included in the fourth and final wave.

Also during the pre-NDA meeting, Novartis had offered to provide an orientation of the datasets for the review team and agency stated they would consider this. As some of the Novartis reside outside the US and will need to procure travel documentation, wondering if the review team has determined if they would like to have this and if they could estimate a timeline for the review session to take place. Any guidance is appreciated.

Thank you

Abbey Abraham
Phone +1 862-778-8998

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
08/10/2016



IND 057120

MEETING MINUTES

Novartis Pharmaceuticals Corporation
Attention: Abbey Abraham, PharmD
Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Mr. Abraham:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for midostaurin.

We also refer to the meeting between representatives of your firm and the FDA on May 24, 2016. The purpose of the meeting was to discuss the adequacy of the proposed content of an NDA for midostaurin for the two proposed indications: 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 [REDACTED] (b) (4) standard induction and consolidation chemotherapy, and the treatment of patients with aggressive systemic mastocytosis or mast cell leukemia [REDACTED] (b) (4)

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call Kimberly Scott, Regulatory Project Manager at (240) 402-4560.

Sincerely,

{See appended electronic signature page}

Donna Przepiorka, MD, PhD
Acting Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: Tuesday, May 24, 2016
10:00AM – 11:00AM (ET)

Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1309
Silver Spring, Maryland 20903

Application Number: IND 057120
Product Name: Midostaurin
Indication: 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, [REDACTED] (b) (4) [REDACTED] standard induction and consolidation chemotherapy.

Treatment of patients with aggressive systemic mastocytosis or mast cell leukemia [REDACTED] (b) (4) [REDACTED]

Sponsor/Applicant Name: Novartis Pharmaceuticals Corporation

Meeting Chair: Donna Przepiorka, MD, PhD
Meeting Recorder: Kimberly Scott, RN, BSN, OCN®

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP)/Division of Hematology Products

Ann Farrell, MD, Division Director
Albert B. Deisseroth, MD, PhD, Clinical Team Leader
Romeo A. de Claro, MD, Clinical Team Leader
Donna Przepiorka, MD, PhD, Acting Clinical Team Leader
Yvette Kasamon, MD, Medical Officer
Ashley Ward, MD, Medical Officer
Theresa Carioti, MPH, Chief, Project Management Staff
Kimberly Scott, BSN, RN, OCN®, Regulatory Health Project Manager

OHOP/Division of Hematology, Oncology, Toxicology (DHOT)

Christopher Sheth, PhD, Supervisory Pharmacologist/Toxicologist
Natalie Simpson, PhD, Pharmacologist/Toxicologist Reviewer

Office of Biostatistics, Division of Biometrics V

Lei Nie, PhD, Team Leader
Chia-Wen Ko, PhD, Reviewer

Division of Molecular Genetics and Pathology/Office of In Vitro Diagnostics and Radiological Health

Allen Williams, PhD, Scientific Reviewer

Office of In Vitro Diagnostics and Radiation Health (OIR)/Division of Molecular Pathology and Genetics

Karen Bijwaard, MS, RAC, Scientific Reviewer

Eastern Research Group Attendee

ERG Christopher Sese, Independent Assessor

SPONSOR ATTENDEES

Renaud Capdeville, MD, Global Program Head
Lisa Rojkjaer, MD, Global Clinical Program Head
Iulian Alecu, MD, Brand Safety Leader,
Taoufik Ouatas, PhD, Site Head, Clinical Pharmacology
Alice Huntsman Labeled, PhD, Program Statistician, Biostatistics
Kannan Natarajan, PhD, Global Head, Biometrics
Shanthi Ganeshan, PhD, North America Region Head, Drug Regulatory Affair
Yuhong Qiu, PhD, Global Program Regulatory Director, Drug Regulatory Affairs
Abbey Abraham, PharmD, Global Program Regulatory Manager, Drug Regulatory Affairs
Gaetano Bonifacio, MD, Sr. Medical Director, US Oncology
Peggy Carter, PhD, US Head, CDx Diagnostic Regulatory

1.0 BACKGROUND

Novartis requested a pre-NDA meeting to discuss the adequacy of the proposed content of the NDA for midostaurin. The objectives of the pre-NDA meeting were to gain agreement that the data from the pivotal Phase III study A2301 and other supportive studies are sufficient to support filing for the proposed indications, and the content of the NDA is complete and adequate to support filing and review.

Midostaurin, 100 mg bid, is being developed as a single agent for patients with ASM/MCL. The clinical development program for ASM/MCL was discussed with the Agency at a pre-NDA meeting on September 2, 2015. Midostaurin, 50 mg bid, is being developed in combination with standard chemotherapy for patients with newly diagnosed FLT3-mutated AML. The clinical development of midostaurin in AML was discussed with the Agency during the End of Phase II

meeting on July 12, 2006. Additional FDA feedback was obtained through a special protocol assessment (SPA) request and the subsequent Type A meeting in 2007, although no SPA agreement was issued. A Type A meeting was held on February 26, 2016 and agreement was reached for a Novartis database lock in March 2016.

Orphan designation of midostaurin was granted for AML in July 2009 and for mastocytosis in April 2010. Breakthrough Designation for midostaurin was granted on January 29, 2016 for the treatment of adult patients with newly diagnosed AML who are FLT3 mutation-positive as detected by an FDA-approved test and who are eligible to receive standard induction and consolidation chemotherapy. Rolling review was granted on April 1, 2016. A companion diagnostic for the FLT3 mutation is in development.

FDA sent Preliminary Comments to Novartis Pharmaceuticals Corporation on May 19, 2016.

2.0 DISCUSSION

The meeting opened with a discussion of the NDA format. FDA clarified that a single NDA with two indications was expected. The Sponsor agreed with the request to submit all elements of the submission under NDA 207997 with two indication subfolders in Module 5 as described below, one for the ASM/MCL indication, and one for the AML indication.

2.1. Registration study and proposed indication

Question 1:

Does the Agency agree that the proposed data package, including the pivotal study (A2301), adequate to support the filing and review of the proposed indication?

FDA Response to Question 1:

The ability of the proposed data package to support the proposed claim in a broader patient population than was included in the pivotal study (i.e. older patients) will be a review issue. We strongly recommend that you provide justification for a limiting the pivotal trial by age for a disease that occurs across a broader age range, and that you explore whether you have sufficient information directly or by extrapolation to support safety and efficacy for any indication in a broader age group, (b) (4)

Discussion:

No discussion occurred.

2.2. Proposed eCTD table of content

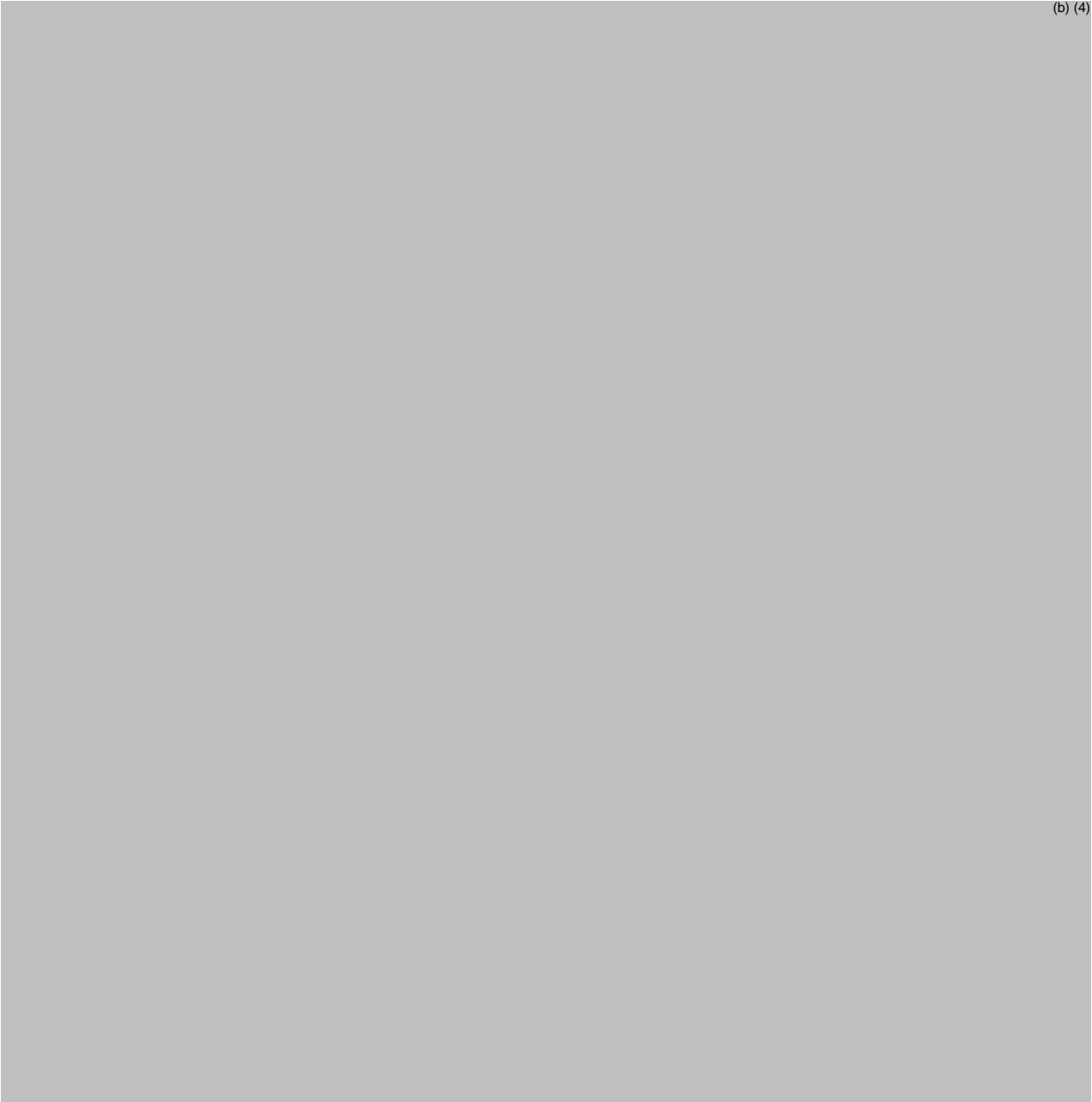
Question 2:

Does the Agency agree with the content of the NDA as outlined in the proposed electronic Common Technical Document (eCTD) table of contents (TOC)?

FDA Response to Question 2:

In general, the structure and content of the TOC appear acceptable, although final determination will be a review issue. See also responses to Questions 3 and 4. From a technical standpoint (not content related), the proposed format for the planned NDA is acceptable. However, please note that there should be separate folders for the AML indication (e.g., 5.3.5 AML) and the ASM/MCL (e.g., 5.3.5 ASM/MCL) indication. The ISS can be placed in the folder for first indication submitted.

(b) (4)



Discussion:

No discussion occurred.

2.3. Integrated Summary of Efficacy

Question 3:

Does the Agency agree with the proposed content and format of the Integrated Summary of Efficacy (ISE)?

FDA Response to Question 3:

We agree with your plan to submit an SCE with all required elements of the ISE in lieu of an ISE as long as the document does not exceed the page limitation. You may also consider submitting a separate SCE for the AML indication and the ASM/MCL indication; the former should include an evaluation of the efficacy results for both the de novo and the relapsed/refractory populations of patients with AML.

We agree with your plan to provide an assessment of efficacy between protocols rather than to pool data from studies of different regimens and different populations. You should, however, include a comprehensive exposure-response analysis for each indication.

The SCE should be located in Module 2.7.3 and the accompanied post-text tables and appendices located in Module 5.3.5.3, file tagged as “ise” if needed. If post-text tables and appendices are submitted separately from the SCE, an annotated index should be included, with, at minimum, the title of the table, listing or appendix, hyperlink to that table, listing or appendix, and a brief description of the contents that includes the study number(s) from which the data described were obtained, if not apparent from the title.

The adequacy of the content of the SCE will be assessed during the filing review of the NDA submission.

For more information on the SCE and the ISE, see the FDA Guidance for Industry on the Integrated Summary of Effectiveness, which can be found at:
<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm079803.pdf>.

We refer you also to the FDA Guidance for the ISE and ISS:
<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm136174.pdf>.

Discussion:

No discussion occurred.

2.4. Integrated Summary of Safety

Question 4:

Does the Agency agree with the proposed pooling strategy and the content of the Integrated Summary of Safety (ISS)?

FDA Response to Question 4:

We do not agree with your plan

(b) (4)

Your proposal will include data for 1370 patients and 500 healthy subjects from 23 studies. The ISS should include pertinent nonclinical data and a detailed analysis of safety across your clinical trials as well as the published literature. Although you are not submitting clinical study reports or data sets for the studies in Table 3-2, you should also provide an overview of safety issues that arose in those studies. If you have a Safety Data Analysis Plan, please submit that in the subfolder with the ISS.

Given the complexity of your development program, however, we suggest that you organize the ISS by analysis and then by indication. For each analysis (demographics, overview of adverse events, serious adverse events, etc), you would include separate analyses by indication (e.g. AML combination therapy, AML monotherapy, ASM/MCL, and other malignancies) as well as a pooled analysis that includes all available data, regardless of indication or use of other anti-cancer agents.

Although it is acceptable to generate a single SCS covering both the AML and ASM/MCL indications, the Agency would prefer a separate SCS for each indication. If you combine them into one SCS, we strongly suggest that you include a discussion of the findings in the context of each proposed indication separately within the submission. In particular, ensure that safety in recipients of monotherapy versus combination therapy are described in aggregate as well as separately. Please also provide separate analyses of all-causality AEs and related AEs.

The adequacy of the content of the SCS and ISS will be assessed during the filing review of the NDA submission.

Discussion:

The Sponsor presented an overview of their contents for the ISS. They outlined the deficiencies in A2301 with regard to available data. The Agency requested specifically that the ISS include A2301 in the dataset for the FDA analyses. The Sponsor indicated they may revise their safety data analyses plan to include additional selective analysis of the larger pool for AEs.

There was additional discussion regarding the Sponsor's proposal

(b) (4)

No agreement was reached. The Agency requested the Sponsor submit a comparative table between an ISS and their plan for the SCS in this NDA as well as a Table of Contents by June 1, 2016.

2.5. Narratives and case report forms

Question 5:

Does the Agency agree with the proposed categories for case report forms and narratives to be included in the dossier?

FDA Response to Question 5:

No. [REDACTED]

(b) (4)

Please submit patient narratives and case-report forms for all of the following on all studies submitted to the NDA as part of the safety package (i.e. all studies listed in Tables 3-1 of the briefing package):

- All deaths that occurred on study, regardless of date of last dose of study drug
- All discontinuations of study drug due to adverse events or patient / investigator decision
- All adverse events of special interest
- All serious adverse events that occurred prior to documented progression and/or initiation of next-line therapy, whichever occurred first

In general, the narrative should describe the following: The nature and intensity of event; the clinical course leading up to event, with an indication of timing relevant to test drug/investigational product administration; relevant laboratory measurements; whether the drug was stopped, and when; countermeasures; post-mortem findings; investigator's opinion on causality and sponsor's opinion on causality, if appropriate. In addition, the following information should be included:

- Patient identifier
- Age and sex of patient
- General clinical condition of patient
- Disease being treated duration (of current episode) of illness
- Relevant concomitant/previous illnesses with details of occurrence/ duration
- Relevant concomitant/previous medication with details of dosage
- Test drug/investigational product administered, drug dose, and length of time administered.

Please also note that Case Report Forms need to be referenced under the study tagging file (STF) of the specific study to which they belong, organized by site as per the specifications and file tagged as “case report form.”

Discussion:

The Sponsor clarified that they do not have narratives for severe or serious AEs that occur commonly in this population. They proposed to submit narratives for the relevant associated AEs for the common events, narratives for withdrawals due to patient or physician decisions (for A2301 only), and narratives for deaths within 30 days in addition to an analysis of post-transplant events. The Agency agreed with this proposal.

2.6. Datasets

Question 6:

Does the Agency find the information provided in the datasets sufficient?

FDA Response to Question 6:

No, the information provided in the datasets is not sufficient. A number of the datasets are lacking necessary information or organized in a confusing manner. We strongly suggest you use the CDISC format for submitting all of your datasets to facilitate review if possible.

We have the following additional comments:

1. You will need to submit an integrated safety data set that includes data from all of the trials included in the ISS (i.e., all trials listed in Tables 3-1 of the briefing package). We suggest that you break this down into two parts to make it a more manageable size: one integrated safety data set should include data from all trials involving patients with hematologic malignancies (AML, ASM/MCL) and the second should include data from all other trials. Include variables denoting which safety subpopulation pool is applicable for each subject and/or event. These integrated safety data sets should include at least:
 - Adverse events
 - Demographics
 - Baseline disease information
 - Medical history
 - Concomitant medications and dates taken
 - Exposure to midostaurin and other study drugs
 - Clinical laboratory tests
 - Vital signs

Please also include the epoch and cycle number for each adverse event. As the datasets to be integrated for the ISS consist of various studies that took place over a number of years, please make sure that the integrated data set uses a uniform CTCAE grading and event terms according to the same MedDRA version.

If the clinical laboratory test data file is too large to submit through the Gateway, you may split the data set, but please describe in the reviewer's guide how the split was made. Clarify specifically how you split the ADLB domain in the ISS data set. Splitting by lab type (e.g. hematology labs in one file, chemistry labs in another file) may help facilitate review.

2. Please include an integrated data set that identifies the tests used to determine response on all of the subjects with AML (i.e. subjects on studies A2301, A2106, A2104, A2104E1, A2104E2 and A2114). This should include at least the following variables: study identification number, site identification number, subject identifier, disease subtype, date of first dose of study drug, response category (e.g. CR, CRp, PR), date of response, epoch/cycle number, study day of response, date of marrow used to identify response, date of ANC used to identify response and date of platelet count used to identify response.

3. Please include an integrated time-to-event data file for all subjects with AML (i.e. subjects on studies A2301, A2106, A2104, A2104E1, A2104E2 and A2114). This should include at least the following variables: study identification number, site identification number, subject number, treatment arm, demographic information, date of first study drug dose, date of CR, date of relapse, date of transplantation if performed after study start, date of last contact, status at last contact (alive, dead or lost to follow-up), proximate cause of death, and root cause of death as determined by the sponsor (e.g. active disease, treatment-related, intercurrent illness, etc). For all deaths on study within 30 days of the last dose of study drug, when the cause of death is listed as disease-related, ensure that the narrative clearly describes the data showing AML.
4. Within adverse event (“AAEV”) and lab value (“ALRS”) datasets, please include:
 - The dose of midostaurin the patient was taking at the time of each AE/lab
 - The chemotherapy cycle the patient was in at the time of each AE/lab
 - Baseline toxicity grade for each row
 - Toxicity grade for all post-treatment measures
 - A TEAE flag that excludes toxicities that were present at baseline without worsening of grade (i.e. only defines a TEAE for toxicities that are new or are a higher grade than at baseline)
 - An SAE flag and an attribution column
 - A shift column for each row that describes the change from baseline (e.g., 0 to -1).
5. In the adverse event (“AAEV”) dataset, please include the full MedDRA hierarchy, by adding the high level group term and the verbatim term. Please also explain the variables AEVNAM1A and AEVNAM2A and why many of the data points under AEVNAM1A are listed as “unavailable.”

If further information is available regarding adverse events coded as “suspected” for AEVREL4C (“AE attributable to other”), it should be included in the datasets. For example, if AE was attributable to the disease under study, or a concomitant medication, or another baseline medical condition.

6. In the lab value (“ALRS”) dataset, integrate laboratory toxicity grading that indicates the directionality of the abnormality. For example, Grade 1 hypoglycemia should be coded as -1, and Grade 2 hyperglycemia should be coded as 2 or +2, as per Section 2.4 (Lab Grades) of the define file. Also, include a lab range indicator that designates values as “LOW” if the lab test range is negative, “HIGH” if the lab test range is positive.
7. There appear to be several different variables to describe epoch and treatment cycle (TPHASE, CYC3N, Phase_1C, others?). Please explain how these variables are intended to be interpreted.

8. In the AERS dataset, please explain the difference between the variables CTC_1C, CTC_2C and CTCGRD1C – which of these represents the CTCAE grade of the adverse event?
9. Please ensure that the demographic dataset contains exact ECOG score for each patient [REDACTED] (b) (4)
10. Ensure that data is submitted regarding patient disposition and post-study therapies.
11. Datasets should contain sufficiently detailed information about exposure to each of the study drugs (total dose received, dates of dose interruptions, dates of dose reductions, amount of dose reduction, etc) to recreate a detailed timeline of exposure to each study drug for each patient.
12. Ensure that there is a single unique subject identifier that is included with every data point (there appear to be several subject identifier variables, and it is not clear how they are interrelated).
13. Please ensure that variables used in in each dataset are consistent (i.e. that a particular variable has the same name in every dataset in which it appears) so that datasets can be combined and/or sorted as needed during review. Please provide the reviewer with instructions regarding the use of variables and flags to identify the set of patients on which primary analyses were performed.
14. Please ensure that all efficacy and safety tables included in the clinical study reports are annotated to indicate which analysis dataset variables were used to produce each table or figure.

The adequacy of the content of the databases will be assessed during the filing review of the submission. We also strongly suggest that you include a Data Analysis Reviewer's Guide that walks the reviewers through the datasets, how they are organized, and how calculated variables were calculated.

Discussion:

The Sponsor offered to provide a dataset orientation for the reviewers. The Agency will consider this offer. The Agency requested that the Sponsor include in the time-to-event data file a variable to indicate the vital status (alive, dead, missing due to the fact that vital status could not be updated) for the data sweep conducted with a April 1, 2015 cutoff date. The Agency also indicated that if other issues with the Sponsor's proposed plan for the data sets were identified, the Agency would send an Information Request.

2.7. Safety update

Question 7: (note: this is Question 6 (2.7) in briefing packet)

[REDACTED] (b) (4)

FDA Response to Question 7:

No. In your Response to Information Request submitted 5/15/2016 you indicated that CPKC412A2301 is on-going. [REDACTED] (b) (4)

We also noted from that Response to Information Request that CPKC412D2201 and CPKC412A2213 are on-going, and the data cutoff dates are 2-5 years ago. We expect that all safety data for the primary submission for ASM/MCL will be current. All safety data should be updated for D2201 and A2213 in the original submission, and a 120-day safety report will be required for the ASM/MCL indication review as well.

Discussion:

No discussion occurred.

2.8. Risk Management

Question 8:

Does the Agency agree that the risk of midostaurin can be adequately managed by labeling and routine pharmacovigilance and there is no need for a risk evaluation and mitigation strategies (REMS)?

FDA Response to Question 8:

At this time, there is insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks, and if it is necessary, what the required elements will be. We will determine the need for a REMS during the review of your application.

Discussion:

No discussion occurred.

2.9. User fee and pediatric Waiver

Question 9:

Does the Agency agree with a user fee waiver and a waiver for pediatric study requirement based on the orphan designation received?

FDA Response to Question 9:

Based upon the information you provided in the briefing document, the submission may meet the requirements for an orphan exemption of the application fee as per Section V.A of the Guidance for Industry User Fee Waivers, Reductions, and Refunds for Drug and Biological Products, “Under section 736(a)(1)(F) of the Act, a human drug application for a product that has been designated as a drug for a rare disease or condition (referred to as an orphan drug) under section 526 of the Act is not subject to an application fee unless the human drug application includes an indication for other than a rare disease or condition.” For such drugs, no request for a waiver is required. When completing the user fee coversheet, the Applicant should indicate that the proposed indication(s) has orphan designation. Please note the final determination for user fee requirements occurs when the application is submitted in its entirety to the Agency.

Regarding pediatric study requirements, 21 CFR 315.55(d) indicates that drugs for which orphan designation has been granted are exempt from the requirement for a pediatric assessment. No request for a waiver is required.

Discussion:

No discussion occurred.

2.10. Financial disclosure

Question 10:

Does the Agency agree with the following ‘covered study’ under the rule ‘Financial Disclosure for Clinical Investigators’?

FDA Response to Question 10:

No, financial disclosure information must be submitted for all clinical trials being submitted as part of the NDA (i.e., all studies listed in Table 3-1 and 3-2 in the briefing package). For each individual trial, complete the Agency’s financial disclosure review form to be included with the submission.

Discussion:

No discussion occurred

2.11. Office of Scientific Investigations

Question 11:

Does the Agency agree with the proposal to include the following items to facilitate OSI inspection preparation and the timeline?

FDA Response to Question 11:

No. You will need to submit the site level dataset with the NDA. The Agency refers you the draft “*Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning*” available at:

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>.

Additional Comments:

We caution that an in-vitro companion diagnostic will be needed for the approval of the AML indication. We encourage you to resolve all outstanding issues regarding that diagnostic as soon as possible.

Discussion:

No discussion occurred.

3.0 OTHER IMPORTANT INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our March 25, 2016 communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to “the Program” under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA’s meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Finally, in accordance with the PDUFA V agreement, FDA has contracted with an independent contractor, Eastern Research Group, Inc. (ERG), to conduct an assessment of the Program. ERG will be in attendance at this meeting as silent observers to evaluate the meeting and will not participate in the discussion. Please note that ERG has signed a non-disclosure agreement.

Information on PDUFA V and the Program is available at <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. The Sponsor indicated they would be revising the timeline of the remaining portions of their rolling review NDA, and would submit the updated timeline to the Agency.

The Sponsor agreed to submit all information for both the AML and ASM/MCL indications under NDA 207997.

All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- A preliminary discussion on the need for a REMS was held and it was concluded that we will determine the need for a REMS during the review of your application.

In addition, we note that a chemistry pre-submission meeting (teleconference) was held on May 16, 2016. We refer you to the minutes of that meeting for any additional agreements that may have been reached.

PREA REQUIREMENTS

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

Because this drug product, for these indications, has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#) including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – “*Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*” (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

Please be advised that the Agency does not make exclusivity determinations pursuant to sections 505(c)(3)(E) and (j)(5)(F) of the Federal Food, Drug, and Cosmetic Act, and 21 CFR 314.108, until after approval of an NDA. As described at 314.50(j), an applicant should include in its NDA a description of the exclusivity to which the applicant believes it is entitled. FDA will consider the applicant’s assertions regarding exclusivity in the review of the application. Please also note that the New Molecular Entity (NME) determination for an application is distinct from and independent of the New Chemical Entity (NCE) determination and any related exclusivity determinations.

FDA has made a preliminary determination that the application for this product would be reviewed as a new molecular entity (NME) and therefore subject to the Program, under PDUFA V. Please note that this is a preliminary determination, based on information available to FDA at this time, and will be re-evaluated at the time your application is submitted. This determination is based on our understanding of the active moiety (21 CFR 314.108(a)) and whether another marketing application containing the same active moiety is approved or marketed. Please also note that the NME determination for an application is distinct from and independent of the new chemical entity (NCE) determination and any related exclusivity determinations, which are made after approval of an NDA.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

The Sponsor also planned to discuss questions 6, 10, and 7 (in that order), but scheduled duration of the meeting did not allow for the additional discussion, and these questions remained open at the end of the meeting. FDA agreed to send written feedback on the Sponsor's proposals for these questions if needed.

The Sponsor also noted that their proposed timeline for rolling submission of the rest of the application would need to be revised. The Sponsor indicated they would submit a revised timeline proposal.

5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
The Agency requested a comparative table between a usual ISS and the planned content of the SCS for this NDA as well as the SCS Table of Contents.	Novartis Pharmaceuticals Corporation	June 1, 2016

6.0 ATTACHMENTS AND HANDOUTS

Please see Novartis email sent on May 23, 2016, "Response to FDA Preliminary Comments on Pre-NDA Meeting Package," and handouts from the Power Point Presentation, "PKC412 (midostaurin) Treatment of patients with newly diagnosed FLT3 mutated AML."

27 Page(s) 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/

DONNA PRZEPIORKA
05/25/2016

Scott, Kimberly

From: Scott, Kimberly
Sent: Wednesday, May 11, 2016 12:32 PM
To: 'Abraham, Abbey'
Cc: Qiu, Yuhong
Subject: NDA 207997 Midostaurin: Presubmission Acknowledgment letter revised
Attachments: NDA 207997 Acknowledge Presubmission .pdf

Importance: High

Good afternoon Abbey,

Please see the attached (revised) copy of the NDA 207997, Midostaurin Acknowledge Presubmission letter. This letter has been revised to reflect the appropriate date of the submission and received date as April 5, 2016.

Please acknowledge receipt of this email.

Thank you,
Kim

From: Abraham, Abbey [<mailto:abbey.abraham@novartis.com>]
Sent: Monday, May 02, 2016 11:21 AM
To: Scott, Kimberly
Cc: Qiu, Yuhong
Subject: RE: NDA 207997 Midostaurin: Presubmission Acknowledgment

Hi Kim

Just one question on the acknowledgement letter. The date of submission is noted as April 12 but we sent via the gateway on April 5th and received acknowledgement of the electronic delivery on the 5th. Is this a typo or was there another reason for the agency's April 12th receipt date?

Thanks

Abbey Abraham
Phone +1 862-778-8998

From: Scott, Kimberly [<mailto:Kimberly.Scott@fda.hhs.gov>]
Sent: Friday, April 29, 2016 5:28 PM
To: Abraham, Abbey
Cc: Qiu, Yuhong
Subject: NDA 207997 Midostaurin: Presubmission Acknowledgment
Importance: High

Good evening Mr. Abraham,

Please see the attached (courtesy copy) presubmission acknowledgement letter for your April 12, 2016 submission for your first section of your New Drug Application, NDA 207797, Midostaurin.

Please acknowledge receipt of this email.

Thank you,

Kim

Kimberly Scott, RN, BSN, OCN®

CDR, U.S. Public Health Service

Regulatory Health Project Manager

Division of Hematology Products

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, Bldg. 22, Rm 2222

Silver Spring, MD 20993

Phone: 240-402-4560 |Kimberly.scott@fda.hhs.gov

3 Pages Have Been Withheld As A Duplicate Copy Of The "Acknowledge Presubmission Letter" dated May 11, 2016 Which Is Located In This Administrative Correspondence Section Of This NDA Approval Package.

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
05/11/2016



NDA 207997

ACKNOWLEDGE PRESUBMISSION

Novartis Pharmaceuticals Corporation
Attention: Abbey Abraham, PharmD
Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Mr. Abraham:

We have received the first section of your New Drug Application (NDA) under the program for step-wise submission of sections of a marketing application under 506 of the Federal Food, Drug, and Cosmetic Act.

Name of Drug Product: Midostaurin, capsules, 25 mg

Date of Submission: April 5, 2016

Date of Receipt: April 5, 2016

Our Reference Number: NDA 207997

We will review this presubmission as resources permit. Presubmissions are not subject to a review clock or to a filing decision by FDA until the application is complete.

Please cite the application listed above at the top of the first page of any communications concerning this supplemental application. Unless you are using the FDA Electronic Submissions Gateway (ESG), send all submissions by overnight mail or courier to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Hematology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, please call me at (240) 402-4560.

Sincerely,

{See appended electronic signature page}

Kimberly Scott, RN, BSN, OCN®
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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
05/11/2016



NDA 207997

ACKNOWLEDGE PRESUBMISSION

Novartis Pharmaceuticals Corporation
Attention: Abbey Abraham, PharmD
Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Mr. Abraham:

We have received the first section of your New Drug Application (NDA)/ under the program for step-wise submission of sections of a marketing application under 506 of the Federal Food, Drug, and Cosmetic Act.

Name of Drug Product: Midostaurin

Date of Submission: April 12, 2016

Date of Receipt: April 12, 2016

Our Reference Number: NDA 207997

This application is subject to the provisions of the Application Integrity Policy (AIP). We will not begin review until the Director, Center for Drug Evaluation and Research, notifies you either that the AIP has been revoked or that an exception to the AIP has been granted in the interest of public health.

Please cite the application listed above at the top of the first page of any communications concerning this supplemental application. Unless you are using the FDA Electronic Submissions Gateway (ESG), send all submissions by overnight mail or courier to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Hematology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets, or patient

information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, please call me at (240) 402-4560.

Sincerely,

{See appended electronic signature page}

Kimberly Scott, RN, BSN, OCN®
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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
04/29/2016



IND 057120

MEETING MINUTES

Novartis Pharmaceuticals Corporation
Attention: Yuhong Qiu, PhD
Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936

Dear Dr. Qiu:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for PKC412 (midostaurin).

We also refer to the meeting between representatives of your firm and the FDA on September 2, 2015. The purpose of the meeting was to discuss the adequacy of the proposed content of a New Drug Application (NDA) for midostaurin.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, contact Kris Kolibab, Regulatory Project Manager, at (240) 402-0277.

Sincerely,

{See appended electronic signature page}

R. Angelo de Claro, MD
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: September 2, 2015; 10:00 AM – 11:00 AM (EST)
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1315
Silver Spring, Maryland 20903

Application Number: IND 057120
Product Name: PKC412 (midostaurin)
Indication: For the treatment of patients with aggressive systemic mastocytosis (ASM) or mast cell leukemia (MCL) (b) (4)

Sponsor/Applicant Name: Novartis Pharmaceuticals Corporation

Meeting Chair: R. Angelo de Claro, MD
Meeting Recorder: Kris Kolibab, PhD

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP), Division of Hematology Products (DHP):

R. Angelo de Claro, MD, Clinical Team Lead
Alexandria Schwarsin, MD, Medical Reviewer
Amy Baird, Chief, Project Management Staff
Kris Kolibab, PhD, Regulatory Project Manager

OHOP, Division of Hematology Oncology Toxicology (DHOT):

Christopher Sheth, PhD, Toxicologist Team Leader
Natalie Simpson, PhD, Toxicologist Reviewer

Office of Clinical Pharmacology (OCP), Division of Clinical Pharmacology V:

Gene Williams, PhD, Team Leader
Sarah Schrieber, PharmD, Pharmacologist

Office of Pharmaceutical Quality (OPQ), Office of New Drug Products (ONDP):

Janice Brown, MS, CMC-Lead

Office of Biostatistics, Division of Biometrics V (DBV)

Lei Nie, PhD, Mathematical Statistician Team Leader
Kallapa Koti, PhD, Mathematical Statistician Reviewer

Office of Business Informatics

Rui Li, MD, MS, Computer Scientist

Office of Scientific Investigations, Division of Good Clinical Practice Compliance

Anthony Orenca, MD, FACP, Medical Officer

SPONSOR ATTENDEES

Renaud Capdeville, MD, Global Program Head, OGD, Novartis
Lisa Rojkaer, MD, Global Clinical Program Head, OGD, Novartis
Alice Huntsman Laped, PhD, Program Statistician, Biostatistics, OGD, Novartis
Catherine Dutreix, PhD, Sr. Fellow, Clinical Pharmacology, OCP, Novartis
Jacqueline Kinyamu-Akunda, DVM, PhD, Director, Preclinical Safety, Novartis
Institutes for BioMedical Research
Gabriela Gruia, MD, Global Head of Drug Regulatory Affairs, OGD, Novartis
Yuhong Qiu, PhD, Global Program Regulatory Director, Drug Regulatory Affairs, Novartis

1.0 BACKGROUND

Novartis Pharmaceuticals Corporation requested a pre-NDA meeting with FDA on June 12, 2015 to discuss the adequacy of the proposed content of a NDA for midostaurin. On June 16, 2015, FDA sent Novartis Pharmaceuticals Corporation the meeting request granted letter.

On August 28, 2015, the Division emailed Novartis Pharmaceuticals Corporation the preliminary responses to the questions contained in the meeting information package.

2. DISCUSSION

2.1. Registration study and proposed indication

Question 1:

Does the Agency agree that data from the pivotal study D2201 and supportive study A2213, together with safety and patient exposure data from the randomized placebo controlled phase III study in AML (RATIFY) adequately support the filing and review of proposed indication 'treatment of patients with ASM or MCL [REDACTED] (b) (4) ' ?

FDA Response to Question 1:

We recommend that you submit the NDA for the treatment of ASM/MCL as soon as possible.

The Agency recognizes the development of treatment in a rare disease with a patient population who has few treatment options and, thus, is interested in the application.

The Agency has several concerns, some of which may be addressed with the presentation of the data:

- **The Agency would want information on why certain patients were enrolled but not included in the Primary Efficacy Population.**
- **The response criteria requires improvement in one C-finding and a lack of progression in other C-findings. Data on all C-findings in patients, regardless of whether or not that C-finding was used to determine response, would need to be included in datasets and discussed in the CSR.**
- **Investigator assessments as well as the SSC assessments would need to be included.**
- **Efficacy narratives for all patients, responders and non-responders, PEP population and enrolled population, would need to be included.**
- **In a single arm trial, it is difficult to differentiate between symptoms that are related to disease and adverse events related to the drug.**

The Agency is concerned that for trial A2213, the response did not need to be confirmed and was based on investigator assessment. Include efficacy narratives for all patients on this trial.

Discussion:

The Sponsor agreed to provide datasets to allow analysis of C-findings.

2.2. KIT D816V companion diagnostic

Question 2:

Does the Agency agree that a companion diagnostic for KIT D816V mutation is not required since midostaurin is active and has similar safety profiles in patients with or without KIT D816V mutation?

FDA Response to Question 2:

Based on your analysis results, a companion diagnostic for KIT D816V mutation is not required.

Discussion:

No discussion occurred.

2.3. Efficacy narrative

Question 3:

Does the Agency agree with the inclusion of the proposed efficacy narratives in the dossier to facilitate the review of the NDA?

FDA Response to Question 3:

The Agency is in agreement with the inclusion of narratives for both patients in the PEP and patients determined to be not eligible for the PEP. To facilitate review, the Agency recommends including further detail on the SSC thought process regarding the individual patients.

For example, in the dossier, a narrative is provided for a patient not included in the PEP. This patient has a transfusion dependent anemia with a baseline HGB of 93 g/L. The basis of ineligibility described is “The patient had a transfusion dependent anemia, but the lack of a second C-finding made this patient ineligible per protocol”. In the protocol it states:

“Patients presenting with the C-Finding of anemia or thrombocytopenia and are receiving RBC or platelet transfusions are required to have another measureable C-Finding present at study entry. An exception to this requirement will be patients presenting with TD anemia, who are allowed to be enrolled into the study even if they don’t have any measurable C-Finding including Hgb <10 g/dL.”

Thus, based on the explanation in the narrative, it is unclear why this patient was not included in the PEP population. Is it secondary to the fact that the anemia could be due to the AHNMD and not due to ASM? More information is needed in each narrative to be included in the NDA submission.

Discussion:

No discussion occurred.

2.4. Summary of clinical efficacy

Question 4:

Does the Agency agree with the proposed content and format of the Summary of Clinical Efficacy (SCE)?

FDA Response to Question 4:

In addition to the proposed content, you should discuss and pool the data across the two trials.

At the meeting, discuss a proposal for the Integrated Summary of Efficacy (ISE), which is a required component of NDA submissions. We refer you to FDA Guidance for the ISE and ISS:

<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm136174.pdf>.

Discussion:

The Sponsor proposal for the ISE is acceptable to the Agency.

The Agency also agrees with the plan not to pool efficacy results for D2201 and A2213, however expects a side by side comparison of the 2 trials to be included SCE/ISE. The Agency requests subgroup analysis of patients with mast cell leukemia to be included.

2.5. Summary of clinical safety

Question 5:

Does the Agency agree with the proposed pooling strategy and the content of the Summary of Clinical Safety (SCS)?

FDA Response to Question 5:

The Agency is in agreement with the proposed pooling strategy.

We recommend that you include an analysis of the safety data from the RATIFY trial when midostaurin was given as a single agent for up to 12 cycles compared to placebo post-consolidation. You can include this analysis in the RATIFY CSR, ISS, or both.

At the meeting, discuss a proposal for the Integrated Summary of Safety (ISS), which is a required component of NDA submissions. We refer you to FDA Guidance for the ISE and ISS:

<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm136174.pdf>.

Discussion:

The Sponsor proposal is acceptable. The Agency clarified that ISS and ISE datasets will be needed to be submitted to the NDA.

2.6. Narratives and case report forms

Question 6:

Does the Agency agree with the proposed categories for case report forms and narratives to be included in the dossier?

FDA Response to Question 6:

Yes.

Discussion:

No discussion occurred.

2.7. Clinical pharmacology package

Question 7:

Does the Agency agree that the clinical pharmacology package is sufficient to support the filing?

FDA Response to Question 7:

Yes, we agree but with the following caveats:

- a. The dose-response and exposure-response (E-R) analyses for the ASM/MCL studies D2201 and A2213 appear appropriate. Additionally submit a pooled exposure-efficacy analyses for studies D2201 and A2213. If data are available, dose-response and exposure-response analyses also need to be conducted for the RATIFY study in AML patients.**
 - i. In your justification for the dose selection for each proposed indication in your NDA, include an integrated dose-response and exposure-response analyses by pooling nonclinical pharmacology, pharmacokinetic, pharmacodynamic, activity, and safety data, and evaluate the frequency of dose reductions and interruptions and time to these dose modifications to support dose selection. Refer to Guidance for Industry entitled “Exposure-Response Relationships – Study Design, Data Analysis and Regulatory Applications” found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf>.**
- b. Given the long duration of the study, it is unclear why enrollment and analysis of the hepatic study are not complete. Can the study be completed and a final report submitted with the NDA? If not, can completion and submission occur early in the review cycle?**

Discussion:

No discussion occurred.

2.8. Electronic datasets

Question 8:

Does the Agency agree with the proposed datasets (non-CDISC format) to be included in the NDA and that the define.pdf file provides adequate supportive documentation on the structure of the datasets?

FDA Response to Question 8:

Your approach is acceptable. Please note, however, that any programs (e.g. SAS) must be submitted as non-executable, ASCII-formatted files. Please refer to the June 2015 Study Data Technical Conformance Guide (SDTCG) for additional relevant technical specifications.

We refer you to the following pharmacometric data and models submission guidelines: <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm>.

Discussion:

The Agency clarified with the Sponsor that analysis data sets should be submitted as SAS transport files. The Sponsor's proposal to submit SAS programs as ASCII files is acceptable. The Agency does not expect efficacy data to be submitted for the RATIFY trial in the ASM/MCL NDA.

2.9. Toxicology package

Question 9:

Does the Agency agree that the toxicology package is adequate to support the registration of midostaurin in the proposed indication?

FDA Response to Question 9:

Yes, we agree.

Discussion:

No discussion occurred.

2.10. Safety update

Question 10:

Does the Agency agree with the proposed content of the safety update?

FDA Response to Question 10:

The Agency is in agreement with the proposed content of the safety update. At the meeting, discuss the timeline for submission of the safety update.

Discussion:

The Sponsor proposes to submit the safety update within the timeframes of a standard NDA review. The Agency noted that the timelines might change based on results of the RATIFY trial.

2.11. Proposed eCTD table of content

Question 11:

Does the Agency agree with the content of the NDA as outlined in the proposed electronic Common Technical Document (eCTD) table of contents (TOC)?

FDA Response to Question 11:

Yes, the proposed format for the planned NDA is acceptable. In section 5.3.3.5, also include your exposure-response analyses reports for the ASM/MCL studies D2201 and A2213 and the AML study RATIFY.

Discussion:

No discussion occurred.

2.12. User fee and pediatric waiver

Question 12:

Does the Agency agree with a user fee waiver and a waiver for pediatric study requirement based the orphan designation received?

FDA Response to Question 12:

Based upon the provided information, the proposal meets the requirements for an orphan exemption of the application fee as per Section V.A of the Guidance for Industry *User Fee Waivers, Reductions, and Refunds for Drug and Biological Products*, “Under section 736(a)(1)(F) of the Act, a human drug application for a product that has been designated as a drug for a rare disease or condition (referred to as an orphan drug) under section 526 of the Act is not subject to an application fee unless the human drug application includes an indication for other than a rare disease or condition.” Applications for orphan designated drugs (and only orphan designated indications) are exempt from user fees – no requests for waivers are required. When completing the user fee coversheet, the Applicant should note that the application is orphan designated, then the calculation of the final amount owed for that application will be \$0.

Please note the final determination for user fee requirements occurs when the application is submitted in its entirety to the Agency.

Regarding pediatric study requirements, 21 CFR 315.55 (d) states pediatric use information does not apply to any drug for an indication or indications for which orphan designation has been granted.

Discussion:

No discussion occurred.

2.13. Financial disclosure

Question 13:

Does the Agency agree that D2201 is the only ‘covered study’ under the rule ‘Financial Disclosure for Clinical Investigators’?

FDA Response to Question 13:

No, the Agency does not agree. We recommend that you include financial disclosure information for the following clinical trials: D2201, A2213, RATIFY, and A2114 (pediatric trial).

Discussion:

No discussion occurred.

2.14. Office of Scientific Investigations (OSI) submission

Question 14:

Does the Agency agree with Novartis proposal to include the following items to facilitate OSI inspection preparation?

FDA Response to Question 14:

The items proposed are required. The Agency strongly recommends submission of the site level dataset. The Agency refers you the draft “Guidance for Industry *Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning*” (available at the following link <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf> for the structure and format of this data set. We recommend submission of this dataset for study A2213 and RATIFY as well. The items proposed are required for A2213 and RATIFY.

Discussion:

The Sponsor proposal is acceptable. The Agency agrees with this late submission within 30 days of NDA submission.

2.15. QT study data

Question 15:

The results of a dedicated QT study (CPKC412A2113) were uploaded into FDA ECG warehouse in July 2010. Does the Agency agree that re-upload is not required?

FDA Response to Question 15:

Yes, we agree that a re-upload will not be required. We have the following additional comment regarding your assessment of the risk of QT prolongation of midostaurin. Based on your reports, it appears that the QT prolongation risk of midostaurin at the therapeutic dose is low. We understand that that this healthy subject study, given its short duration, is not meant to address directly the long-acting metabolite, which accumulates over 3-4 weeks. Therefore, this QT study may not be adequate to fulfill the regulatory requirement of QT evaluation for midostaurin. Additional data regarding the QT effect of long-acting metabolites at the steady state is expected and should be included in your NDA, if available. Since continuation of the ECG monitoring across the clinical program is being conducted, we are agreeable for you to cross-reference the study reports/dataset submitted to your IND in the NDA submission, and include additional QT data from other studies that may address the concern outlined above. The adequacy of your QT assessment in your clinical program remains a review issue. Please also refer to comments conveyed in two previous email correspondences dated June 22, 2015.

Discussion:

No discussion occurred.

3.0 OTHER MEETING INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.

The Agency was able to agree with the Clinical, Statistical, Clinical Pharmacology, and Non-clinical components of the NDA submission for ASM/MCL indication. Regarding the CMC component, refer to meeting minutes dated July 31, 2015 for CMC meeting on July 24, 2015.

All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- A preliminary discussion on the need for a REMS was held and it was concluded that a need for the REMS will be made during the review of the application and the Agency will notify the sponsor once a determination for a need for a REMS occurs.
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. See above for agreement for late submission of site-level data sets.

Discussion:

The Agency discussed with the Sponsor regarding the expedited programs available including rolling review, fast track designation, and breakthrough therapy designation. The Agency noted the timelines may need to be changed based on granting of the expedited programs. The Division would be supportive of a breakthrough therapy designation request (BTDR) for AML indication if overall survival results are statistically significant and clinically meaningful.

At this time, the Sponsor intends to submit the NDA for ASM/MCL and AML indications at the same time citing that data transfer from the Cooperative Group and CMC components as potentially limiting steps for an earlier submission.

PREA REQUIREMENTS

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

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#) including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [PLLR Requirements for Prescribing Information](#) websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential in the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, “Product name, NDA/BLA 012345, Establishment Information for Form 356h.”

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

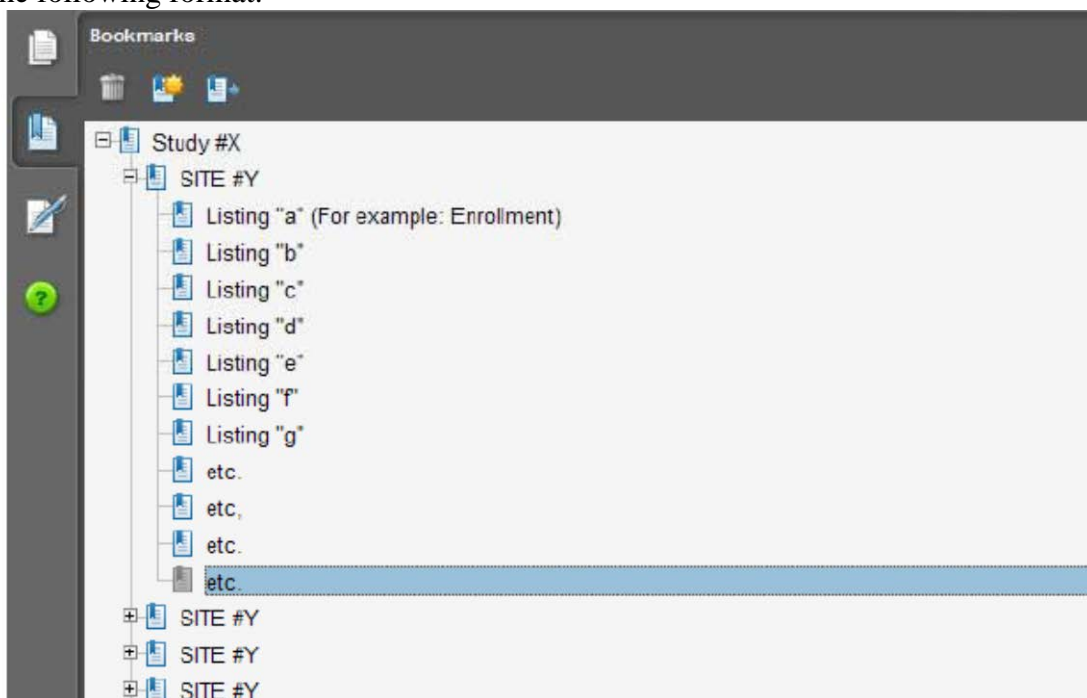
1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:

- a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
 3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
 - a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
 - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
 4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
 5. For each pivotal trial provide original protocol and all amendments (or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated

- b. Subject listing for treatment assignment (randomization)
 - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry *Providing*

Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning (available at the following link

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Attachment 1
Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item¹	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

¹ Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1

(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page

(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

5.0 ACTION ITEMS

None.

6.0 ATTACHMENTS AND HANDOUTS

The Sponsor provided the attached handouts for the meeting.

11 Page(s) 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/

ROMEO A DE CLARO
09/03/2015

MEETING MINUTES

MEETING DATE: July 12, 2006 **TIME:** 2:30 **LOCATION:** 1315

IND: 57,120 **Meeting Request Receipt Date:** May 15, 2006
FDA Response Date: May 18, 2006
Briefing Document Receipt Date: June 12, 2006

DRUG: PKC412 oral gelcaps **INDICATION:** AML

SPONSOR: Novartis **TYPE of MEETING:** EOP2

FDA PARTICIPANTS: Robert Justice, M.D., Dir., DDOP
Ramzi Dagher, M.D., Medical Team Leader, DDOP (Chair)
Nancy Scher, M.D., Medical Officer, DDOP
David Morse, Ph.D., Pharm. Supervisor, DDOP
Hans Rosenfeldt, Ph.D., Pharmacologist, DDOP
Roshni Ramchandani, Ph.D., Clin. Pharm. Reviewer, OCP
Chia-wen Ko, Ph.D., Statistician, OPSS
Shenghui Tang, Ph.D., Statistician, OPSS
Francis Kalush, Ph.D., HFZ-440, CDRH/OIVD/DIHD
Robert Becker, M.D., HFZ-440, CDRH/OIVD/DIHD
Arthur Flatau, Patient Consultant (by phone)
Joann Minor, HF-12, OSHI
Patricia Delaney, HF-12, OSHI
Dotti Pease for Ann Staten, Project Manager, DDOP

SPONSOR:

John Rediske, Ph.D., Drug Regulatory Affairs, Novartis
Giorgio Massimini, M.D., Clinical Development, Novartis
Frances Duffy-Warren, Ph.D., Drug Regulatory Affairs, Novartis
Lixia Wang, Ph.D., Biostatistics, Novartis
Xiaoming Li, Ph.D., Biostatistics, Novartis
Penny Phillips, Ph.D., Biomarker Development, Novartis
Richard Stone, M.D., Clinical Investigator (CALGB)
Prem Narang, Ph.D., Drug Regulatory Affairs, Novartis
Harry Bloom, Ph.D., Project Manager, Novartis
Debra Aleknavage, Reg. Affairs, Novartis

MEETING OBJECTIVES: Discuss the development plan for PKC412 to support the indication of [REDACTED] (b) (4) [REDACTED] AML patients [REDACTED] (u) (4) [REDACTED] with activating mutations of the FLT-3 gene.

BACKGROUND: PKC412 is an inhibitor of protein kinase C as well as an inhibitor of vascular endothelial growth factor. Protein kinase C may be a pathological mediator that plays a role in cancer, psoriasis, inflammatory diseases, diabetes and CNS disorders. PKC412 is a targeted agent against FLT3 and thus, in combination with chemotherapy, should provide improved therapeutic benefit to AML patients with FLT3 mutations.

FDA's draft responses to the sponsor's questions were faxed to Novartis on July 5 and Novartis decided to retain the face-to-face meeting as scheduled. Discussion is indicated in bold italics.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

1. Does the Agency agree that the preclinical safety studies conducted and planned for PKC412, the parent compound will be sufficient for registration?

FDA: The non-clinical studies of PKC412 that have been put forward by Novartis in support of IND 57,120 appear sufficient for registration pending submission of the additional studies proposed in this meeting package, and pending review.

2. We believe that the proposed clinical pharmacology program including drug-drug interaction (DDI) studies with PKC412 is adequate to support the initial registration package. Does the Agency agree?

FDA: Yes. Your clinical pharmacology plan is acceptable.

However, we urge you to conduct the hepatic impairment study and you may consider submitting an interim report comparing moderately impaired patients with control patients in a reduced study design.

Additional Protocol-Related Comment:

We recommend that you collect PK samples, using sparse sampling, for measurement of PKC412 and its metabolites in your proposed phase 3 study. This would enable evaluation of exposure-response relationships for measures of effectiveness and toxicity.

3. The selected patient population for the proposed Ph III study is "newly diagnosed, FLT3 mutated AML patients less than 60 years of age". Does the Agency agree with the at risk selected patient population is appropriate to support registration for the proposed indication?

FDA: Yes. However, please see the responses to questions 11 and 12 regarding the assay sensitivity and specificity.

4. Is the proposed consensus chemotherapy regimen acceptable for the pivotal trial?

FDA: Yes

5. Does the Agency agree that the safety and efficacy profile of PKC412 demonstrated in Studies 2104 and 2106 supports the choice of the proposed dose of 50 mg orally twice daily and the sequential treatment regimen for the Phase III trial?

FDA: Yes

6. Does the Agency agree that the addition of a maintenance phase to the treatment regimen is appropriate for the Phase III trial?

FDA: Yes. Please see also question number 7.

Discussion: Discuss how question 6 links with question 7. FDA noted that this reference is to the FDA's recommendation for SPA in the response to question 7.

7.

[Redacted text block]

(b) (4)

[Large redacted text block]

(b) (4)

(b) (4)

DISCUSSION: FDA noted the clarification and encouraged Novartis to submit an SPA for this trial.

In Acute Leukemia, Complete Response Rate with Duration has been considered a validated surrogate for Clinical Benefit. (b) (4)

Therefore, please submit your protocol and Statistical analysis Plan for Special protocol Assessment. In addition, this may require further discussion with ODAC.

SPONSOR:

- SPA with ODAC member consultations or ODAC discussion of EFS endpoint ?
- Timeframe for FDA review of EFS endpoint.

DISCUSSION: FDA strongly recommends the submission of an SPA and will probably get an ODAC consultant to help us. Leukemia endpoints were discussed at a workshop in June 2005 and will be discussed at an ODAC meeting in the future.

8. (b) (4)
Does the Agency agree that this represents sufficient improvement in patient benefit to support full approval of PKC412?

FDA: This will be a review issue. Please see response to question 7.

9. Does the Agency agree that a single, multi-center, randomized, double-blind, placebo-controlled phase III trial (given the statistical design aspects noted above) is adequate to support the approval of PKC412 for the indication (b) (4)

AML patients with activating FLT3 mutations”?

FDA: In order for a single randomized trial to support an NDA, the trial must be well designed, flawlessly executed, and internally consistent and provide statistically and clinically persuasive efficacy findings so that a second trial would be ethically or practically impossible to perform. Please see response to question 7 above and questions 11 and 12 below.

10. Does the Agency agree that the proposed clinical data package will provide adequate safety data for approval in the proposed indication?

FDA: It appears that the safety data base will be adequate.

11. Does the Agency agree with the current plan to use multiple laboratories to implement the FLT3 mutation assay used for patient selection in the proposed phase III trial?

FDA: We have too little information about the specifications and the performance characteristics of the mutation assay(s) to answer firmly. Please identify the sites at which FLT3 testing will be done. Please provide a full description of the materials and procedures for test performance. Please describe your methodology or provide the protocol through which intra-laboratory validation and inter-laboratory cross-validation of the assays will be accomplished. Some features to consider are those described in the "Analytical Test Validation" section of the "Drug-Diagnostic Co-Development Concept Paper" currently published by FDA at <http://www.fda.gov/cder/genomics/pharmacoconceptfn.pdf>.

SPONSOR:

- *Will submit requested information by end of September*
- *Will both DODP and CDRH be involved in review of the assay validation proposal?*

FDA – Submit everything through CDER, and we will consult CDRH.

- *Request a 15 day review cycle*

FDA – A 15-day turn around is doubtful, but submitting electronically (by e-mail) would help. We still would need to have an internal discussion (CDER and CDRH) before we could convey our comments.

12. (b) (4)

Does the Agency agree?

FDA: No. Given successful demonstration of validity within and across laboratories for the clinical study (Question 11), the performance of those tests across the entire testing

community after drug registration remains unknown. The primary concerns from a device perspective are 1) well established and satisfactory analytical characteristics (e.g. reproducibility within and across assays and laboratories) and 2) the ability to trace the clinical utility of the (any) test at each site back to the trials that are executed to support licensing of the drug. From a practical perspective, this means establishing the clinical utility of the test using samples from patients studied in the pivotal drug trial. FDA recommends clearance or approval of a test or test(s) supporting the recommendation in the drug label. If this is not accomplished at the time that the drug is registered, then FDA recommends as a condition of approval the development of a standardized test as has been required in other circumstances.

SPONSOR:

- *The current trial will test benefit of PKC412 in poor prognosis AML patients presenting with mutations in Flt3.*
- *No data will be generated in this trial comparing outcomes of patients with Flt 3 mutations vs. patients with wild type Flt 3.*
- *The association of Flt3 mutation with poor prognosis is well established and will not be re-confirmed in this planned pivotal trial.*

-  (b) (4)

DISCUSSION: *Data supporting the clinical utility of the test could be obtained from other sources in addition to this clinical trial; however, an approved kit would still be recommended at the time of NDA approval.*

Additional FDA Comments:

Based on the limited data base we recommend that you provide additional data concerning the mutation negative patients and response to the drug. Please contact the Center for Devices and Radiological Health for additional information.

ACTION ITEMS:

Novartis will submit an SPA for this study in the near future. They will try to give us a few weeks notice before submitting it so that we can get started clearing an ODAC consultant.

Dotti Pease
Chief, Project Management Staff

Concurrence Chair: _____
Ramzi Dagher, M.D.
Medical Team Leader

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

/s/

Ramzi Dagher
7/18/2006 11:57:28 AM

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

/s/

Dotti Pease
7/18/2006 01:39:42 PM

LATE-CYCLE COMMUNICATION
DOCUMENTS

207997Orig1s000

207997Orig2s000



NDA 207997

LATE-CYCLE MEETING MINUTES

Novartis Pharmaceuticals Corporation
Attention: Abbey Abraham, PharmD
Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Abraham:

Please refer to your New Drug Application (NDA) dated August 29, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for RYDAPT (midostaurin) capsules, 25 mg.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on January 10, 2017.

A copy of the official minutes of the LCM is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call Kimberly Scott, Regulatory Project Manager at (240) 402-4560.

Sincerely,

{See appended electronic signature page}

Donna Przepioraka, MD, PhD
Cross-Discipline Team Lead
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: Tuesday, January 10, 2017
2:00PM – 3:00PM (ET)

Teleconference Number: 1-866-755-6294
Passcode: [REDACTED] (b) (4)

Application Number: NDA 207997
Product Name: RYDAPT (midostaurin)

Indication:

- Original 1: Treatment of adult patients with advanced systemic mastocytosis.
- Original 2: 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.

Applicant Name: Novartis Pharmaceuticals Corporation

Meeting Chair: Donna Przepiorka, MD, PhD

Meeting Recorder: Kimberly Scott

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP)/Division of Hematology Products

Ann Farrell, MD, Division Director
Albert B. Deisseroth, MD, PhD, Supervisory Associate Division Director
Donna Przepiorka, MD, PhD, Cross-Discipline Team Lead
Ashley Ward, MD, Medical Officer
Theresa Carioti, MPH, Chief, Project Management Staff
Kimberly Scott, BSN, RN, OCN®, Regulatory Health Project Manager
Barry W. Miller, MS, CRNP, Acting Deputy Director Safety
Diane Leaman, BS, Safety Regulatory Project Manager

OHOP/Division of Hematology, Oncology, Toxicology (DHOT)

Christopher Sheth, PhD, Supervisory Pharmacologist/Toxicologist
Natalie Simpson, PhD, Pharmacologist/Toxicologist Reviewer

Office of Biostatistics, Division of Biometrics V

Lei Nie, PhD, Statistics Team Leader
Chia-Wen Ko, PhD, Statistics Reviewer

Office of Translational Sciences (OTS)/Office of Clinical Pharmacology (OCP)/Division of Clinical Pharmacology V

Nitin Mehrotra, M Pharm, PhD, Pharmacometrics Team Lead

Stacy Shord, PharmD, Team Lead
Sriram Subramaniam, Pharm D, Clinical Pharmacology Reviewer

Office of Surveillance and Epidemiology (OSE), Office of Medication Error Prevention and Risk Management (OMEPRM), Division of Medication Error Prevention and Analysis (DMEPA)

Leeza Rahimi, PharmD, Safety Evaluator

Division of Molecular Genetics and Pathology/Office of In Vitro Diagnostics and Radiological Health

Allen Williams, PhD, Scientific Reviewer

Office of Pharmaceutical Quality/Office of New Drug Product/Division of New Drug Product I

Anamitro Banerjee, PhD, Acting Branch Chief

APPLICANT ATTENDEES

Renaud Capdeville, Vice President, Global Program Head
Taoufik Ouatas, Site Head, Oncology Clinical Pharmacology
Zheng Gu, Multi Program Head, Integrated Medical Safety
Iulian Alecu, Senior Director, Integrated Medical Safety
Noah Berkowitz, Executive Director, Global Clinical Program Head
Allison Florance, Executive Director, Biostatistics
Alice Huntsman-Labed, Director, Biostatistics
Karen Sinclair, Senior Statistician, Biostatistics
Jacqueline Kinyamu-Akunda, Director, Preclinical Safety
Elizabeth Purdy, Senior Manager, Regulatory Affairs, CMC
Sheryl LeRoy, Oncology Franchise Head, Regulatory Affairs, CMC
Eva Tiecke, Associate Director, Precision Medicine
Marilyn Fritzemeier, Director, CDx Diagnostic Regulatory
Valerie Campello Iddison, Vice President, Global Medical Affairs
Karen Habucky, Head, US Clinical Strategy - Leukemia
Shanthi Ganeshan, Vice President, North America Region Head, Drug Regulatory Affairs
Yuhong Qiu, Senior Director, Drug Regulatory Affairs
Abbey Abraham, Director, Drug Regulatory Affairs

1.0 BACKGROUND

NDA 207997 was submitted on August 29, 2016 for RYDAPT (midostaurin).

Proposed indications:

- Original 1: Treatment of adult patients with advanced systemic mastocytosis.
- Original 2: 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.

PDUFA goal date: April 28, 2017

FDA issued a Background Package in preparation for this meeting on January 6, 2017.

2.0 DISCUSSION

1. Introductory Comments: (Kimberly Scott, RPM/Donna Przepiorka, CDTL)

Discussion:

FDA explained that this application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting does not address the final regulatory decision for the application. The objective of the meeting is share information about the deficiencies identified to date and to discuss the status of the review.

2. Discussion of Substantive Review Issues:

- Dose optimization for use of midostaurin for treatment of mastocytosis

Discussion:

FDA indicated there was a concern regarding the proposed starting dose of midostaurin 100 mg BID for treatment of mastocytosis, since there was a high rate of treatment interruptions and dose modifications using this dose. FDA inquired about (b) (4)

FDA pointed out that availability of data from a single dose level, lack of control arm, and multiple treatment interruptions and dose modifications makes it difficult to utilize exposure-efficacy analysis towards dosing recommendations. Applicant acknowledged this limitation in the analysis.

- (b) (4)

Discussion:

(b) (4)
the Applicant also indicated they were open to discussion of other approaches to clarify the RATIFY treatment plan in labeling.

- Treatment effect by molecular subgroup for patients with AML

Discussion:

FDA acknowledged the Applicant's submission of the subgroup analysis of RATIFY by NPM1 mutation and identified the inconsistencies in the treatment effect as a potential issue that would require further explanation before concluding that the inconsistencies were random chance. FDA indicated that the specific information needed would be detailed in an Information Request to be sent to the Applicant shortly after the meeting.

FDA also inquired whether the Applicant still planned to submit [REDACTED] (b) (4) [REDACTED]. The Applicant indicated that the additional analyses were planned, but the exact data of availability was not yet firm.

3. Discussion of Minor Review Issues:

- Concomitant use of strong CYP3A4 inhibitors with midostaurin

Discussion:

FDA reiterated that the intended population had a high rate of use of strong cytochrome P450 (CYP) 3A inhibitors, and expressed concern regarding the exposure and tolerability of midostaurin in the presence of strong CYP3A inhibitors, particularly at the early phase of dosing and at steady state due to the time dependent kinetics of midostaurin. As discussed earlier, this is further complicated by the lack of recording of dates and times of dosing and pharmacokinetic sampling for the majority of the patients in the RATIFY trial. FDA inquired if the Applicant had any additional information or plans to address this issue. The Applicant indicated that there were no additional information and indicated that based on the adverse events collected at the cycle level in the RATIFY trial, tolerability does not appear to be an issue.

4. Additional Applicant Data: (Applicant)

Discussion:

The Applicant indicated that they have additional data scheduled for submission during this review cycle.

5. Information Requests:

Discussion:

The Applicant acknowledged FDA's request for new [REDACTED] (b) (4) [REDACTED] and confirmed that the response will be submitted by Friday, January 13, 2017.

6. REMS or Other Risk Management Actions:

Discussion:

FDA indicated that there is no request for a REMS planned at this time.

7. Postmarketing Requirements/Postmarketing Commitments: 5 minutes

Discussion:

FDA indicated that the review is still on-going, and PMRs or PMCs have not been finalized at this time. FDA will discuss PMRs and PMCs with the Applicant at a later date.

8. Major Labeling Issues:

Discussion:

FDA indicated that labeling review was on-going, and there were still plans to send the first set of comments in about 4 weeks, but FDA wanted the Applicant to be aware of 3 issues with the Prescribing Information that were being discussed. FDA intends to send labeling comments by the February 7, 2017 goal date.

- Boxed warning regarding use during pregnancy

Discussion:

FDA has a concern that since standard induction chemotherapy is routinely administered to pregnant patients in the 2nd and 3rd trimester, a boxed warning about the potential hazards from fetal exposure to midostaurin might be warranted.

- Limitation of use statement regarding lack of efficacy of midostaurin as monotherapy for treatment of relapsed or refractory FLT3-mutated AML

Discussion:

FDA reiterated that given the extensive amount of data showing no efficacy for midostaurin monotherapy for the relapsed/refractory population, a limitation of use statement was being considered.

- Display response rates for mastocytosis by IWG criteria

Discussion:

FDA acknowledged recent major changes in the mastocytosis response criteria accepted internationally and shared that including in Section 14 the results of the mastocytosis studies using the new criteria was under consideration.

(b) (4)

9. Review Plans:

Discussion:

The Applicant acknowledged the on-going Sponsor and clinical site inspections. FDA indicated that the review process is otherwise continuing, and the goal date is unchanged.

10. Wrap-up and Action Items:

- The Applicant requested additional information about a [REDACTED] ^{(b) (4)}. Since the [REDACTED] ^{(b) (4)} is not handled by the Division, FDA agreed to provide information for the appropriate contact off-line.
- FDA will send an information request about the NPM1 subgroup analysis [REDACTED] ^{(b) (4)} according to the timeline described above.
- The Applicant will provide a response to the CMC IR by January 13, 2017.

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

/s/

DONNA PRZEPIORKA
01/18/2017



NDA 207997

**LATE CYCLE MEETING
BACKGROUND PACKAGE**

Novartis Pharmaceuticals Corporation
Attention: Abbey Abraham, PharmD
Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Abraham:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for RYDAPT (midostaurin) capsules, 25 mg.

We also refer to the Late-Cycle Meeting (LCM) scheduled for January 10, 2017. Attached is our background package, including our agenda, for this meeting.

Please email me a list of your attendees as well as a teleconference number for the meeting at Kimberly.scott@fda.hhs.gov, by Friday, January 6 2017.

If you have any questions, call Kimberly Scott, Regulatory Project Manager, at (240) 402-4560.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, MD
Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: Tuesday, January 10, 2017
Teleconference Number: TBA

Application Number: NDA 207997
Product Name: RYDAPT (midostaurin)

Indication:

- Original 1: Treatment of adult patients with advanced systemic mastocytosis.
- Original 2: 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.

Applicant Name: Novartis Pharmaceuticals Corporation

FDA ATTENDEES (tentative)

Office of Hematology and Oncology Products (OHOP)/Division of Hematology Products

Ann Farrell, MD, Division Director
Albert B. Deisseroth, MD, PhD, Clinical Team Leader
Donna Przepiorka, MD, PhD, Acting Clinical Team Leader
Yvette Kasamon, MD, Medical Officer
Ashley Ward, MD, Medical Officer
Theresa Carioti, MPH, Chief, Project Management Staff
Kimberly Scott, BSN, RN, OCN®, Regulatory Health Project Manager
Kelly Miller, PharmD, Regulatory Project Manager
Wan Lee, PharmD, Regulatory Project Manager
Diane Leaman, BS, Safety Regulatory Project Manager

OHOP/Division of Hematology, Oncology, Toxicology (DHOT)

Christopher Sheth, PhD, Supervisory Pharmacologist/Toxicologist
Natalie Simpson, PhD, Pharmacologist/Toxicologist Reviewer

Office of Biostatistics, Division of Biometrics V

Lei Nie, PhD, Statistics Team Leader
Chia-Wen Ko, PhD, Statistics Reviewer

Office of Translational Sciences (OTS)/Office of Clinical Pharmacology (OCP)/Division of Clinical Pharmacology V

Stacy Shord, PharmD, Team Lead
Sriram Subramaniam, Pharm D, Clinical Pharmacology Reviewer

Office of Surveillance and Epidemiology (OSE), Office of Medication Error Prevention and Risk Management (OMEPRM), Division of Medication Error Prevention and Analysis (DMEPA)

Hina Mehta, PharmD, Team Lead
Leeza Rahimi, PharmD, Safety Evaluator

Division of Molecular Genetics and Pathology/Office of In Vitro Diagnostics and Radiological Health

Allen Williams, PhD, Scientific Reviewer

Office of Pharmaceutical Quality/Office of New Drug Product/Division of New Drug Product I

Anamitro Banerjee, PhD, Acting Branch Chief
Sherita McLamore-Hines, PhD, Acting Quality Assessment Lead
Nina Ni, PhD, CMC Reviewer

Office of Pharmaceutical Quality/Office of Process and Facilities/Division of Process Assessment I

Bogdan Kurtyka, PhD, Acting Quality Assessment Lead

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

1. Discipline Review Letters

No Discipline Review letters have been issued to date.

2. Substantive Review Issues

Clinical (Original 1):

1. There is insufficient justification for the 100 mg BID starting dose of midostaurin for treatment of advanced systemic mastocytosis. Based on the pharmacokinetic data provided, by 28 days of midostaurin dosed at 100 mg BID versus 50 mg BID, steady-state levels are notably quite similar. Further, over 50% of patients with advanced systemic mastocytosis required dose modification due to toxicity. Given that steady-state levels of 100 mg BID were similar to those with 50 mg BID, that there were frequent dose modifications due to toxicity for patients who started with 100 mg BID, and that the active metabolite CPG6525421 has a very long $t_{1/2\beta}$ (>400 hours), the proposed recommended starting dose of 100 mg BID may not be appropriate.

Clinical (Original 2):

2. You have evidence of lack of efficacy of midostaurin as monotherapy for treatment of relapsed or refractory FLT3-mutated AML. This may warrant a limitation of use statement in the prescribing information.
3.  (b) (4)
, but you have not submitted data to support this recommendation.
4. You state that midostaurin is a multikinase inhibitor, with activity including inhibition of other kinases known to be active in AML, but you are pursuing an indication for treatment of patients with FLT3-mutated AML specifically. Since AML cells may have more than one kinase mutation, and you have not provided subgroup analyses of efficacy outcomes in Study A2301 (RATIFY) by genetic mutation at diagnosis, it is not clear that you have targeted the correct AML molecular subgroup for your indication.

3. Minor Review Issues

Clinical Pharmacology

1. The exposure and tolerability of midostaurin in presence of strong cytochrome P450 inhibitors, particularly, at the early phase of midostaurin administration (i.e., up to 8 days after consecutive dosing) and at steady state (by 28-day after consecutive dosing) following consecutive dosing, have not been adequately demonstrated in the clinical trials. Midostaurin shows time-dependent pharmacokinetics with the maximal trough concentrations observed by 8 days and steady-state achieved by 28 days after consecutive dosing.

ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

REMS OR OTHER RISK MANAGEMENT ACTIONS

No issues related to risk management have been identified to date

LCM AGENDA

1. Introductory Comments: 5 minutes
(Kimberly Scott, RPM/Donna Przepiorka, CDTL)
Welcome, Introductions, Ground rules, Objectives of the meeting
2. Discussion of Substantive Review Issues –20 minutes
Each issue will be introduced by FDA and followed by a discussion.
 - Dose optimization for use of midostaurin for treatment of mastocytosis
 -  (b) (4)
 - Treatment effect by molecular subgroup for patients with AML
3. Discussion of Minor Review Issues – 10 minutes
 - Concomitant use of strong CYP3A4 inhibitors with midostaurin
4. Additional Applicant Data – 10 minutes (Applicant)
5. Information Requests – 5 minutes
 - Clinical
 - Clinical Pharmacology
 - CMC: due January 6, 2017
6. REMS or Other Risk Management Actions
None planned.

7. Postmarketing Requirements/Postmarketing Commitments –5 minutes
8. Major labeling issues – 10 minutes
 - Boxed warning regarding use during pregnancy
 - Limitation of use statement regarding lack of efficacy of midostaurin as monotherapy for treatment of relapsed or refractory FLT3-mutated AML
 - Display response rates for mastocytosis by IWG criteria
9. Review Plans – 5 minutes
10. Wrap-up and Action Items – 5 minutes

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
01/06/2017