

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205755Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 205755

SUPPL #

HFD #

Trade Name Zykadia

Generic Name ceritinib

Applicant Name Novartis Pharmaceuticals Corporation

Approval Date, If Known

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)

c) 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:

d) Did the applicant request exclusivity?

YES NO

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

The applicant did not specify the number of years.

e) 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

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
Explain:

NO
Explain:

Investigation #2

YES
Explain:

NO
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: Karen Boyd, M.S.
Title: Senior Regulatory Project Manager
Date: 4/14/14

Name of Office/Division Director signing form: Patricia Keegan, M.D.
Title: Director, Division of Oncology Products 2

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/

KAREN C BOYD
04/28/2014

PATRICIA KEEGAN
04/29/2014

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 205755 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Zykadia Established/Proper Name: ceritinib Dosage Form: capsules		Applicant: Novartis Pharmaceuticals Corporation Agent for Applicant (if applicable):
RPM: Karen Boyd		Division: CDER/OHOP/DOP2
NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></p> <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <ul style="list-style-type: none"> <input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i> <p>Date of check: _____</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>
❖ Actions		
<ul style="list-style-type: none"> Proposed action: <u>April 29, 2014</u> User Fee Goal Date is <u>August 24, 2014</u> Previous actions <i>(specify type and date for each action taken)</i> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR <input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		<input checked="" type="checkbox"/> Received by OPDP, 4/1/14
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority: Standard Priority
 Chemical classification (new NDAs only): NDA Chemical Type 1, NME (New molecular entity).
(confirm chemical classification at time of approval)

- | | |
|--|---|
| <input type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input checked="" type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input checked="" type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input checked="" type="checkbox"/> Breakthrough Therapy designation | |

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR
 Submitted in response to a PMC
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS: MedGuide
 Communication Plan
 ETASU
 MedGuide w/o REMS
 REMS not required

Comments:

❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	<input type="checkbox"/> Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other: Burst
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters (including approval letter with final labeling)	Action(s) and date(s) Approval, 4/29/14
Labeling	
❖ Package Insert (write submission/communication date at upper right of first page of PI)	
<ul style="list-style-type: none"> Most recent draft labeling (if it is division-proposed labeling, it should be in track-changes format) 	<input checked="" type="checkbox"/> Included 4/10/14
<ul style="list-style-type: none"> Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included 12/24/13
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (write submission/communication date at upper right of first page of each piece)	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> Most-recent draft labeling (if it is division-proposed labeling, it should be in track-changes format) 	<input checked="" type="checkbox"/> Included 4/10/14
<ul style="list-style-type: none"> Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included 12/24/13
❖ Labels (full color carton and immediate-container labels) (write submission/communication date on upper right of first page of each submission)	
<ul style="list-style-type: none"> Most-recent draft labeling 	<input checked="" type="checkbox"/> Included 3/14/14
❖ Proprietary Name	
<ul style="list-style-type: none"> Acceptability/non-acceptability letter(s) (indicate date(s)) Review(s) (indicate date(s)) 	03/25/14 03/24/14
❖ Labeling reviews (indicate dates of reviews)	RPM: <input checked="" type="checkbox"/> 2/7/14 DMEPA: <input checked="" type="checkbox"/> 3/24/14, 2/4/14 DMPP/PLT (DRISK): <input checked="" type="checkbox"/> None OPDP: <input checked="" type="checkbox"/> 3/27/14 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Other: <input checked="" type="checkbox"/> Nonclinical: 4/9/14 Patient Labeling: 3/28/14 Maternal Health: 3/21/14
Administrative / Regulatory Documents	
❖ Administrative Reviews (e.g., RPM Filing Review ⁴ /Memo of Filing Meeting) (indicate date of each review)	2/21/14
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Committee	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary (signed by Division Director)	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

⁴ Filing reviews for scientific disciplines should be filed with the respective discipline.

<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director’s Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC : N/A If PeRC review not necessary, explain: <u>PMHS staff notified of Orphan Designation on 3/25/14, and they informed the division that a pediatric page is not required.</u> 	
<ul style="list-style-type: none"> ❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters) (<i>do not include previous action letters, as these are located elsewhere in package</i>) 	Compliance Teleconference: 4/17/14 (uploaded 4/29/14) Compliance Information Request: 4/11/14 (uploaded 4/15/14) Information Request: 4/9/14 Labeling to Sponsor: 4/7/14 Labeling Teleconference: 4/7/14 Labeling to Sponsor: 4/7/14 PMR negotiations: 4/4/14 CMC Teleconference: 4/3/14 (uploaded 4/8/14) Compliance Teleconference: 4/3/14 (uploaded 4/28/14) Compliance Teleconference: 4/2/14 (uploaded 4/28/14) Labeling to Sponsor: 4/2/14 Labeling Teleconference: 4/1/14 (uploaded 4/9/14) PMR negotiations: 3/31/14 (uploaded 4/1/14) Labeling to Sponsor: 3/31/14 (uploaded 4/1/14) Labeling to Sponsor: 3/28/14 LCM Background Package: 3/27/14 Proprietary Name Request Withdrawn: 3/26/14 PMR negotiations: 3/25/14 (uploaded 3/26/14) Biopharm Tcon: 3/24/14 (uploaded 4/11/14) Labeling to Sponsor: 3/21/14 CMC Tcon: 3/19/14 (uploaded 4/11/14) NDA Methods Validation: 3/19/14 CMC IR: 3/18/14 Proprietary Name submission: 3/17/14 (uploaded 3/18/14) Clinical IR: 3/14/14 Clinical IR: 3/14/14 Clinical/Clin Pharm Tcon: 3/14/14 (uploaded 4/11/14) Acknowledge proprietary name withdrawal: 3/12/14 Clinical IR: 3/13/14 (uploaded

	<p>3/26/14) Clinical IR: 3/12/14 Response to question on IR: 3/10/14 Container labeling IR: 3/7/14 CMC IR: 3/7/14 Clin Pharm IR: 3/6/14 Agenda for midcycle communication: 3/6/14 Nonclinical IR: 3/6/14 Clinical IR: 3/4/14 (uploaded 3/5/14) Nonclinical IR: 3/4/14 (uploaded 3/5/14) CMC IR: 2/27/14 CMC/Microbiology: 2/24/14 Clinical IR: 2/21/14 Filing letter: 2/21/14 Clinical IR: 2/21/14 CMC IR: 2/20/14 Clin Pharm IR: 2/18/14 Biopharma IR: 2/18/14 Clin Pharm IR: 2/14/14 (uploaded 2/18/14) Clinical IR: 2/13/14 Clinical IR: 2/11/14 Clin Pharm IR: 2/7/14 Advice—Proprietary Name: 2/4/14 (uploaded 2/6/14) Clinical IR: 2/5/14 DMEPA Teleconference: 2/4/14 (uploaded 2/5/14) Memo (Verbal): 1/31/14 Labeling to Sponsor: 1/31/14 Clinical IR: 1/29/14 DMEPA Teleconference: 1/27/14 (uploaded 1/29/14) CMC Microbiology IR: 1/22/14 Clinical IR: 1/22/14 Clin Pharm IR: 1/17/14 Acknowledgement Letter: 1/6/14 Clin Pharm IR: 1/3/14 Acknowledge Presubmission: 12/20/14 Acknowledge Presubmission: 12/11/14</p>
<p>❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)</p>	<p>Team meeting: 4/29/14 Wrap Up meeting: 4/8/14 (uploaded 4/25/14) Labeling meeting: 4/7/14 Labeling meeting: 3/31/14 (uploaded 4/25/14) Team/Labeling meeting: 3/27/14 (uploaded 4/25/14) Labeling meeting: 3/20/14 (uploaded 4/17/14)</p>

	<p>Labeling meeting: 3/18/14 (uploaded 4/17/14) Team Meeting: 3/18/14 (uploaded 4/24/14) Labeling meeting: 3/14/14 (uploaded 4/17/14) Labeling meeting: 3/13/14 (uploaded 4/17/14) Internal PMR meeting: 3/11/14 (uploaded 4/22/14) Team meeting: 3/4/14 (uploaded 4/22/14) Labeling meeting: 3/4/14 (uploaded 4/17/14) Internal PMR meeting: 3/3/14 (uploaded 4/15/14) Internal meeting (Discuss Midcycle Communication): 3/3/14 (uploaded 4/15/14) Midcycle meeting minutes: 2/25/14 (uploaded 4/15/14) Team Meeting: 2/18/14 (uploaded 4/7/14) Planning meeting minutes: 1/3/14 (uploaded 2/14/14)</p>
❖ Minutes of Meetings	
<ul style="list-style-type: none"> If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> 11/22/13, 8/14/13
<ul style="list-style-type: none"> EOP2 meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> 5/15/13
<ul style="list-style-type: none"> Mid-cycle Communication (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> 3/7/14
<ul style="list-style-type: none"> Late-cycle Meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> 3/28/14
<ul style="list-style-type: none"> Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) 	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> Date(s) of Meeting(s) 	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> 4/29/14
Division Director Summary Review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> 4/19/14
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> 4/11/14
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> 8
Clinical	
❖ Clinical Reviews	
<ul style="list-style-type: none"> Clinical Team Leader Review(s) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> No separate review, concurrence in primary review
<ul style="list-style-type: none"> Clinical review(s) (<i>indicate date for each review</i>) 	Joint clinical and biostatistics primary and secondary review: 03/25/14

	Filing Review: 01/21/14
<ul style="list-style-type: none"> Social scientist review(s) (if OTC drug) (indicate date for each review) 	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (indicate date of review/memo) 	Financial Disclosure review: 4/17/14
<ul style="list-style-type: none"> Clinical reviews from immunology and other clinical areas/divisions/Centers (indicate date of each review) 	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> Controlled Substance Staff review(s) and Scheduling Recommendation (indicate date of each review) 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> Risk Management <ul style="list-style-type: none"> REMS Documents and REMS Supporting Document (indicate date(s) of submission(s)) REMS Memo(s) and letter(s) (indicate date(s)) Risk management review(s) and recommendations (including those by OSE and CSS) (indicate date of each review and indicate location/date if incorporated into another review) 	N/A N/A <input checked="" type="checkbox"/> 3/25/14
<ul style="list-style-type: none"> OSI Clinical Inspection Review Summary(ies) (include copies of OSI letters to investigators) 	<input checked="" type="checkbox"/> 3/24/14
Clinical Microbiology <input checked="" type="checkbox"/> None	
<ul style="list-style-type: none"> Clinical Microbiology Team Leader Review(s) (indicate date for each review) 	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) (indicate date for each review)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
<ul style="list-style-type: none"> Statistical Division Director Review(s) (indicate date for each review) 	<input checked="" type="checkbox"/> No separate review, concurrence in primary review
Statistical Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> No separate review, concurrence in primary review
Statistical Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> Joint clinical and biostatistics primary and secondary review: 03/25/14 Filing review: 1/21/14
Clinical Pharmacology <input type="checkbox"/> None	
<ul style="list-style-type: none"> Clinical Pharmacology Division Director Review(s) (indicate date for each review) 	<input checked="" type="checkbox"/> No separate review, concurrence in primary review
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> No separate review, concurrence in primary review
Clinical Pharmacology review(s) (indicate date for each review)	<input type="checkbox"/> None Primary review: 3/25/14 QT-IRT review: 3/8/14 Filing review: 1/21/14
<ul style="list-style-type: none"> OSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters) 	<input checked="" type="checkbox"/> None requested

Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• Division Director Review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> 4/9/14
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> 3/27/14
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> Primary review: 3/25/14 Filing review: 1/21/14
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> 4/8/14
• Branch Chief/Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review, concurrence in primary review
• Product quality review(s) including ONDQA biopharmaceutics reviews (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> CMC DP primary and secondary review: 4/3/14 CMC DS primary and secondary review: 3/26/14 Biopharmaceutics Primary review: 3/25/14 Biopharmaceutics Filing Review: 1/24/14 CMC Filing Review: 1/21/14
❖ Microbiology Reviews <input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (<i>indicate date of each review</i>) <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) (<i>indicate date of each review</i>)	<input type="checkbox"/> Not needed Primary and secondary review: 3/6/14 Filing review: 1/14/14
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	See CMC DP review, page 75, signed 4/3/14
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	

❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within 2 years of action date) (<i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁵</i>) <input checked="" type="checkbox"/> CGMP/Facilities Filing Review	Date completed: 4/3/14 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable 1/22/14
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within 30 days of action date) (<i>original and supplemental BLAs</i>)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation (<i>check box only, do not include documents</i>)	<input type="checkbox"/> Completed <input checked="" type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

⁵ i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
• Finalize 505(b)(2) assessment	<input type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input checked="" type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Not applicable
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

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/s/

KAREN C BOYD
05/01/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: April 29, 2014
From: Karen Boyd, M.S., DOP2/OHOP/CDER
Subject: Team meeting: NDA 205755

NDA: 205755
Product: Ceritinib (LDK 378) capsules, 150mg
Submission Date: December 24, 2013
Received Date: December 24, 2013
Sponsor: Novartis Pharmaceuticals Corporation
PDUFA Date: August 24, 2014

Proposed Indication: Treatment of patients with (b) (4) metastatic non small cell lung cancer (NSCLC) who have (b) (4).
(b) (4)

Attendees: Richard Pazdur, Jonathan Jarow, Patricia Keegan, Gideon Blumenthal, Sean Khozin, Erik Laughner, Teicher Agosto, Karen Jones, Emily Fox, Robert Wittorf, Mahesh Ramanadham, Liang Zhou, Tamy Kim, Donghao Lu, David Doleski, Jean Tang, Karen Boyd

Meeting Summary:

1. Office of Compliance gave an update on the inspection on the (b) (4) facility.
2. FDA received a copy of the form FDA 483 issued to the site this morning.
3. Office of Compliance representatives had a conversation with the inspection team to understand and assess the significance of the form FDA 483 observations.
4. Office of Compliance deemed facility is acceptable in terms of manufacture of the API
(b) (4)

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KAREN C BOYD
04/29/2014

MEMORANDUM OF TELECON

DATE: April 17, 2014

APPLICATION NUMBER: NDA 205755

BETWEEN:

Novartis Pharmaceuticals Corporation

AND

Office of Compliance:

David Doleski
Mahesh Ramanadham
Robert Wittorf

Office of New Drug Quality Assessment:

Ali Al Hakim
Liang Zhou
Teicher Agosto

Division of Oncology Products:

Karen Jones
Gideon Blumenthal
Karen Boyd
Sean Khozin

SUBJECT: (b) (4) Manufacturer

Background:

NDA 205755 is indicated for the treatment of patients with (b) (4) metastatic NSCLC who have (b) (4). The first rolling submission was submitted on November 27, 2014 followed by submissions on December 12, 2013 and December 24, 2014. EERs for the application were submitted on January 14, 2014. On (b) (4) (b) (4) an import alert was issued for (b) (4) which is the manufacturer for (b) (4). They Agency requested a teleconference with the sponsor to address questions regarding the (b) (4) site.

The Call:

The questions are as follows:

1. Please identify lot numbers and dates of manufacture for (b) (4) commercial API (b) (4) manufactured at (b) (4). Please provide release results and a comparison of release results to material manufactured at the (b) (4) site.

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

8. What assurance do you have that lots manufactured were released by appropriate QA procedures?

Drafted: T. Agosto 4/28/2014
Revised: R. Wittorf, 4/29/2014
Finalized: T. Bouie 4/29/2014

Teicher N. Agosto
Regulatory Health Project Manager

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/s/

TEICHER N AGOSTO
04/29/2014

MEMORANDUM OF TELECON

DATE: April 2, 2014 and April 3, 2014

APPLICATION NUMBER: NDA 205755

BETWEEN:

Novartis Pharmaceuticals Corporation

AND

Office of Compliance:

David Doleski
Alicia Mozzachio
Mahesh Ramanadham
Carmelo Rosa
Robert Wittorf

Office of New Drug Quality Assessment:

Ali Al Hakim
Liang Zhou
Donghao Lu
Jean Tang
Teicher Agosto
Teshara G. Bowie

Division of Oncology Products:

Karen Jones
Gideon Blumenthal
Karen Boyd
Sean Khozin

SUBJECT: (b) (4) Manufacturer

Background:

NDA 205755 is indicated for the treatment of patients with (b) (4) metastatic NSCLC who have (b) (4). The first rolling submission was submitted on November 27, 2014 followed by submissions on December 12, 2013 and December 24, 2014. EERs for the application were submitted on January 14, 2014. On (b) (4) (b) (4) an import alert was issued for (b) (4) which is the manufacturer for (b) (4).

APRIL 2, 2014 TELECONFERENCE:

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The Agency expressed that it is important to provide accurate information in the application regarding the location of the facilities used to manufacture material in support of the application. In this regard it is important to differentiate the location where the lots to support the application are located as compared to the location to be used for future manufacturing. Novartis agreed to share with the FDA their un-redacted audit reports, quality agreements and SOPs. Novartis also agreed to provide a genealogy of the drug substance batches, (b) (4).

Teshara G. Bouie
Regulatory Health Project Manager

Drafted: T. Bouie 4/4/2014

Revised: R. Wittorf, M. Ramanadham, A. Mozzachio, D. Doleski 4/24/2014

Finalized: T. Bouie 4/28/2014

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/s/

TESHARA G BOUIE
04/28/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: March 27, 2014
From: Karen Boyd, M.S., DOP2/OHOP/CDER
Subject: Team/Labeling Meeting: NDA 205755

FDA's proposed labeling revisions as discussed during the March 27, 2014, labeling meeting:

Attendees: Patricia Keegan, Sean Khozin, Gideon Blumenthal, Hong Zhao, Ruby Leong, Brian Booth, Nam Atiqur Rahman, Whitney Helms, Liang Zhou, Pengfei Song, Sharon Mills, Karen Boyd, Qunyh-Van Tran, Naomi Redd, Miriam Dinatale

Sections discussed include:

- 1: Indications and Usage
- 2: Dosage and Administration
- 5: Warnings and Precautions
- 6: Adverse Reactions
- 7: Drug Interactions
- 12.3: Clinical Pharmacology: Pharmacokinetics
- 14: Clinical Studies

Other topics discussed during the meeting:

- Late Cycle meeting agenda and objectives reviewed with the team
- Novartis' counter-proposal to FDA's PMR on the food effect of ceritinib

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/s/

KAREN C BOYD
04/25/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: March 31, 2014
From: Karen Boyd, M.S., DOP2/OHOP/CDER
Subject: Labeling Meeting: NDA 205755

FDA's proposed labeling revisions as discussed during the March 31, 2014, labeling meeting:

Attendees: Patricia Keegan, Sean Khozin, Gideon Blumenthal, Hong Zhao, Ruby Leong, Brian Booth, Nam Atiqur Rahman, Whitney Helms, Liang Zhou, Pengfei Song, Sharon Mills, Karen Boyd, Qunyh-Van Tran, Naomi Redd, Miriam Dinatale, Jeanine Best

Sections discussed include:

- 5.7: Warnings and Precautions: Embryofetal Toxicity
- 8.1: Use in Specific Populations: Pregnancy
- 8.7: Use in Specific Populations: Females and Males of Reproductive Potential
- 12.1: Clinical Pharmacology: Mechanism of Action
- 12.2: Clinical Pharmacology: Pharmacodynamics
- 13: Nonclinical Toxicology
- 17: Patient Counseling Information
- Patient Information

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/s/

KAREN C BOYD
04/25/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: April 8, 2014
From: Karen Boyd, M.S., DOP2/OHOP/CDER
Subject: Wrap Up Meeting Minutes: NDA 205755

NDA: 205755
Product: Ceritinib (LDK 378) capsules, 150mg
Submission Date: December 24, 2013
Received Date: December 24, 2013
Sponsor: Novartis Pharmaceuticals Corporation
Target Action Date: April 17, 2014
PDUFA Date: August 24, 2014

Proposed Indication: Treatment of patients with [REDACTED]^{(b) (4)} metastatic non small cell lung cancer (NSCLC) who have [REDACTED]^{(b) (4)}.

Attendees: Richard Pazdur, Jonathan Jarow, Patricia Keegan, Gideon Blumenthal, Sean Khozin, Tamy Kim, John Leighton, Whitney Helms, Margaret Brower, Emily Fox, Shenghui Tang, Lijun Zhang, Ruby Leong, Hong Zhao, Donghao Lu, Jean Tang, Ali Al Hakim, Liang Zhou, Karen Boyd, Naomi Redd, Okpo Eradiri, Liang Zhou, Qi Liu, Otto Townsend, Hong Zhou, Brian Booth, Cynthia LaCivita, Kevin Wright, Miriam Dinatale, Jeanine Best, Rosemary Addy, Melanie Pierce, Jessica Cole, Barbara Fuller, Denise Pica-Branco, Karen Jones, Robert Wittorf, Mahesh Ramanadham, David Doleski, Lauren Iacono-Connor, Peter Waldron, Jeff Summers, Kira Leishear.

Meeting Summary:

1. RPM went over important review goal dates with the team
2. Discipline Specific Reviews of the Application:
 - a. All primary and secondary reviews are complete.
 - b. Outstanding issues:
 - i. Robert Wittorf provided an update on a potential compliance issue with a foreign site that makes [REDACTED]^{(b) (4)} for ceritinib.
3. Pending Consults
 - a. All consults are in DARRTs.
 - b. Inspections: Clinical inspections are complete. Facility inspections are pending.
4. Discussion of Proposed Action to be Taken
 - a. Clinical: Approve
 - b. P/T: Approve
 - c. CMC: Approve
 - d. Biopharmaceuticals: Approve
 - e. Clin Pharm: Approve

- f. Stats: Approve
5. Labeling Discussion: The labeling negotiations are complete for the package insert and patient package insert. Novartis will send final draft labeling to the NDA by no later than COB Wednesday, April 9, 2014. DMEPA, OPDP and CMC are satisfied with the changes Novartis made to the container label and request no additional changes. Ms. Jones had a question about how Novartis plans to attach the label [REDACTED]^{(b)(4)}. Ms. Boyd will follow up with an information request to Novartis.
 6. Discussion of sign-off procedure and schedule
 - a. Drs. Pazdur and Keegan discussed sign-off procedure and schedule with the team.

Action items from the meeting:

- KB will send an IR to Novartis [REDACTED]^{(b)(4)}.
- KB will set up a meeting with senior management to discuss the potential compliance issue further.

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/s/

KAREN C BOYD
04/25/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: March 18, 2014
From: Karen Boyd, M.S., DOP2/OHOP/CDER
Subject: Team Meeting #3 Minutes: NDA 205755

NDA: 205755
Product: Ceritinib (LDK 378) capsules, 150mg
Submission Date: December 24, 2013
Received Date: December 24, 2013
Sponsor: Novartis Pharmaceuticals Corporation
Target Action Date: April 17, 2014
PDUFA Date: August 24, 2014

Proposed Indication: Treatment of patients with [REDACTED] (b) (4) metastatic non small cell lung cancer (NSCLC) who have [REDACTED] (b) (4).

Attendees: Patricia Keegan, Gideon Blumenthal, Sean Khozin, Whitney Helms, Margaret Brower, Emily Fox, Donghao Lu, Karen Boyd, Naomi Redd, Okpo Eradiri, Shenghui Tang, Liang Zhou, Qi Liu, Otto Townsend, Hong Zhou, Brian Booth, Ruby Leong. Kevin Wright, Miriam Dinatale, Jeanine Best.

Meeting Summary:

- Review team updates:
 - Biopharmaceuticals' review is ongoing and will be on time. Biopharmaceuticals is waiting on a March 21, 2014 response to IR submission from Novartis.
 - CMC's review is ongoing. For the drug product stability, CMC is considering granting an expiration date of 18 months, based on the data provided by Novartis so far.
 - Nonclinical review is complete.
 - Clinical Pharmacology: The draft primary review is complete. It is under secondary review right now and will be signed by the deadline.
 - Clinical: Review is ongoing and will be on time.
- Inspections update:
 - Clinical inspection:
 - Novartis and Alice Shaw's inspection are complete.
 - The South Korea inspection will start [REDACTED] (b) (4) and will take about 2 weeks.
- PMR update:
 - The team discussed potential PMRs
 - RPM Boyd will send out a PMR template form for the review team to fill out.
- Proprietary Name Review Update
 - The name Zykadia was deemed acceptable after the OSE review.

Action items from the meeting:

1. RPM Boyd will set up a teleconference with Novartis for next Monday to discuss their dissolution specifications.
2. RPM Boyd will send out the PMR/PMC template to the team.
3. Review team will complete their primary reviews by March 25, 2014.

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/s/

KAREN C BOYD
04/24/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: March 4, 2014
From: Karen Boyd, M.S., DOP2/OHOP/CDER
Subject: Team Meeting #2 Minutes: NDA 205755

NDA: 205755
Product: Ceritinib (LDK 378) capsules, 150mg
Submission Date: December 24, 2013
Received Date: December 24, 2013
Sponsor: Novartis Pharmaceuticals Corporation
Target Action Date: April 17, 2014
PDUFA Date: August 24, 2014

Proposed Indication: Treatment of patients with [REDACTED] (b) (4) metastatic non
small cell lung cancer (NSCLC) who have [REDACTED] (b) (4)
[REDACTED]

Attendees: Gideon Blumenthal, Sean Khozin, Whitney Helms, Karen Boyd, Cynthia LaCivita, Naomi Redd, Kevin Wright, Miriam Dinatale, Kira Leishear, Tracy Salaam, Afrouz Nayernama, Sarah Doff

Meeting Summary:

- OSE went over their preliminary safety findings and their draft risk evaluation and mitigation strategy assessment with the clinical team, based on their review of the data submitted to the NDA thus far (including the updated safety and efficacy update). No REMS was submitted with the application and OSE is assessing whether or not a REMS is needed.

Action items from the meeting:

1. OSE and clinical will continue with their review.

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/s/

KAREN C BOYD
04/22/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Center for Drug Evaluation and Research

Memorandum

Date: March 11, 2014
From: Karen Boyd, M.S., DOP2/OHOP/CDER
Subject: Meeting on potential PMR: NDA 205755

Date and Time: March 11, 2014, 2pm-3pm

Attendees: Gideon Blumenthal, Sean Khozin, Ruby Leong, Pengfei Song, Qi Liu, Nam Atik Rahman, Brian Booth, Lijun Zhang, Shenghui Tang, Karen Boyd.

Meeting Summary:

- Continued discussion between clinical, clin pharm and stats to discuss the following: lower dose of ceritinib with food.
- Discussion of the protocol Novartis submitted to IND 109272 entitled, “A randomized, open-label crossover study to evaluate the relative bioavailability of [REDACTED] (b)(4) [REDACTED] of LDK378 in comparison to the reference LDK378 capsule formulation and the effect of a [REDACTED] (b)(4) on the pharmacokinetics of LDK378 capsules in healthy subjects”

Action items:

1. Ms. Boyd will schedule a sponsor teleconference with Novartis during the week of March 11th to discuss this potential PMR.

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/s/

KAREN C BOYD
04/22/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: March 4, 2014
From: Karen Boyd, M.S., DOP2/OHOP/CDER
Subject: Labeling Meeting Memo: NDA 205755

FDA's proposed labeling revisions as discussed during the March 4, 2014, labeling meeting:

Attendees: Patricia Keegan, Sean Khozin, Gideon Blumenthal, Margaret Brower, Emily Fox, Whitney Helms, Karen Boyd, Quynh-Van Tran, Otto Townsend, Ali Al Hakim, Liang Zhou, Jean Tang, Donghao Lu, Morgan Walker, Jeanine Best, Denise Pica-Branco, Miriam Dinatale

Sections discussed include:

- 3: Dosage Forms and Strengths
- 8: Use in Specific Populations
- 11: Description
- 13: Nonclinical Toxicology
- 16: How Supplied/Storage and Handling

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KAREN C BOYD
04/17/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: March 13, 2014
From: Karen Boyd, M.S., DOP2/OHOP/CDER
Subject: Labeling Meeting Memo: NDA 205755

FDA's proposed labeling revisions as discussed during the March 13, 2014, labeling meeting:

Attendees: Patricia Keegan, Sean Khozin, Gideon Blumenthal, Karen Boyd, Quynh-Van Tran, Lijun Zhang, Sharon Mills, Naomi Redd

Sections discussed include:

- 1: Indications and Usage
- 5: Warnings and Precautions
- 14: Clinical Studies

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/s/

KAREN C BOYD
04/17/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: March 14, 2014

From: Karen Boyd, M.S., DOP2/OHOP/CDER

Subject: Labeling Meeting Memo: NDA 205755

FDA's proposed labeling revisions as discussed during the March 14, 2014, labeling meeting:

Attendees: Patricia Keegan, Sean Khozin, Gideon Blumenthal, Hong Zhao, Ruby Leong, Pengfei Song, Brian Booth, Eric Brodsky, Margaret Brower, Emily Fox, Whitney Helms, Sharon Mills, Karen Boyd, Qunyh-Van Tran, Debbie Bietzell, Naomi Redd

Sections discussed include:

- 2: Dosage and Administration
- 7: Drug Interactions
- 12: Clinical Pharmacology

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/s/

KAREN C BOYD
04/17/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Memorandum

Date: March 18, 2014
From: Karen Boyd, M.S., DOP2/OHOP/CDER
Subject: Labeling Meeting Memo: NDA 205755

FDA's proposed labeling revisions as discussed during the March 18, 2014, labeling meeting:

Attendees: Patricia Keegan, Sean Khozin, Gideon Blumenthal, Hong Zhao, Ruby Leong, Pengfei Song, Brian Booth, Sharon Mills, Karen Boyd, Qunyh-Van Tran, Naomi Redd, Miriam Dinatale

Sections discussed include:

- 12.2: Pharmacodynamics
- 12.3: Pharmacokinetics
- 2.2: Dose Modifications
- 2.3: Dose Modification for Strong CYP3A4 Inhibitors
- 6: Adverse Reactions
- 10: Overdosage
- 17: Patient Counseling Information

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KAREN C BOYD
04/17/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Memorandum

Date: March 20, 2014
From: Karen Boyd, M.S., DOP2/OHOP/CDER
Subject: Labeling Meeting Memo: NDA 205755

FDA's proposed labeling revisions as discussed during the March 20, 2014, labeling meeting:

Attendees: Patricia Keegan, Sean Khozin, Gideon Blumenthal, Hong Zhao, Ruby Leong, Whitney Helms, Liang Zhou, Karen Dowdy

Sections discussed include:

- 2.1: Recommended Dosing
- 11: Description
- 16: How Supplied/Storage and Handling
- Highlights

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/s/

KAREN C BOYD
04/17/2014

From: [Bouie, Teshara](#)
To: [Agosto, Teicher](#)
Subject: FW: Questions for Novartis regarding (b) (4) (NDA 205755)
Date: Monday, April 14, 2014 9:42:25 AM

From: Doleski, David
Sent: Friday, April 11, 2014 6:13 PM
To: Grande, Frank
Cc: Bruckheimer, Michael; Bouie, Teshara; Boyd, Karen; Rosa, Carmelo R
Subject: Questions for Novartis regarding (b) (4) site (NDA 205755)

Hi Frank, We have some additional questions regarding manufacturing of the (b) (4) at the (b) (4) site. Could you provide answers to the questions below to us next week? We would like to have a conference call on Tuesday or Wednesday in order to discuss your responses.

1. We have reviewed the information you have provided April 4, 2014. Within audit report, ID (b) (4), for the inspection occurring (b) (4), you cite the potential for cross contamination of (b) (4) manufactured within the same facility as the (b) (4) as a "major" concern. Please describe actions being taken to prevent (b) (4) from being introduced into the (b) (4). Please be specific.

2. Describe the testing performed that provides assurance of the purity of the (b) (4) (b) (4).

3. During the April 4, 2014 teleconference, Novartis stated that representatives have been on-site for the manufacturing of the (b) (4) at both facilities. Please provide additional information outlining the specific roles and responsibilities of these individuals with respect to manufacturing of the (b) (4) (b) (4).

Please let me know if you have any questions or concerns.

Regards,

Dave

David Doleski
Director, Division of Good Manufacturing Practice Assessment (DGMPA)
Office of Manufacturing and Product Quality (OMPQ)
Office of Compliance
CDER, FDA
phone 301-796-2627
e-mail: david.doleski@fda.hhs.gov

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/s/

TEICHER N AGOSTO
04/15/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: February 25, 2014
From: Karen Boyd, M.S., DOP2/OHOP/CDER
Subject: Midcycle Meeting Minutes: NDA 205755

NDA: 205755
Product: Ceritinib (LDK 378) capsules, 150mg
Submission Date: December 24, 2013
Received Date: December 24, 2013
Sponsor: Novartis Pharmaceuticals Corporation
Target Action Date: April 17, 2014
PDUFA Date: August 24, 2014

Proposed Indication: Treatment of patients with [REDACTED] (b) (4) metastatic non small cell lung cancer (NSCLC) who have [REDACTED] (b) (4)

Attendees: Richard Pazdur, Jonathan Jarow, Patricia Keegan, Gideon Blumenthal, Sean Khozin, Ruby Leong, Pengfei Song, Nam Atik Rahman, Brian Booth, Yuzhuo Pan, Lijun Zhang, Shenghui Tang, Donghao Lu, Zhe Jean Tang, Liang Zhou, Ali Al-Hakim, Emily Fox, Margaret Brower, Whitney Helms, Barbara Scepura, Karen Boyd, Cynthia LaCivita, Naomi Redd, Wana Manitpisitkui, Otto Townsend, Okpo Eradiri, Kira Leishear, Kevin Wright, Peter Waldron, Jessica Cole, Miriam Dinatale, Ping Zhao, Lee Pai-Scherf, Sarah Dorff, Quynh-Van Tran, Nitin Mehrotra, Abhilasha Nair, Rosane Charlab Orbach, Morgan Walker.

Presentation Schedule:

Regulatory Project Manager/Clinical inspections
Clinical/Statistical
Clinical Pharmacology
CMC/Biopharmaceutics
Facility inspections
Nonclinical
DRISK

Meeting Summary:

- **Clinical inspections:** Inspections are ongoing at MGH, Fox Chase and Novartis. Inspections at [REDACTED] (b) (4) are expected to start on [REDACTED] (b) (4), and inspections at the Seoul, South Korea site are expected to start March 17, 2014.
- **Clinical/Statistical:**
 - Majority of patients experienced GI toxicity. Potential postmarketing studies are under consideration to evaluate the food effect of ceritinib.
 - Additional adverse events including hepatotoxicity, QT prolongation, pneumonitis

and bradycardia are likely class effects. Adverse events that may be linked to ceritinib include hyperglycemia (~10% with ~3% requiring dose adjustment), convulsions (~5%) and acute pancreatitis (~10% with clinical and laboratory features).

- Favorable risk-benefit profile
 - ORR of large magnitude and duration in a population of patients with limited standard treatment options.
 - Overall manageable toxicity profile.
- **Clinical Pharmacology**
 - The proposed dosing regimen (750 mg QD) is under review and appears to be acceptable.
 - In vivo DDI potential appears to be adequately evaluated with CYP3A modulators (inhibitors or inducers), but not with CYP3A substrates. A PMR will be requested for DDI studies with sensitive CYP3A and CYP2C9 substrates.
 - The impact of PK, safety, and dose adjustment on hepatic and renal impairment patients is under review.
 - 4 Potential PMRs were proposed.
- **CMC/Biopharmaceuticals**
 - Drug Substance:
 - Potential genotoxic impurity with (b) (4) is under investigation.
 - Updated stability data from the batches manufactured using the (b) (4) (b) (4) are needed from the sponsor.
 - Drug substance specifications (acceptance criteria) are missing for particle size, (b) (4).
 - Drug Product:
 - DMF: FDA needs specific information for the container/closure system (e.g. pages and volumes of each DMF) from the sponsor.
 - Further information on the proposed storage condition for the drug product: Stored 25 °C (77 °F) in tight container is needed from the sponsor.
 - Further information on the proposed shelf life of (b) (4) months is needed from the sponsor.
 - The shelf life may be extended as additional data becomes available.
 - Biopharmaceuticals:
 - FDA is waiting for the applicant's response on an information request for the following items:
 - Bridging of 2 sites that manufactured clinical batches
 - In-vitro drug release stability data at all dissolution sampling time points
 - Clarification on rapid dissolution rate for BCS Class 4 drug.
- **Facilities Review:** No unresolvable issues. 10 sites listed in the application, 9 acceptable, 1 pending [laboratory site that was inspected (b) (4)].
- **Nonclinical:**
 - Pharmacology studies generally support the mechanism of action.
 - Findings in the animals were generally predictive of the clinical findings. The target organs were pancreas, bile and biliopancreatic ducts, GI and liver. Additionally, there was a significant increase in transaminases, moderate QT prolongation and pulmonary phospholipidosis at higher doses in rats.

- Pregnancy category D is recommended.
- Impurity concerns are under review.
- **DRISK:**
 - No REMS submitted
 - Follow up meeting with clinical team is proposed to discuss adverse events such as hepatotoxicity, ILD/pneumonitis, QT interval prolongation, and other AEs of potential concern from ongoing review from clinical team.

Action items from the meeting:

1. Midcycle Communication Meeting: Ms. Boyd will set up a 30 minute meeting with the team to discuss the midcycle communication
2. PLAIR request: Ms. Boyd will send Novartis' email to CMC and they will follow up to find out the status of the denial.
3. ^{(b) (4)} Container labeling—CMC will send Ms. Boyd any additional comments on the ^{(b) (4)} container label.
4. SGE: Ms. Boyd will follow up with Caleb and Dianne to find out the status, and will set up SGE meetings.
5. IRs: Ms. Boyd will be expecting a combined CMC and non-clinical IR regarding the potential impurities

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/s/

KAREN C BOYD
04/15/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: March 3, 2014
From: Karen Boyd, M.S., DOP2/OHOP/CDER
Subject: Meeting to discuss Midcycle Communication: NDA 205755

Date and Time: March 3, 2014, 12pm-1pm

Attendees: Richard Pazdur, Jonathan Jarow, Patricia Keegan, Gideon Blumenthal, Sean Khozin, Ruby Leong, Pengfei Song, Nam Atik Rahman, Brian Booth, Lijun Zhang, Shenghui Tang, Donghao Lu, Zhe Jean Tang, Liang Zhou, Ali Al-Hakim, Emily Fox, Margaret Brower, Whitney Helms, Karen Boyd, Cynthia LaCivita, Naomi Redd, Otto Townsend, Okpo Eradiri, Kira Leishear, Jessica Cole, Miriam Dinatale, Quynh-Van Tran, Morgan Walker.

Meeting Summary:

- Discussion of each discipline's team leader approved draft responses to the midcycle communication template with senior management. This included significant review issues, outstanding Information Requests and major safety concerns/risk management.
- Discuss who is required to attend the midcycle communication meeting on Friday (March 7, 8:30-9:30am).

Action items:

1. Ms. Boyd will circulate latest template to the team for responses, with the goal of sending the draft agenda to the company by Thursday, March 6th.

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04/15/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: March 3, 2014
From: Karen Boyd, M.S., DOP2/OHOP/CDER
Subject: Meeting on potential PMR: NDA 205755

Date and Time: March 3, 2014, 1:30pm-2pm

Attendees: Gideon Blumenthal, Sean Khozin, Ruby Leong, Pengfei Song, Nam Atik Rahman, Brian Booth, Lijun Zhang, Shenghui Tang, Karen Boyd.

Meeting Summary:

- Preliminary discussion between clinical, clin pharm and stats to discuss the following: lower dose of ceritinib with food.
- Further discussion is needed to sketch out a potential PMR.

Action items:

1. Ms. Boyd will schedule a follow on meeting to continue the discussion.

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KAREN C BOYD
04/15/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Memorandum

Date: March 24, 2014
From: Karen Boyd, M.S., DOP2/OHOP/CDER
Subject: NDA 205755: Biopharmaceutics and CMC Teleconference with Novartis

Date and Time of Teleconference: March 24, 2014, 1pm-1:45pm

FDA Attendees:

Patricia Keegan, Director, DOP2
Gideon Blumenthal, Clinical Team Leader, DOP2
Sean Khozin, Clinical Reviewer, DOP2
Karen Boyd, Senior Regulatory Project Manager, DOP2
Okpo Eradiri, Biopharmaceutics Reviewer, ONDQA
Angelica Dorantes, Biopharmaceutics Team Leader, ONDQA
Ali Al Hakim, Branch Chief, ONDQA/DNDQAI
Liang Zhou, CMC Team Leader, ONDQA/DNDQAI
Jean Tang, CMC reviewer, ONDQA/DNDQAI

Novartis Attendees:

Bertrand Sutter, Senior Fellow, Technical Research and Development
Simon Ensslin, PhD, Fellow, Pharmaceutical and Analytical Development
Diane Zezza, PhD, Global Head Regulatory Affairs CMC
Frank Grande, Associate Director, Regulatory Affairs CMC
Margaret Dugan, MD, Senior Vice President, Global Program Head
Yvonne Lau, PhD, Senior Fellow, Oncology Clinical Pharmacology
Gabriela Gruia, MD, Global Head Drug Regulatory Affairs
Shanthi Ganeshan, PhD, Vice President, North America Region Head, Drug Regulatory Affairs
Nina Gutman, PharmD, Senior Associate Director, Drug Regulatory Affairs

Discussion: FDA communicated the following recommended dissolution acceptance criterion to Novartis: We acknowledge receipt of the dissolution data for 3 registration stability batches (1010000660, 1010000958 and 1010001326) at the 9-month stability time point. Your proposed dissolution specification of $Q = \frac{(b)}{(4)}\%$ at $\frac{(b)}{(4)}$ min is not acceptable. Based on our review of all the dissolution profiles at release and at the 9-month stability time point, we are recommending a dissolution acceptance criterion of $Q = \frac{(b)}{(4)}\%$ at 15 min.

Novartis accepted this recommended dissolution acceptance criterion, and agreed to update the Specifications Table. Novartis will formally submit the Specifications Table to the NDA and will send a courtesy copy to Karen Boyd by email by Wednesday, March 26, 2014.

FDA and Novartis had a further discussion on the (b) (4), DMF reference, and stability data.

Regarding the (b) (4), FDA requests that Novartis propose a PMC to test the (b) (4) method and specification for the LDK378 drug product since they do not have a method in place.

Regarding the DMF, FDA needs the DMF information, and FDA can't take an action without it. Novartis committed to contacting their DMF holders as soon as possible, and will do their best to provide the information by Wednesday, March 26, 2014.

Regarding the stability data, FDA agreed to allow Novartis to submit the 9 month stability data for the 3 registration stability batches (batches 1010000660, 1010000958 and 1010001326) and up to 24 months for one batch from supportive stability (batch AEUS/2012-0023) in May 2014. This will be listed as a PMC.

Action items:

- By Wednesday, March 26, 2014, Novartis will submit
 - Updated stability data
 - DMF Information
 - Revised testing Monograph
 - Timeline for the PMC on (b) (4) content

Call concluded.

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KAREN C BOYD
04/11/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: March 19, 2014
From: Karen Boyd, M.S., DOP2/OHOP/CDER
Subject: NDA 205755: CMC Teleconference with Novartis

Date and Time of Teleconference: March 19, 2014, 2:15pm-3:00pm

FDA Attendees:

Ali Al Hakim, Liang Zhou, Donghao Lu, Jean Tang, Robert Wittorf, Jewell Martin, Teicher Agosto, Karen Boyd

Novartis Attendees:

Nina Gutman – Regulatory Affairs
Anne Frederick – Global Lead, Regulatory Affairs
Frank Grande – Regulatory CMC

Novartis is seeking clarification on the following items from the March 17, 2014 information request:

- Comment number 4 requests that the mean mass specification be revised. As noted in the attached response, the result is recorded in mg and covers the prosed range. Novartis is concerned that revising the specification as requested may lead to unnecessary laboratory calculations and errors. Novartis would like to further understand the need to include the % in the result. Can the Agency please provide a rational for inclusion of the % in the specification?
- Comment number 6 requests information on the container closure system. It is Novartis's understanding that all the requested information (specifications for the bottles ^{(b)(4)}) was already included in the attachments to the response submitted via e-mail on 12-Mar-2014. Is additional information being requested that was not provided in the 12-Mar-2014 response?

Discussion during the meeting:

FDA and Novartis discussed comments 4 and 6, stated above.

Regarding comment #4, Novartis understands that both % and ranges of the mean mass will be added to the DP specification for the purpose of the clarification.

Regarding comment #5, Novartis acknowledges that the urgency of submission of DMF information is critical to complete the review, and will request DMF holder to provide necessary information as soon as possible.

In addition, the team discussed comment 3 from the March 17, 2014 information request. FDA does not know (b) (4) the drug product. Novartis mentioned that they do not have a method in place to determine (b) (4) the drug product. FDA responded that Novartis could use the USP (b) (4) method and clarification procedure which is already worked out. Novartis acknowledged FDA's concern but responded that they do not have a method in place so they would need more time to submit this information. They potentially could submit this information by March 26, 2014.

FDA also cannot find critical information in the DMF, and we need Novartis to submit this information by March 26, 2014.

Based on the data submitted thus far, FDA is not comfortable giving a (b) (4) month shelf life for the drug product. Novartis acknowledged this.

Action items:

- Novartis will submit a timeline on when they can provide the method and specification (b) (4) by March 26, 2014.
- DMF: Novartis will submit information by March 26, 2014.

Call concluded.

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KAREN C BOYD
04/11/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Memorandum

Date: March 14, 2014
From: Karen Boyd, M.S., DOP2/OHOP/CDER
Subject: Teleconference with Novartis to discuss potential PMC/PMRs related to the food effect of ceritinib: NDA 205755

Date and Time of Teleconference: March 14, 2014, 12pm-1pm

FDA Attendees: Patricia Keegan, Gideon Blumenthal, Sean Khozin, Shenghui Tang, Lijun Zhang, Hong Zhao, Ruby Leong, Pengfei Song, Qi Liu, Brian Booth, Nam Atiqur Rahman, Jeff Summers

Novartis Attendees:

Margaret Dugan, M.D., Senior VP, Global Program Head
Andrew Joe, M.D., Senior Global Clinical Leader
Ben Cheng, M.D., Brand Safety Leader
Nassir Habboubi, M.D., VP, US Clinical Development and Medical Affairs
Margarida Geraldes, Ph.D., Director, Biostatistics
Yvonne Lau, Ph.D., Senior Fellow, Oncology Clinical Pharmacology
Shanthi Ganeshan, Ph.D., North America Region Head, Drug Regulatory Affairs
Anne Frederick, Ph.D., Executive Director, Global Program Regulatory Director
Nina Gutman, Pharm.D., Senior Associate Director, Drug Regulatory Affairs

Meeting Purpose: Meeting with Novartis to discuss potential PMC/PMRs related to the food effect of ceritinib

Discussion during the meeting: Novartis presented slides with answers to the following FDA questions (sent via email on March 12, 2014):

1. There are reports that patients have been treated with 600 mg with food to alleviate GI AEs, which may lead to confusion regarding how to appropriately dose ceritinib. How do you plan to address this dosing issue?
2. We received the protocol amendment for Study CLDK378A2108 that proposes to include a new cohort to evaluate the effect of a (b) (4) on the pharmacokinetics of ceritinib in healthy subjects.
 - a. What is the overall development goal of this study?
 - b. How would this study address the issue of administering ceritinib with food to improve GI tolerability in patients?
 - c. If patients mistakenly took 750 mg with a regular meal, they would likely experience serious AEs. How would you address this possibility?

3. (b) (4)

Novartis presented their slides (attached) to these questions. Discussion between FDA and Novartis followed and FDA expressed concerns that the recommended dose of 750 mg in the fasted state is not tolerable as the majority of patients experienced gastrointestinal toxicities. FDA commented that Novartis' proposed study (b) (4) was inadequate. As currently designed, Arm 1 was ceritinib 750 mg in the fasted condition and Arm 2 was ceritinib 750 mg with a (b) (4). Novartis thought that a (b) (4) would not increase the exposure but improve GI tolerability. FDA expressed concerns about this thought as restricting patients to taking a (b) (4) raise a compliance issue. FDA recommended adding an additional arm to test a lower dose of ceritinib with a meal and to conduct the trial in patients with ALK-positive NSCLC. Novartis should identify the dose of ceritinib that would be needed when taken with a meal to match exposures of 750 mg ceritinib in the fasted state.

Action item:

- Novartis will provide FDA with a description of the postmarketing trial of testing a lower dose with food, as well as timelines by COB Tuesday, March 18, 2014.

Call concluded.

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KAREN C BOYD
04/11/2014

Boyd, Karen

From: Boyd, Karen
Sent: Wednesday, April 09, 2014 8:35 AM
To: Gutman, Nina
Subject: NDA 205755: Information Request on Container label

Importance: High

Hi Nina,

Since Novartis will only have a container (and not a carton), what is Novartis' plan to attach/package the labels with the container? Please respond via email by COB today followed by a formal submission to your NDA.

Please confirm receipt.

Thanks,
Karen

Karen Boyd, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
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Email: Karen.Boyd@fda.hhs.gov
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KAREN C BOYD
04/09/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Center for Drug Evaluation and Research

Memorandum

Date: April 1, 2014
From: Karen Boyd, M.S., DOP2/OHOP/CDER
Subject: Teleconference with Novartis to discuss labeling: NDA 205755

Date and Time of Teleconference: April 1, 2014, 11am-12pm

FDA Attendees: Joseph Gootenberg, Gideon Blumenthal, Sean Khozin, Whitney Helms, Margaret Brower, Emily Fox, Hong Zhao, Ruby Leong, Brian Booth, Shenghui Tang, Lijun Zhang, Miriam Dinatale, Sharon Mills, Jeannine Best, Quynh-Van Tran, Naomi Redd, Jean Tang

Novartis Attendees:

Margaret Dugan, MD, Senior VP, Global Program Head
Andrew Joe, MD, Senior Global Clinical Leader
Margarida Geraldes, PhD, Director, Biostatistics
Yvonne Lau, PhD, Senior Fellow, Oncology Clinical Pharmacology
Nassir Habboubi, MD, VP, US Clinical Development and Medical Affairs
Alicia Rossiter, MD, FCP, Executive Director / Group Head, Integrated Medical Safety, Oncology
Amy Lambert, PhD, DABT, Associate Director, Preclinical Safety
Nanxin Li, PhD, Associate Director Oncology, Genomics Institute of the Novartis Research Foundation
Shanthi Ganeshan, PhD, North America Region Head, Drug Regulatory Affairs
Anne Frederick, PhD, Executive Director, Global Program Regulatory Director
Nina Gutman, PharmD, Senior Associate Director, Drug Regulatory Affairs

Sections covered include:

- 2.1: Dosing and Administration
- 2.2: Dose Modifications
- 5.1: Warnings and Precautions: Severe or Persistent Gastrointestinal Toxicity
- 5.5 Warnings and Precautions: Hyperglycemia
- 5.7 Warnings and Precautions: Embryofetal Toxicity
- 7.1. Drug Interactions: Effect of Other Drugs on Ceritinib
- 8.1 Use in Specific Populations: Pregnancy
- 8.7: Use in Specific Populations: Females and Males of Reproductive Potential
- 12.1: Clinical Pharmacology: Mechanism of Action
- 12.3: Clinical Pharmacology: Pharmacokinetics
- 13.2: Nonclinical Toxicology: Animal Toxicity and/or Pharmacology
- Highlights

Discussion: Novartis agreed with FDA's proposed changes to 2.1, 2.2, 5.1, 5.5, 5.7, 7.1, 8.1,

8.7, 12.1, 13.2, and highlights. Novartis and FDA disagreed with the wording of Zykadia taken with food found in 12.3. FDA proposed alternative wording for Novartis' consideration.

Action items:

- Novartis will work off-line on section 12.3, and will send alternative wording for FDA's consideration
- FDA and Novartis will schedule a follow up meeting to discuss sections 12.3, 17 and the Patient Package Insert.

Call concluded.

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KAREN C BOYD
04/09/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Memorandum

Date: April 3, 2014
From: Karen Boyd, M.S., DOP2/OHOP/CDER
Subject: Teleconference with Novartis to communicate CMC expiratory dating: NDA 205755

Date and Time of Teleconference: April 3, 2014, 12pm-12:15pm

FDA Attendees: Ali Al Hakim, Donghao Lu, Jean Tang, Liang Zhou, Karen Boyd

Novartis Attendees:

Frank Grande, Regulatory Liaison, Global Regulatory--CMC
Anne Frederick, PhD, Executive Director, Global Program Regulatory Director
Nina Gutman, PharmD, Senior Associate Director, Drug Regulatory Affairs

FDA communicated the following to Novartis:

FDA will grant expiratory dating for the drug substance at (b) (4) months and for the drug product at 18 months, assuming the facility issues are resolved.

Call concluded.

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KAREN C BOYD
04/08/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Center for Drug Evaluation and Research

Memorandum

Date: April 7, 2014
From: Karen Boyd, M.S., DOP2/OHOP/CDER
Subject: Teleconference with Novartis to discuss labeling: NDA 205755

Date and Time of Teleconference: April 7, 2014, 1pm-1:15pm

FDA Attendees: Patricia Keegan, Sean Khozin, Gideon Blumenthal, Hong Zhao, Ruby Leong, Barbara Fuller, Karen Boyd, Lijun Zhang, Brian Booth, Quynh-Van Tran, Afrouz Nayernama

Novartis Attendees:

Margaret Dugan, MD, Senior VP, Global Program Head
Andrew Joe, MD, Senior Global Clinical Leader
Margarida Geraldes, PhD, Director, Biostatistics
Yvonne Lau, PhD, Senior Fellow, Oncology Clinical Pharmacology
Gabriela Gruia, MD, Global Head Drug Regulatory Affairs
Shanthi Ganeshan, PhD, North America Region Head, Drug Regulatory Affairs
Anne Frederick, PhD, Executive Director, Global Program Regulatory Director

Sections covered include:

- 5.4: QT Interval Prolongation
- 12.2: Pharmacokinetics
- Patient Information
- Highlights
- 6.1 Clinical Trials Experience

Agreements reached: FDA agreed to Novartis' proposed revisions to section 5.4, 12.2 and highlights. FDA did not agree with Novartis' proposal in the Patient information section, (b) (4)
Instead, FDA and
Novartis reached agreement (b) (4)

Call concluded.

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KAREN C BOYD
04/07/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: April 7, 2014
From: Karen Boyd, M.S., DOP2/OHOP/CDER
Subject: Labeling Meeting Memo: NDA 205755

FDA's proposed labeling revisions as discussed during the April 7, 2014, labeling meeting:

Attendees: Patricia Keegan, Sean Khozin, Gideon Blumenthal, Hong Zhao, Ruby Leong, Nam Atiqur Rahman, Liang Zhou, Emily Fox, Whitney Helms, Barbara Fuller, Karen Boyd, Quynh-Van Tran, Lijun Zhang, Brian Booth

Sections discussed include:

- 2.1: Dosing and Administration
- 2.2: Dose Modification for Adverse Reactions
- 5.1: Warnings and Precautions: Severe or Persistent Gastrointestinal Toxicity
- 5.2: Hepatotoxicity
- 5.3: Interstitial Lung Disease (ILD)/Pneumonitis
- 5.4: QT Interval Prolongation
- 5.5: Hyperglycemia
- 6: Adverse Reactions
- 12.3: Pharmacokinetics
- 13.2: Animal Toxicity and/or Pharmacology
- 14: Clinical Studies
- 17: Patient Counseling Information
- Patient Information

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KAREN C BOYD
04/07/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Memorandum

Date: February 18, 2014
From: Karen Boyd, M.S., DOP2/OHOP/CDER
Subject: Team Meeting #1 Minutes: Ceritinib: NDA 205755

NDA: 205755
Product: Ceritinib (LDK 378) capsules, 150mg
Submission Date: December 24, 2013
Received Date: December 24, 2013
Sponsor: Novartis Pharmaceuticals Corporation
Target Action Date: April 17, 2014
PDUFA Date: August 24, 2014

Proposed Indication: Treatment of patients with [REDACTED] ^{(b) (4)} metastatic non small cell lung cancer (NSCLC) who have [REDACTED] ^{(b) (4)}.

Attendees: Gideon Blumenthal, Sean Khozin, Whitney Helms, Emily Fox, Liang Zhou, Naomi Redd, Janice Pohlman, Qi Liu, Naomi Redd, Kevin Wright, Cynthia LaCivita, Lijun Zhang, Ruby Leong, Hong Zhao, Jean Tang, Donghao Lu, Okpo Eradiri, Pengfei Song, Qi Liu, Jessica Cole, Robert Wittorf, Otto Townsend, Morgan Walker, Quynh-Van Tran, Miriam Dinatale, Denise Pica-Branco, Brian Booth

Meeting Summary:

- Update: Novartis will be submitting a new patient information label via email by COB Wednesday, February 19, which includes the safety and efficacy updates. We will use that label as a starting point for our discussions at the labeling meetings.
- Novartis submitted their safety and efficacy update (October 31, 2013 cutoff) in multiple parts starting on February 10th.
 - Raw Data submitted February 10, 2014
 - Derived Data submitted February 12, 2014
 - SCE and SCE appendix 1 submitted February 14, 2014
 - SCS addendum and associated appendix will be submitted by Feb 20, 2014
- Proprietary name review update: DMEPA is currently reviewing Novartis' proposed proprietary name, [REDACTED] ^{(b) (4)}
- Discipline Review Updates: Each discipline gave their update during their midcycle practice presentation.
- Inspection update: The Seoul, South Korea site is currently scheduled for inspection March 17-April 4, 2014. The other sites (Mass General, Novartis) are ongoing and a little behind due to the weather on the east coast. We are not planning for a facilities inspection at this time.

ACTION ITEMS:

1. Review team should update their midcycle slides by COB February 19th based on feedback from the team meeting.
2. RPM Boyd will send out an information request clarifying with the applicant if they have an approved USAN name.

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KAREN C BOYD
04/07/2014

Boyd, Karen

From: Boyd, Karen
Sent: Monday, April 07, 2014 4:29 PM
To: 'Frederick, Anne'
Cc: Gutman, Nina
Subject: NDA 205755: Draft Label
Attachments: NDA_205755_draft_label_to_Novartis_after_tcon_4_7_14.docx

Importance: High

Hi Anne,

Attached is latest draft label. For transparency, I kept the changes tracked that we discussed and agreed upon during our call today. From FDA's perspective, there are no outstanding issues left to discuss on the label, and we would like you to formally submit a final draft label to the NDA that is properly formatted and incorporates all of the agreed upon changes. Please submit the final draft label by **COB Wednesday, April 9, 2014**.

If you have any questions or concerns, please let me know.

Please confirm receipt.

Thanks,
Karen

Karen Boyd, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
Email: Karen.Boyd@fda.hhs.gov
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KAREN C BOYD
04/07/2014

Boyd, Karen

From: Boyd, Karen
Sent: Monday, April 07, 2014 11:24 AM
To: 'Frederick, Anne'
Cc: 'Gutman, Nina'
Subject: NDA 205755: Draft ZYKADIA Label
Attachments: NDA_205755_draft_label_to_Novartis_4_7_14.docx

Importance: High

Hi Anne,

Attached is the latest draft of the Zykadia label for discussion at today's 1pm teleconference.

We accepted the changes that we agreed with and provide alternative language and comments on the parts that we did not. Please note: we did not review the highlights section yet. At the meeting at 1pm, please be prepared to discuss this version of the label.

If you have any questions or concerns, please let me know.

Please confirm receipt.

Thanks,
Karen

Karen Boyd, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
Email: Karen.Boyd@fda.hhs.gov
Phone: 301-796-7032
Fax: 301-796-9849

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KAREN C BOYD
04/07/2014

Boyd, Karen

From: Boyd, Karen
Sent: Friday, April 04, 2014 6:19 PM
To: 'Gutman, Nina'
Cc: 'Frederick, Anne'
Subject: NDA 205755: PMR/PMCs: Request for formal submission

Importance: High

Hi Nina (or Anne),

Regarding the proposed PMRs and PMCs for NDA 205755, I need to make sure all of the proposed PMR/PMCs are formally submitted to the NDA ASAP. Your submission should include the PMR/PMC, milestone and associated timelines. If you formally submitted the proposed PMR already, please indicate that in your submission and the date of that submission. Here is the list of the ones that we have been discussing:

- a. Subpart H Post-Marketing Requirement: Conduct and submit the results of a multicenter, randomized study or studies establishing the superiority of ceritinib over standard therapy in adult patients with ALK-rearranged (ALK-positive) metastatic NSCLC who have been previously treated with crizotinib or in adult patients with previously untreated ALK-positive metastatic NSCLC.

Final Protocol Submission	Submitted 4/2013
Study/Trial Completion:	04/30/2019
Final Report Submission:	10/31/2019

- b. Post-Marketing Requirement: Conduct a clinical trial to evaluate the systemic exposure and safety of 450 mg ceritinib taken with a meal and 600 mg ceritinib taken with a light meal as compared with that of 750 mg ceritinib taken in the fasted state in metastatic ALK-positive NSCLC patients

- **Interim analysis:**

- Draft protocol submission: Jul-2014
- Final protocol submission: Sep-2014 (assuming FDA provides comments on the draft protocol within 30 days of submission)
- Interim analysis completion: Apr-2016
- Interim analysis report submission: Jul-2016

- **Final analysis:**

- Draft protocol submission: Jul-2014
- Final protocol submission: Sep-2014 (assuming FDA provides comments on the draft protocol within 30 days of submission)
- Trial completion: Feb-2017
- Final report submission: Aug-2017

- c. Post-Marketing Requirement: Complete a pharmacokinetic trial to determine the appropriate dose of ceritinib in patients with hepatic impairment in accordance with the FDA Guidance for Industry entitled "Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling."

Final Protocol Submission: submitted;
Study/Trial Completion: 01/31/2016;
Final Report Submission: 06/30/2016.

- d. Post-Marketing Requirement: Conduct a clinical trial to evaluate the effect of repeat doses of ceritinib on the single dose pharmacokinetics of midazolam (a sensitive CYP3A4 substrate) in accordance with the FDA Guidance for Industry entitled “Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations.”

Final Protocol Submission: 09/30/2014;
Study/Trial Completion: 08/31/2016;
Final Report Submission: 02/28/2017.

- e. Post-Marketing Requirement: Conduct a clinical trial to evaluate the effect of repeat doses of ceritinib on the single dose pharmacokinetics of warfarin (a sensitive CYP2C9 substrate) in accordance with the FDA Guidance for Industry entitled “Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations.”

Final Protocol Submission: 09/30/2014;
Study/Trial Completion: 08/31/2016;
Final Report Submission: 02/28/2017.

- f. Post-Marketing Requirement: Conduct a clinical trial to evaluate if proton pump inhibitors, H₂-receptor antagonists, and antacids alter the bioavailability of ceritinib and to determine how to dose ceritinib with regard to concomitant gastric acid reducing agents.

Final Protocol Submission: 01/31/2015;
Study/Trial Completion: 08/31/2015;
Final Report Submission: 02/29/2016.

- g. Post Marketing Commitment: Submit a revised testing monograph (TM) that will include a ^{(b) (4)} method and specification for LDK378 drug product (capsule content) as post-approval commitment.

The updated TM will be submitted by 30-April-2014.

- h. Post Marketing Commitment: Submit 9 months stability data for the 3 registration stability batches (batches 1010000660, 1010000958 and 1010001326) and up to 24 months for one batch from supportive stability (batch AEUS/2012-0023).

The updated stability data will be submitted by 16-May-2014.

If you have any questions or concerns, please let me know.

Please confirm receipt.

Thanks,
Karen

Karen Boyd, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
Email: Karen.Boyd@fda.hhs.gov
Phone: 301-796-7032
Fax: 301-796-9849

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/s/

KAREN C BOYD
04/04/2014

Boyd, Karen

From: Boyd, Karen
Sent: Wednesday, April 02, 2014 6:36 PM
To: 'Gutman, Nina'
Subject: NDA 205755: Draft Patient label and Patient Package Insert
Attachments: NDA_205755_draft_patient_label_4_2_14.docx; NDA_205755_PPI_draft_4_2_14.doc

Hi Nina,

Attached is the latest draft PI and PPI for NDA 205755. This label, and most of the changes, were discussed and agreed upon during our teleconference on April 1, 2014. In addition, during our phone conversation on April 1, 2014, you mentioned the following additional changes for section 17 and the patient package insert (PPI).

- Section 17: Take out “ (b) (4) ” in the second to last bullet.
- PPI: Remove (b) (4) from “What is the most important information I should know about ZYKADIA?”
- PPI: Remove “ (b) (4) .”

To improve the efficiency, we addressed these items specifically in the label and accepted the rest of the edits. We also added language to the highlights section that needs to be included for accelerated approval and made a few minor changes to highlights and 13.1.

By noon on Friday, please send me back the label via email with your proposed changes tracked, followed by a formal submission to the NDA. For the items that you agree with, please accept those changes. For those that you don't agree with, please add a comment and provide alternative language for us to consider. For section 12.3, we received your proposal and we can discuss that on Monday. So, there is no need to add your proposal into the label at this time.

If you have any questions or concerns, please let me know.

Please confirm receipt.

Thanks,
Karen

Karen Boyd, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
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Food and Drug Administration
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/s/

KAREN C BOYD
04/02/2014

Boyd, Karen

From: Boyd, Karen
Sent: Monday, March 31, 2014 5:31 PM
To: 'Gutman, Nina'
Subject: NDA 205755: Draft PMR language

Importance: High

Hi Nina,

Attached is our proposed language for this PMR. As discussed during the late cycle meeting, please provide reasonable timelines for Final Protocol submission, Study/Trial Completion, and Final Report submission as soon as possible.

1. Subpart H Post-Marketing Requirement: Conduct and submit the results of a multicenter, randomized study or studies establishing the superiority of ceritinib over standard therapy in adult patients with ALK-rearranged (ALK-positive) metastatic NSCLC who have been previously treated with crizotinib or in adult patients with previously untreated ALK-positive metastatic NSCLC.

Please confirm receipt.

Thanks,
Karen

Karen Boyd, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
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/s/

KAREN C BOYD
04/01/2014

Boyd, Karen

From: Boyd, Karen
Sent: Monday, March 31, 2014 5:27 PM
To: 'Gutman, Nina'
Subject: NDA 205755: Draft ceritinib labeling
Attachments: NDA_205755_patient_label_3_31_14.docx; NDA_205755_PPI_3_31_14.doc

Importance: High

Hi Nina,

Attached are FDA's suggested updates to the patient label and patient package insert. Many of these updates to the PI were discussed and agreed upon during the March 28, 2014 late cycle meeting. We also had the opportunity to review the nonclinical, maternal health and QT-IRT sections, and our changes are included in this version. For items that we agreed with, we accepted your change. For the items we did not agree with, our changes are tracked and we also inserted some comments.

We would like to discuss both of these labels at our 11am meeting tomorrow. Please be prepared to let us know if you accept our changes or if further discussion is needed.

If you have any questions, please don't hesitate to contact me.

Please confirm receipt of this email.

Thanks,
Karen

Karen Boyd, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
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/s/

KAREN C BOYD
04/01/2014

Boyd, Karen

From: Boyd, Karen
Sent: Friday, March 28, 2014 10:00 AM
To: 'Gutman, Nina'
Subject: NDA 205755: Draft labeling
Attachments: NDA_205755_Draft_label_to_Sponsor_3_28_14.docx

Importance: High

Hi Nina,

Attached is FDA's response to your proposed label, submitted via email on March 27, 2014, for NDA 205755. For items that we agreed with, we accepted your change. For the items we did not agree with, our changes are tracked and we also inserted some comments.

We would like to discuss this at the late cycle meeting today. Please be prepared to let us know if you accept our changes or if further discussion is needed. As discussed earlier today, we do not plan on discussing the non-clinical, maternal health, and patients labeling sections. The QT-IRT section also is flagged for discussion next week.

If you have any questions, please don't hesitate to contact me.

Please confirm receipt of this email.

Thanks,
Karen

Karen Boyd, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
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Food and Drug Administration
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/s/

KAREN C BOYD
03/28/2014

Boyd, Karen

From: Boyd, Karen
Sent: Thursday, March 13, 2014 3:58 PM
To: 'Gutman, Nina'
Subject: NDA 205755: Clinical Information Request

Importance: High

Hi Nina,

Please refer to your November 27, 2013, December 12, 2013, and December 24, 2013 rolling submission regarding New Drug Application (NDA) 205755.

Please respond to the following clinical information request via email by COB EST on **Monday, March 17, 2014**, followed by a formal submission to your NDA.

- Please provide narratives for patients who experienced syncope in Study X2101.

If you have any questions, please let me know.

Please confirm receipt.

Thanks,
Karen

Karen Boyd, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
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/s/

KAREN C BOYD
03/26/2014

Boyd, Karen

From: Boyd, Karen
Sent: Tuesday, March 25, 2014 5:16 PM
To: 'Gutman, Nina'
Subject: NDA 205755: PMR Follow up

Importance: High

Hi Nina,

Thank you for sending along the proposed PMR and associated timelines to test a lower dose of ceritinib with food.

We do not agree with your proposal (listed below) or the associated timeline. Instead, we propose the following language for the PMR and request that you send us a reasonable timeline for completion of the study:

PMR: Conduct a clinical trial to evaluate the safety, efficacy, and pharmacokinetics of 450 mg ceritinib taken with a meal as compared with that of 750 mg ceritinib taken in the fasted state in metastatic ALK-positive NSCLC patients.

By 2pm EST on Thursday, March 27, 2014, please send me an email with the following information:

1. Determination if Novartis agrees with this proposed PMR, listed above.
2. Proposed milestones/timeline for completion of this proposed PMR.

If Novartis disagrees, we request that you propose alternate language/timelines by 2pm EST on Thursday, March 27, 2014.

If you have any questions or concerns, please let me know.

Please confirm receipt.

Thanks,
Karen

Karen Boyd, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
Email: Karen.Boyd@fda.hhs.gov
Phone: 301-796-7032
Fax: 301-796-9849

From: Gutman, Nina [<mailto:nina.gutman@novartis.com>]
Sent: Wednesday, March 19, 2014 6:02 PM
To: Boyd, Karen
Subject: RE: Follow up from today's call and timelines

Dear Karen,

As promised below please find the proposed PMR and associated timelines to test a lower dose of ceritinib with food.

PMR:

(b) (4)

Timelines:

- Draft protocol submission: Oct-2014
- Final protocol submission: Dec-2014
- Trial completion: Jun-2019
- Final report submission: Dec-2019

Please confirm receipt and let me know if you have any questions.

Best regards,

Nina

Nina Gutman, Pharm.D.

Senior Associate Director, Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation
One Health Plaza, 315/5450A
East Hanover, NJ 07936
USA

Cell + (b) (6)

Phone +1 862 778-1767

Fax +1 973 781-8265

nina.gutman@novartis.com

www.novartis.com

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/s/

KAREN C BOYD
03/26/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205755

**PROPRIETARY NAME REQUEST
WITHDRAWN**

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936

ATTENTION: Yanina Gutman, Pharm.D.
Senior Associate Director, Drug Regulatory Affairs

Dear Dr. Gutman:

Please refer to your New Drug Application (NDA) dated and received December 24, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ceritinib Capsules, 150 mg.

We acknowledge receipt of your March 19, 2014, correspondence, on March 19, 2014, notifying us that you are withdrawing your request for a review of the proposed proprietary name (b) (4). This proposed proprietary name request is considered withdrawn as of March 19, 2014.

We note that you have submitted a new request for proprietary name in your submission dated March 19, 2014.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Kevin Wright, Pharm.D., Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3621. For any other information regarding this application, contact Karen Boyd, Regulatory Project Manager, in the Office of New Drugs at (301) 796-7032.

Sincerely,

{See appended electronic signature page}

Kevin Wright, Pharm.D.
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

KEVIN WRIGHT
03/26/2014



NDA 205755

MID-CYCLE COMMUNICATION

Novartis Pharmaceuticals Corporation
Attention: Yanina Gutman, Pharm.D.
Senior Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936

Dear Dr. Gutman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ceritinib capsules, 150 mg.

We also refer to the teleconference between representatives of your firm and the FDA on March 7, 2014. 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, call me at (301) 796-7032.

Sincerely,

{See appended electronic signature page}

Karen C. Boyd, M.S.
Senior Regulatory Project Manager
Division of Oncology Products 2
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: March 7, 2014, 8:30am-9:30am

Application Number: NDA 205755

Product Name: Ceritinib

Indication: Treatment of patients with (b) (4) metastatic non-small cell lung cancer (NSCLC) who have (b) (4)

Applicant Name: Novartis Pharmaceuticals Corporation

Meeting Chair: Gideon Blumenthal, M.D.

Meeting Recorder: Karen Boyd

FDA ATTENDEES

Patricia Keegan, M.D., Director, OHOP/DOP2

Gideon Blumenthal, M.D., Clinical Team Leader, OHOP/DOP2

Sean Khozin, M.D., Clinical Reviewer, OHOP/DOP2

Karen Boyd, M.S., Senior Regulatory Project Manager, OHOP/DOP2

Shenghui Tang, Ph.D., Biostatistics Team Leader, OB/DBV

Margaret Brower, Ph.D., Non-clinical Reviewer, OHOP/DHOT

Emily Fox, Ph.D., Non-clinical Reviewer, OHOP/DHOT

Whitney Helms, Ph.D., Non-clinical Team Leader, OHOP/DHOT

Jean Tang, Ph.D., Product Quality Reviewer, ONDQA/DNDQAI

Donghao Lu, Ph.D., Product Quality Reviewer, ONDQA/DNDQAI

Liang Zhou, Ph.D., Product Quality Team Leader, ONDQA/DNDQAI

Ali Al Hakim, Ph.D., Product Quality Branch Chief, ONDQA/DNDQAI

Okpo Eradiri, Ph.D., Biopharmaceutics Reviewer, OPS/ONDQA

Ruby Leong, Ph.D., Clinical Pharmacology Reviewer, OCP/DCPV

Pengfei Song, Ph.D., Pharmacometrics Reviewer, OCP/DCPV

Qi Liu, Pharmacometrics Team Leader, OCP/DCPV

Brian Booth, Supervisory Pharmacologist, OCP/DCPV

Naomi Redd, Pharmacist, OSE/OMEPRM/DRISK

EASTERN RESEARCH GROUP

Patrick J. Zhou, Independent Assessment Contractor

APPLICANT ATTENDEES

Margaret Dugan, M.D., Senior VP, Global Program Head

Andrea Kay, M.D., VP, Senior Global Clinical Program Head

Andrew Joe, M.D., Senior Global Clinical Leader

Alicia Rossiter, M.D., FCP, Executive Director / Group Head, Integrated Medical Safety

Ben Cheng, M.D., Brand Safety Leader
Nassir Habboubi, M.D., VP, US Clinical Development and Medical Affairs
Margarida Geraldes, Ph.D., Director, Biostatistics
Yvonne Lau, Ph.D., Senior Fellow, Oncology Clinical Pharmacology
Frank Grande, Associate Director, Global Regulatory Chemistry, Manufacturing, and Controls
Erika Zannou, Ph.D., TRD Franchise Head Oncology
Anne Frederick, Ph.D., Executive Director, Global Program Regulatory Director
Nina Gutman, Pharm.D., Senior Associate Director, Drug Regulatory Affairs

NOTE: The meeting agenda topics were provided to Novartis on March 6, 2014, to facilitate discussion.

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/Statistics:

1. A potential acute pancreatitis signal is under investigation and may be included in section 6 of the product labeling.

DISCUSSION DURING THE MEETING: Novartis submitted a response to an FDA information request regarding this issue, and asked if it was clear or if they needed to provide any additional information. FDA responded that Novartis' response to the information request was under review and no further information was needed at this time.

2. Potential postmarketing studies are under consideration to evaluate the food effect of ceritinib.

DISCUSSION DURING THE MEETING: Novartis asked if FDA could expand on this potential postmarketing study. FDA expressed concern that some treating oncologists may reduce the dose of ceritinib to potentially alleviate the GI toxicity issues. The correct dose reduction while still maintaining efficacy is unknown. FDA is looking into the possibility of a postmarketing study to further understand if lower doses of ceritinib with food will decrease the GI toxicities while maintaining efficacy and exposure.

CMC

Drug Substance:

3. Potential genotoxic impurity with (b) (4) is under investigation.
4. FDA needs updated stability data from the batches manufactured using the (b) (4).
5. Drug substance specifications (acceptance criteria) are missing for particle size, (b) (4)

CMC Drug Product:

6. DMF: FDA needs specific information for the container/closure system (e.g. pages and volumes of each DMF).
7. FDA needs further information on the proposed storage condition for the drug product: Stored 25 °C (77 °F) in tight container.
8. FDA needs further information on the proposed shelf life of (b) (4) months.
 - i. The shelf life may be extended as additional data becomes available.

DISCUSSION DURING THE MEETING (CMC Drug Substance and Drug Product issues 3-8): Novartis acknowledged receipt of the CMC information requests and plans to submit a response to most of the items according to the provided timeline. However, they plan to submit their response to the stability data request, to support the proposed (b) (4) month shelf life, in May 2014 and asked if this timing would be acceptable. FDA responded that they could not make a determination without reviewing the documents. Once Novartis submits the documents, then FDA can make a determination.

Biopharmaceuticals:

9. Novartis's justification for the proposed dissolution acceptance criterion is not based on multipoint release and stability data.

DISCUSSION DURING THE MEETING: FDA stated that justification for the proposed dissolution acceptance criterion is not based on multipoint release and stability data. Novartis plans to submit multipoint dissolution data on three registration batches at the 9-month pull point by the end of March or early April 2014. FDA is trying to determine if there will be sufficient time to review this data without impacting internal timelines.

Nonclinical:

10. No significant review issues at this time, assuming that Novartis satisfactorily addresses the March 4, 2014, and March 6, 2014, nonclinical and CMC information requests.

DISCUSSION DURING THE MEETING: No further discussion occurred during the meeting.

Clinical Pharmacology:

11. Potential postmarketing studies are under consideration (i.e. to evaluate the effect of hepatic impairment and gastric acid reducing agents on the pharmacokinetics of ceritinib and to evaluate the effect of ceritinib on the pharmacokinetics of CYP3A4 and CYP2C9 sensitive substrates).

DISCUSSION DURING THE MEETING: Novartis asked if FDA could expand on the potential acid reducing agent postmarketing study. Novartis stated that population pharmacokinetic (PK) analysis showed similar exposures in patients with and without acid reducing agents. FDA stated that the population PK analysis does not take the time course of acid reducing agent co-administration into consideration. Furthermore, the population PK analysis also showed a decreased absorption rate constant when ceritinib was concomitantly administered with proton pump inhibitors (PPI) and H₂-receptor antagonists (H₂RA), which signaled that ceritinib bioavailability may also be affected by acid reducing agents such as PPIs and H₂RAs. Therefore, FDA recommended a postmarketing study to evaluate the magnitude of effect of acid reducing agents on the PK of ceritinib.

3.0 INFORMATION REQUESTS

The following information requests (reproduced below) are outstanding as of March 7, 2014: information requests made on February 27, March 4 (2), and March 6, 2014 (2). Novartis should submit the requested information per the requested timeline as stated in the information requests.

CMC Drug Product (DP) (Information Request sent 2/27/14, due 3/11/14):

12. Clarify if the (b)(4) is a critical step or not and whether it is within the validated range. Provide scientific reasons or justification if the step is not considered to be a critical step.
13. Propose acceptance criteria for (b)(4) in the DP specification and provide updated DP specification.
14. In the section 3.2.P.8.1, specify the capsule counts in the HDPE bottle and the size of the HDPE bottle in both tables 2-1 and 3-1.
15. Provide initial stability starting date for both supportive and registration batches.
16. For the test of “Mean mass of contents” in the drug product specification, provide the range using % of the target weight as well as the weight range in mg.
17. Confirm the batches used in the supportive stability studies are same as the batches placed in the registration stability studies because it is unclear in the submission when you only mentioned that “These two clinical batches are representative of the registration stability batches and the commercial product.” If yes, provide information such as manufacturing process, capsule shell used including type, color, size, etc.
18. Provide any updated stability data for both supportive stability and registration stability batches when they become available (e.g. at 12 month test point).
19. In the tables 3-4 and 3-6 of the section of 3.2.P.8.1 (supportive stability studies batch # AEUS/2011-0076, AEUS/2012-0023), clarify if the qualified impurities at (b)(4) are from process impurities of drug substance since the same impurities are not

found in the registration stability batches (batch #: 1010000660, 1010000958 and 1010001326). If yes, relate these two process impurities to the specified impurity in drug substance. If not, provide justification for the impurity/degradation profiles difference between the supportive stability batches and registration batches.

CMC Drug Substance (DS) (Information Request sent 2/27/14, due 3/11/14):

20. (b) (4) is a potential genotoxic impurity and was tested in (b) (4) batches as the corresponding (b) (4) at (b) (4). Is there a direct method to monitor the level of (b) (4) in drug substance (as you have monitored it in (b) (4) batches for NMT (b) (4)%)?
21. Provide any updated stability data from the batches, C0002, C0004 and C0005 (manufactured using the (b) (4)).
22. The acceptance criterion for LDK378 Appearance was proposed to be “white to almost white or light yellow or light brown powder”. This is a wide color range and may not effectively serve the intended purpose for quality control.
23. To ensure the batch to batch consistency, add drug substance specification (acceptance criteria) for particle size at (b) (4).
24. Add a drug substance specification (acceptance criterion) for (b) (4) to confirm that the drug substance has (b) (4).
25. Add a drug substance specification (acceptance criterion) for residual solvent, (b) (4).
26. The impurity names were specified for (b) (4). Provide similar information for (b) (4).

Nonclinical and CMC (Information Request sent 3/4/14, Due 3/7/14)

27. You have indicated that batch #0850001 used for Study 0970057-01 qualified impurities (b) (4) at (b) (4)% and (b) (4)% respectively. This study was an exploratory non-GLP study, and cannot be used for qualification purposes. This same batch was used for Study 0970416 which was GLP compliant. Please confirm that the impurity levels documented for impurities (b) (4) were identical when administered to animals in both studies.
28. Please confirm that (b) (4) is impurity # (b) (4).
29. You have indicated that the Ames assay (Study 0970421) documented 7 potential genotoxic compounds which were later found to be below (b) (4) with the exception of the (b) (4). Please document where these data for the specific genotoxic compounds are located in Study #0970421.

Clinical (Information Request sent 3/4/14, Due 3/7/14)

30. Please provide a summary of any cardiac assessments (including the results of echocardiography and ECGs) in patients who experienced edema (particularly lower extremity edema) in study X2101.

Clinical Pharmacology (Information Request sent 3/6/14, Due 3/13/14)

31. Given that ceritinib demonstrates pH-dependent solubility in vitro and becomes poorly soluble as pH increases, co-administration of gastric acid reducing agents may increase gastrointestinal pH and affect the pharmacokinetics of ceritinib. Please propose postmarketing requirement (PMR) language and provide milestone timelines for completion of a clinical trial to evaluate if gastric acid reducing agents (e.g., proton pump inhibitors, H₂-receptor antagonists, antacids) alter the bioavailability of ceritinib.

Nonclinical and CMC (Information Request sent 3/6/14, Due 3/11/14)

32. Please confirm that impurity (b)(4) identified in clinical batches with a (b)(4) of (b)(4) is the same impurity identified as (b)(4) in nonclinical batch #0850001 used to justify the proposed specification for this impurity.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

Adverse events of concern (primarily hepatotoxicity and potentially, pancreatitis) are still being discussed. FDA's preliminary review indicates that a REMS may not be needed at this time.

5.0 ADVISORY COMMITTEE MEETING

There are no plans at this time for an advisory committee meeting.

6.0 LATE-CYCLE MEETING/OTHER PROJECTED MILESTONES

The proposed date for the late cycle meeting is March 28, 2014, from 12:00 pm-1:00 pm. FDA also plans to send the draft label to Novartis by March 24, 2014.

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/s/

KAREN C BOYD
03/25/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 205755

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936

ATTENTION: Yanina Gutman, Pharm.D.
Senior Associate Director, Drug Regulatory Affairs

Dear Dr. Gutman:

Please refer to your New Drug Application (NDA) dated and received December 24, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ceritinib Capsules, 150 mg.

We also refer to your March 19, 2014, correspondence, received March 19, 2014, requesting review of your proposed proprietary name, Zykadia. We have completed our review of the proposed proprietary name, Zykadia and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your March 19, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Kevin Wright, Pharm.D., Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3621. For any other information regarding this application, contact Karen Boyd, Regulatory Project Manager, in the Office of New Drugs at (301) 796-7032.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES on behalf of KELLIE A TAYLOR
03/25/2014

Boyd, Karen

From: Boyd, Karen
Sent: Friday, March 21, 2014 7:03 PM
To: 'Gutman, Nina'
Subject: NDA 205755: Draft Proposed Labeling
Attachments: NDA_205755_Draft_label_to_Sponsor_3_21_14.docx

Importance: High

Hi Nina,

Attached is FDA's draft proposed labeling for NDA 205755. Our changes are tracked and we also inserted some comments. Please respond to all of our comments in the label and use tracked changes to record any edits to the label. In areas of the label that you agree with FDA's proposed edits, please accept the tracked change to aid in reviewability. Please note: all of our changes are based on the updated label that you submitted through the gateway on 2/21/14.

Please send us back an updated tracked changes version of the label in WORD format via email by **noon EST on Thursday, March 27, 2014**, followed by a formal amendment to the NDA.

If you have any questions, please let me know.

Please confirm receipt of this email.

Thanks,
Karen

Karen Boyd, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
Email: Karen.Boyd@fda.hhs.gov
Phone: 301-796-7032
Fax: 301-796-9849

19 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

KAREN C BOYD
03/21/2014



NDA 205755

**REQUEST FOR METHODS
VALIDATION MATERIALS**

Novartis Pharmaceuticals Corporation
Attention: Yanina Gutman, PharmD
One Health Plaza
East Hanover, NJ 07936

Dear Yanina Gutman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for (b)(4) (Ceritinib, LDK378) 150 mg capsules.

We will be performing methods validation studies on (b)(4) (Ceritinib, LDK378) 150 mg capsules, as described in NDA 205755.

In order to perform the necessary testing, we request the following sample materials and equipments:

Method, current version

- AM40001B (AS5001769) drug substance – Assay by HPLC
- AM30001B (AS5001769) drug substance – Related Substances
- 53501.01 Identity, assay and degradation products by HPLC in Drug Product

Samples and Reference Standards

- 2 x 250 mg LDK378 reference substance
- 2 x 250 mg LDK378-NXA reference substance
- 500 mg LDK378 drug substance
- 100 (b)(4) (Ceritinib, LDK378) 150 mg capsules
- (b)(4) impurity (b)(4) or reference material containing impurity
- (b)(4) impurity (b)(4) or reference material containing impurity

Equipment

(b)(4)
(b)(4)

Please include the MSDSs and the Certificates of Analysis for the sample and reference materials.

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: MVP Sample Custodian
645 S Newstead
St. Louis, MO 63110

Please notify me upon receipt of this FAX. You may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (michael.trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy, Ph.D.
MVP coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MICHAEL L TREHY
03/19/2014

Wright, Kevin

From: Gutman, Nina <nina.gutman@novartis.com>
Sent: Monday, March 17, 2014 11:06 AM
To: Wright, Kevin
Cc: Kang, Sue
Subject: RE: NDA 205755 - Proprietary name submission

Dear Dr. Wright,

Thank you very much for your email and for the feedback. Novartis will assess the feedback and will follow-up as soon as possible.

Best regards,
Nina

Nina Gutman, Pharm.D.
Senior Associate Director, Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation
One Health Plaza, 315/5450A
East Hanover, NJ 07936
USA

Cell + (b) (6)
Phone +1 862 778-1767
Fax +1 973 781-8265
nina.gutman@novartis.com
www.novartis.com

From: Wright, Kevin [mailto:Kevin.Wright@fda.hhs.gov]
Sent: Monday, March 17, 2014 10:15 AM
To: Gutman, Nina
Cc: Kang, Sue
Subject: RE: NDA 205755 - Proprietary name submission

Dr. Gutman,

Please refer to your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Ceritinib Capsules, 150 mg.

We also refer to your correspondence dated and received February 6, 2014, requesting review of your proposed proprietary name, (b) (4)

The proposed proprietary name, (b) (4) was misinterpreted as (b) (4) in the FDA Prescription Simulation Study (written study). We are concerned this misinterpretation may be indicative of name confusion that would occur if the proposed name were to be allowed in the marketplace. This type of finding generally serves as the basis of rejecting a proposed name.

Since your product has been granted breakthrough designation, as a courtesy, we have conducted a preliminary analysis of your alternate name Zykadia. Our preliminary assessment of the alternate name Zykadia did not identify any potential risk of name confusion. Therefore, in the interest of time, we recommend you consider

amending your Request for Proprietary Name Review to indicate Zykadia as your primary proposed proprietary name.

Best regards,

Kevin Wright, PharmD

Safety Evaluator | DMEPA | OMEPRM | OSE | CDER | FDA | 301.796.3621 kevin.wright@fda.hhs.gov

 Thinking green when printing

From: Gutman, Nina [<mailto:nina.gutman@novartis.com>]

Sent: Monday, March 17, 2014 10:09 AM

To: Wright, Kevin

Subject: RE: NDA 205755 - Proprietary name submission

Hello Dr. Wright,

I hope that this email finds you well.

Would you be able to kindly provide a status update on the 3 proposed proprietary names that were submitted for ceritinib?

Thank you very much for your time and consideration.

Best regards,

Nina

Nina Gutman, Pharm.D.

Senior Associate Director, Drug Regulatory Affairs

Novartis Pharmaceuticals Corporation

One Health Plaza, 315/5450A

East Hanover, NJ 07936

USA

Cell + [REDACTED] (b) (6)

Phone +1 862 778-1767

Fax +1 973 781-8265

nina.gutman@novartis.com

www.novartis.com

From: Gutman, Nina

Sent: Wednesday, February 05, 2014 1:37 PM

To: 'Kevin.Wright@fda.hhs.gov'

Cc: 'Sue.Kang@fda.hhs.gov'

Subject: RE: NDA 205755 - Proprietary name submission

Dear Dr. Wright,

As promised, attached please find a request for FDA to review the following proposed proprietary names for ceritinib (in order of preference):

- Primary: [REDACTED] (b) (4)™
- Alternate 1: ZYKADIA™
- Alternate 2: [REDACTED] (b) (4)

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/s/

KEVIN WRIGHT
03/18/2014



NDA 205755

INFORMATION REQUEST

Novartis Pharmaceuticals Corporation
Attention: Yanina Gutman, Pharm.D.
Senior Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936

Dear Dr. Gutman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ceritinib capsules, 150 mg.

We also refer to your original NDA submission.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a written response by March 18, 2014, in order to continue our evaluation of your NDA.

1. In section 3.2.P.3.4, you describe the (b) (4)

[Redacted]

Please provide the following:

[Redacted] (b) (4)

2. (b) (4)

[Redacted]

3. Your response provided is not acceptable. (b) (4)

[Redacted]

If you have any questions, please contact Jewell Martin, Regulatory Project Manager, at (301) 796-2072.

Sincerely,

{See appended electronic signature page}

Ali H. Al Hakim, PhD
Branch Chief, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research=

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/s/

ALI H AL HAKIM
03/18/2014

Boyd, Karen

From: Boyd, Karen
Sent: Friday, March 14, 2014 5:23 PM
To: 'Gutman, Nina'
Subject: NDA 205755: Clinical Information Request

Importance: High

Hi Nina,

Please refer to your November 27, 2013, December 12, 2013, and December 24, 2013 rolling submission regarding New Drug Application (NDA) 205755.

Please respond to the following clinical information request via email by **noon EST on Thursday, March 20, 2014**, followed by a formal submission to your NDA.

- Please provide information on Novartis' plans to investigate the safety and efficacy of LDK378 in non-small cell lung cancer patients whose tumors have ROS1 mutations.

If you have any questions, please let me know.

Please confirm receipt.

Thanks,
Karen

Karen Boyd, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
Email: Karen.Boyd@fda.hhs.gov
Phone: 301-796-7032
Fax: 301-796-9849

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/s/

KAREN C BOYD
03/14/2014

Boyd, Karen

From: Boyd, Karen
Sent: Friday, March 14, 2014 5:20 PM
To: 'Gutman, Nina'
Subject: NDA 205755: Clinical Information Request

Hi Nina,

Please refer to your November 27, 2013, December 12, 2013, and December 24, 2013 rolling submission regarding New Drug Application (NDA) 205755.

Please respond to the following clinical information request via email by COB EST on **Tuesday, March 18, 2014**, followed by a formal submission to your NDA.

Please preform a risk ratio analysis of the incidence of hyperglycemia (glucose greater than 250 mg/dL based on laboratory values) in the following cohorts of patients in study X2101 treated at 750mg of LDK378:

- Patients on glucocorticoids versus all others
- Patients with a history of diabetes at baseline versus all others
- Patients with hyperglycemia (glucose above 160 mg/dL) at baseline versus all others
- Patients with hyperglycemia (glucose above 200 mg/dL) at baseline versus all others

If you have any questions, please let me know.

Please confirm receipt.

Thanks,
Karen

Karen Boyd, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
Email: Karen.Boyd@fda.hhs.gov
Phone: 301-796-7032
Fax: 301-796-9849

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/s/

KAREN C BOYD
03/14/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 109272
NDA 205755

**PROPRIETARY NAME REQUEST
WITHDRAWN**

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936

ATTENTION: Yanina Gutman, Pharm.D.
Senior Associate Director, Drug Regulatory Affairs

Dear Dr. Gutman:

Please refer to:

- Your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Ceritinib Capsules, 150 mg
- Your New Drug Application (NDA) dated and received November 27, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ceritinib Capsules, 150 mg

We acknowledge receipt of your January 29, 2014, correspondence, received on January 29, 2014, notifying us that you are withdrawing your request for a review of the proposed proprietary name (b)(4). This proposed proprietary name request is considered withdrawn as of January 29, 2014.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Kevin Wright, Pharm.D., Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3621. For any other information regarding this application, contact Karen Boyd, MS, Regulatory Project Manager in the Office of New Drugs (OND) at (301) 796-7032.

Sincerely,

{See appended electronic signature page}

Kevin Wright, Pharm.D.
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

KEVIN WRIGHT
03/12/2014

Boyd, Karen

From: Boyd, Karen
Sent: Wednesday, March 12, 2014 2:15 PM
To: 'Gutman, Nina'
Subject: NDA 205755: 3/14/14 Teleconference: Questions to Address

Hi Nina,

FDA requests that your 10 minute presentation at this Friday's potential PMC/PMR teleconference discussing the food effect on ceritinib includes answers to the following questions. As discussed, please send me a draft of your slides addressing these questions by COB tomorrow, March 13, 2014.

1. There are reports that patients have been treated with 600 mg with food to alleviate GI AEs, which may lead to confusion regarding how to appropriately dose ceritinib. How do you plan to address this dosing issue?
2. We received the protocol amendment for Study [REDACTED] (b) (4) that proposes to include a new cohort to evaluate the effect of a [REDACTED] (b) (4) on the pharmacokinetics of ceritinib in healthy subjects.
 - a. What is the overall development goal of this study?
 - b. How would this study address the issue of administering ceritinib with food to improve GI tolerability in patients?
 - c. If patients mistakenly took 750 mg with a regular meal, they would likely experience serious AEs. How would you address this possibility?
3. [REDACTED] (b) (4)

If you have any questions, please let me know.

Please confirm receipt.

Thanks,
Karen

Karen Boyd, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
Email: Karen.Boyd@fda.hhs.gov
Phone: 301-796-7032
Fax: 301-796-9849

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/s/

KAREN C BOYD
03/12/2014

Boyd, Karen

From: Boyd, Karen
Sent: Monday, March 10, 2014 3:31 PM
To: 'Gutman, Nina'
Cc: Frederick, Anne
Subject: RE: NDA 205755: Clinical Pharmacology Information Request

Importance: High

Hi Nina and Anne,

Here is our response to your proposal received via email on 3/7/14, in response to our 3/6/14 clinical pharmacology information request regarding the trial to assess the impact of gastric acid reducing agents on the PK of ceritinib:

FDA does not agree with your proposal. Given numerous confounding factors, population pharmacokinetic analyses with acid reducing agents as time independent covariates cannot adequately address our concern on the impact of coadministration of acid reducing agents on the pharmacokinetics of ceritinib, and cannot provide accurate information on how to dose ceritinib with regard to acid reducing agents. FDA recommends a dedicated drug-drug interaction study to evaluate the impact of acid reducing agents on the pharmacokinetics of ceritinib and to allow for a determination on how to dose ceritinib with regard to acid reducing agents.

If you have any questions, please let me know.

Please confirm receipt.

Thanks,
Karen

Karen Boyd, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
Email: Karen.Boyd@fda.hhs.gov
Phone: 301-796-7032
Fax: 301-796-9849

From: Gutman, Nina [<mailto:nina.gutman@novartis.com>]
Sent: Friday, March 07, 2014 4:54 PM
To: Boyd, Karen
Cc: Frederick, Anne
Subject: RE: NDA 205755: Clinical Pharmacology Information Request

Hi Karen,

I am writing to follow-up on yesterday's clinical pharmacology information request regarding the trial to assess the impact of gastric acid reducing agents on the PK of ceritinib as well as our discussion this morning.

As per the feedback provided by FDA during today's mid-cycle teleconference, Novartis understands that the current population PK analysis is not sufficient to assess the impact of gastric acid reducing agents on the population PK parameters because the model did not take the time course of the gastric acid reducing agents into consideration. To address FDA's concern, Novartis proposes to code the gastric acid reducing agents as time independent covariates, coded as 1 if the comedication is used by the patient during 80% of the ceritinib treatment period or 0 for the patient otherwise. Since most gastric acid reducing agents are given as daily treatment and the effects of PPIs on gastric pH are long-acting, the approach described above should be sufficient to capture the effect of gastric acid reducing agents on the PK parameters of ceritinib. We believe that this addresses FDA's concern about not capturing the treatment duration of the concomitant medication.

Can you please follow-up with your team and let us know if our proposal is acceptable? We would very much appreciate your input by close of day Monday, 10-Mar-2014 (if possible).

Thanks in advance!

Best regards,
Nina

Nina Gutman, Pharm.D.
Senior Associate Director, Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation
One Health Plaza, 315/5450A
East Hanover, NJ 07936
USA

Cell (b) (6)
Phone +1 862 778-1767
Fax +1 973 781-8265
nina.gutman@novartis.com
www.novartis.com

From: Boyd, Karen [<mailto:Karen.Boyd@fda.hhs.gov>]
Sent: Thursday, March 06, 2014 2:24 PM
To: Gutman, Nina
Subject: NDA 205755: Clinical Pharmacology Information Request
Importance: High

Hi Nina,

Please see attached for a clinical pharmacology information request for NDA 205755.

Please confirm receipt.

Thanks,
Karen

Karen Boyd, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products

Center for Drug Evaluation and Research
Food and Drug Administration
Email: Karen.Boyd@fda.hhs.gov
Phone: 301-796-7032
Fax: 301-796-9849

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/s/

KAREN C BOYD
03/10/2014



NDA 205755

INFORMATION REQUEST

Novartis Pharmaceuticals Corporation
Attention: Yanina Gutman, Pharm.D.
Senior Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936

Dear Dr. Gutman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ceritinib capsules, 150 mg.

We also refer to your original NDA submission.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a written response by March 12, 2014, in order to continue our evaluation of your NDA.

1. Provide the specifications and test methods for the bottles and caps.
2. Include resolution in the system suitability criteria for the analytical procedure for impurities in the drug product or provide justification for not including it.
3. As indicated in the submission the color of capsule shell used in the registration stability is opaque blue cap with white body. However, Tables 3-4, 3-5 and 3-6 in the "Registration Stability Report – Data tables" in the section P.8.3. describe the color of capsule shell is (b)(4) (cap and body). Please clarify the discrepancy.
4. Provide the comparison table of supporting stability and registration stability in terms of packaging, protocols, formulation (e.g. capsule shell size, color), etc.
5. Your application references DMF (b)(4) for gelatin capsules. However, your application should specify the type of gelatin capsules used. Further, your LOA should include specific reference to where the supporting information in DMF (b)(4) can be found (e.g., dates of submission, volume, page as appropriate).

6. Your application references DMF (b)(4) for HDPE bottle. However, your application should specify the type of HDPE bottle used. Further, your LOA should include specific reference to where the supporting information in DMF (b)(4) can be found (e.g., dates of submission, volume, page as appropriate).
7. Your application references DMF (b)(4) for HDPE bottle. However, your application should specify the type of HDPE bottle used. Further, your LOA should include specific reference to where the supporting information in DMF (b)(4) can be found (e.g., dates of submission, volume, page as appropriate).
8. Your application references DMF (b)(4) for (b)(4) information. Your LOA should include specific reference to where the supporting information in DMF (b)(4) can be found (e.g., dates of submission, volume, page as appropriate).
9. Your application references DMF (b)(4) for (b)(4) information. Your LOA should include specific reference to where the supporting information in DMF (b)(4) can be found (e.g., dates of submission, volume, page as appropriate).
10. Your application references DMF (b)(4) for (b)(4) information. Your LOA should include specific reference to where the supporting information in DMF (b)(4) can be found (e.g., dates of submission, volume, page as appropriate).

If you have any questions, please contact Jewell Martin, Regulatory Project Manager, at (301) 796-2072.

Sincerely,

{See appended electronic signature page}

Ali H. Al Hakim, PhD
Branch Chief, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

ALI H AL HAKIM
03/07/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: March 6, 2014
From: Karen Boyd, M.S., DOP2/OHOP/CDER
Subject: NDA 205755: Nonclinical/CMC Information Request

Hi Nina,

Please refer to your November 27, 2013, December 12, 2013, and December 24, 2013 rolling submission regarding New Drug Application (NDA) 205755.

Please respond to the following nonclinical/CMC information request via email by COB EST on Monday, March 10, 2014, followed by a formal submission to your NDA.

- Please confirm that impurity (b) (4) identified in clinical batches with a (b) (4) of (b) (4) is the same impurity identified as (b) (4) in nonclinical batch #0850001 used to justify the proposed specification for this impurity.

Thanks,
Karen

Karen Boyd, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

KAREN C BOYD
03/06/2014

MEMORANDUM

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

DATE: March 6, 2014

TO: Nina Gutman, Pharm.D., Novartis Pharmaceuticals Corporation

FROM: Karen Boyd, M.S., Senior Regulatory Project Manager, CDER/OHOP/DOP2

SUBJECT: Agenda for Midcycle Communication

APPLICATION/DRUG: Ceritinib

Meeting Date and Time: March 7, 2014, 8:30am-9:30am

Application Number: NDA 205755

Product Name: Ceritinib

Indication: Treatment of patients with (b) (4) metastatic non-small cell lung cancer (NSCLC) who have (b) (4)

Applicant Name: Novartis Pharmaceuticals Corporation

Meeting Chair: Gideon Blumenthal, M.D.

Meeting Recorder: Karen Boyd, M.S.

FDA ATTENDEES (tentative)

Patricia Keegan, M.D., Director, OHOP/DOP2

Gideon Blumenthal, M.D., Clinical Team Leader, OHOP/DOP2

Sean Khozin, M.D., Clinical Reviewer, OHOP/DOP2

Karen Boyd, M.S., Senior Regulatory Project Manager, OHOP/DOP2

Lijun Zhang, Ph.D., Biostatistics Reviewer, OB/DBV

Shenghui Tang, Ph.D., Biostatistics Team Leader, OB/DBV

Margaret Brower, Ph.D., Non-clinical Reviewer, OHOP/DHOT

Emily Fox, Ph.D., Non-clinical Reviewer, OHOP/DHOT

Whitney Helms, Ph.D., Non-clinical Team Leader, OHOP/DHOT

Jean Tang, Ph.D., Product Quality Reviewer, ONDQA/DNDQAI

Donghao Lu, Ph.D., Product Quality Reviewer, ONDQA/DNDQAI

Liang Zhou, Ph.D., Product Quality Team Leader, ONDQA/DNDQAI

Ali Al Hakim, Ph.D., Product Quality Branch Chief, ONDQA/DNDQAI

Okpo Eradiri, Ph.D., Biopharmaceutics Reviewer, OPS/ONDQA

Ruby Leong, Ph.D., Clinical Pharmacology Reviewer, OCP/DCPV
Pengfei Song, Ph.D., Pharmacometrics Reviewer, OCP/DCPV
Qi Liu, Pharmacometrics Team Leader, OCP/DCPV

APPLICANT ATTENDEES

Margaret Dugan, M.D., Senior VP, Global Program Head
Andrea Kay, M.D., VP, Senior Global Clinical Program Head
Andrew Joe, M.D., Senior Global Clinical Leader
Alicia Rossiter, M.D., FCP, Executive Director / Group Head, Integrated Medical Safety
Ben Cheng, M.D., Brand Safety Lead
Nassir Habboubi, M.D., VP, US Clinical Development and Medical Affairs
Margarida Geraldes, Ph.D., Director, Biostatistics
Yvonne Lau, PhD, Senior Fellow, Oncology Clinical Pharmacology
Frank Grande, Associate Director, Global Regulatory Chemistry, Manufacturing, and Controls
Nanxin Li, PhD, Associate Director, Drug Discovery
Shanthi Ganeshan, Ph.D., VP, North America Region Head, Drug Regulatory Affairs
Anne Frederick, Ph.D., Executive Director, Global Program Regulatory Director
Nina Gutman, Pharm.D., Senior Associate Director, Drug Regulatory Affairs

1. Introductions
2. Introductory Comments
3. Significant Review Issues

Clinical/Statistics:

- a. Potential acute pancreatitis signal is under investigation and may be included in section 6 of the product labeling.
- b. Potential postmarketing studies are under consideration to evaluate the food effect of ceritinib.

CMC Drug Substance:

- c. Potential genotoxic impurity with (b) (4).
- d. Need updated stability data from the batches manufactured using the (b) (4).
- e. Drug substance specifications (acceptance criteria) are missing for particle size, (b) (4).

CMC Drug Product:

- f. DMF: Need specific information for the container/closure system (e.g. pages and volumes of each DMF)
- g. The proposed storage condition for drug product: Stored 25 °C (77 °F) in tight container.
- h. The proposed shelf life: (b) (4) months.
 - i. The shelf life may be extended as additional data becomes available.

Biopharmaceuticals:

- i. Justification for the proposed dissolution acceptance criterion is not based on multipoint release and stability data.

Nonclinical:

- j. No significant review issues at this time, assuming that Novartis satisfactorily addresses the March 4, 2014 Nonclinical and CMC Information request.

Clinical Pharmacology:

- k. Potential postmarketing studies are under consideration (e.g., to evaluate the effect of hepatic impairment and gastric acid reducing agents on the pharmacokinetics of ceritinib and to evaluate the effect of ceritinib on the pharmacokinetics of CYP3A4 and CYP2C9 sensitive substrates).

4. Information Requests

The following information requests are outstanding as of today: information requests made on February 27, March 4, 2014 (2), and March 6, 2014. Please submit the requested information per the requested timeline as stated in the information requests.

CMC Drug Product (DP) (Information Request sent 2/27/14, due 3/11/14):

- a. Clarify if the (b) (4) is a critical step or not and whether it is within the validated range. Provide scientific reasons or justification if the step is not considered to be a critical step.
- b. Propose acceptance criteria for (b) (4) in the DP specification and provide updated DP specification.
- c. In the section 3.2.P.8.1, specify the capsule counts in the HDPE bottle and the size of the HDPE bottle in both tables 2-1 and 3-1.
- d. Provide initial stability starting date for both supportive and registration batches.

- e. For the test of “Mean mass of contents” in the drug product specification, provide the range using % of the target weight as well as the weight range in mg.
- f. Confirm the batches used in the supportive stability studies are same as the batches placed in the registration stability studies because it is unclear in the submission when you only mentioned that “These two clinical batches are representative of the registration stability batches and the commercial product.” If yes, provide information such as manufacturing process, capsule shell used including type, color, size, etc.
- g. Provide any updated stability data for both supportive stability and registration stability batches when they become available (e.g. at 12 month test point).
- h. In the tables 3-4 and 3-6 of the section of 3.2.P.8.1 (supportive stability studies batch # AEUS/2011-0076, AEUS/2012-0023), clarify if the qualified impurities at (b) (4) are from process impurities of drug substance since the same impurities are not found in the registration stability batches (batch #: 1010000660, 1010000958 and 1010001326). If yes, relate these two process impurities to the specified impurity in drug substance. If not, provide justification for the impurity/degradation profiles difference between the supportive stability batches and registration batches.

CMC Drug Substance (DS) (Information Request sent 2/27/14, due 3/11/14):

- i. (b) (4) is a potential genotoxic impurity and was tested in (b) (4) batches as the corresponding (b) (4) at (b) (4). Is there a direct method to monitor the level of (b) (4) in drug substance (as you have monitored it in (b) (4) batches for NMT (b) (4)%)?
- j. Provide any updated stability data from the batches, C0002, C0004 and C0005 (manufactured using the (b) (4)).
- k. The acceptance criterion for LDK378 Appearance was proposed to be “white to almost white or light yellow or light brown powder”. This is a wide color range and may not effectively serve the intended purpose for quality control.
- l. To ensure the batch to batch consistency, add drug substance specification (acceptance criteria) for particle size at (b) (4).
- m. Add a drug substance specification (acceptance criterion) for (b) (4) to confirm that the drug substance has (b) (4).

- n. Add a drug substance specification (acceptance criterion) for residual solvent, (b) (4).
- o. The impurity names were specified for (b) (4). Provide similar information for (b) (4).

Nonclinical and CMC (Information Request sent 3/4/14, Due 3/7/14)

- p. You have indicated that batch #0850001 used for Study 0970057-01 qualified impurities (b) (4) at (b) (4)% and (b) (4)% respectively. This study was an exploratory non-GLP study, and cannot be used for qualification purposes. This same batch was used for Study 0970416 which was GLP compliant. Please confirm that the impurity levels documented for impurities (b) (4) were identical when administered to animals in both studies.
- q. Please confirm that (b) (4) is impurity # (b) (4).
- r. You have indicated that the Ames assay (Study 0970421) documented 7 potential genotoxic compounds which were later found to be below (b) (4) with the exception of the (b) (4). Please document where these data for the specific genotoxic compounds are located in Study #0970421.

Clinical (Information Request sent 3/4/14, Due 3/7/14)

- s. Please provide a summary of any cardiac assessments (including the results of echocardiography and ECGs) in patients who experienced edema (particularly lower extremity edema) in study X2101.

Clinical Pharmacology (Information Request sent 3/6/14, Due 3/13/14)

- t. Given that ceritinib demonstrates pH-dependent solubility in vitro and becomes poorly soluble as pH increases, coadministration of gastric acid reducing agents may increase gastrointestinal pH and affect the pharmacokinetics of ceritinib. Please propose postmarketing requirement (PMR) language and provide milestone timelines for completion of a clinical trial to evaluate if gastric acid reducing agents (e.g., proton pump inhibitors, H₂-receptor antagonists, antacids) alter the bioavailability of ceritinib.

5. Major Safety Concerns/Risk Management Update

Adverse events of concern (primarily hepatotoxicity and potentially pancreatitis) are still being discussed. Our preliminary review indicates that a REMS may not be needed at this time.

6. Advisory Committee Meeting Plans

There are no plans at this time for an advisory committee meeting.

7. Proposed Date for Late-Cycle Meeting/Other Projected Milestones
The proposed date for the late cycle meeting is March 28, 2014, from 12:00 pm-1:00 pm.

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/s/

KAREN C BOYD
03/06/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: March 6, 2014
From: Karen Boyd, M.S., DOP2/OHOP/CDER
Subject: NDA 205755: Clinical Pharmacology Information Request

Hi Nina,

Please refer to your November 27, 2013, December 12, 2013, and December 24, 2013 rolling submission regarding New Drug Application (NDA) 205755.

Please respond to the following clinical pharmacology information request via email by COB EST on March 13, 2014, followed by a formal submission to your NDA.

- Given that ceritinib demonstrates pH-dependent solubility in vitro and becomes poorly soluble as pH increases, coadministration of gastric acid reducing agents may increase gastrointestinal pH and affect the pharmacokinetics of ceritinib. Please propose postmarketing requirement (PMR) language and provide milestone timelines for completion of a clinical trial to evaluate if gastric acid reducing agents (e.g., proton pump inhibitors, H2-receptor antagonists, antacids) alter the bioavailability of ceritinib.

Thanks,
Karen

Karen Boyd, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

KAREN C BOYD
03/06/2014

Boyd, Karen

From: Boyd, Karen
Sent: Tuesday, March 04, 2014 4:42 PM
To: 'Gutman, Nina'
Subject: NDA 205755: Nonclinical/CMC Information Request

Importance: High

Hi Nina,

Please see below for a non-clinical and CMC information request for NDA 205755:

1. You have indicated that batch #0850001 used for Study 0970057-01 qualified impurities (b) (4) at (b) (4)% and (b) (4)% respectively. This study was an exploratory non-GLP study, and cannot be used for qualification purposes. This same batch was used for Study 0970416 which was GLP compliant. Please confirm that the impurity levels documented for impurities (b) (4) were identical when administered to animals in both studies.
2. Please confirm that (b) (4) is impurity # (b) (4).
3. You have indicated that the Ames assay (Study 0970421) documented 7 potential genotoxic compounds which were later found to be below (b) (4) with the exception of the (b) (4). Please document where these data for the specific genotoxic compounds are located in Study #0970421.

Please respond to this request via email by COB Friday, March 7, 2014, followed by a formal submission to your NDA.

Please confirm receipt.

Thanks,
Karen

Karen Boyd, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
Email: Karen.Boyd@fda.hhs.gov
Phone: 301-796-7032
Fax: 301-796-9849

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/s/

KAREN C BOYD
03/05/2014

Boyd, Karen

From: Boyd, Karen
Sent: Tuesday, March 04, 2014 4:44 PM
To: 'Gutman, Nina'
Subject: NDA 205755: Clinical Information Request

Hi Nina,

Please see below for a clinical information request for NDA 205755:

1. Please provide a summary of any cardiac assessments (including the results of echocardiography and ECGs) in patients who experienced edema (particularly lower extremity edema) in study X2101.

Please respond to this request via email by COB Friday, March 7, 2014, followed by a formal submission to your NDA.

Please confirm receipt.

Thanks,
Karen

Karen Boyd, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
Email: Karen.Boyd@fda.hhs.gov
Phone: 301-796-7032
Fax: 301-796-9849

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/s/

KAREN C BOYD
03/05/2014



NDA 205755

INFORMATION REQUEST

Novartis Pharmaceuticals Corporation
Attention: Yanina Gutman, Pharm.D.
Senior Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936

Dear Dr. Gutman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ceritinib capsules, 150 mg.

We also refer to your original NDA submission.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a written response by March 11, 2014, in order to continue our evaluation of your NDA.

Drug Product (DP):

1. Clarify if the (b)(4) is a critical step or not and whether it is within the validated range. Provide scientific reasons or justification if the step is not considered to be a critical step.
2. Propose acceptance criteria for (b)(4) in the DP specification and provide updated DP specification.
3. In the section 3.2.P.8.1, specify the capsule counts in the HDPE bottle and the size of the HDPE bottle in both tables 2-1 and 3-1.
4. Provide initial stability starting date for both supportive and registration batches.
5. For the test of "Mean mass of contents" in the drug product specification, provide the range using % of the target weight as well as the weight range in mg.
6. Confirm the batches used in the supportive stability studies are same as the batches placed in the registration stability studies because it is unclear in the submission when

you only mentioned that “These two clinical batches are representative of the registration stability batches and the commercial product.” If yes, provide information such as manufacturing process, capsule shell used including type, color, size, etc.

7. Provide any updated stability data for both supportive stability and registration stability batches when they become available (e.g. at 12 month test point).
8. In the tables 3-4 and 3-6 of the section of 3.2.P.8.1 (supportive stability studies batch # AEUS/2011-0076, AEUS/2012-0023), clarify if the qualified impurities at (b) (4) are from process impurities of drug substance since the same impurities are not found in the registration stability batches (batch #: 1010000660, 1010000958 and 1010001326). If yes, relate these two process impurities to the specified impurity in drug substance. If not, provide justification for the impurity/degradation profiles difference between the supportive stability batches and registration batches.

Drug Substance (DS):

9. (b) (4) is a potential genotoxic impurity and was tested in (b) (4) batches as the corresponding (b) (4) at (b) (4). Is there a direct method to monitor the level of (b) (4) in drug substance (as you have monitored it in (b) (4) batches for NMT (b) (4))?
10. Provide any updated stability data from the batches, C0002, C0004 and C0005 (manufactured using the (b) (4)).
11. The acceptance criterion for LDK378 Appearance was proposed to be “white to almost white or light yellow or light brown powder”. This is a wide color range and may not effectively serve the intended purpose for quality control.
12. To ensure the batch to batch consistency, add drug substance specification (acceptance criteria) for particle size at (b) (4).
13. Add a drug substance specification (acceptance criterion) for (b) (4) to confirm that the drug substance has (b) (4).
14. Add a drug substance specification (acceptance criterion) for residual solvent, (b) (4) (b) (4).
15. The impurity names were specified for (b) (4) Provide similar information for (b) (4)

If you have any questions, please contact NAME, Regulatory Project Manager, at (301) 796-2072.

Sincerely,

{See appended electronic signature page}

Ali H. Al Hakim, PhD
Branch Chief, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

ALI H AL HAKIM
02/27/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: February 24, 2014
From: Karen Boyd, M.S., DOP2/OHOP/CDER
Subject: NDA 205755: CMC/Microbiology Information Request

Dear Dr. Gutman,

Please refer to your November 27, 2013, December 12, 2013, and December 24, 2013 rolling submission regarding New Drug Application (NDA) 205755.

Please respond to the following CMC/Microbiology information request by COB EST Monday, March 3, 2014, followed by a formal submission to the NDA:

- Please submit a revised specification that reflects the [REDACTED] ^{(b) (4)} testing for microbial enumeration studies.

Thanks,
Karen

Karen Boyd, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

KAREN C BOYD
02/24/2014

Boyd, Karen

From: Boyd, Karen
Sent: Friday, February 21, 2014 5:00 PM
To: 'Gutman, Nina'
Subject: NDA 205755: Clinical Information Request

Importance: High

Hi Dr. Gutman,

Please see below for a clinical information request for NDA 205755. Please respond via email to Karen Boyd by **noon EST on Monday, February 24, 2014**, followed a formal submission to the NDA.

1. The following patients treated at all dose levels had AE's leading to discontinuation (study X2101, dataset AAEV) n= 29. Table 1-2 of the safety update (page 18) says 26 patients. Explain the discrepancy.

SID1A
0002_90002
0041_90028
0041_90045
0062_90004
0064_90003
0064_90004
0064_90006
0081_90176
0082_00014
0121_90014
0121_90022
0121_90026
0121_90027
0141_90035
0175_00017
0201_90020
0201_90080
0502_00006
0502_90030
0504_90052
0504_90054
0505_00002
0505_90046
0506_90016
0507_00008
0507_90010
0507_90033
0507_90035
0507_90038

2. The following patients treated at 750mg had AE's leading to discontinuation (study X2101, dataset AAEV) n= 26. Table 1-2 of the safety update (page 18) says 24 patients. Explain the discrepancy.

SID1A
0002_90002
0041_90028
0041_90045
0062_90004
0064_90003
0064_90004
0064_90006
0081_90176
0082_00014
0121_90014
0121_90022
0121_90026
0121_90027
0141_90035
0201_90020
0201_90080
0502_00006
0502_90030
0504_90052
0504_90054
0505_90046
0506_90016
0507_90010
0507_90033
0507_90035
0507_90038

If you have any questions, please let me know.

Please confirm receipt.

Thanks,
Karen

Karen Boyd, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
Email: Karen.Boyd@fda.hhs.gov
Phone: 301-796-7032
Fax: 301-796-9849

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/s/

KAREN C BOYD
02/21/2014



NDA 205755

**FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED**

Novartis Pharmaceuticals Corporation
Attention: Yanina Gutman, Pharm.D.
Senior Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936

Dear Dr. Gutman:

Please refer to your New Drug Application (NDA) dated December 24, 2013, received December 24, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for ceritinib capsules, 150 mg.

We also refer to your presubmissions dated November 27, 2013, and December 12, 2013, and your NDA amendments dated January 8, January 24, January 29, February 3, February 5, February 10 (2), February 12, February 14 (2), February 18 (2), February 19, February 20 (2), and February 21, 2014.

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. 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> . Therefore, the user fee goal date is August 24, 2014.

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 as early as March 24, 2014, but no later than May 27, 2014. In addition, the planned date for our internal

mid-cycle review meeting is February 25, 2014. We are not currently planning to hold an advisory committee meeting to discuss this application.

During our filing review of your application, we identified potential review issues as communicated to you via electronic mail (email) information requests dated January 3, January 17, January 22 (2), January 29, February 5, February 7, February 11, February 13, February 14, February 18 (2), February 20, and February 21, 2014. The following information requests are outstanding as of today: information requests made on February 7, February 11, February 18, February 20, and February 21, 2014. Please submit the requested information per the requested timeline as stated in the information requests.

In addition, we are providing the following additional potential review issues that have not been previously communicated:

1. The NDA does not contain the expected proposed postmarketing requirement (PMR), including milestones (e.g., study completion date, submission of final study report), for completion of the hepatic impairment study CLDK378A2110 as agreed to during the November 22, 2013 pre-NDA meeting. Please submit the proposed PMR to the NDA.
2. The Form 3674 included in the NDA was not signed by the authorized sponsor representative, Dr. Yanina Gutman. Resubmit the Form 3674 signed by Dr. Gutman.

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.

In addition, we informed you on January 31, 2014 of specific instances where you failed to comply with FDA Guidances for content and format of product labeling. We acknowledge receipt of revised labeling formally submitted to the NDA on February 21, 2014. The revised labeling will be used as the basis for further labeling discussions.

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

We will review this application under the provisions of 21 CFR 314 Subpart H – Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses. Unless we otherwise inform you, as required by 21 CFR 314.550, you must submit during the preapproval review period copies of all promotional materials, including promotional labeling and advertisements, intended for dissemination or publication within 120 days following marketing approval (i.e., your launch campaign). During the preapproval review period, please submit, in triplicate, a detailed cover letter (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) and patient PI (as applicable). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and patient PI (as applicable), 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, call Ms. Karen Boyd, Senior Regulatory Project Manager, at (301) 796-7032.

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure(s):

Appendix of outstanding information requests:

Information request sent February 7, 2014; response requested February 25, 2014:

1. Conduct the following exposure-response analyses using the updated datasets that you plan to submit for “Safety and Efficacy Update” on February 25, 2014. Please submit the results with relevant datasets, data define file, and programs along with your planned “Safety and Efficacy Update” to your NDA. Please use two exposure datasets in all of the following analyses: 1) Updated average $C_{\text{trough, ss}}$ observed at dose level of 750 mg; and 2) Population PK post hoc estimates of $C_{\text{trough, ss}}$ (e.g., at Day 1 of Cycle 2) at all dose levels from 50 mg to 750 mg.
 - a. Conduct multivariable step-wise logistic regression analyses to select significant covariates besides exposure and evaluate their impacts on ORR. If time allows, please also update your analyses for Figures 3-2 through 3-6 for individual AEs.
 - b. Conduct analyses to evaluate the relationship between exposure and each of the following dose changes: reduction, delay, and discontinuation.
 - c. Conduct analyses to evaluate the relationship between exposure and Grade 3 or above AEs.
 - d. Conduct survival analyses to evaluate the relationship between exposure (by quartiles) and each of the following endpoints: PFS, and time to the first dose change.
 - e. Evaluate the relationship between exposure (by quartiles) and time to response, and duration of response in responders.

Information request sent February 11, 2014; response requested February 18, 2014 (new due date of February 21, 2014 for part 1 (below) okayed by Karen Boyd, FDA received Part 2 and 3 on February 18, 2014):

2. Based on the updated safety datasets with a cut-off date of October 31, 2013, patients in Table-1 exhibited features suggestive of acute pancreatitis, including gastrointestinal symptoms with amylase and/or lipase elevations. Please perform an assessment of the association between the use of LDK378 and acute pancreatitis using the **updated safety database** with the cut-off date of October 31, 2013. As part of this assessment, include information regarding challenge-de-challenge-re-challenge, imaging, laboratory, and clinical parameters in addition to concomitant medications and other pertinent variables.

Table 1. Patients in CLDK378X2101 with features suggestive of acute pancreatitis

0041_90020
0061_90001
0061_90002
0061_90098
0061_90142
0062_90003
0081_00108
0081_90138

0121_00009
0141_90035
0161_90060
0175_90020
0175_90029
0201_00008
0201_90011
0201_90025
0201_90063
0501_90001
0502_00006
0502_90015
0502_90016
0502_90029
0504_00023
0504_00025
0504_90037
0504_90044
0504_90045
0504_90048
0504_90050
0504_90057
0504_90066
0504_90078
0505_90039
0505_90049
0505_90051
0506_90012
0506_90015
0507_00008

Information request sent February 18, 2014; response requested February 28, 2014:

3. The clinical batches of your proposed drug product were manufactured at two manufacturing sites in Switzerland and the United States. Submit to the NDA, comparative dissolution data of representative batches from the two sites demonstrating similarity in dissolution profiles between the two manufacturing sites.
4. The dissolution data from stability samples are reported for only the proposed specification time point of (b) (4) min. Please submit the complete dissolution profile data for the clinical and registration batches, i.e., report the data at all sampling time points. In the event that only the (b) (4) min time point results were recorded, please collect and provide the

complete dissolution profile data (n=12) for the clinical and registration batches at the current stability time point and thereafter (submit the data as soon as they become available).

5. We note the investigative experiments that were conducted to select the dissolution equipment, medium, as well as paddle speed. (b) (4)

modifications of the dissolution medium to obtain a profile more representative of the drug product's expected in-vivo release rate.

Information request sent February 20, 2014; response requested as soon as possible (informal response received by Ms. Karen Boyd via email on February 20, 2014):

6. Clarify if ceritinib is an approved USAN name.

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/s/

PATRICIA KEEGAN
02/21/2014

Boyd, Karen

From: Boyd, Karen
Sent: Friday, February 21, 2014 12:36 PM
To: 'Gutman, Nina'
Subject: NDA 205755: Clinical Information Request

Importance: High

Hi Nina,

Please see below for a clinical information request for NDA 205755.

In the updated summary of clinical safety (page 10), it says "in Study X2101, a total of 45 (14.8%) on-treatment deaths were reported" but in dataset ACMPDTH there are 49 on treatment deaths listed. Please explain the discrepancy.

Please submit a response via email by COB today (February 21, 2014), followed by a formal submission to the NDA.

Please confirm receipt.

Thanks,
Karen

Karen Boyd, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
Email: Karen.Boyd@fda.hhs.gov
Phone: 301-796-7032
Fax: 301-796-9849

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/s/

KAREN C BOYD
02/21/2014

Boyd, Karen

From: Boyd, Karen
Sent: Thursday, February 20, 2014 10:35 AM
To: 'Gutman, Nina'
Subject: NDA 205755: Information Request

Importance: High

Hi Nina,

Is ceritinib an approved USAN name?

Please submit your response ASAP via email followed by a formal submission to the NDA.

Please confirm receipt.

Thanks,
Karen

Karen Boyd, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
Email: Karen.Boyd@fda.hhs.gov
Phone: 301-796-7032
Fax: 301-796-9849

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/s/

KAREN C BOYD
02/20/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: February 18, 2014
From: Karen Boyd, M.S., DOP2/OHOP/CDER
Subject: NDA 205755: Clinical Pharmacology Information Request

Dear Dr. Gutman,

Please refer to your November 27, 2013, December 12, 2013, and December 24, 2013 rolling submission regarding New Drug Application (NDA) 205755.

Please respond to the following clinical pharmacology information request:

1. Derive exposure endpoint $C_{ss, average}$ for each individual in your study X2101. To calculate $C_{ss, average}$, please divide the individual average dose intensity by the oral clearance at steady state (CL_{ss}/F) that estimated for each individual in your final population PK model.
 - a. Please submit the dataset containing subject identifier (SID1A), dose intensity (DOSINT1N) and population PK estimated CL_{ss}/F by **noon EST on Wednesday, February 19, 2014.**
 - b. Please also conduct exposure-response analyses for efficacy endpoints using $C_{ss, average}$ and submit the results by **COB EST on Monday, February 24, 2014.**
2. Evaluate the impact of dose reduction, dose delay, or occurrence of Grade 3+ AEs on the PFS in your study X2101, particularly at dose level of 750 mg. Please submit your results and interpretations by **COB EST on Monday, February 24, 2014.**

If you have any questions, please don't hesitate to let me know.

Thanks,
Karen

Karen Boyd, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

KAREN C BOYD
02/18/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: February 18, 2014
From: Karen Boyd, M.S., DOP2/OHOP/CDER
Subject: NDA 205755: Biopharmaceuticals Information Request

Dear Nina,

Please refer to your November 27, 2013, December 12, 2013, and December 24, 2013 rolling submission regarding New Drug Application (NDA) 205755.

Please respond to the following biopharmaceuticals information request via email to Karen Boyd (karen.boyd@fda.hhs.gov) by **COB EST Friday, February 28, 2014**, followed by a formal submission to your NDA.

1. The clinical batches of your proposed drug product were manufactured at two manufacturing sites in Switzerland and the United States. Submit to the NDA, comparative dissolution data of representative batches from the two sites demonstrating similarity in dissolution profiles between the two manufacturing sites.
2. The dissolution data from stability samples are reported for only the proposed specification time point of ^{(b) (4)} min. Please submit the complete dissolution profile data for the clinical and registration batches, i.e., report the data at all sampling time points. In the event that only the ^{(b) (4)} min time point results were recorded, please collect and provide the complete dissolution profile data (n=12) for the clinical and registration batches at the current stability time point and thereafter (submit the data as soon as they become available).
3. We note the investigative experiments that were conducted to select the dissolution equipment, medium, as well as paddle speed. ^{(b) (4)}

modifications of the dissolution medium to obtain a profile more representative of the drug product's expected in-vivo release rate.

If you have any questions, please don't hesitate to contact me.

Thanks,
Karen

Karen Boyd, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration

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KAREN C BOYD
02/18/2014

Boyd, Karen

From: Jones, Karen
Sent: Friday, February 14, 2014 6:09 PM
To: nina.gutman@novartis.com
Cc: Boyd, Karen
Subject: Novartis NDA 205755 ceritinib NDA/Clinical Pharmacology

Hello Dr. Gutman,

On behalf of Karen Boyd, please find below an information request from our clinical pharmacology team for NDA 205755 for ceritinib:

- Please refer to your responses to the FDA Information Request on February 13, 2014. It is noted that the quartile with the highest systemic exposure tends to have the shortest duration of response (DOR) compared to other quartiles (Figure 2-10). In addition, it is noted that the dose level of 750 mg appears to have the shortest duration of response (DOR) compared to other dose levels ranging from 400 mg to 700 mg. Please explore potential underlying reasons and provide a written response by COB on February 17, 2014.

Please reply to confirm receipt of this request.

Thank you.

Karen

Karen D. Jones
Chief, Project Management Staff
Division of Oncology Products 2

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/s/

KAREN C BOYD
02/18/2014

Planning Meeting Minutes
January 14, 2014

NDA: 205755
Product: Ceritinib (LDK 378) capsules, 150mg
Submission Date: December 24, 2013
Received Date: December 24, 2013
Sponsor: Novartis Pharmaceuticals Corporation

Proposed Indication: Treatment of patients with (b) (4) metastatic non small cell lung cancer (NSCLC) who have (b) (4)

Attendees: Richard Pazdur, Jonathan Jarow, Patricia Keegan, Karen Boyd, Karen Jones, Sean Khozin, Gideon Blumenthal, Lijun Zhang, Shenghui Tang, Ruby Leong, Hong Zhao, Sarah Dorff, Margaret Brower, Emily Fox, Whitney Helms, Jean Tang, Donghao Lu, Liang Zhou, Ali Al Hakim, Okpo Eradiri, Naomi Redd, Cynthia LaCivita, Jessica Cole, Otto Townsend, Lauren Iacono-Connor, Kevin Wright, Morgan Walker, Barbara Fuller, Quynh Tran, Miriam Dinatale, Robert Wittorf, Barb Sceपुरa, Peter Waldron, Afrouz Nayernama

Discussion Topics:

- Sponsor requested Priority Review. FDA agrees to grant priority review.
- FDA decided to expedite review clock to a 4 month clock. Target action date is 4/17/14.
- Safety and Efficacy Update: Novartis proposes to submit their safety and efficacy update by February 25, 2014. FDA agrees to this extension even through it is beyond the 60-day window agreed upon during the pre-NDA meeting.
- Discussion of the status of the proprietary name review, as the (b) (4) name is unacceptable. The review team did not have any additional comments for the proprietary name review denied letter. OSE will conduct a teleconference with Novartis and ask them to submit new possible names as soon as possible.
- OSI inspections sites include Novartis, CRO, South Korea, Massachusetts General Hospital and Fox Chase.
- No facilities inspections are needed at this time.
- No preclinical study site audits are needed.
- SGEs and patient representative: Sean and Gideon submitted potential names to Dianne Spillman and Caleb Briggs. Goal is to have SGE meetings by mid- to late March.
- Patient Labeling and OPDP agreed to a 1 week turnaround versus a 2-week turnaround on the labeling review.
- An ODAC meeting is not needed.
- Goal is to have filing issues ready for the Day 60/filing letter.
- Labeling meetings will start after the midcycle meeting. RPM Boyd will schedule 6 meetings.

- Team meetings will occur monthly.

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KAREN C BOYD
02/14/2014

Boyd, Karen

From: Boyd, Karen
Sent: Thursday, February 13, 2014 12:47 PM
To: 'Gutman, Nina'
Cc: 'anne.frederick@novartis.com'
Subject: NDA 205755: Clinical Information Request

Importance: High

Hi Nina and Anne,

In addition to our question on the completeness of dataset [arskdh], can you also explain the values for the [BORRSN] variable (see table below) in detail, in particular, 2, 4, 5?

Please provide the answers to both of these questions via email as soon as possible, followed by a formal submission to the NDA.

Please confirm receipt.

BORRSN	
<i>Code</i>	<i>Value</i>
1	No valid post-baseline assessment
2	All post baseline assessments have overall response UNK
3	New anti neoplastic therapy started before first post-baseline assessment
4	SD too early
5	PD too late

Thanks,
Karen

Karen Boyd, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
Email: Karen.Boyd@fda.hhs.gov
Phone: 301-796-7032
Fax: 301-796-9849

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/s/

KAREN C BOYD
02/13/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: February 11, 2014
From: Karen Boyd, M.S., DOP2/OHOP/CDER
Subject: NDA 205755: Clinical Information Request

Dear Nina,

Please refer to your November 27, 2013, December 12, 2013, and December 24, 2013 rolling submission regarding New Drug Application (NDA) 205755.

Please respond to the following clinical information request via email to Karen Boyd (karen.boyd@fda.hhs.gov) by **COB EST Tuesday, February 18, 2014**, followed by a formal submission to your NDA.

1. Based on the updated safety datasets with a cut-off date of October 31, 2013, patients in Table-1 exhibited features suggestive of acute pancreatitis, including gastrointestinal symptoms with amylase and/or lipase elevations. Please perform an assessment of the association between the use of LDK378 and acute pancreatitis using the **updated safety database** with the cut-off date of October 31, 2013. As part of this assessment, include information regarding challenge-de-challenge-re-challenge, imaging, laboratory, and clinical parameters in addition to concomitant medications and other pertinent variables.

Table 1. Patients in CLDK378X2101 with features suggestive of acute pancreatitis

0041_90020
0061_90001
0061_90002
0061_90098
0061_90142
0062_90003
0081_00108
0081_90138
0121_00009
0141_90035
0161_90060
0175_90020
0175_90029
0201_00008
0201_90011
0201_90025
0201_90063
0501_90001

0502_00006
0502_90015
0502_90016
0502_90029
0504_00023
0504_00025
0504_90037
0504_90044
0504_90045
0504_90048
0504_90050
0504_90057
0504_90066
0504_90078
0505_90039
0505_90049
0505_90051
0506_90012
0506_90015
0507_00008

2. Provide narratives for the following patients who experienced convulsions:
0201_90017
0201_90035
0201_90044
3. Using the **updated efficacy database** with the cut-off date of October 31, 2013, identify patients in CLDK378X2101 who progressed on LDK378 with CNS as the primary site of relapse. Submit a dataset with these patients (one row/patient) including core variables (e.g., age, race, study arm).

If you have any questions, please don't hesitate to let me know.

Thanks,
Karen

Karen Boyd, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

KAREN C BOYD
02/11/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: February 7, 2014
From: Karen Boyd, M.S., DOP2/OHOP/CDER
Subject: NDA 205755: Clinical Pharmacology Information Request

Dear Nina,

Please refer to your November 27, 2013, December 12, 2013, and December 24, 2013 rolling submission regarding New Drug Application (NDA) 205755. This information request seeks additional exposure-response evidence to support your proposed dosing regimen.

Please conduct the following exposure-response analyses using the current datasets for safety, efficacy, and exposure. Please submit the results with relevant datasets, data define file, and programs to the NDA by COB EST on Thursday, February 13, 2014.

1. Conduct multivariable step-wise logistic regression analyses to select significant covariates besides exposure and evaluate their impacts on ORR.
2. Conduct analyses to evaluate the relationship between exposure and Grade 3 or above AEs.
3. Conduct analyses to evaluate the relationship between exposure and each of the following dose changes: reduction, delay, and discontinuation.
4. Conduct survival analyses to evaluate the relationship between exposure (by quartiles) and each of the following endpoints: PFS, time to the first dose change.
5. Evaluate the relationship between exposure (by quartiles) and time to response and duration of response in responders.

In addition, please conduct the following exposure-response analyses using the updated datasets that you plan to submit for "Safety and Efficacy Update" on February 25, 2014. Please submit the results with relevant datasets, data define file, and programs along with your planned "Safety and Efficacy Update" to your NDA by COB EST on Tuesday, February 25, 2014. Please use two exposure datasets in all of the following analyses: 1) Updated average C_{trough}, ss observed at dose level of 750 mg; and 2) Population PK post hoc estimates of C_{trough}, ss (e.g., at Day 1 of Cycle 2) at all dose levels from 50 mg to 750 mg.

1. Conduct multivariable step-wise logistic regression analyses to select significant covariates besides exposure and evaluate their impacts on ORR. If time allows, please also update your analyses for Figures 3-2 through 3-6 for individual AEs.
2. Conduct analyses to evaluate the relationship between exposure and each of the following dose changes: reduction, delay, and discontinuation.

3. Conduct analyses to evaluate the relationship between exposure and Grade 3 or above AEs.
4. Conduct survival analyses to evaluate the relationship between exposure (by quartiles) and each of the following endpoints: PFS, and time to the first dose change.
5. Evaluate the relationship between exposure (by quartiles) and time to response, and duration of response in responders.

Please note that we encourage you to conduct and submit other relevant analyses besides the above requested analyses.

If you have any questions, please let me know.

Thanks,
Karen

Karen Boyd, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration

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KAREN C BOYD
02/07/2014

Wright, Kevin

From: Gutman, Nina <nina.gutman@novartis.com>
Sent: Wednesday, February 05, 2014 1:37 PM
To: Wright, Kevin
Cc: Kang, Sue
Subject: RE: NDA 205755 - Proprietary name submission
Attachments: req-comm.pdf; appendix-1.pdf

Dear Dr. Wright,

As promised, attached please find a request for FDA to review the following proposed proprietary names for ceritinib (in order of preference):

- Primary: (b) (4)™
- Alternate 1: ZYKADIA™
- Alternate 2: (b) (4)

Please note that these documents will be submitted officially to NDA 205755 via the FDA Electronic Submissions Gateway tomorrow.

Please let me know if you have any questions/concerns.

Thanks in advance for your time and review.

Best regards,
Nina

Nina Gutman, Pharm.D.
Senior Associate Director, Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation
One Health Plaza, 315/5450A
East Hanover, NJ 07936
USA

Cell + (b) (6)
Phone +1 862 778-1767
Fax +1 973 781-8265
nina.gutman@novartis.com
www.novartis.com

From: Wright, Kevin [mailto:Kevin.Wright@fda.hhs.gov]
Sent: Tuesday, February 04, 2014 2:33 PM
To: Gutman, Nina
Cc: Kang, Sue
Subject: RE:NDA 205755 - Proprietary name submission

Dr. Gutman,

Thank you for a productive meeting this morning. I would like to follow up with you regarding the submission of (b) (4) as a proprietary name for Ceritinib NDA 205755. In order, for the DMEPA review team to consider (b) (4) for this application you will need to withdraw the name from (b) (4) IND (b) (4). Then submit a request for review under Ceritinib NDA 205755.

Best regards,

Kevin Wright, PharmD

Safety Regulatory Project Manager | OSE | CDER | FDA | 301.796.3621 | kevin.wright@fda.hhs.gov

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From: Gutman, Nina [<mailto:nina.gutman@novartis.com>]
Sent: Tuesday, February 04, 2014 9:58 AM
To: Wright, Kevin
Cc: Kang, Sue
Subject: RE: IND 109272/NDA 205755 - Proprietary name submission

Dear Dr. Wright,

Given the abbreviated timelines for the review of the trade name, Novartis wants to better understand the Agency's approach on the following points to enable us to send the most appropriate names in the formal submission for a most meaningful evaluation:

- Novartis would like to obtain initial feedback from DMEPA on two clones of (b) (4) ((b) (4) and (b) (4))
- Novartis would like to better understand the process and timelines for reviewing a proposed trade name that previously received conditional approval from DMEPA (specifically, (b) (4) which received conditional approval on 08-Nov-2013 for (b) (4))

We look forward to this morning's discussion.

Best regards,
Nina

Nina Gutman, Pharm.D.
Senior Associate Director, Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation
One Health Plaza, 315/5450A
East Hanover, NJ 07936
USA

Cell + (b) (6)
Phone +1 862 778-1767
Fax +1 973 781-8265
nina.gutman@novartis.com
www.novartis.com

From: Wright, Kevin [<mailto:Kevin.Wright@fda.hhs.gov>]
Sent: Tuesday, February 04, 2014 8:05 AM
To: Gutman, Nina

Cc: Kang, Sue
Subject: RE: IND 109272/NDA 205755 - Proprietary name submission

Dr. Gutman,

Good morning, please forward the questions Novartis would like to discuss during our teleconference.

The attendees from the Agency include:

Alice Tu, Pharm.D., Team Leader, Safety Evaluator
Kevin Wright, Pharm.D., Safety Regulatory Project Manager
Otto Townsend, Pharm.D., Safety Evaluator
Sue Kang, MS, Team Leader, Safety Regulatory Project Manager (tentative)

Best regards,

Kevin Wright, PharmD

Safety Regulatory Project Manager | OSE | CDER | FDA | 301.796.3621 kevin.wright@fda.hhs.gov

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From: Gutman, Nina [<mailto:nina.gutman@novartis.com>]
Sent: Monday, February 03, 2014 4:49 PM
To: Wright, Kevin
Cc: Kang, Sue
Subject: RE: IND 109272/NDA 205755 - Proprietary name submission

Dear Dr. Wright,

Can you please tell me who will be attending the meeting from FDA's side tomorrow?

Thanks in advance!

Best regards,
Nina

Nina Gutman, Pharm.D.
Senior Associate Director, Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation
One Health Plaza, 315/5450A
East Hanover, NJ 07936
USA

Cell + (b) (6)
Phone +1 862 778-1767
Fax +1 973 781-8265

From: Wright, Kevin [<mailto:Kevin.Wright@fda.hhs.gov>]
Sent: Monday, February 03, 2014 10:38 AM
To: Gutman, Nina
Cc: Kang, Sue
Subject: RE: IND 109272/NDA 205755 - Proprietary name submission

Dr. Gutman,

Thank you for confirming our teleconference. We look forward to speaking with you and your team tomorrow.

Thanks,

Kevin

From: Gutman, Nina [<mailto:nina.gutman@novartis.com>]
Sent: Monday, February 03, 2014 10:21 AM
To: Wright, Kevin
Cc: Kang, Sue
Subject: RE: IND 109272/NDA 205755 - Proprietary name submission

Dear Dr. Wright,

Yes, my team is available tomorrow, 04-Feb-2014 at 10:30 AM. Thank you so very much for accommodating the TC request on such short notice.

The following individuals will attend the TC:

- Margaret Dugan, MD, Senior Vice President, Global Program Head
- Dorothy Linvill-Neal, Global Head, Name Creation & Regulatory Strategy
- Sudipta Rao, Sr. Trademark Attorney
- Suman Shirodkar, MD, Global Disease Lead Lung
- Shanthi Ganeshan, PhD, Vice President, North America Region Head, Drug Regulatory Affairs
- Anne Frederick, PhD, Executive Director, Global Program Regulatory Director
- Nina Gutman, PharmD, Senior Associate Director, Drug Regulatory Affairs

You can use the following call-in information for the meeting:

United States (toll free): [REDACTED] (b) (4)

Passcode: [REDACTED] (b) (4)

Best regards,
Nina

Nina Gutman, Pharm.D.
Senior Associate Director, Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation
One Health Plaza, 315/5450A
East Hanover, NJ 07936
USA

Cell + [REDACTED] (b) (6)
Phone +1 862 778-1767

Fax +1 973 781-8265
nina.gutman@novartis.com
www.novartis.com

From: Wright, Kevin [<mailto:Kevin.Wright@fda.hhs.gov>]
Sent: Monday, February 03, 2014 9:44 AM
To: Gutman, Nina
Cc: Kang, Sue
Subject: RE: IND 109272/NDA 205755 - Proprietary name submission

Dr. Gutman,

Good morning, the DMEPA team is available for a 30 minute teleconference on Tuesday, February 4 at 10:30 am (EST). Is your team available at this time?

Best regards,

Kevin Wright, PharmD

Safety Regulatory Project Manager | OSE | CDER | FDA | 301.796.3621 | kevin.wright@fda.hhs.gov

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From: Gutman, Nina [<mailto:nina.gutman@novartis.com>]
Sent: Sunday, February 02, 2014 9:37 PM
To: Wright, Kevin
Cc: Kang, Sue
Subject: RE: IND 109272/NDA 205755 - Proprietary name submission

Dear Dr. Wright,

Novartis was informed by DOP2 last week that FDA plans to take action on our application in April 2014. As such, I am writing to see if DMEPA would be able to accommodate a short teleconference with Novartis by Wednesday, 05-Feb-2014 to discuss next steps pertaining to our proposed trade name submission. Please let me know at your earliest convenience.

Thanks in advance!

Best regards,
Nina

Nina Gutman, Pharm.D.

Senior Associate Director, Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation
One Health Plaza, 315/5450A
East Hanover, NJ 07936
USA

Cell + [REDACTED] (b) (6)
Phone +1 862 778-1767
Fax +1 973 781-8265
nina.gutman@novartis.com
www.novartis.com

From: Wright, Kevin [<mailto:Kevin.Wright@fda.hhs.gov>]
Sent: Wednesday, January 29, 2014 12:29 PM
To: Gutman, Nina
Cc: Kang, Sue
Subject: RE: IND 109272/NDA 205755 - Proprietary name submission

Dr. Gutman,

Please find the meeting minutes from our January 27, 2014 teleconference attached. You can officially submit a primary name and two alternate names. Please list the alternate proprietary names in order of preference. The team will begin to review your primary name and conduct a preliminary safety assessment for your alternate names.

Thanks,

Kevin Wright, PharmD

Safety Regulatory Project Manager | OSE | CDER | FDA | 301.796.3621 | kevin.wright@fda.hhs.gov

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From: Gutman, Nina [<mailto:nina.gutman@novartis.com>]
Sent: Wednesday, January 29, 2014 6:43 AM
To: Wright, Kevin
Cc: Kang, Sue
Subject: RE: IND 109272/NDA 205755 - Proprietary name submission

Dear Dr. Wright,

As requested, Novartis plans to send a letter to FDA today to withdraw the proposed proprietary name [REDACTED] (b) (4). The letter will be sent to NDA 205755 via Sequence No. 0006. The letter is also attached to this email for your reference.

Also, thank you very much for your willingness to do a quick screen of a few proposed proprietary names. We very much appreciate your flexibility.

Given the abbreviated timelines, would it be possible for Novartis to submit 1 proposed and 2 alternate proprietary names officially for formal review by DMEPA (rather than for a quick screen)? We would of course prioritize these names in our submission. If so, would it be possible for DMEPA to screen all 3 names in parallel?

Thanks in advance for your time and consideration.

Best regards,
Nina

Nina Gutman, Pharm.D.

Senior Associate Director, Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation
One Health Plaza, 315/5450A
East Hanover, NJ 07936
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Cell + [REDACTED] (b) (6)
Phone +1 862 778-1767
Fax +1 973 781-8265
nina.gutman@novartis.com
www.novartis.com

From: Wright, Kevin [<mailto:Kevin.Wright@fda.hhs.gov>]
Sent: Monday, January 27, 2014 3:53 PM
To: Gutman, Nina
Cc: Kang, Sue
Subject: RE: IND 109272/NDA 205755 - Proprietary name submission

Dr. Gutman,

The letter can be addressed Kellie Taylor:

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

From: Gutman, Nina [<mailto:nina.gutman@novartis.com>]
Sent: Monday, January 27, 2014 3:46 PM
To: Wright, Kevin
Cc: Kang, Sue
Subject: RE: IND 109272/NDA 205755 - Proprietary name submission

Hi Dr. Wright,

Thanks for your speedy feedback and the very helpful information.

Should we decide to withdraw the name [REDACTED] (b) (4) by 29-Jan-2014, to whom should we address the letter?

Best regards,
Nina

Nina Gutman, Pharm.D.

Senior Associate Director, Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation
One Health Plaza, 315/5450A
East Hanover, NJ 07936
USA

Cell + (b) (6)
Phone +1 862 778-1767
Fax +1 973 781-8265
nina.gutman@novartis.com
www.novartis.com

From: Wright, Kevin [<mailto:Kevin.Wright@fda.hhs.gov>]
Sent: Monday, January 27, 2014 3:18 PM
To: Gutman, Nina
Cc: Kang, Sue
Subject: RE: IND 109272/NDA 205755 - Proprietary name submission

Dr. Gutman,

Good afternoon. I spoke with the DMEPA review team regarding your request. The team would like to conduct a Prescription Simulation Study on the proposed proprietary names. February 18 is the earliest the team would be able to provide you feedback on any of the proposed proprietary names (3). Also, I would encourage your team to consider submitting proprietary names that are sufficiently different from one another to help expedite the review process.

Lastly, I would like to reiterate, the team would like for you to let us know by close of business Wednesday, January 29 of your decision to withdraw your request for proprietary name.

Best regards,

Kevin

From: Gutman, Nina [<mailto:nina.gutman@novartis.com>]
Sent: Monday, January 27, 2014 11:12 AM
To: Wright, Kevin
Subject: RE: IND 109272/NDA 205755 - Proprietary name submission

Dear Dr. Wright,

Thank you very much for the very informative teleconference today.

During the call, DMEPA kindly agreed to do an initial scan of up to 3 names. Can you please let me know how long it will take DMEPA to provide preliminary feedback on the 3 names? I ask because we do not want to delay the official submission of the proposed trade name(s).

Thanks in advance for your time and response.

Best regards,

Nina

Nina Gutman, Pharm.D.

Senior Associate Director, Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation
One Health Plaza, 315/5450A
East Hanover, NJ 07936
USA

Cell + (b) (6)
Phone +1 862 778-1767
Fax +1 973 781-8265
nina.gutman@novartis.com
www.novartis.com

From: Gutman, Nina
Sent: Monday, January 27, 2014 8:49 AM
To: 'Kevin.Wright@fda.hhs.gov'
Subject: RE: IND 109272/NDA 205755 - Proprietary name submission

Hi Dr. Wright,

I am just writing to confirm our meeting this morning at 10 AM.

The following individuals will attend the meeting:

- Margaret Dugan, MD, Senior Vice President, Global Program Head
- Dorothy Linvill-Neal, Global Head, Name Creation & Regulatory Strategy
- Sudipta Rao, Sr. Trademark Attorney
- Shanthy Ganeshan, PhD, Vice President, North America Region Head, Drug Regulatory Affairs
- Anne Frederick, PhD, Executive Director, Global Program Regulatory Director
- Nina Gutman, PharmD, Senior Associate Director, Drug Regulatory Affairs

You can use the following call-in information for the meeting (this is the same number that I provided previously):

United States (toll free): (b) (4)
Passcode: (b) (4)

Best regards,
Nina

Nina Gutman, Pharm.D.

Senior Associate Director, Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation
One Health Plaza, 315/5450A
East Hanover, NJ 07936
USA

Cell + (b) (6)
Phone +1 862 778-1767
Fax +1 973 781-8265
nina.gutman@novartis.com
www.novartis.com

From: Gutman, Nina
Sent: Tuesday, January 21, 2014 9:58 AM

To: 'Kevin.Wright@fda.hhs.gov'
Subject: RE: IND 109272/NDA 205755 - Proprietary name submission

Hi Dr. Wright,

I am writing to confirm Novartis availability for a teleconference on Monday, 27-Jan-2014 at 10 AM.

Best regards,
Nina

Nina Gutman, Pharm.D.
Senior Associate Director, Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation
One Health Plaza, 315/5450A
East Hanover, NJ 07936
USA

Cell + [REDACTED] (b) (6)
Phone +1 862 778-1767
Fax +1 973 781-8265
nina.gutman@novartis.com
www.novartis.com

From: Wright, Kevin [<mailto:Kevin.Wright@fda.hhs.gov>]
Sent: Tuesday, January 21, 2014 9:53 AM
To: Gutman, Nina
Subject: RE: IND 109272/NDA 205755 - Proprietary name submission

Dr. Gutman,

Thank you for your help!

From: Gutman, Nina [<mailto:nina.gutman@novartis.com>]
Sent: Tuesday, January 21, 2014 9:50 AM
To: Wright, Kevin
Subject: RE: IND 109272/NDA 205755 - Proprietary name submission

Hi Dr. Wright,

I am still confirming availability for 27-Jan-2014. I understand that we will not have a call at 10 AM today.

Nina

Nina Gutman, Pharm.D.
Senior Associate Director, Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation
One Health Plaza, 315/5450A
East Hanover, NJ 07936
USA

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Phone +1 862 778-1767
Fax +1 973 781-8265
nina.gutman@novartis.com
www.novartis.com

From: Gutman, Nina
Sent: Tuesday, January 21, 2014 8:56 AM
To: 'Kevin.Wright@fda.hhs.gov'
Cc: 'Sue.Kang@fda.hhs.gov'
Subject: RE: IND 109272/NDA 205755 - Proprietary name submission

Hi Dr. Wright,

I am checking our availability for Monday, 27-Jan. I will follow-up as soon as possible this morning.

Best regards,
Nina

Nina Gutman, Pharm.D.
Senior Associate Director, Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation
One Health Plaza, 315/5450A
East Hanover, NJ 07936
USA

Cell + (b) (6)
Phone +1 862 778-1767
Fax +1 973 781-8265
nina.gutman@novartis.com
www.novartis.com

From: Wright, Kevin [<mailto:Kevin.Wright@fda.hhs.gov>]
Sent: Tuesday, January 21, 2014 8:53 AM
To: Gutman, Nina
Cc: Kang, Sue
Subject: RE: IND 109272/NDA 205755 - Proprietary name submission

Dr. Gutman,

Good morning. The Food and Drug Administration is closed today. The DMEPA review team would like to reschedule our t-conference for Monday (1/27) at 10 am.

From: Gutman, Nina [<mailto:nina.gutman@novartis.com>]
Sent: Tuesday, January 21, 2014 8:03 AM
To: Wright, Kevin
Subject: RE: IND 109272/NDA 205755 - Proprietary name submission

Hi Dr. Wright,

I hope that this email finds you well.

I am writing to confirm that our teleconference today is still going to happen (I ask because I am not sure if FDA is closed due to snow).

Also, please note that Anne Frederick will not be joining the call today.

Best regards,
Nina

Nina Gutman, Pharm.D.

Senior Associate Director, Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation
One Health Plaza, 315/5450A
East Hanover, NJ 07936
USA

Cell + (b) (6)
Phone +1 862 778-1767
Fax +1 973 781-8265
nina.gutman@novartis.com
www.novartis.com

From: Wright, Kevin [<mailto:Kevin.Wright@fda.hhs.gov>]
Sent: Thursday, January 16, 2014 10:02 AM
To: Gutman, Nina
Subject: RE: IND 109272/NDA 205755 - Proprietary name submission

Hi Dr. Gutman,

Thank you for the update.

From: Gutman, Nina [<mailto:nina.gutman@novartis.com>]
Sent: Thursday, January 16, 2014 10:00 AM
To: Wright, Kevin
Subject: RE: IND 109272/NDA 205755 - Proprietary name submission

Hi Dr. Wright,

Suman Shirodkar, MD, Global Brand Leader, will join us for the teleconference on 21-Jan-2014.

Best regards,
Nina

Nina Gutman, Pharm.D.

Senior Associate Director, Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation
One Health Plaza, 315/5450A
East Hanover, NJ 07936
USA

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Fax +1 973 781-8265
nina.gutman@novartis.com
www.novartis.com

From: Gutman, Nina
Sent: Wednesday, January 15, 2014 1:18 PM
To: 'Kevin.Wright@fda.hhs.gov'
Subject: RE: IND 109272/NDA 205755 - Proprietary name submission

Dear Dr. Wright,

I confirm that my team is available for a teleconference with DMEPA on Tuesday, 21-Jan-2014 from 10-10:30 AM.

The following individuals will attend the meeting:

- Margaret Dugan, MD, Senior Vice President, Global Program Head
- Dorothy Linvill-Neal, Global Head, Name Creation & Regulatory Strategy
- Sudipta Rao, Sr. Trademark Attorney
- Shanthy Ganeshan, PhD, Vice President, North America Region Head, Drug Regulatory Affairs
- Anne Frederick, PhD, Executive Director, Global Program Regulatory Director
- Nina Gutman, PharmD, Senior Associate Director, Drug Regulatory Affairs

You can use the following call-in information for the meeting:

United States (toll free): [REDACTED] (b) (4)

Passcode: [REDACTED] (b) (4)

Please let me know if you have any questions/concerns.

Best regards,

Nina

Nina Gutman, Pharm.D.

Senior Associate Director, Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation
One Health Plaza, 315/5450A
East Hanover, NJ 07936
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Cell + [REDACTED] (b) (6)

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Fax +1 973 781-8265

nina.gutman@novartis.com

www.novartis.com

From: Wright, Kevin [<mailto:Kevin.Wright@fda.hhs.gov>]

Sent: Wednesday, January 15, 2014 11:36 AM

To: Gutman, Nina

Subject: RE: IND 109272/NDA 205755 - Proprietary name submission

Dr. Gutman,

Unfortunately, I cannot share DMEPA's rationale for denying the proposed name.

From: Gutman, Nina [<mailto:nina.gutman@novartis.com>]

Sent: Wednesday, January 15, 2014 10:36 AM

To: Wright, Kevin

Subject: RE: IND 109272/NDA 205755 - Proprietary name submission

Dear Dr. Wright,

Thank you very much for your email. I will check my team's availability and will get back to you as soon as possible.

Would you be able to share with me the reason for why the proposed name is unacceptable?

Best regards,
Nina

Nina Gutman, Pharm.D.

Senior Associate Director, Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation
One Health Plaza, 315/5450A
East Hanover, NJ 07936
USA

Cell + [REDACTED] (b) (6)
Phone +1 862 778-1767
Fax +1 973 781-8265
nina.gutman@novartis.com
www.novartis.com

From: Wright, Kevin [<mailto:Kevin.Wright@fda.hhs.gov>]
Sent: Wednesday, January 15, 2014 10:09 AM
To: Gutman, Nina
Subject: RE: IND 109272/NDA 205755 - Proprietary name submission

Dr. Gutman,

Good morning. The DMEPA review team would like to schedule a 30 minute teleconference with you and your review team regarding your proprietary name submission under NDA 205755 Ceritinib.

Please let me know if you are available for this teleconference on Tuesday, January 21, 2014 from 10:00 - 10:30 AM (EST). Also, please provide me with call-in information and a list of attendees.

The agenda and FDA attendees are as follows:

Agenda

- 1) Introductions
- 2) Purpose of meeting - Discuss the proposed proprietary name, [REDACTED] (b) (4) FDA has concluded that your proposed name is unacceptable.
- 3) Regulatory Path Forward
- 4) Closing remarks

FDA Attendees

Alice Tu, Team Leader, Safety Evaluator, DMEPA
Otto Townsend, Safety Evaluator, DMEPA
Kevin Wright, Safety Regulatory Project Manager, OSE

From: Gutman, Nina [<mailto:nina.gutman@novartis.com>]
Sent: Tuesday, December 24, 2013 9:39 AM
To: Wright, Kevin
Subject: RE: IND 109272/NDA 205755 - Proprietary name submission

Dear Dr. Wright,

I am writing to inform you that the last part of the [REDACTED] (b) (4) (ceritinib, LDK378) NDA was submitted to FDA this morning (NDA 205755, Sequence No. 0002).

As you know, the proposed proprietary name, (b) (4) was originally submitted to FDA for review on 31-Oct-2013 (IND No. 109272, Serial No. 0242). This proposed name was resubmitted in Part 1 of the rolling NDA on 27-Nov-2013 (NDA No. 205755, Sequence No. 0000). At the time of resubmission of the proposed proprietary name, Novartis requested that the proprietary name review timelines be converted from IND (180 days) to NDA (90 days) timelines.

Can you please confirm that we should expect to hear back from FDA regarding the acceptability of the proposed name (b) (4) by 27-Feb-2014?

Thanks in advance and Happy Holidays!

Best regards,
Nina

Nina Gutman, Pharm.D.
Senior Associate Director, Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation
One Health Plaza, 315/5450A
East Hanover, NJ 07936
USA

Cell + (b) (6)
Phone +1 862 778-1767
Fax +1 973 781-8265
nina.gutman@novartis.com
www.novartis.com

From: Kang, Sue [<mailto:Sue.Kang@fda.hhs.gov>]
Sent: Tuesday, December 10, 2013 1:19 PM
To: Gutman, Nina
Cc: Wright, Kevin
Subject: RE: IND 109272/NDA 205755 - Proprietary name submission

Nina,

Thank you for this update. We will share this information with the DMEPA team reviewing your Request for Proprietary Name submission. I have cc'd Kevin Wright on this email. He will be your new point of contact regarding your proprietary name submission for IND 109272/ NDA 205755.

Kevin Wright, Pharm.D.
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
301-796-3621
kevin.wright@fda.hhs.gov

Kind regards,

Sue Kang
Team Leader, Project Management Staff
Office of Surveillance and Epidemiology

From: Gutman, Nina [<mailto:nina.gutman@novartis.com>]
Sent: Friday, December 06, 2013 2:07 PM
To: Kang, Sue
Subject: RE: IND 109272/NDA 205755 - Proprietary name submission

Dear Ms. Kang,

I am writing to let you know that the recommended INN for LDK378 is **ceritinib**. This INN will be released into the public domain by the WHO in the forthcoming list of recommended INNs. Please note that the Request for Proprietary Name review for (b) (4) which was originally submitted to IND 109,272 was resubmitted to NDA 205755 on 27-Nov as part of the rolling NDA.

Please let me know if you have any questions/concerns.

I hope you have a great weekend!

Best regards,
Nina

Nina Gutman, Pharm.D.
Senior Associate Director, Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation
One Health Plaza, 315/5450A
East Hanover, NJ 07936
USA

Cell + (b) (6)
Phone +1 862 778-1767
Fax +1 973 781-8265
nina.gutman@novartis.com
www.novartis.com

From: Kang, Sue [<mailto:Sue.Kang@fda.hhs.gov>]
Sent: Wednesday, November 13, 2013 7:38 AM
To: Gutman, Nina
Subject: RE: IND 109272 - Proprietary name submission

Nina,

The 90-day review time will start when you submit your Request for Proprietary Name review.

You do not have to have labels and labeling to submit a request for name review to the NDA, but you do need to ensure that you provide a complete submission based on the guidance at the link below.

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075068.pdf>

I hope this answers your questions below.

Kind regards,

Sue Kang

Team Leader, Project Management Staff
Office of Surveillance and Epidemiology

From: Gutman, Nina [<mailto:nina.gutman@novartis.com>]
Sent: Tuesday, November 12, 2013 2:34 PM
To: Kang, Sue
Subject: RE: IND 109272 - Proprietary name submission

Dear Ms. Kang,

Thank you very much for your email.

We were planning to resubmit the Request for Proprietary Name Review in late Nov/early Dec as part of the rolling NDA. Unfortunately, the proposed prescribing information and container label will not be available in time for this submission.

Will the 90-day review time start only after the proposed prescribing information and the proposed container label are submitted?

Best regards,
Nina

Nina Gutman, Pharm.D.
Senior Associate Director, Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation
One Health Plaza, 315/5450A
East Hanover, NJ 07936
USA

Cell + [REDACTED] (b) (6)
Phone +1 862 778-1767
Fax +1 973 781-8265
nina.gutman@novartis.com
www.novartis.com

From: Kang, Sue [<mailto:Sue.Kang@fda.hhs.gov>]
Sent: Tuesday, November 12, 2013 2:23 PM
To: Gutman, Nina
Subject: IND 109272 - Proprietary name submission

Dr. Gutman,

This email is to notify you that the Division of Medication Error Prevention and Analysis (DMEPA) received your Request for Proprietary Name review on 10/31/2013 for "LDK378" IND 109272. In your cover letter you request that the proprietary name review timelines be converted from IND (180 days) to NDA (90 days) timelines at the time of submission of the rolling NDA.

I would like to inform you that you will need to submit another Request for Proprietary Name review once you submit your NDA. Please make sure your Request for Proprietary Name review includes FDA Form 356h, and a cover letter stating "REQUEST FOR PROPRIETARY NAME" on the first page of the submission. Also, this submission should contain the proposed labels and labeling or a reference to the submission containing the labels and labeling.

If you have any questions or comments regarding this email, please contact me.

Kind regards,

Sue Kang
Team Leader, Project Management Staff
Office of Surveillance and Epidemiology

THIS MESSAGE IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PREDECISIONAL, PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER LAW.

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/s/

KEVIN WRIGHT
02/06/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: February 5, 2014
From: Karen Boyd, M.S., DOP2/OHOP/CDER
Subject: NDA 205755: Clinical Information Request

Dear Nina,

Please refer to your November 27, 2013, December 12, 2013, and December 24, 2013 rolling submission regarding New Drug Application (NDA) 205755. Please also refer to your amendment, received via the electronic gateway on February 5, 2014, containing 8 SAEs and 112 non-serious AEs that were omitted from the clinical database at the time of the ceritinib NDA.

Please also refer to your February 5, 2014, phone conversation with Ms. Karen Boyd and Dr. Sean Khozin regarding the clinical datasets. As discussed, please submit the Safety and Efficacy update including the datasets as soon as possible. If the full update is not available, please send the Safety Update for CLDK378X2101 (including the datasets) as soon as possible, followed by the complete submission by February 25, 2014. Expedited submission of the updates would minimize the impact of your February 5, 2014, amendment regarding the omitted safety information on FDA's review timelines.

In reference to your February 5, 2014, amendment containing communication on the omissions to the NDA 205755 safety database, we request that following be submitted as an amendment to the NDA by COB EST Monday, February 10, 2014:

1. Please submit a breakdown of the number of omitted adverse events by center name.
2. Please indicate if Novartis intends to amend the Clinical Study Report to account for these omissions.

If you have any questions, please don't hesitate to let me know.

Thanks,
Karen

Karen Boyd, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

KAREN C BOYD
02/05/2014

MEMORANDUM of TELECONFERENCE

MEETING DATE: February 4, 2014
TIME: 10:30-11:00 am (EST)
LOCATION: CDER WO 3302
APPLICATION: NDA 205755
DRUG NAME: (b) (4) (ceritinib)
TYPE OF MEETING: Teleconference

MEETING CHAIR: Alice Tu, Pharm.D.
MEETING RECORDER: Kevin Wright, Pharm.D.

FDA ATTENDEES:

Office of Surveillance and Epidemiology

Kevin Wright, Pharm.D., Safety Regulatory Project Manager

Office of Medication Error Prevention and Risk Management

Division of Medication Error Prevention and Analysis

Alice Tu, Pharm.D., Acting Team Leader, Safety Evaluator

Otto Townsend, Pharm.D., Safety Evaluator

SPONSOR ATTENDEES:

Suman Shirodkar, MD Global Brand Leader

Margaret Dugan, MD, Senior Vice President, Global Program Head

Dorothy Linvill-Neal, Global Head, Name Creation & Regulatory Strategy

Sudipta Rao, Sr. Trademark Attorney

Shanthi Ganeshan, PhD, Vice President, North America Region Head, Drug Regulatory Affairs

Anne Frederick, PhD, Executive Director, Global Program Regulatory Director

Nina Gutman, PharmD, Senior Associate Director, Drug Regulatory Affairs

BACKGROUND:

MEETING OBJECTIVE:

The Applicant requested this teleconference to discuss a path forward with a proprietary name submission under NDA 205755.

DISCUSSION:

- The Applicant began the teleconference by stating they understand the rationale for the DMEPA's denial of the proposed proprietary name, (b) (4) under IND 109272 and NDA 205755. The Applicant stated they have reviewed their process to identify viable proprietary names for the Agency's consideration. The Applicant also stated the proprietary name, (b) (4) was found acceptable by the (b) (4) and they would like to keep the US trademark as close to (b) (4) as possible.
- The Applicant stated they have conducted a preliminary assessment (orthographic, phonetic, and POCA) of two clone proprietary names, (b) (4) and (b) (4). The Applicant would like to get feedback from the Agency on which name to submit.

- The Agency stated at this time we cannot give you feedback on which name is more viable. We would need to conduct a preliminary assessment of each name before we are able to determine which name may be a more viable candidate. However, we recommended the Applicant to review the results of their analysis and determine which name is supported by the data. The Agency recommended the Applicant to submit data in support of the proprietary name.
- The Applicant stated they are considering two other proprietary names, Zykadia and (b) (4). The Applicant stated that (b) (4) was reviewed and conditionally approved by the Agency in November 2013 for (b) (4). The Applicant asked if they can submit (b) (4) as the proposed proprietary name to NDA 205755 considering the abbreviated timelines.
- The Agency stated that the proprietary name, (b) (4), can be submitted to this NDA since the name was never marketed but the Agency would get back to the Applicant on the logistics of the submission. We also pointed out to the Applicant that our determination on the acceptability of (b) (4) for this NDA (b) (4).
- At this point, the Agency clarified the Applicant's order of name preference for this NDA submission. The Applicant stated, at this point, their primary proposed proprietary name will be either (b) (4) or (b) (4) secondary alternate is Zykadia, and the third alternate is (b) (4). The Applicant asked how the timelines of their application approval would impact DMEPA's ability to review these three names. The Applicant asked if the Agency would conduct a full review of the three proposed proprietary names.
- The Agency stated due to limited resources, the priority would go to the primary proprietary name which would receive a full assessment. The alternate proprietary names would receive a preliminary analysis. Additionally, the Agency will expedite the review process in an effort to meet the application goal date. The Agency will also maintain open communication with the Applicant to facilitate a collaborative and expeditious review process.
- Call end at approximately 10:25 AM (EST).

ACTION ITEMS:

- The Agency will inform the Applicant on how to submit a proprietary name that was approved under a different application.
- The Applicant will submit a request for proprietary name review by next week. The request will list the proprietary names in order of preference.

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/s/

CHI-MING TU
02/05/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: January 31, 2014
From: Karen Boyd, M.S., DOP2/OHOP/CDER
Subject: NDA 205755: Communication to Sponsor

On January 30, 2014, RPM Karen Boyd communicated via telephone to Nina Gutman, sponsor-representative for NDA 205755, that FDA is looking to take an early action on NDA 205755. We have until August to review the application, but we hope to take an action as early as April 2014. Nina acknowledged my comment and appreciated the agency's transparency.

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/s/

KAREN C BOYD
01/31/2014

Boyd, Karen

From: Boyd, Karen
Sent: Friday, January 31, 2014 9:19 AM
To: 'Gutman, Nina'
Cc: Pierce, Melanie
Subject: NDA 205755: FDA initial edits to proposed labeling
Attachments: NDA_205755_FDA initial edits to proposed labeling_1_31_14.doc

Importance: High

Hi Nina,

Attached are FDA's initial edits to your proposed labeling for NDA 205755. Our changes are tracked and we also inserted some comments. Please respond to all of our comments in the label and use tracked changes to record any edits to the label. In areas of the label that you agree with FDA's proposed edits, please accept the tracked change to aid in reviewability.

Please send us back an updated tracked changes label in WORD format with the proposed changes incorporated by **COB EST Wednesday, February 19, 2014**. Please send me a courtesy copy via email, and then submit a formal amendment to the NDA.

If you have any questions, please let me know.

Please confirm receipt.

Thanks,
Karen

Karen Boyd, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
Email: Karen.Boyd@fda.hhs.gov
Phone: 301-796-7032
Fax: 301-796-9849

14 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

KAREN C BOYD
01/31/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: January 29, 2014
From: Karen Boyd, M.S., DOP2/OHOP/CDER
Subject: NDA 205755: Clinical Information Request

Dear Nina,

Please refer to your November 27, 2013, December 12, 2013, and December 24, 2013 rolling submission regarding New Drug Application (NDA) 205755.

Below is a clinical information request. Please formally submit your response to the NDA by **COB EST Wednesday, February 5, 2014.**

- For study LDK378X2101, format the following datasets to the current version of CDISC/Study Data Tabulation Model (SDTM) version 1.1, SDTM Implementation Guide (SDTMIG) version 3.1.1:

Demography = DMG
Concomitant medications = CMD
Adverse events = AEV
Relevant medical history conditions= CND
Laboratory results = LRS2
Vital signs = VSN

Please ensure that exposure and disposition data for study LDK378X2101 are provided in the requested CDISC/SDTM format.

If you have any questions regarding this information request, please don't hesitate to contact me.

Thanks,
Karen

Karen Boyd, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

KAREN C BOYD
01/29/2014

MEMORANDUM of TELECONFERENCE

MEETING DATE: January 27, 2014
TIME: 10:00-10:30 am (EST)
LOCATION: CDER WO 4440
APPLICATION: NDA 205755/IND 109272
DRUG NAME: (b) (4) (ceritinib)
TYPE OF MEETING: Teleconference

MEETING CHAIR: Chi-Ming (Alice) Tu, Pharm.D.
MEETING RECORDER: Kevin Wright, Pharm.D.

FDA ATTENDEES:

Office of Surveillance and Epidemiology

Kevin Wright, Pharm.D., Safety Regulatory Project Manager
Sue Kang, MS, Team Leader, Safety Regulatory Project Manager

Office of Medication Error Prevention and Risk Management

Division of Medication Error Prevention and Analysis

Alice Tu, Pharm.D., Acting Team Leader
Otto Townsend, Pharm.D., Safety Evaluator

SPONSOR ATTENDEES:

Suman Shirodkar, MD Global Brand Leader
Margaret Dugan, MD, Senior Vice President, Global Program Head
Dorothy Linvill-Neal, Global Head, Name Creation & Regulatory Strategy
Sudipta Rao, Sr. Trademark Attorney
Shanthi Ganeshan, PhD, Vice President, North America Region Head, Drug Regulatory Affairs
Anne Frederick, PhD, Executive Director, Global Program Regulatory Director
Nina Gutman, PharmD, Senior Associate Director, Drug Regulatory Affairs

BACKGROUND:

On March 6, 2013, under IND 109272 the Agency granted breakthrough designation therapy to ceritinib for treatment of patients with (b) (4) metastatic non-small cell lung cancer who have (b) (4).

On October 31, 2013, the Applicant submitted a request for proprietary name review for (b) (4) under IND 109272.

On November 27, 2013, in the original submission for NDA 205755, the Applicant requested review of the proprietary name, (b) (4) for Ceritinib.

MEETING OBJECTIVE:

FDA requested this teleconference to notify the applicant of our concerns with their proposed proprietary name, (b) (4).

DISCUSSION:

- The Agency began the teleconference by stating they completed their preliminary review of the name and found it unacceptable because the proposed proprietary name shares phonetic similarity to (b) (4). The proposed proprietary name, (b) (4) was interpreted in the Prescription Simulation Study as (b) (4).
- The applicant asked the Agency if this error was an actual error or cited as a potential error. Also, the applicant inquired if the Agency conducted a Failure Mode Effects Analysis (FMEA) between the name pair. The Agency replied that (b) (4) was not cited as a potential error but instead a participant actually interpreted the tested name (b) (4) as the existing drug product name (b) (4) in the verbal simulation study. The Agency clarified that they did perform a FMEA, however, our post-marketing experience shows that names with significant phonetic and orthographic similarities are often confused despite differences in product characteristics. Examples of highly similar name pairs where errors occurred are “Cerebyx and Celebrex”, “Advair and Advicor”, and “(b) (4) and Durezol”.
- At this point, the Agency recommended the applicant to withdraw their proposed proprietary name, (b) (4) by close of business Wednesday, January 29, 2014 and submit a new “Request for New Proprietary Name” as soon as possible.
- The applicant understood the recommendation and informed the Agency that they will need to discuss with their management before responding by Wednesday.
- The applicant asked the Agency if we would consider a “clone name” as an alternate proposed proprietary name. For example, if the applicant submitted “(b) (4)” as a proposed proprietary name, would this “clone” be a more viable candidate. The Agency replied that it would be a review issue and we cannot predict whether (b) (4) would lead to name confusion without conducting a prescription simulation study. However, our preliminary thoughts are the beginning of the names “(b) (4) and (b) (4)” still sound similar. More specifically, the first syllables, (b) (4) are both alveolar, affricate phonemes.
- The applicant asked if they could submit a list of potential proprietary names to the Agency in order to conduct a preliminary review prior to submitting another proprietary name officially to their pending NDA. The Agency stated typically our review process provides you the option to submit a primary name and an alternate name. However, we recognize that the Agency has granted your application “Breakthrough Therapy Designation” therefore you may submit up to three names for a preliminary assessment.
- Call ended approximately 10:20 AM (EST).

ACTION ITEMS:

- The applicant will provide the Agency with a list of three potential names for preliminary review.
- The applicant must inform the Agency by close of business Wednesday, January 29, 2014 if they plan on withdrawing their proposed proprietary name, (b) (4).

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/s/

CHI-MING TU
01/29/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: January 22, 2014
From: Karen Boyd, M.S., DOP2/OHOP/CDER
Subject: NDA 205755: CMC Microbiology Information Request

Dear Nina,

Please refer to your November 27, 2013, December 12, 2013, and December 24, 2013 rolling submissions regarding New Drug Application (NDA) 205755.

Please respond to the following CMC microbiology information request via email to Karen Boyd (karen.boyd@fda.hhs.gov) by **COB EST Wednesday, February 19, 2014**, followed by a formal submission to your NDA.

You propose to perform (b) (4) for the Microbial Limits test for drug product release. (b) (4) for drug products (b) (4) by regulation (21 CFR 211.165 (a) and (b).) If a drug product release specification includes tests and acceptance criteria for a given attribute, then the test must be performed (b) (4). However, microbial limits testing may be omitted from the product release specification provided adequate (b) (4) are established and documented. If you wish to omit the microbial limits specification, more information on your process is needed. Address the following points:

1. Identify and justify critical control points in the manufacturing process that could affect microbial load of the drug product.
2. Describe microbiological monitoring and acceptance criteria for the critical control points that you have identified. Verify the suitability of your testing methods for your drug product. Conformance to the acceptance criteria established for each critical control point should be documented in the batch record in accordance with 21 CFR 211.188.
3. Describe activities taken when microbiological acceptance criteria are not met at control points.

In addition to these points, address the following:

4. You should minimally perform microbial limits testing at the initial stability testing time point. Provide an updated stability schedule to reflect this testing.
5. In the absence of historical data, you should perform quarterly microbial limits testing on stability batches for the first year of stability. Following the first year, testing may be performed annually.

If you choose to omit microbial limits testing for release, then remove the microbial limits tests and acceptance criteria from the drug product release specification. Alternatively, you may retain a microbial limits specification for product release, but testing must be performed on (b) (4)

(b) (4) drug product produced.

Please submit a revised drug product release specification for whichever microbial limits testing alternative that you select.

If you have any questions regarding this information request, please don't hesitate to contact me.

Thanks,
Karen

Karen Boyd, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

KAREN C BOYD
01/22/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: January 22, 2014
From: Karen Boyd, M.S., DOP2/OHOP/CDER
Subject: NDA 205755: Clinical Information Request

Dear Nina,

Please refer to your November 27, 2013, December 12, 2013, and December 24, 2013 rolling submissions regarding New Drug Application (NDA) 205755.

Please respond to the following clinical information request via email to Karen Boyd (karen.boyd@fda.hhs.gov) by **COB EST Monday, January 27, 2014**, followed by a formal submission to your NDA.

- Submit an amendment to your Financial Disclosure Certification confirming that Novartis acted with due diligence to obtain financial disclosure information but was unable to do so for all the investigators in Study CLDK378X2101 and state the reason(s) why 5 out of 127 financial disclosures were not collected.

Thanks,
Karen

Karen Boyd, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

KAREN C BOYD
01/22/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: January 17, 2014
From: Karen Boyd, M.S., DOP2/OHOP/CDER
Subject: NDA 205755: Clinical Pharmacology Information Request

Dear Nina,

Please refer to your December 24, 2013 submission regarding New Drug Application (NDA) 205755.

Please respond to the clinical pharmacology question stated below via email to Karen Boyd (karen.boyd@fda.hhs.gov) by **COB EST Friday, January 24, 2014**, followed by a formal submission to your NDA.

1. Please submit a study report for your PBPK simulations using SimCYP software to predict the effect of ketoconazole and rifampin on the pharmacokinetics (PK) of ceritinib after multiple dosing [reference studies LDK378A2104 and LDK378A2106].

The study report should include the purpose of the simulations, assumptions being made, detailed process of PBPK model building and verification, a summary of model input parameters of ceritinib, version of SimCYP being used, simulation results, and conclusions. The parameters can be compiled in the table format with parameter name, parameter values (mean and/or variability), source of the parameter values and assumptions being made. In addition, any modification of the default values of the system and/or drug parameter input of a particular version of the software should be declared and justified.

Specifically for ceritinib, we recommend you construct your PBPK model by considering time-dependent inhibition of CYP3A4. The model should be optimized in order to delineate the nonlinear PK observed in ALK-positive cancer patients ([study LDK378X2101], [study LDK378X1101]) and single dose PK in healthy subjects ([Study LDK378A2101], [Study LDK378A2104], [Study LDK378A2105] and [Study LDK378A2106]). Next, the model should be independently verified by comparing simulated effect of enzyme inhibitor or inducer on ceritinib PK with that observed from drug interaction studies (LDK378A2104 and LDK378A2106 for the effect of ketoconazole and rifampin, respectively). In addition, any modification of the model after verification step should be justified. You should use your final ceritinib model to simulate the scenarios described below:

- a. 750 mg once daily (QD) ceritinib at steady state in the presence of a strong CYP3A4 inhibitor (ketoconazole 200 mg twice daily, BID).
- b. 750 mg QD ceritinib at steady state in the presence of a strong CYP3A4 inducer (rifampin 600 mg QD).

In addition, please use your final ceritinib model to simulate the following scenarios:

- c. 750 mg QD ceritinib at steady state in the presence of a moderate CYP3A4 inhibitor (fluconazole 200 mg QD).
- d. 750 mg QD ceritinib at steady state in patients with mild, moderate and severe hepatic impairment.
- e. Effect of 750 mg ceritinib at steady state on the PK of midazolam after a single oral dose (5 mg) and the effect of a single dose of 750 mg ceritinib on the PK of midazolam after a single oral dose (5 mg) when midazolam is administered with ceritinib.

Please provide the model files used to generate the final PBPK simulations (e.g. drug model files, population files, and workspace files, .cmp, .lbr, and .wks). These files should be executable by the FDA reviewers using Simcyp. Software specific excel files such as parameter estimation data files and simulation outputs should be submitted as MS Excel files. Study report(s) should be provided as PDF files (screenshots can be incorporated if required).

If you have any questions, please let me know.

Thanks,
Karen

Karen Boyd, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

KAREN C BOYD
01/17/2014



NDA 205755

NDA ACKNOWLEDGMENT

Novartis Pharmaceuticals Corporation
Attention: Yanina Gutman, Pharm.D.
Senior Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936

Dear Dr. Gutman:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: (b) (4) (ceritinib) capsules, 150 mg

Date of Application: December 24, 2013

Date of Receipt: December 24, 2013

Our Reference Number: NDA 205755

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 22, 2014, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Products 2
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

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, call me at (301) 796-7032.

Sincerely,

{See appended electronic signature page}

Karen Boyd, M.S.
Senior Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

KAREN C BOYD
01/06/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: January 3, 2014
From: Karen Boyd, M.S., DOP2/OHOP/CDER
Subject: NDA 205755: Clinical Pharmacology Information Request

Dear Nina,

In reference to your NDA 205755 received December 24, 2013, please fill out the attached clinical pharmacology form and send it back to me via email by COB EST on Wednesday, January 8, 2013. Please then follow with a formal submission to your NDA.

Thanks,
Karen

Karen Boyd, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
Email: Karen.Boyd@fda.hhs.gov
Phone: 301-796-7032
Fax: 301-796-9849

Highlights of Clinical Pharmacology

Therapeutic dose	Include 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) Cmax and AUC
	Multiple Dose	Mean (%CV) Cmax 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)
	Tmax	<ul style="list-style-type: none"> • Median (range) for parent • Median (range) for metabolites
Distribution	Vd/F or Vd	Mean (%CV)
	% bound	Mean (%CV)
Elimination	Route	<ul style="list-style-type: none"> • Primary route; percent dose eliminated • Other routes
	Terminal t _{1/2}	<ul style="list-style-type: none"> • Mean (%CV) for parent • Mean (%CV) for metabolites
	CL/F or CL	Mean (%CV)
Intrinsic Factors	Age	Specify mean changes in Cmax and AUC
	Sex	Specify mean changes in Cmax and AUC
	Race	Specify mean changes in Cmax and AUC
	Hepatic & Renal Impairment	Specify mean changes in Cmax and AUC
Extrinsic Factors	Drug interactions	Include listing of studied DDI studies with mean changes in Cmax and AUC
	Food Effects	Specify mean changes in Cmax and AUC and meal type (i.e., high-fat, standard, low-fat)
Expected High Clinical	Describe worst case scenario and expected fold-change in Cmax and	

Exposure Scenario	AUC. The increase in exposure should be covered by the supra-therapeutic dose.
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KAREN C BOYD
01/03/2014



NDA 205755

ACKNOWLEDGE NDA PRESUBMISSION

Novartis Pharmaceuticals Corporation
Attention: Yanina Gutman, Pharm.D.
Senior Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936

Dear Dr. Gutman:

We have received the second section of your New Drug Application (NDA) under the program for step-wise submission of sections of an NDA (section 506 of the Federal Food, Drug, and Cosmetic Act) for the following:

Name of Drug Product: (b) (4) (ceritinib) capsules, 150 mg

Date of Submission: December 12, 2013

Date of Receipt: December 12, 2013

Our Reference Number: NDA 205755

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 NDA 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 Oncology Products 2
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, call me at (301) 796-7032.

Sincerely,

{See appended electronic signature page}

Karen Boyd, M.S.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

KAREN C BOYD
12/20/2013



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 109272

MEETING MINUTES

Novartis Pharmaceuticals, Corporation
Attention: Yanina Gutman, PharmD
Senior Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Gutman:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for "LDK378."

We also refer to the meeting between representatives of your firm and the FDA on November 22, 2013. The purpose of the meeting was to discuss the content of the NDA and content and format of the Safety and Efficacy Update.

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, call Melanie Pierce at (301) 796-1273.

Sincerely,

{See appended electronic signature page}

Melanie Pierce
Senior Regulatory Health Project Manager
Division of Oncology Products 2
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: November 22, 2013; 10:00 AM
Meeting Location: CDER WO Bldg 22; room 1309

Application Number: IND 109272
Product Name: LDK378
Indication: Treatment of patients with [REDACTED] (b) (4) metastatic non-
small cell lung cancer (NSCLC) who have [REDACTED] (b) (4)
[REDACTED] (b) (4) crizotinib

Sponsor/Applicant Name: Novartis Pharmaceuticals

Meeting Chair: Gideon Blumenthal
Meeting Recorder: Melanie Pierce

Office of Hematology Oncology Products

Jonathan Jarow Acting Associate Director

Office of Hematology Oncology Products

Division of Oncology Products 2

Patricia Keegan, MD Director
Gideon Blumenthal, MD Clinical Team Leader
Sean Khozin, MD Clinical Reviewer
Melanie Pierce, BSc Project Manager

Office of Hematology Oncology Products

Division of Hematology Oncology Toxicology

Whitney Helms, PhD Pharmacology/Toxicology Supervisor

Office of Clinical Pharmacology V

Hong Zhao, PhD Clinical Pharmacology Team Leader
Ruby Leong, PhD Clinical Pharmacology Reviewer
Rosane Charlab Orbach Genomics Reviewer
Christian Grimstein Genomics Reviewer

Meeting Minutes
Type B-Pre-NDA**Office of Biostatistics****Division of Biostatistics V**

Shanghai Tang, PhD

Somesh Chattopadhyay, PhD

Statistical Team Leader

Statistical Reviewer

Office of New Drugs Quality Assessment

Liang Zhou, PhD

Quality Team Leader

Office of Scientific Investigations

Lauren Iacono-Connor

OSI Investigator

NOVARTIS ATTENDEES

Margaret Dugan, MD,

Miguel Izquierdo, MD, PhD,

Andrew Joe, MD,

Anthony Boral, MD, PhD,

Alicia Rossiter, MD,

Senior VP Global Program Head

Senior Global Clinical Program Head

Senior Global Clinical Leader

Executive Director Clinical Research Physician

Executive Director, Group Head Integrated Medical
Safety

Margarida Geraldes, PhD,

Yi-Yang (Yvonne) Lau, PhD,

Lucine Karjian,

Director, Biostatistics

Senior Fellow Oncology Clinical Pharmacology

Director, Global Regulatory Chemistry

Manufacturing and Controls (CMC)

Luigi Catanzariti, PhD,

Executive Director, Novartis Companion

Diagnostics

Mirna DiPano,

Senior Associate Director, Companion Diagnostics

Regulatory Affairs

Ken Culver, MD,

Director, Clinical Research Physician, US Clinical

Development and Medical Affairs

Gabriela Gruia, MD,

Senior VP and Global Head, Drug Regulatory

Affairs and Oncology Submissions Management

Shanthi Ganeshan, PhD, VP,

North America Region Head, Drug Regulatory

Affairs

Anne Frederick, PhD,

Executive Director, Global Program Regulatory

Director

Nina Gutman, PharmD,

Senior Associate Director, Drug Regulatory Affairs

Meeting Minutes
Type B-Pre-NDA

BACKGROUND

Regulatory Background:

On November 20, 2012, an End-of-Phase 1/Pre-Phase 3 meeting was held with the FDA to discuss the ongoing phase I study (CLDK378X2101), the proposed phase III study (CLDK378A2303, in ALK-positive NSCLC patients previously treated with chemotherapy and crizotinib), and the proposed clinical pharmacology program for LDK378.

On March 6, 2013, Breakthrough Therapy Designation was granted for LDK378 for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) that is ALK-positive as detected by an FDA-approved test and which has progressed during treatment with crizotinib or where patients are intolerant to crizotinib.

On May 13, 2013, preliminary comments were issued to Novartis in response to Novartis' March 18, 2013 meeting request to obtain FDA guidance on drug substance starting materials and drug substance and drug product stability data for the NDA submission for the treatment of patients with (b) (4) metastatic non-small cell lung cancer (NSCLC) who have (b) (4) (b) (4) crizotinib. After receipt of FDA's comments, Novartis elected to cancel the meeting.

On May 15, 2013, an End-of-Phase 2 meeting was held to discuss the clinical development program of LDK378 in previously untreated patients with (b) (4) metastatic non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive. The protocols discussed during the meeting was Protocol CLDK378A2301, an open-label, randomized, active-controlled, multi-center, active-controlled, phase III trial in 348 previously untreated adult patients with ALK-positive, stage IIIB or IV, non-squamous NSCLC (b) (4)

On May 20, 2013, FDA issued Written Responses to Novartis in response to Novartis' February 22, 2013 meeting request. The purpose of the meeting was to discuss the content and format of the NDA submission for LDK378 in the treatment of patients with (b) (4) metastatic non-small cell lung cancer (NSCLC) who have (b) (4) crizotinib.

In the briefing package, Novartis stated that the NDA submission will be based on Study CLDK378X2101, entitled "A phase I, multicenter, open-label dose escalation study of LDK378, administered orally in adult patients with tumors characterized by genetic abnormalities in anaplastic lymphoma kinase" and a phase 1 Japanese study, CLDK378X1101. CLDK378X2101 is a first-in-human, open-label study investigating the safety and anti-tumor activity of LDK378 in patients with tumors confirmed to have genetic abnormalities in ALK.

CLDK378X2101 is a first-in-human, open-label study investigating the safety and anti-tumor activity of LDK378 in patients with tumors confirmed to have genetic abnormalities in ALK.

Meeting Minutes
Type B-Pre-NDA

There are two phases of the study, an escalation phase and an expansion phase. The expansion phase started after the MTD/RDE had been estimated. There are 4 arms in which enrollment occurred in parallel. Arm 1A, Arm 1B and Arm 2 would each enroll up to 100 patients, and Arm 3 would enroll approximately 10 patients.

- (Arm 1A) Patients with ALK-translocated NSCLC who had disease progression during treatment or within 2 weeks of the last dose of an ALK inhibitor and planned initiation of LDK378 within 60 days of the last dose of the prior ALK inhibitor,
- (Arm 1B) Patients with ALK-translocated NSCLC who were previously treated with an ALK inhibitor and do not meet the criteria for Arm 1A, above.
- (Arm 2) Patients with ALK-translocated NSCLC not previously treated with an ALK inhibitor, and
- (Arm 3) Patients with tumors other than NSCLC with genetic abnormalities in ALK

Patients may continue treatment with LDK378 until the patient experiences unacceptable toxicity that precludes any further treatment, disease progression, and/or treatment is discontinued at the discretion of the investigator or by patient request.

Tumor response evaluations were determined by the local investigators, based on RECIST version 1.0. Additionally, tumor response evaluations would undergo blinded central review.

The Efficacy Analysis Set (EAS) will be the primary data set used (data cutoff date August 2, 2013) for the analysis of tumor response data (ORR, DOR, and PFS based on investigator assessments) and for the analysis of OS. This dataset is a subset of the FAS and consists of patients who received the first dose of LDK378 at least 18 weeks prior to the analysis cutoff date.

The Central Efficacy Analysis Set (CEAS) will be used for the analysis of tumor response data based on independent central review assessments. This data set is a subset of the EAS and consists of patients

- who received the first dose of LDK378 at least 18 weeks prior to the analysis cutoff date, and
- for whom EITHER the baseline scan and at least one post-baseline scan are available and can be evaluated by the Blinded Independent Review Committee (BIRC) OR no post-baseline scan was performed in the study due to early death or discontinuation.

Novartis plans to present the primary efficacy results for patients at the RD of 750 mg/day as follows:

- Prior ALK inhibitor therapy (Arms 1A and 1B combined)

- Disease progression during treatment with last prior ALK inhibitor therapy (or within 2 weeks of last dose)
- No disease progression during treatment with (or within 2 weeks of last dose of) last prior ALK inhibitor therapy
- ALK inhibitor therapy naïve (Arm 2)
- All NSCLC

Summary of ORR based on investigator assessment in the EAS population is shown in Table 1.

Table 1. Summary of best overall response based on Investigator assessment in ALK-positive NSCLC patients from the 750 mg/day treatment dose group, by prior ALK inhibitor status based on data cutoff date of August 2, 2013 (EAS – NSCLC 750 mg)

	NSCLC with prior ALK inhibitor			NSCLC ALK inhibitor naïve patients	All NSCLC patients ^(a)
	All patients with prior ALK inhibitor	Patients with PD during last prior ALK inhibitor ^(b)	Patients without PD during last prior ALK inhibitor ^(c)		
	N=121	N=110	N=11	N=59	N=180
Best overall response, n (%)					
Complete response (CR)	2 (1.7)	2 (1.8)	0 (0.0)	1 (1.7)	3 (1.7)
Partial response (PR)	65 (53.7)	61 (55.5)	4 (36.4)	40 (67.8)	105 (58.3)
Stable disease (SD)	23 (19.0)	22 (20.0)	1 (9.1)	13 (22.0)	36 (20.0)
Progressive disease (PD)	13 (10.7)	12 (10.9)	1 (9.1)	0 (0.0)	13 (7.2)
Unknown	18 (14.9)	13 (11.8)	5 (45.5)	5 (8.5)	23 (12.8)
Overall response rate (ORR) (CR or PR), n (%)	67 (55.4)	63 (57.3)	4 (36.4)	41 (69.5)	108 (60.0)
95% CI	(46.1-64.4)	(47.5-66.7)	(12.9-69.2)	(56.1-80.8)	(52.4-67.2)

^(a)This table presents data for patients with ALK-positive NSCLC in the 750 mg/day treatment dose group who received the first dose of LDK378 at least 18 weeks prior to the analysis cut-off date, EAS-NSCLC 750 mg group.

^(b) Patients who had PD during treatment with last prior ALK inhibitor therapy (or within 2 weeks of last dose).

^(c) Patients who did not have PD during treatment with last prior ALK inhibitor therapy (or within 2 weeks of last dose).

^(d) All patients includes ALK-positive NSCLC patients treated with LDK378 750 mg/day.

Best overall response is based on investigator's assessment of disease status using RECIST 1.0 criteria.

CR and PR are confirmed by repeat assessments performed not less than 4 weeks after the criteria for response are first met.

Exact binomial 95% Confidence Interval

The most common adverse events (n = 246), incidence ≥ 25% in ALK-positive NSCLC patients were diarrhea (83.7%), nausea (77.6%), vomiting (56.1%), alanine aminotransferase (ALT) increased (36.6%), fatigue (35.8%), abdominal pain (31.7%), decreased appetite (31.7%), and aspartate aminotransferase (AST) increased (26.8%). The most common grade 3/4 adverse events (incidence ≥ 4%) in ALK-positive NSCLC patients were ALT increased (21.5%), AST increased (7.7%), hyperglycemia (5.3%), lipase increased (5.3%), diarrhea (5.3%), blood alkaline phosphatase increased (4.5%), pneumonia (4.5%), nausea (4.1%), and fatigue (4.1%). Novartis plans to submit an NDA in late Dec-2013 to seek Accelerated Approval for LDK378 for the treatment of patients with (b) (4) metastatic NSCLC who have (b) (4)

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AVAILABLE
COPY

Sponsor Submitted Questions and FDA Response:

1. 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: Yes, FDA agrees with the content of the NDA as outlined in the proposed eCTD table of contents.

Discussion during the meeting: Novartis acknowledged FDA's responses and there was no discussion during the meeting.

2. Does the Agency agree that the data from the registration Study X2101 are adequate to substantiate the efficacy and safety of LDK378 and that the robust results of this study support filing these data in support of the proposed indication?

FDA Response: Yes, FDA agrees that data from X2101 and the supportive studies appear to be adequate to allow a substantive benefit-risk evaluation of LDK378 in Novartis' proposed NDA. The final indication will be assessed by examining the submitted data in a benefit-risk analysis at the time of review.

Discussion during the meeting: Novartis acknowledged FDA's responses and there was no discussion during the meeting

3. Does the Agency agree with the proposed timelines for submission of the NDA documents?

FDA Response: Since data presented in the current meeting package confirm that Novartis' clinical development program for LDK378 in NSCLC continues to meet the criteria for Breakthrough Therapy designation, FDA generally agrees with the proposed timelines for submission of the NDA documents. However, Novartis should submit the labeling documents at the time of the original NDA submission in late November 2013/early December 2013. The initial labeling documents do not need to be in the structured product labeling (SPL) format. Novartis should submit the labeling documents in the SPL format no later than 30 days after the last component of the original NDA submission. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). Please also see FDA's response to question 8.

Novartis' Response submitted via email on 11.21.13: Novartis plans to submit the following to FDA as part of the rolling NDA in late Nov-2013:

- Module 1
 - Section 1.1.2: Application form: FDA form 356h

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- Section 1.1.3: User fee cover sheet: FDA form 3397, orphan drug designation
- Section 1.2: Cover letter, FDA form 3674
- Section 1.12.4: Request for comments and advice
- Section 1.12.14: Environmental analysis
- Module 2
 - Section 2.6.2: Pharmacology Written Summary
 - Section 2.6.3: Pharmacology Tabulated Summary
- Module 4
 - All Module 4 documents with the exception of three embryo-fetal development reports which will be submitted in late Dec-2013
- Module 5
 - Section 5.3.2.2: Reports of hepatic metabolism and drug interaction studies

Novartis will submit the labeling documents with the last piece of the rolling NDA (summary documents [Module 2] and clinical study reports [Module 5]) in late Dec-2013 as finalization of the label requires information contained in these modules of the NDA.

Novartis will submit the labeling in SPL format within 30 days of the original NDA submission.

Discussion during the meeting: Novartis stated that they plan to submit the first part of the NDA the week of November 25, 2013 and the second (and final) part will be submitted in late December. In addition, Novartis expressed understanding that labeling in SPL format can be submitted within 30 days of the final component of the NDA. See agreements reached.

4. Novartis believes that this application is exempt from a user fee as LDK378 has been granted an orphan drug designation *'for the treatment of patients with NSCLC that is ALK-positive'*.

Does the Agency agree that a user fee waiver will be accepted?

FDA Response: Yes, FDA agrees that a user fee waiver will be accepted. Novartis should notify FDA that it is claiming the orphan exemption when it completes and submits the User Fee Coversheet, Form FDA 3397, which should be included in the NDA with a brief statement claiming the orphan exception in the cover letter.

Discussion during the meeting: Novartis acknowledged FDA's responses and there was no discussion during the meeting.

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5. Does the Agency agree to grant a waiver for pediatric studies in this application?

FDA Response: FDA acknowledges that Novartis does not intend to conduct studies in pediatric subjects with lung cancer. Because this drug product for this indication has an orphan drug designation, you are exempt from the requirements of the Pediatric Research Equity Act.

Discussion during the meeting: Novartis acknowledged FDA's responses and there was no discussion during the meeting.

6. In the Type C written feedback issued by FDA on 20-May-2013, FDA noted that the primary analysis for registration Study X2101 should be based on the Full Analysis Set (FAS; this data set consists of all patients who received at least one full or partial dose of LDK378). In the response to FDA dated 10-Jun-2013 (Serial No. 0119), Novartis provided a rationale for basing the primary efficacy analysis on the EAS which is a subset of the FAS and consists of ALK-positive NSCLC patients who received the first dose of LDK378 at least 18 weeks prior to the analysis cut-off date. In the amended Type C written feedback issued by FDA on 18-Jul-2013, FDA recommended further discussion on this topic during the pre-NDA meeting when more data are available.

Does the Agency agree that the primary analysis of tumor response (ORR per Investigator assessment and DOR per Investigator assessment) will be based on the ALK-positive NSCLC patients in the 750 mg/day treatment dose group who were previously treated with an ALK inhibitor and who received their first dose of LDK378 at least 18 weeks prior to the analysis cut-off date?

FDA Response: FDA reiterates its previous response from the July 18, 2013 meeting. The primary analysis should best be based on full analysis set (FAS), consisting of all patients who receive at least one full or partial dose of LDK378. Results from the efficacy analysis set (EAS) should be submitted as supportive evidence. FDA will take into account Novartis' concerns regarding the lack of sufficient follow up and limited data on the duration of response with the FAS at the time of NDA review.

Novartis should also perform a concordance analysis of tumor response between investigator and Blinded Independent Review Committee (BIRC) tumor assessments.

Novartis' Response submitted via email on 11.21.13:

Primary analysis set:

Novartis will provide the efficacy results based on the Full Analysis Set (FAS, ALK-positive NSCLC patients who received at least one dose of LDK378 regardless of length of follow-up) and the Efficacy Analysis Set (EAS, ALK-positive NSCLC patients

who received their first dose of LDK378 at least 18 weeks prior to the analysis cut-off date).

As described in the protocol for Study X2101, Novartis has conducted the primary analyses of anti-tumor activity of LDK378 based on ORR and DOR per Investigator assessment for the EAS. The rationale for performing the analyses on this patient population was that it allowed sufficient follow-up time for tumor assessments and confirmation of response for the ORR calculation since tumor assessments are conducted every 6 weeks (Study X2101 protocol, Section 9).

Assessing the anti-tumor activity of LDK378 based on FAS provides a biased assessment since the ORR assessment then heavily depends on the accrual rate. For this reason Novartis considers the EAS to be the appropriate primary analysis set for assessment of efficacy.

At the time of the original submission, the EAS will contain 180 ALK-positive NSCLC patients in the 750 mg dose group. However, at the time of the Efficacy Update, the EAS will include 52 more ALK-positive NSCLC patients (232) in the 750 mg dose group with appropriate follow-up.

Novartis believes that the efficacy results based on the FAS are supportive of those observed for the primary analysis set (EAS).

Analysis of concordance between Investigator and BIRC assessment of overall response

Novartis has performed a concordance analysis of best overall response between Investigator and BIRC assessments (Table 2-1). A description of the discordances will be included in the clinical study report.

Table -2 Best overall response assessed by Investigator versus BIRC (CEAS)

	Investigator BOR results		Central radiology review BOR results				
			CR n (%)	PR n (%)	SD n (%)	PD n (%)	Unknown n (%)
NSCLC LDK378 750 mg (N=177)	CR (n=3)	[1]	0	3 (100)	0	0	0
		[2]	0	3 (3.4)	0	0	0
	PR (n=104)	[1]	1 (1.0)	75 (72.1)	16 (15.4)	10 (9.6)	2 (1.9)
		[2]	1 (100)	75 (84.3)	16 (41.0)	10 (35.7)	2 (10.0)
	SD (n=35)	[1]	0	11 (31.4)	20 (57.1)	4 (11.4)	0
		[2]		11 (12.4)	20 (51.3)	4 (14.3)	0
	PD (n=12)	[1]	0	0	1 (8.3)	9 (75.0)	2 (16.7)
		[2]	0	0	1 (2.6)	9 (32.1)	2 (10.0)
	Unknown (n=23)	[1]	0	0	2 (8.7)	5 (21.7)	16 (69.6)

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	[2]	0	0	2 (5.1)	5 (17.9)	16 (80.0)
Total		1	89	39	28	20

N: The total number of patients in Central efficacy analysis set.

n: Number of patients who are at the corresponding category

CR: complete response, PR: partial response, SD: stable disease; PD: progressive disease

^[1] row percent rates are calculated as the number of patients in the corresponding cell (e.g. CR/CR) divided by the total number of patients corresponding to that particular row as per investigator assessment (e.g. all patients with investigator BOR result = CR)

^[2] column percent rates are calculated as the number of patients in the corresponding cell (e.g. CR/CR) divided by the total number of patients corresponding to that particular column as per central radiology review (e.g. all patients with central radiology review BOR result = CR)

The 32% discordance of best overall response between Investigator and BIRC is in the range of what has been published in the literature (Ford 2009).

Discussion during the meeting: FDA finds Novartis' proposal inconsistent with FDA's approach, which will be to conduct the primary analyses of ORR in the full analysis set supported by the EAS results. FDA acknowledges Novartis' concerns that the primary analysis is affected by accrual rates. The efficacy update may mitigate these concerns. Novartis stated that the efficacy update will include investigator-determined and IRC-determined response. FDA agreed to review all of the available data including investigator- and IRC-determined ORR in the FAS and EAS in order to arrive at a decision regarding approval; FDA stated that the exact data that will be included in the label will be a review decision.

Novartis agreed to provide the analysis of concordance between the IRC- and investigator-determined responses.

7. Novartis believes that the risks associated with treatment with LDK378 can be managed adequately with appropriate labeling and routine pharmacovigilance activities. Does the Agency agree?

FDA Response: Yes, FDA generally agrees. However, the final assessment of the risks of LDK378 and the appropriate risk mitigation strategies will be determined during the NDA review.

Discussion during the meeting: Novartis acknowledged FDA's responses and there was no discussion during the meeting.

8. Does the Agency agree with the content of the Safety and Efficacy Update as outlined in the proposed eCTD TOC as well as the format of the data to be presented in the Summary of Clinical Safety (SCS) addendum and the Summary of Clinical Efficacy (SCE) addendum?

FDA Response: Yes, FDA agrees with Novartis' proposal with regard to content; however, the timing of submission of the safety and efficacy update should be within 60

days of submission of the final component of the NDA. Please submit updated data and an addendum to the clinical study report with the updated analyses in the Safety and Efficacy update.

Novartis' Response submitted via email on 11.21.13: To avoid providing the same information twice for Study X2101, Novartis proposes to update the safety information via an addendum to the SCS only.

The SCS addendum will contain information from registration Study X2101 as well as from other ongoing studies.

- For Study X2101, the SCS addendum will include the following information:
 - Patient disposition
 - Duration of exposure
 - Dose reductions and dose interruptions
 - Overall summary of adverse events (AEs) including deaths, AEs suspected to be drug related, SAEs, AEs leading to discontinuation, and AEs leading to dose adjustment or interruption
 - Hematology and chemistry laboratory summaries
 - AEs and laboratory data associated with evaluations of AEs of special interest such as hepatotoxicity, interstitial lung disease/pneumonitis, and QT interval prolongation
- In Study X1101, at the time of the data cut-off for the original NDA, only 6 of 19 patients were ongoing in the dose-escalation phase. As of 31-Oct-2013, no patients were enrolled in the expansion phase. As such, Novartis will only provide an overview of SAEs and deaths reported from the Novartis global pharmacovigilance database between 03-Aug-2013 and 31-Oct-2013
- For Studies A2201 and A2203, Novartis will update the information provided in the original NDA, including:
 - Patient disposition (including number of patients treated, number of patients who discontinued treatment, primary reason for discontinuation, and number of patients ongoing)
 - Demographics (including age, gender, sex, and ECOG performance status)
 - Duration of exposure
 - AEs leading to study drug discontinuation
 - AEs requiring dose adjustment or delay (interruption)
- For all other ongoing studies (X2102, X2103, A2201, A2203, A2303, A2301, and A2402), SAEs and deaths reported from the Novartis global pharmacovigilance database between 03-Aug-2013 and 31-Oct-2013 will be provided.

Novartis will not provide datasets for the ongoing studies with the exception of the registration study, X2101.

The SCE addendum will include updated efficacy information from Study X2101 only. Specifically, analyses will be provided for ORR, DOR, PFS, and OS by Investigator and BIRC assessment.

Novartis plans to submit the Safety and Efficacy Update within 60 days of the original submission.

Discussion during the meeting: Novartis clarified that the narratives of SAEs and deaths will be provided for all ongoing studies in SCS appendix 3 of module 5. FDA agreed to accept listings of the SAEs and deaths from study X1101 in the SCS addendum rather than as an updated clinical study report. Novartis will provide updated datasets for the X2101 trial in the safety update. FDA agreed to the content and timing of the safety update.

ADDITIONAL CLINICAL COMMENT:

9. For the confirmatory trial, FDA may consider superiority or non-inferiority designs comparing unapproved (or approved under subpart H) ALK inhibitors with crizotinib, using overall response rate as the primary endpoint. In addition, FDA would entertain the formation of a master protocol testing pairwise comparisons of several ALK inhibitors against a common control (crizotinib) in patients who have not previously received ALK-targeted therapy for the treatment of ALK rearrangement-positive metastatic NSCLC.

Novartis' Response submitted via email on 11.21.13: Novartis wishes to reaffirm that ongoing Study A2303 (*'A phase III multicenter, randomized study of oral LDK378 versus standard chemotherapy in adult patients with ALK rearranged [ALK-positive] locally advanced or metastatic NSCLC who have been treated previously with one chemotherapy regimen [platinum doublet] and crizotinib'*) will be used to confirm the clinical benefit of LDK378 in ALK-positive NSCLC patients previously treated with an ALK inhibitor. Of note, the fully accrued Study A2201 (*'A phase II, multicenter, single-arm study of oral LDK378 in adult patients with ALK-activated non-small cell lung cancer previously treated with chemotherapy and crizotinib'*) will further support the assessment of clinical benefit in this patient population.

As discussed during the teleconference on 12-Nov-2013, Novartis is not in favor of participating in a 'master protocol' described above. (b) (4)

[REDACTED]

Discussion during the meeting: FDA stated that the ongoing Study A2303, which is anticipated to complete accrual fourth quarter, 2014, is acceptable in design to confirm clinical benefit. FDA encourages Novartis to submit the final results of Studies A2201 and A2203 when available and acknowledges Novartis' plan to conduct a head-to-head trial against crizotinib when additional data are available to support assumptions for the design of this study.

FDA acknowledges Novartis' plans to complete Study A2301 for first-line treatment in comparison to chemotherapy; however, FDA expressed concerns that this is not the optimal study due to concerns of equipoise.

GENERAL ADDITIONAL COMMENTS:

10. Although Novartis is required to provide a listing of all manufacturing facilities in the NDA submission, it would greatly facilitate the review of the application if the manufacturing site information is provided prior to the NDA submission (preferably at the time of the meeting). 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.

Novartis' Response submitted via email on 11.21.13: The requested information was provided as Appendix 7 in the pre-NDA briefing package. This information will also be provided in FDA Form 356h which will be submitted in late Nov-2013 as part of the rolling NDA. Please note that the sites will be ready for inspection at the time of the original submission (late Dec-2013).

Discussion during the meeting: FDA acknowledges Novartis' response.

11. To facilitate FDA's review of the clinical investigator's sites, please provide a response to the "OSI requests/requirements for and NDA/BLA" memo sent on October 9, 2013 to be discussed during the pre-NDA meeting.

Novartis' Response submitted via email on 11.21.13: Novartis will provide the information requested for registration Study X2101 for Parts I and II as soon as it becomes available and no later than at the time of the original NDA submission in late Dec-2013. Novartis is not planning to provide the site level datasets for the pilot program (Part III of the OSI request).

Discussion during the meeting: FDA finds Novartis' proposal acceptable as long as parts 1 and 2 come in prior or with the final submission. FDA will accept parts 1 and 2

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separately if they can be provided earlier than the last component of the rolling submission.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.

Discussion during meeting: FDA and Novartis are in agreement with the contents as proposed in the briefing package and as clarified through this meeting.

- Discussion on the need for a REMS was held and it was concluded that:

Discussion during meeting: FDA acknowledges that Novartis does not intend to submit a REMS. FDA agrees, that based on the information submitted to date, a REMS will not be required to ensure safe and effective use of LDK378.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. We agreed that the following minor application components may be submitted within 30 calendar days after the submission of the original application:

LATE COMPONENT – Administrative Information (module 1-1.14.1.3)

Discussion during meeting: FDA agreed that Novartis may submit labeling in SPL format within the first 30 calendar days of the last component of the application.

In addition, we note that a chemistry pre-submission meeting was scheduled to be held on May 14, 2013 but you elected to cancel after receipt of our preliminary comments of May 13, 2013. We refer you to the minutes of that meeting and to the July 10, 2013 meeting cancellation correspondence 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, 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. As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements of Prescribing Information website including the Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products, regulations, 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. We encourage you to use the SRPI checklist as a quality assurance tool before you submit your proposed PI.

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.				

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Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

ISSUES REQUIRING FURTHER DISCUSSION

- Please see action items below

ACTION ITEMS

- There are no action items

ATTACHMENTS AND HANDOUTS

- There are no attachments or handouts

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

/s/

MELANIE B PIERCE
12/19/2013



NDA 205755

ACKNOWLEDGE NDA PRESUBMISSION

Novartis Pharmaceuticals Corporation
Attention: Yanina Gutman, Pharm.D.
Senior Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936

Dear Dr. Gutman:

We have received the first section of your New Drug Application (NDA) under the program for step-wise submission of sections of an NDA (section 506 of the Federal Food, Drug, and Cosmetic Act) for the following:

Name of Drug Product: (b) (4) (ceritinib) capsules, 150 mg

Date of Submission: November 27, 2013

Date of Receipt: November 27, 2013

Our Reference Number: NDA 205755

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 NDA 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 Oncology Products 2
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, call me at (301) 796-7032.

Sincerely,

{See appended electronic signature page}

Karen Boyd, M.S.
Regulatory Health Project Manager
Division of Oncology Products 2
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/

KAREN C BOYD
12/11/2013



IND 109272

**MEETING REQUEST-
WRITTEN RESPONSES**

Novartis Pharmaceuticals, Corporation
Attention: Anne Frederick, Ph.D.
Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Frederick:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act "LDK378."

We also refer to your submission dated February 22, 2013, containing a Type C meeting request. The purpose of the requested meeting was to request a meeting to discuss the content and format of the NDA submission for LDK378 in the treatment of patients with (b) (4) metastatic non-small cell lung cancer (NSCLC) who have (b) (4) crizotinib, to your June 10, 2013 and July 18, 2013 requests for clarification regarding question 4.

Further reference is made to our Meeting Granted letter dated March 15, 2013, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your March 21, 2013 background package.

If you have any questions, call Melanie Pierce, Senior Regulatory Health Project Manager at (301) 796-1273.

Sincerely,

{See appended electronic signature page}

Melanie Pierce
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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Page 2

Enclosure:
Written Responses



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

WRITTEN RESPONSES

Meeting Type: Type C
Meeting Category: Other

Application Number: IND 109272
Product Name: LDK378
Indication: Treatment of patients with [REDACTED] (b) (4) metastatic non-small cell lung cancer (NSCLC) who have [REDACTED] (b) (4) [REDACTED] crizotinib.

Sponsor/Applicant Name: Novartis Pharmaceuticals
Regulatory Pathway: 505(b)(1)

BACKGROUND

Regulatory Background:

On February 22, 2013, Novartis Pharmaceuticals requested a meeting to discuss the content and format of the NDA submission for LDK378 in the treatment of patients with [REDACTED] (b) (4) metastatic non-small cell lung cancer (NSCLC) who have [REDACTED] (b) (4) crizotinib.

On November 20, 2012, an End-of-Phase 1/Pre-Phase 3 meeting was held with the FDA to discuss the ongoing phase I study (CLDK378X2101), the proposed phase III study (CLDK378A2303, in ALK-positive NSCLC patients previously treated with chemotherapy and crizotinib), and the proposed clinical pharmacology program for LDK378.

On March 6, 2013, Breakthrough Therapy Designation was granted for LDK378 for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) that is ALK-positive as detected by an FDA-approved test and which has progressed during treatment with crizotinib or where patients are intolerant to crizotinib.

Proposed Pivotal Trial:

The NDA will be based on the ongoing Study CLDK378X2101, entitled "A phase I, multicenter, open-label dose escalation study of LDK378, administered orally in adult patients with tumors characterized by genetic abnormalities in anaplastic lymphoma kinase" and a phase 1 Japanese study, CLDK378X1101. CLDK378X2101 is a first-in-human, open-label study investigating the safety and anti-tumor activity of LDK378 in patients with tumors confirmed to have genetic abnormalities in ALK. There are two phases of the study, an escalation phase and an expansion phase. The expansion phase started after the MTD/RDE had been estimated. There are 4 arms in which enrollment occurred in parallel. Arm 1A, Arm 1B and Arm 2 would each enroll up to 100 patients, and Arm 3 would enroll approximately 10 patients.

Written Response

- (Arm 1A) Patients with ALK-translocated NSCLC who had disease progression during treatment or within 2 weeks of the last dose of an ALK inhibitor and planned initiation of LDK378 within 60 days of the last dose of the prior ALK inhibitor,
- (Arm 1B) Patients with ALK-translocated NSCLC who were previously treated with an ALK inhibitor and do not meet the criteria for Arm 1A, above.
- (Arm 2) Patients with ALK-translocated NSCLC not previously treated with an ALK inhibitor, and
- (Arm 3) Patients with tumors other than NSCLC with genetic abnormalities in ALK

Patients may continue treatment with LDK378 until the patient experiences unacceptable toxicity that precludes any further treatment, disease progression, and/or treatment is discontinued at the discretion of the investigator or by patient request.

Tumor response evaluations were determined by the local investigators, based on RECIST version 1.0. Additionally, tumor response evaluations would be undergo blinded central review.

The Efficacy Analysis Set (EAS) will be the primary data set used for the analysis of tumor response data (ORR, DOR, and PFS based on investigator assessments) and for the analysis of OS. This data set is a subset of the FAS and consists of patients who received the first dose of LDK378 at least 18 weeks prior to the analysis cutoff date.

The Central Efficacy Analysis Set (CEAS) will be used for the analysis of tumor response data based on independent central review assessments. This data set is a subset of the EAS and consists of patients

- who received the first dose of LDK378 at least 18 weeks prior to the analysis cutoff date, and
- for whom EITHER the baseline scan and at least one post-baseline scan are available and can be evaluated by the Blinded Independent Review Committee (BIRC) OR no post-baseline scan was performed in the study due to early death or discontinuation.

The primary clinical study report (CSR) will be produced based on an analysis cutoff date defined to ensure that a minimum of 120 NSCLC patients in the 750 mg dose group (from dose escalation or dose expansion) who have received prior treatment with crizotinib, have received the first dose of LDK378 at least 18 weeks prior to the analysis cutoff date. Within this analysis, patients treated during the escalation phase will be pooled with those receiving the same dosing regimen during expansion phase.

As of the October 24, 2012 data snapshot, 111 patients have been treated across a dose range of 50 mg to 750 mg daily and the maximum tolerated dose (MTD) was established as 750 mg daily. The majority of the responses were observed at doses of 400 mg and above, with just two responses at lower doses (1 at 200 mg and 1 at 300 mg). As of the data snapshot date, a total of

Written Response

77 ALK-positive NSCLC patients treated at doses of ≥ 400 mg were evaluable for tumor response (at least 1 post-baseline tumor assessment or discontinued treatment). Tumor assessments were performed by local review as per the protocol every 2 cycles (6 weeks) and were based on RECIST (v1.0). Best overall response rates are summarized in Table 1.

Table 1. Summary of best overall response in ALK-positive NSCLC patients treated at doses of 400 - 750 mg in Study CLDK378X2101

Response rate (RECIST v1.0)	N	CR ^a	CR + PR	CR + PR + uPR ^b
All NSCLC, ≥ 400 mg/d	77	1 (1%)	34 (44%)	56 (73%)
NSCLC, at 750 mg	41	0	15 (37%)	29 (71%)
ORR by prior crizotinib treatment				
NSCLC prior crizotinib, ≥ 400 mg/d	57	1 (2%)	27 (47%)	44 (77%)
NSCLC prior crizotinib, 750 mg/d	27	0	11 (41%)	20 (74%)
NSCLC crizotinib naive, ≥ 400 mg/d	20	0	7 (35%)	12 (60%)
NSCLC crizotinib naive, 750 mg/d	14	0	4 (29%)	9 (64%)
a CR is confirmed				
b uPR, partial response documented on only 1 occasion at the time of the database snapshot				

Among the most common adverse events with LDK378 in Study CLDK378X2101 in patients treated at 750 mg daily (n=62) were diarrhea (71%), nausea (65%), fatigue (24%), decreased appetite (21%), and ALT increased (18%). Grade 3-4 adverse events included hyperglycemia (6%), ALT increased (3%), diarrhea (3%), and anemia (5%).

General Comment: FDA is providing general advice to facilitate preparation of a future NDA. Following analysis and submission of top-line results, a pre-NDA meeting should be held to reach agreement on the content and format of the proposed NDA and agreement on late submissions, if any.

Sponsor Submitted Questions and FDA Response:

CLINICAL/STATISTICS:

- Does the FDA agree with Novartis' proposal for providing patient narratives in the NDA submission?

FDA Responses: Yes. FDA agrees with Novartis' proposal.

Novartis' Response submitted June 10, 2013: Novartis would like to clarify that the agreed upon patient narratives and CRFs will be provided for patients in the following studies:

- CLDK378X2101: A phase I, multicenter, open-label dose escalation study of LDK378, administered orally in adult patients with tumors characterized by genetic abnormalities in ALK

Written Response

- CLDK378X1101: A phase I, multicenter, open-label dose escalation study of LDK378 administered orally in Japanese patients with tumors characterized by genetic alterations in ALK
- CLDK378A2101: A randomized, open label, three-treatment, two period cross-over study to determine the relative bioavailability of LDK378 administered either with a low-fat low-calorie or high-fat high-calorie meal compared to fasted condition in healthy subjects
- CLDK378A2104: An open-label, two-period, single-sequence study to estimate the effect of ketoconazole on the pharmacokinetics of a single 450 mg oral dose of LDK378 in healthy volunteers
- CLDK378A2105: An open-label, single center, phase I study to determine the absorption, distribution, metabolism, and excretion (ADME) of LDK378 after a single oral administration of 750 mg [¹⁴C]LDK378 in healthy male volunteers
- CLDK378A2106: An open-label, two-period, single-sequence study to estimate the effect of rifampin on the pharmacokinetics of a single 750 mg oral dose of LDK378 in healthy volunteers

Serious adverse event (SAE) and death listings will be provided for all other ongoing studies as previously described in Question 3.

FDA response July 18, 2013: FDA agrees with the proposal for providing patient narratives in the NDA submission for the studies Novartis has stated above.

2. Does the Agency agree that the statistical methodology and proposed analyses for the pivotal study are adequate to support the filing of LDK378 in the proposed indication?

FDA Responses: No. FDA does not agree with the proposed analyses. Efficacy analyses must clearly distinguish between patients who were enrolled in Study CLDK378X2101 after disease progression during treatment with prior ALK inhibitor therapy (or within 2 weeks of the last dose as defined in the protocol) and those who discontinued prior ALK inhibitor therapy for reasons other than disease progression independent of the timing of planned initiation of LDK378. Furthermore, the datasets provided should include the nature of disease progression on prior ALK inhibitor therapy (radiologic vs. clinical) and the type of prior ALK inhibitor therapy (crizotinib vs. other) for each patient.

Novartis' Response submitted June 10, 2013: Novartis agrees to provide efficacy analyses distinguishing between a) patients who were enrolled in Study CLDK378X2101 after disease progression during treatment with a prior ALK inhibitor therapy (or within 2 weeks of the last dose as defined in the protocol); and b) all other patients who were previously treated with an ALK inhibitor and who do not meet the criteria in a). As requested, the datasets will include the type of prior ALK inhibitor therapy (crizotinib vs. other) for each patient. However, the nature of disease progression on prior ALK inhibitor therapy (radiologic vs. clinical) was not collected, and therefore it will not be available.

Written Response

FDA Response July 18, 2013: FDA agrees with Novartis's response on providing efficacy analyses that distinguish between a) patients who were enrolled in Study CLDK378X2101 after disease progression during treatment with a prior ALK inhibitor therapy (or within 2 weeks of the last dose as defined in the protocol); and b) all other patients who were previously treated with an ALK inhibitor and who do not meet the criteria in a). FDA acknowledges that Novartis cannot report on the nature of disease progression on prior ALK inhibitor therapy since the data was not collected.

In addition, we have the following comments regarding the analysis plan for Study CLDK378X2101.

- a. The primary analysis based on efficacy analysis set is not acceptable. The primary analysis should be based on full analysis set (FAS), consisting of all patients who receive at least one full or partial dose of LDK378, as defined in the briefing document.

Novartis response to point "a" submitted June 10, 2013: Novartis believes that the proposed analysis plan for the pivotal study CLDK378X2101 in which the primary efficacy analysis is based on overall response rate (ORR) by investigator assessment using the Efficacy Analysis Set (EAS; this data set is a subset of the FAS and consists of patients who received the first dose of LDK378 at least 18 weeks prior to the analysis cut-off date) is appropriate and should be considered acceptable by the Agency. Patients enrolled within 18 weeks prior to the data cut-off will not have sufficient follow-up for assessment and/or confirmation of response, or if response was assessed, data on the duration of response will be limited. Therefore, an efficacy analysis based on the FAS (i.e., including those patients in the denominator) will be too conservative and will not reflect the true efficacy of LDK378. In this context, the use of the EAS, including patients who received the first dose of LDK378 at least 18 weeks before data cut-off and counting patients without a post-baseline scan due to early death or discontinuation as non-responders, will provide a more meaningful set of data to adequately characterize the efficacy of LDK378. This approach will not introduce any bias in the assessment of efficacy since the cut-off was prospectively defined in the protocol, and patients in the EAS will be included solely on the basis of the time of their enrollment into the study with respect to the data cut-off.

FDA Response to item "a" July 18, 2013: The primary analysis should best be based on full analysis set (FAS), consisting of all patients who receive at least one full or partial dose of LDK378, as defined in the briefing document. Results from the efficacy analysis set (EAS) should be submitted as supportive evidence. FDA will take into account Novartis' concerns regarding the lack of sufficient follow-up and limited data on the duration of response with the FAS at the time of NDA review. FDA recommends further discussions on this topic during the pre-NDA meeting when more data is available.

- b. FDA recommends the analysis using the blinded independent central review (BIRC) assessments as the primary analysis and the analysis using investigator

Written Response

assessments as the supportive analysis. Therefore, FDA strongly recommends that scans for all patients be retrieved for retrospective BIRC review.

- c. In the primary efficacy analysis conducted by central review assessment of the full analysis set population, patients who did not have BIRC assessments or no post-baseline scan performed in the study due to early death or discontinuation should be categorized as a non-responder.

Novartis' response to points "b" and "c" submitted June 10, 2013: In the protocol for Study CLDK378X2101, assessment of response by investigator was prospectively defined as the primary assessment of response. The original protocol did not include BIRC for assessment of response. Novartis is implementing a retrospective collection of imaging exams (i.e., MRI, CT scans) for BIRC as agreed upon with FDA on 20-Nov-2012 during the End-of phase I/Pre-phase III meeting.

Every effort will be made to retrieve scans for all patients; however, due to the retrospective nature of the exercise, this ambitious goal may not be achieved. More realistically, experience shows that for some patients it will not be possible to retrieve the scans. Since the analysis of response as determined by BIRC was not originally planned in the protocol and will be based on imaging collected retrospectively, it should not be used as the primary analysis of efficacy. In addition, attributing a non-response to missing CT scans (this will likely be the case due to the retrospective collection of scans) in this setting would result in a highly conservative analysis not reflective of the true efficacy of LDK378. Note that patients without a post-baseline scan due to early death or discontinuation will be counted as non-responders as noted in the definition of Central Efficacy Analysis Set (CEAS). Therefore, Novartis proposes that it is more appropriate to use investigator assessment based on EAS as the primary efficacy analysis and the analysis using BIRC assessment based on the CEAS as the supportive analysis. In addition, Novartis will provide a sensitivity analysis of efficacy using investigator assessment based on the FAS.

The approach proposed by Novartis has been acceptable in a similar situation for another ALK inhibitor. The initial NDA submission for crizotinib was based on ongoing trials in which the primary efficacy endpoint was ORR by investigator assessment and included only patients with appropriate follow-up for evaluation of response. Only discontinuations, SAEs, and deaths were provided for the other patients enrolled with more limited follow-up in these trials. In addition, in these trials, a retrospective collection of scans was also implemented, and efficacy assessed by an independent radiology review panel was provided as supportive data, although in a smaller number of patients. Accordingly, the label for crizotinib reflects only the data of the primary efficacy analysis by investigator assessment for patients with adequate follow-up for evaluation of response.

FDA Response to items "b" and "c" submitted June 10, 2013: FDA agrees with using BIRC assessments as supportive analysis.

Written Response

- d. The definition of duration of response should be defined as the time from first documented response (PR or CR) to the date of first documented disease progression or death due to any cause.

Novartis' response to point "d" submitted June 10, 2013: Novartis confirms that we agree with FDA's proposal; duration of response will be defined as the time from first documented response (PR or CR) to the date of first documented disease progression or death due to any cause.

- e. While it is acceptable to provide the results of PFS and OS, these are not interpretable in a single arm study.

3. Does the Agency agree with the proposed strategy for the Summary of Clinical Safety (SCS) and for the Summary of Clinical Efficacy (SCE)?

FDA Responses: The proposed overview of information in the SCS and SCE appear to be acceptable. The proposed presentation of efficacy analyses in the SCE is not acceptable. Novartis should include additional analyses of efficacy as outlined in FDA's response to question 2.

Please see FDA's response to question 4 regarding presentation of datasets in a single format using a uniform version of MedDRA for clinical safety.

4. Does the Agency agree with Novartis' proposal for the submission of electronic datasets?

FDA Responses: Yes. FDA generally agrees with Novartis' proposal for the submission of electronic datasets as outlined under Novartis' Position statement for Question 4. Furthermore, categorization of adverse events should be based on a single MedDRA version in a pooled dataset that includes all the patients in the safety population.

Please see additional clinical pharmacology recommendations (comments 16-19) on datasets submission

Novartis' response submitted June 10, 2013: As described in the Novartis proposal, safety data will not be pooled across studies as:

- The number of patients in the phase I study in Japanese patients, CLDK378X1101, is very small compared to the number of patients in the same dose group and subgroup in the pivotal study CLDK378X2101
- Study CLDK378X1101 has only 3 patients in the 750 mg dose group with prior treatment with an ALK inhibitor and only 2 patients in the 750 mg dose who are ALK inhibitor naïve
- Only SAE and death listings will be provided for the ongoing phase II and phase III studies.

However, a common MedDRA version will be used for datasets, and reporting of adverse events for the pivotal study (CLDK378X2101) as well as the Phase I Japanese study (CDK378X1101).

Written Response

Safety analyses in the Summary of Clinical Safety will be presented for each of these two trials separately.

FDA Response July 17, 2013: FDA agrees with Novartis's proposal on the method of presenting the safety data for studies CLDK378X1101 and CLDK378X2101. FDA recommends pooling the safety data across the pivotal study CLDK378X2101 and the ongoing phase II and phase III studies. For the ongoing phase II and phase III studies, provide SAEs, deaths, and any adverse events (regardless of grade) leading to treatment modification/discontinuation.

Novartis' response submitted via email July 29, 2013: As for other Novartis Oncology submissions previously accepted by FDA, we propose to provide SAE and death listings for the ongoing phase II and phase III studies from the Novartis global pharmacovigilance safety database. This database collects all SAEs (and deaths) reported to Novartis for all ongoing studies. The database structure of the Novartis global pharmacovigilance safety database is not compatible with that from the clinical databases; hence pooling safety data from the pivotal study (CLDK378X2101) with data from the Novartis global pharmacovigilance safety database for the ongoing phase II and phase III studies would not be possible. Furthermore, as the Novartis global pharmacovigilance safety database only collects SAEs (and deaths), Novartis would not be able to provide AEs leading to discontinuation or dose modification.

As such, Novartis requests that FDA accept our proposal to provide SAE and death listings only for the ongoing studies (other than the pivotal study [CLDK378X2101] and the study in Japanese patients [CLDK378X1101]) from the Novartis global pharmacovigilance safety database. Data sets would not be provided for the ongoing phase II and phase III studies.

FDA Response July 30, 2013: Novartis' proposal to provide SAE and death listings for ongoing phase 2 and 3 studies (listed in table 2-1 of your July 29, 2013 communication), is acceptable. Based on Novartis' explanation, FDA agrees that providing listings of AEs leading to discontinuation or dose modification is not required for these ongoing studies.

5. Does the Agency agree with the proposed content of the 90-Day Safety Update, including additional efficacy data from Study CLDK378X2101?

FDA Responses: Yes. The proposed content of the 90-Day Safety Update appears acceptable including the plan to provide longer-term efficacy data from patients in Study CLDK378X2101 included in the original NDA.

CLINICAL PHARMACOLOGY COMMENTS:

Please address the following clinical pharmacology related questions in the NDA submission:

Written Response

6. What is the basis for selecting the dose(s) and dosing regimen used in the registration trial(s)?
7. What are the exposure-response relationships (dose-response, exposure-response) for efficacy?
8. What are the exposure-response relationships (dose-response, exposure-response) for safety?
9. How is the QT prolongation potential of LDK378 assessed? What are the conclusion and proposed labeling description?
10. What are the characteristics of absorption, distribution, metabolism and excretion of LDK378?
11. What are the effects of food on the bioavailability of LDK378? And what is the dosing recommendation with regard to meals or meal types?
12. What influence do the intrinsic factors (as listed below but not limited to) have on LDK378 exposure and/or its pharmacodynamic response? What is their clinical impact? What dose and dosing regimen adjustments are recommended?
 - a. gender
 - b. race
 - c. weight
 - d. disease
 - e. genetic polymorphism
 - f. hepatic impairment
 - g. renal impairment
13. What influence do the extrinsic factors (as listed below but not limited to) have on LDK378 exposure and/or its pharmacodynamic response? What is their clinical impact? What dose and dosing regimen adjustments are recommended?
 - a. concomitant medications
 - b. CYP and/or transporter based drug-drug interactions
 - c. diet
 - d. smoking

In addition, please apply the following advice in preparing clinical pharmacology sections of the NDA submission:

14. Submit bioanalytical method(s) and validation reports for clinical pharmacology and biopharmaceutics studies.

Written Response

15. Provide complete datasets for clinical pharmacology and biopharmaceutics studies. The datasets should not be limited to PK/PD. For example, domains related to safety (e.g., AE's), demographics, non-PK laboratory values, concomitant drug use should be included. All of these are important in identifying patterns of potential clinical pharmacology related causes of clinical safety outcomes and facilitating exploratory exposure-response analyses and population PK analyses.
16. Provide all concentration-time and derived PK parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
17. Present the PK parameter data as geometric mean with coefficient of variation (and mean \pm standard deviation) and median with range as appropriate in the study reports.
18. Provide a table listing of patients with renal or hepatic impairment who have received LDK378, organized by trial number. Include available renal and hepatic function parameters such as SCr, CLCr calculated by the Cockcroft Gault equation and/or eGFR calculated by MDRD, AST/ALT, Total Bilirubin, etc for each patient in the listing. Also, provide a summary of the following information for each patient: PK and PD data, safety, and clinical efficacy.

Novartis' Response submitted June 10, 2013: Per FDA's guidance, Novartis will provide table listings of patients with renal and hepatic impairment who received LDK378 in Study CLDK378X2101. The respective table listings will include all requested renal and hepatic function parameters. In addition, the table listings will provide a summary of select PK parameters and safety and efficacy endpoints. Please note that PD endpoints will not be provided as these data are not available from the ongoing phase I trial, CLDK378X2101.

FDA Response July 18, 2013: Novartis's proposal to provide table listings of patients with renal and hepatic impairment who received LDK378 in Study CLDK378X2101 is reasonable.

19. Submit the following datasets to support the population PK analysis:
 - a. SAS transport files (*.xpt) for all datasets used for model development and validation
 - b. Description of each data item provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets
 - c. Model codes or control streams and output listings for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. Submit these files as ASCII text files with *.txt extension (e.g., myfile_ctl.txt, myfile_out.txt)

Written Response

- d. Model development decision tree and/or table which gives an overview of modeling steps

For the population analysis reports, submit:

- e. Standard model diagnostic plots
- f. Individual plots for a representative number of subjects including observed concentrations, the individual prediction line and the population prediction line
- g. Model parameter names and units in tables. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1).
- h. Summary of the report describing the clinical application of modeling results.

Refer to the following pharmacometric data and models submission guidelines <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm> for more information.

- 20. Explore exposure-response (measures of effectiveness, biomarkers and toxicity) relationships for LDK378 and its major active metabolite(s) in the targeted patient population and include the results of this exploratory analysis in the NDA submission. Refer to Guidance for Industry found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf> and <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf> for more information.
- 21. Submit the following items for QTc study/assessment:
 - a. Copy of the QT/QTc study protocol
 - b. Copy of the Investigator's Brochure
 - c. Annotated CRF
 - d. Define file which describes the contents of the electronic data sets
 - e. Electronic data sets as SAS transport files (in CDISC SDTM format – if possible) and all the SAS codes for the analyses
 - f. ECG waveforms to the ECG warehouse (www.ecgwarehouse.com)
 - g. Completed Highlights of Clinical Pharmacology Table

Novartis' response submitted June 10, 2013: Novartis would like to clarify that no QT/QTc study will be conducted in healthy volunteers, and therefore, a study protocol will not be included in the NDA. The proposed QT assessment plan was described in Question 6 in the End-of-phase I/Pre-phase III meeting briefing book for the Type B meeting held on 20-Nov-2012. Due to potential tolerability issues of administering multiple doses of LDK378 to healthy volunteers and as LDK378 has over a 4-fold accumulation at steady-state, the conduct of a single-dose QT study at substantial multiples of the anticipated maximum therapeutic exposure or a multiple-dose QT study

Written Response

at clinically relevant doses in healthy volunteers is not feasible. Additionally, performing such a stand-alone study in ALK-positive NSCLC patients would be difficult in terms of recruitment and completion.

LDK378 has an IC₅₀ of 0.4 μM in the hERG channel assay indicating the potential for QT prolongation. In monkeys, there were no LDK378-related effects in hemodynamic parameters or in ECG parameters (P duration, PR, QRS, QT and QTc intervals) at doses as high as 250 mg/kg. Preliminary data from patients treated in the ongoing phase I study (CLDK378X2101) at doses of 50-750 mg suggest that LDK378 may have a concentration- dependent effect on the QT interval. One patient (700 mg QD dose; <1%) had a QTc > 500 ms and 2 (<1.5%) patients (1 at 700 mg QD dose, 1 at 750 mg QD dose) had an increase from baseline QTc > 60 ms.

Additional cardiac assessments will be conducted in adult ALK-positive NSCLC patients. Novartis plans to monitor QTc in all patients. As an alternative to a thorough QT/QTc study, QTc will be monitored more extensively in subsets of patients in several studies:

- approximately 60 patients across two phase II studies (CLDK378A2201 and CLDK378A2203),
- approximately 100 patients (50 patients in each of the LDK378 and chemotherapy arms) in the confirmatory Phase III study in patients who have received prior chemotherapy (platinum doublet) and prior crizotinib (CLDK378A2303), and
- approximately 60 patients (30 patients in each of the LDK378 and standard first-line chemotherapy) in the Phase III study in previously untreated adult patients (CLDK378A2301).

In addition, the phase I study (CLDK378X2101) includes ECG collection with time-matched LDK378 plasma concentrations. Given the wide range of doses studied in this trial (50 to 750 mg), these data will enable a characterization of the LDK378 concentration-QTc relationship.

A summary of the ECG and PK assessment schedule for the Phase I, II and III studies is provided in Table 1-1 (refer to document submitted by Novartis). Triplicate ECGs along with time-matched LDK378 plasma concentrations at pre-dose and at various post-dose timepoints, including anticipated T_{max} (approximately 6 hour post-dose) during Cycle 1, Day 1 and Cycle 2, Day 1 (steady-state), will be obtained for the Phase II and III studies.

A central ECG laboratory will be used to read the ECGs collected in the Phase I, II and III studies. The readers will be blinded to date and time of ECG collection, and in the Phase III study, they will be blinded to study treatment. Mean changes from baseline and associated 90% CIs for ECG parameters (including QTc, PR and QRS) will be provided by time point. The concentration-QTc relationship will be characterized.

Written Response

The QTc assessment from Study CLDK378X2101 will be provided to support the accelerated NDA filing of LDK378. Associated raw and analysis (derived) datasets, annotated CRF, and define files will be provided as noted in Section 2.4 of the Type C briefing document submitted to FDA on 16-Apr-2013 (Serial No. 0100).

FDA Response July 18, 2013: Novartis's plan not to conduct QT/QTc studies in healthy volunteers is acceptable.

PREA REQUIREMENTS

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit a Pediatric Study Plan (PSP) within 60 days of an End-of-Phase 2 (EOP2) meeting held on or after November 6, 2012. If an EOP2 meeting will not occur, then:

- if your marketing application is expected to be submitted prior to January 5, 2014, you may either submit a PSP 210 days prior to submitting your application or you may submit a pediatric plan with your application as was required under the Food and Drug Administration Amendments Act (FDAAA).
- if your marketing application is expected to be submitted on or after January 5, 2014, the PSP should be submitted as early as possible and at a time agreed upon by you and FDA. We strongly encourage you to submit a PSP prior to the initiation of Phase 3 studies. In any case, the PSP must be submitted no later than 210 days prior to the submission of your application.

The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. For additional guidance on submission of the PSP, including a PSP Template, please refer to:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm> . In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov.

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/s/

MELANIE B PIERCE

08/14/2013



IND 109272

MEETING MINUTES

Novartis Pharmaceuticals, Corporation
Attention: Anne Frederick, Ph.D.
Executive Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Frederick:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for "LDK378."

We also refer to the meeting between representatives of your firm and the FDA on May 15, 2013. The purpose of the meeting was to discuss the clinical development program of LDK378 in previously untreated patients with (b) (4) metastatic non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive.

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Melanie Pierce, Senior Regulatory Health Project Manager at (301) 796-1273.

Sincerely,

{See appended electronic signature page}

Melanie Pierce
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:

Meeting Minutes
Additional DOP2 CDISC Guidance
DOP2's End-of-Phase 2 General Advice for Planned Marketing Applications



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End of Phase 2

Meeting Date and Time: May 15, 2013; 3:00 p.m.
Meeting Location: White Oak Bldg 22, Room 1309

Application Number: EOP2 109272
Product Name: LDK378
Indication: Treatment of previously untreated patients with (b) (4) (b) (4) metastatic non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive

Sponsor/Applicant Name: Novartis Corporation
Meeting Chair: Gideon Blumenthal
Meeting Recorder: Melanie Pierce

FDA ATTENDEES

Office of Hematology Oncology Products

Richard Pazdur Director
Anthony Murgio Associate Director for Regulatory Science

Office of Hematology Oncology Products

Division of Oncology Products 2

Patricia Keegan Director
Gideon Blumenthal Team Leader
Sean Khozin Clinical Reviewer
Melanie Pierce Project Manager

Office of Clinical Pharmacology V

Stacy Shord Clinical Pharmacology Reviewer

BACKGROUND

On March 1, 2013, Novartis Pharmaceuticals requested a meeting to discuss clinical development program of LDK378 in previously untreated patients with ██████████ (b) (4) metastatic non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive.

On November 20, 2012, an End-of-Phase 1/Pre-Phase 3 meeting was held with the FDA to discuss the ongoing phase 1 study (Protocol CLDK378X2101), the proposed phase 3 study (Protocol CLDK378A2303 to be conducted in ALK-positive NSCLC patients previously treated with chemotherapy and crizotinib), and the proposed clinical pharmacology program for LDK378.

On March 6, 2013, Breakthrough Therapy Designation was granted for LDK378 for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) that is ALK-positive as detected by an FDA-approved test and which has progressed during treatment with crizotinib or where patients are intolerant to crizotinib.

LDK378 has shown activity in advanced NSCLC patients with ALK-rearrangements in the ongoing Protocol CLDK378X2101, entitled “A phase I, multicenter, open-label dose escalation study of LDK378, administered orally in adult patients with tumors characterized by genetic abnormalities in anaplastic lymphoma kinase.” As of the October 24, 2012 data snapshot, 111 patients have been treated across a dose range of 50 mg to 750 mg daily and the maximum tolerated dose (MTD) was established as 750 mg daily. The majority of the responses were observed at doses of 400 mg and above, with just two responses at lower doses (1 at 200 mg and 1 at 300 mg). As of the data snapshot date, a total of 77 ALK-positive NSCLC patients treated at doses of ≥400 mg were evaluable for tumor response (at least 1 post-baseline tumor assessment or discontinued treatment). Tumor assessments were performed by local review as per the protocol every 2 cycles (6 weeks) and were based on RECIST (v1.0). Best overall response rates are summarized in Table 1.

Table 1. Summary of best overall response in ALK-positive NSCLC patients treated at doses of 400 - 750 mg in Study CLDK378X2101

Response rate (RECIST v1.0)	N	CR ^a	CR + PR	CR + PR + uPR ^b
All NSCLC, ≥400 mg/d	77	1 (1%)	34 (44%)	56 (73%)
NSCLC, at 750 mg	41	0	15 (37%)	29 (71%)
ORR by prior crizotinib treatment				
NSCLC prior crizotinib, ≥400 mg/d	57	1 (2%)	27 (47%)	44 (77%)
NSCLC prior crizotinib, 750 mg/d	27	0	11 (41%)	20 (74%)
NSCLC crizotinib naive, ≥400 mg/d	20	0	7 (35%)	12 (60%)
NSCLC crizotinib naive, 750 mg/d	14	0	4 (29%)	9 (64%)
a CR is confirmed				
b uPR, partial response documented on only 1 occasion at the time of the database snapshot				

Among the most common adverse events with LDK378 in Study CLDK378X2101 in patients treated at 750 mg daily (n=62) were diarrhea (71%), nausea (65%), fatigue (24%), decreased appetite (21%), and ALT increased (18%). Grade 3-4 adverse events included hyperglycemia (6%), ALT increased (3%), diarrhea (3%), and anemia (5%).

Proposed Clinical Trials:

Novartis plans to conduct two Phase 3 trials of LDK378 in previously untreated patients with (b) (4) metastatic, ALK-positive NSCLC.

Study Protocol CLDK378A2301 is an open-label, randomized, active-controlled, multi-center, active-controlled, phase III trial in 348 previously untreated adult patients with ALK-positive, stage IIIB or IV, non-squamous NSCLC. Randomization will be stratified by WHO performance status (0 versus 1, 2), prior adjuvant chemotherapy (yes vs. no), and whether the patient has brain metastases at screening (presence vs. absence). Eligible patients will be randomly assigned in a 1:1 ratio to two treatment arms:

- Experimental: LDK378 (first oral dose defines Day 1, continuous daily dosing)
- Control: reference chemotherapy (pemetrexed [500 mg/m²] plus cisplatin [75 mg/m²] or carboplatin [AUC 5-6])

Treatment will continue until disease progression according to RECIST 1.1 as determined by BIRC, unacceptable toxicity that precludes further treatment, pregnancy, start of a new anticancer therapy, discontinues treatment at the discretion of the patient or investigator, lost to follow-up, or study is terminated by the sponsor. Patients randomized to the reference chemotherapy treatment will be allowed to crossover to LDK378 treatment while being followed in the study after a Blinded Independent Review Committee (BIRC) has documented disease progression.

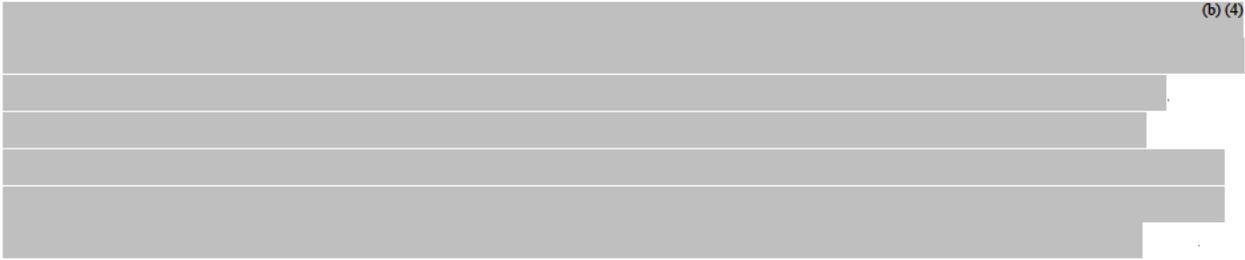
The primary endpoint is PFS as determined by a Blinded Independent Review Committee (BIRC) according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 guidelines every 6 weeks until Month 33, and every 9 weeks afterwards. PFS is defined as the time from the date of randomization to the date of the first radiologically documented disease progression or death due to any cause. Assuming that the median PFS is 8 months in the reference chemotherapy arm and 12.9 months in the LDK378 arm, a total of 205 events (documented by BIRC) are needed to detect a hazard ratio of 0.62 with 90% power at a one-sided alpha level of 2.5%. The primary analysis will be a stratified log-rank test performed on the ITT population.

(b) (4)

The trial is also designed to test OS. The OS analyses will be performed only if the primary efficacy endpoint PFS is statistically significant favoring the LDK378 group. (b) (4)

(b) (4)

(b) (4)

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Other secondary endpoints include overall response rate (ORR), duration of response (DOR), and disease control rate (DCR). A statistical procedure is not proposed to adjust for multiplicity in testing the secondary endpoints besides OS.

(b) (4)

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Sponsor Submitted Questions and FDA Response:

CLINICAL:

Study CLDK378A2301:

1. Does the Agency agree with Novartis' proposal to obtain a first-line indication for LDK378?

FDA Response: Yes, Novartis' strategy to seek a first line metastatic ALK-positive NSCLC indication is acceptable.

Discussion during meeting: FDA stated that study 2301 is not required to support the initial marketing application for LDK378. FDA also asked whether the trial could be performed in the US, that is, would such a trial be considered ethical and feasible to conduct in the US. Novartis stated that this trial design will likely be required by the EU regulatory authorities and will be performed primarily outside of the US (EU (b) (4)). Novartis will attempt to complete accrual within 2 years. FDA confirmed that the trial design could be used to support a label expansion for non-small cell lung cancer and to verify clinical benefit.

- 2.



3. Does the Agency agree with the patient population for both trials, as defined by their Eligibility criteria, in particular to restrict the population to nonsquamous NSCLC in Study CLDK378A2301?

FDA Response: No. Inclusion of stage IIIB patients who are candidates for definitive multimodal therapy is not acceptable. Inclusion of nonsquamous stage IV NSCLC patients is acceptable.

Discussion during meeting: Novartis agrees that the protocol inclusion criterion will be limited to IIIB patients who are not candidates for definitive multimodal therapy.

4. Does the Agency agree that the PFS endpoint is adequate to demonstrate a clinically relevant benefit of LDK378 versus standard therapy in previously untreated patients with ALK rearranged newly diagnosed stage IIIB or IV NSCLC?

FDA Response: Yes. PFS is an acceptable primary endpoint. However, please note that in order to provide substantial evidence of effectiveness, the magnitude of PFS effect should be large, clinically meaningful and highly statistically significant. In addition, the trial should demonstrate a favorable benefit-risk profile for LDK378-treated patients.

Discussion during meeting: There was no further discussion during the meeting.

5. Does the Agency agree that pemetrexed-based platinum doublet chemotherapy followed by pemetrexed maintenance is an appropriate comparator for the first-line treatment of untreated patients with ALK-positive, stage IIIB or IV, nonsquamous NSCLC?

FDA Response: Yes. FDA agrees that pemetrexed-based platinum doublet chemotherapy followed by pemetrexed maintenance in Novartis' proposed trial is acceptable as there are no data comparing ALK-inhibitor therapy with platinum doublet chemotherapy with or without maintenance in the first-line treatment of ALK-rearranged NSCLC patients. The lack of data establishing an improvement in PFS or OS with ALK-inhibitors in the first-line treatment of NSCLC maintains the condition of equipoise. FDA recognizes that it will be difficult to enroll patients in the United States to this study given the availability of crizotinib for the first-line treatment of ALK-rearranged NSCLC patients. See response to question 3 regarding eligibility criteria.

Discussion during meeting: Please see discussion under item 1 above.

6. Does the Agency agree to allow crossover from reference chemotherapy to LDK378 after disease progression is confirmed by the BIRC?

FDA Response: Yes, Novartis' decision to allow crossover from reference chemotherapy to LDK378 following progression is appears appropriate. In the Case Report Form (CRF), Novartis should collect information on subsequent therapies on all patients post progression.

Discussion during meeting: There was no further discussion during the meeting.

7. Does the Agency agree that the proposed sample size, testing strategy, and design operating characteristics for the assessment of efficacy are adequate?

FDA Response: Yes, however, FDA reminds Novartis that the PFS interim analysis at 35% information will not be acceptable to support a superiority claim, as stated in the protocol since “there is no plan to stop the study for efficacy at the interim analysis” and the estimation of the treatment effect is likely to be unstable.

Discussion during meeting: There was no further discussion during the meeting.

(b) (4)

Additional Discussion during the meeting: Novartis intends to file their application in December, 2013. The data will be presented at ASCO.

ADDITIONAL CLINICAL COMMENTS:

10. Exclude patients with uncontrolled diabetes mellitus in Protocols CLDK378A2301 (b) (4) (b) (4).

Discussion during meeting: Novartis agreed to exclude patients with uncontrolled diabetes mellitus in protocols 2301 (b) (4)

11. Since patients may derive benefit from subsequent standard of care therapy, FDA recommends re-consenting patients in the LDK378 arms of Protocol CLDK378A2301 (b) (4) after documented disease progression if Novartis intends

to continue to treat these patients with LDK378. [REDACTED]

(b) (4)

Discussion during meeting: Novartis intends to use the original consent form to provide this information to patients. FDA acknowledges Novartis' position.

Consider exploratory analyses of ORR, DOR, and PFS as measured by volumetric CT versus standard RECIST v1.1 assessments.

Discussion during meeting: There was no further discussion during the meeting.

12.

(b) (4)

ISSUES REQUIRING FURTHER DISCUSSION:

- See action items below

ACTION ITEMS:

- There are no action items

ATTACHMENTS AND HANDOUTS:

- Attendees list
- Additional DOP2 CDISC Guidance
- DOP2's End-of-Phase 2 General Advice for Planned Marketing Applications

PREA PEDIATRIC STUDY PLAN

The Food and Drug Administration Safety and Innovation Act of 2012 changes the timeline for submission of a PREA Pediatric Study Plan and includes a timeline for the implementation of these changes. You should review this law and assess if your application will be affected by these changes. If you have any questions, please email the Pediatric Team at Pedsdrugs@fda.hhs.gov.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, “Guidance for Industry Assessment of Abuse Potential of Drugs”, available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>.

Additional DOP2 CDISC Guidance

The following two tables identify variables and domains that the division uses in conducting standardized analyses on data for marketing or licensing applications. Following the tables is a description of the Tumor Identification (TU), Tumor Results (TR), Response (RS), domains and variables therein. These are provided because DOP2 uses these domains and variables in analysis tools developed by FDA. (b) (4)

we request that you implement the use of this SDTM format with all your upcoming submissions.

Please use the draft CDISC *Oncology Disease-Specific Therapeutic Area Supplement to the SDTM Implementation Guide* (<http://www.cdisc.org/sdtm>) for submitting tumor identification, results, and response data to DOP2 as soon as they become available.

Please follow the guidance as provided in the CDER Data Standards Issues Document that can be found at:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

Table 1: Variables that DOP2 requires for analyses of OS, PFS, RR, Disposition, and Adverse Reactions

Domain	Variable Name	Variable Label	Required Variable Values	Currently Available	CDISC Core	CDISC Data Type	CDISC Code List
ADSL	STRATA<N>	Based on definition of strata variable	0,1	No		Num	0,1
AE	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
AE	AEBODSYS	Body System or Organ Class	--	Yes	Exp	Char	
AE	AEDECOD	Dictionary-Derived Term	--	Yes	Req	Char	
AE	AETOXGR	Standard Toxicity Grade	--	Yes	Perm	Char	
AE	AESTDTC	Start Date/Time of Adverse Event	--	Yes	Exp	Char	ISO 8601
CM	CMCAT	Category for Medication	ANTI-CANCER	Yes	Perm	Char	--
CM	CMDECOD	Standardized Disposition Term	--	Yes	Perm	Char	NCOMPLT (Completion/Reason for Non-Completion)

CM	CMENDTC	End Date/Time of Disposition Event	--	Yes	Exp	Char	ISO 8601
CM	CMSTDTC	Start Date/Time of Disposition Event	--	Yes	Exp	Char	ISO 8601
CM	CMSTDY	Study Day of Start of Medication	--	Yes	Perm	Num	--
CM	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
DM	AGE	Age	--	Yes	Req	Num	--
DM	AGEU	Age Units	--	Yes	Exp	Char	AGEU
DM	ARM	Description of Planned Arm	--	Yes	Req	Char	--
DM	ACTARM		--	New			--
DM	ARMCD	Planned Arm Code	--	Yes	Req	Char	--
DM	COUNTRY	Country	--	Yes	Req	Char	ISO 3166 3- char. code
DM	DTHDTC	Date of Death	--	New		Char	ISO 8601
DM	DTHFL	Subject Death Flag	Y	New		Char	--
DM	ETHNIC	Ethnicity	--	Yes	Perm	Char	--
DM	RACE	Race	--	Yes	Exp	Char	--
DM	RFPENDTC	Date/Time of End of Participation	--	New		Char	ISO 8601
DM	SEX	Sex	--	Yes	Req	Char	M, F, U
DM	SITEID	Study Site Identifier	--	Yes	Req	Char	--
DM	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
DS	DSCAT	Category for Disposition Event	PROTOCOL MILESTONE	Yes	Perm	Char	DSCAT
DS	DSDECOD	Standardized Disposition Term	DEATH, RANDOMIZED, LOST TO FOLLOW-UP, ALIVE, ADVERSE EVENT, PROGRESSIVE DISEASE	Yes	Req	Char	NCOMPLT (Completion/Reason for Non-Completion)
DS	DSDTC	Date/Time of Collection	--	Yes	Perm	Char	ISO 8601

DS	DSSCAT	Subcategory for Disposition Event	STUDY DISCONTINUATION, TREATMENT DISCONTINUATION, STUDY TERMINATION	Yes	Perm	Char	--
DS	DSSTDTC	Start Date/Time of Disposition Event	--	Yes	Exp	Char	ISO 8601
DS	DSSTDY	Study Day of Start of Disposition Event	--	Yes	Perm	Num	--
DS	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
EX	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
EX	EXSTDTC	Start Date/Time of Treatment	--	Yes	Exp	Char	ISO 8601
EX	EXENDTC	End Date/Time of Treatment	--	Yes	Perm	Char	ISO 8601
LB	LBBLFL	Baseline Flag	Y	Yes	Exp	Char	NY
LB	LBNRIND	Reference Range Indicator	HIGH, LOW	Yes	Exp	Char	--
LB	LBTEST	Lab Test or Examination Name	--	Yes	Req	Char	--
LB	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
MH	MHDECOD	Dictionary-Derived Term	--	Yes	Perm	Char	--
MH	MHENDTC	End Date/Time of Medical History Event	--	Yes	Perm	Char	ISO 8601
MH	MHSTDTC	Start Date/Time of Medical History Event	--	Yes	Perm	Char	ISO 8601
MH	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
RS	RSACPTFL	Accepted Record Flag	Y	Yes	Perm	Char	Y or Null
RS	RSDTC	Date/Time of Response Assessment	--	Yes	Exp	Char	ISO 8601

RS	RSEVAL	Evaluator	INVESTIGATOR	Yes	Exp	Char	EVAL
RS	RSSTAT	Response Assessment Status	NOT DONE	Yes	Perm	Char	ND
RS	RSSTRESC	Response Assessment Result in Std Format	CR or COMPLETE RESPONSE, PR or PARTIAL RESPONSE, SD or STABLE DISEASE, PD or PROGRESSIVE DISEASE, NE or NOT EVALUABLE	Yes	Exp	Char	--
RS	RSTESTCD	Response Assessment Short Name	OVRLRESP, looks for TGRES, NTGRES & BESTRESP	Yes	Req	Char	--
RS	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
RS	VISIT	Visit name	Must contain "UNSCH" for unscheduled	Yes	Perm	Char	
SV	SVSTDTC	Start Date/Time of Visit	--	Yes	Exp	Char	ISO 8601
SV	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
TA	ANCHDTC	Anchor date of assessment schedule	Variable in ADSL - no name determined	NEW		Char	
TA	MAXPRD	Maximum length of assessment schedule		NEW		Char	ISO 8601 Duration
TA	MINPRD	Minimum length of assessment schedule		NEW		Char	ISO 8601 Duration
TA	STOFFSET	Start time from anchor date		NEW		Char	ISO 8601 Duration
TA	TGTPRD	Length of assessment schedule		NEW		Char	ISO 8601 Duration
TR	TRACPTFL	Accepted Record Flag	Y	Yes	Perm	Char	Y or Null
TR	TRDTC	Date/Time of Tumor Measurement	--	Yes	Exp	Char	ISO 8601
TR	TREVAL	Evaluator	INVESTIGATOR	Yes	Exp	Char	EVAL

TR	TRLINKID	Link ID	--	Yes	Exp	Char	--
TR	TRLNKGRP		--	NEW		Char	--
TR	TRSTAT	Tumor Assessment Status	NOT DONE	Yes	Perm	Char	ND
TR	TRSTRESC	Character Result/Finding in Std. Format	If TRTESTCD equals "TUMSTATE" Looks for PRESENT, ABSENT, UNEQUIVOCAL PROGRESSION	Yes	Exp	Char	--
TR	TRSTRESN	Numeric Result/Finding in Std. Format	--	Yes	Exp	Num	--
TR	TRTESTCD	Tumor Assessment Short Name	LDIAM, TUMSTATE, Looks for SUMLDIAM	Yes	Exp	Char	--
TR	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
TS	DCUTDTC	Data cut off date	--	New		Char	ISO 8601
TS	TSPARMCD	Trial Summary Parameter Short Name	PSSDDUR, PSCDUR	New	Req	Char	--
TS	TSVAL	Parameter Value	ISO Duration	New	Req	Char	--
TU	TUACPTFL	Accepted Record Flag	Y	Yes	Perm	Char	Y or Null
TU	TUDTC	Date/Time of Tumor Identification	--	Yes	Exp	Char	ISO 8601
TU	TUEVAL	Evaluator	INVESTIGATOR	Yes	Exp	Char	EVAL
TU	TULINKID	Link ID	--	Yes	Exp	Char	--

TU	TULOC	Location of Tumor	--	Yes	Exp	Char	LOC
TU	TUMETHOD	Method of Identification	--	Yes	Exp	Char	
TU	TUSTRESC	Tumor Identification Result Std. Format	NEW	Yes	Exp	Char	
TU	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--

Please ensure that the following domains and variables are included in your CDISC data submissions. Although the CDISC Implementation guide lists many variables as permissible, in order for DOP2 to conduct efficient and timely reviews of the clinical trial data, most permissible variables should be considered as required variables. Please consult with the division on any permissible variables that you intend not to include in your data files so we can determine the impact this will have on the review process and the acceptability of the omission.

Table 2: Additional variables in SDTM and ADaM that are necessary for efficient review

DOMAIN	VARAIBLE	DATA TYPE
ADaM		
ADSL	STUDYID	C
ADSL	USUBJID	C
ADSL	TRT01A	C
ADSL	TRT01P	C
ADSL	ARM	C
ADSL	AGE	N
ADSL	AGEGR1	C
ADSL	SEX	C
ADSL	RACE	C
ADSL	TRTEDT	N
ADSL	TRTEDTM	N
ADSL	TRTSDT	N
ADSL	TRTSDTM	N
ADSL	DEATHDSC	C
SDTM		
AE	STUDYID	C
AE	USUBJID	C
AE	AEDECOD	C
AE	AEBODSYS	C
AE	AEREL	C
AE	AESEV	C
AE	AETOXGR	C

AE	AESTDTC	C
AE	AEENDTC	C
AE	AESTDY	N
AE	AEENDY	N
AE	AEDUR	C
CM	STUDYID	C
CM	USUBJID	C
CM	CMDECOD	C
CM	CMSTDTC	C
CM	CMENDTC	C
CM	CMENDY	N
CM	CMSTDY	N
CM	CMDUR	C
DM	STUDYID	C
DM	USUBJID	C
DM	AGE	N
DM	SEX	C
DM	RACE	C
DM	ARM	C
DM	RFENDTC	C
DM	RFSTDTC	C
DS	STUDYID	C
DS	USUBJID	C
DS	DSDECOD	C
DS	DSCAT	C
DS	DSSTDTC	C
DS	DSSTDY	N
EX	STUDYID	C
EX	USUBJID	C
EX	EXTRT	C
EX	EXDOSE	N
EX	EXSTDTC	C
EX	EXENDTC	C
EX	EXSTDY	N
EX	EXENDY	N
EX	EXDUR	C
LB	STUDYID	C
LB	USUBJID	C
LB	LBTEST	C
LB	LBSTRESN	N
LB	LBSTNRHI	N
LB	LBSTNRLO	N
LB	LBDTC	C
LB	LBDY	N
MH	STUDYID	C
MH	USUBJID	C
MH	MHDECOD	C
MH	MHBODSYS	C

VS	STUDYID	C
VS	USUBJID	C
VS	VSTEST	C
VS	VSSTRESN	N
VS	VSDTC	C
VS	VSDY	N

CDISC Oncology Domains

Introduction

Assessment of the change in tumor burden is an important feature of the clinical evaluation of cancer therapeutics: both tumor shrinkage (objective response) and disease progression are useful endpoints in cancer clinical trials⁽¹⁾. RECIST (Response Evaluation Criteria in Solid Tumors)⁽²⁾ has been widely adopted in solid tumor clinical trials where the primary endpoints are objective response or progression and is accepted by regulatory authorities as an appropriate guideline for these assessments. The SDTM domains presented here were developed with RECIST Criteria in mind. However, the domains are intended to represent data collected in clinical trials where tumors are identified and then repeatedly measured/assessed at subsequent timepoints and used in an evaluation of response(s). As such these domains would be equally applicable for criteria other than RECIST e.g. Chesson classification⁽³⁾ in the assessment lymphomas, or, MacDonald Response⁽⁴⁾ in the assessment of malignant gliomas.

The tumor assessment package consists of three SDTM domains based on the SDTM Findings Observation Class. The three domains are related but each domain has a distinct purpose:

TU (Tumor Identification): The TU domain represents data that uniquely identifies tumors. The tumors are identified by an investigator and/or independent assessor and in RECIST terms this equates to the identification of Target, Non-Target or New tumors. A record in the TU domain contains the following information: a unique tumor ID value; anatomical location of the tumor; method used to identify the tumor; role of the individual identifying the tumor; and timing information.

TR (Tumor Results): The TR domain represents quantitative measurements and/or qualitative assessments of the tumors identified in the TU domain. These measurements are usually taken at baseline and then at each subsequent assessment to support response evaluations. A record in the TR domain contains the following information: a unique tumor ID value; test and result; method used; role of the individual assessing the tumor; and timing information.

Clinically accepted evaluation criteria expect that a tumor identified by the tumor ID is the same tumor at each subsequent assessment. The TR domain does not include anatomical location information on each measurement record because this would be a duplication of information already represented in TU. This duplication of data was a deciding factor in multi-domain approach to representing this data.

RS (Response): The RS domain represents the response evaluation determined from the data in TR. Data from other sources (in other SDTM domains) might also be used in an assessment of response for example, MacDonald Response Criteria includes a neurological aspect.

New variables:

--LINKID – The organization of data across the TU and TR domains requires a relrec relationship in order to link the data between the 2 domains. A dataset to dataset link would be the most appropriate linking mechanism. Utilizing one of the existing ID variables is not possible in this case because all three of the variables (GRPID, REFID & SPID) are needed (see examples). Therefore a new ID variable --LINKID is being proposed in order to support the linking requirements. The --LINKID variable is specifically designed to support a relrec dataset to dataset relationship. Values of LINKID could concatenate values of other variables when more than one variable are needed to do join data rows.

--ACPTFL – The Acceptance Flag identifies those records that have been determined to be the accepted assessments/measurements by an independent assessor. This flag should not be used by a sponsor for any other data censoring purpose. This would be used in cases where multiple assessors (e.g. RADIOLOGIST 1 & RADIOLOGIST 2) provide assessments or evaluations at the same timepoint or an overall evaluation.

--EVALID – The Evaluator Specified variable is used in conjunction with TREVAL to provide an additional level of detail. When multiple assessors play the role identified in TREVAL, values of EVALID will attribute a row of data to a

particular assessor. For example TREVAL="INDEPENDENT ASSESSOR" and TREVALID="RADIOLOGIST 1". The --EVALID variable is not subject to Controlled Terminology. When --EVALID is populated --EVAL must also be populated.

References:

- (1) E.A. Eisenhauera,* , P. Therasseb, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1) *EUROPEAN JOURNAL OF CANCER* 45 (2009) 228–247
- (2) RECIST Criteria - <http://www.eortc.be/recist/>
- (3) Bruce D. Cheson, Beate Pfistner, et al. Revised Response Criteria for Malignant Lymphoma *Journal of Clinical Oncology*. Vol 25 Number 5 Feb 10 2007
- (4) DR Macdonald, TL Cascino, et al. Response criteria for phase II studies of supratentorial malignant glioma *Journal of Clinical Oncology*, Vol 8, 1277-1280

1. Oncology Domains:

1.1. TUMOR IDENTIFICATION - TU

tu.xpt, Tumor Identification - Findings, Version 3..x.x One record per identified tumor per visit per subject, Tabulation

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
STUDYID	Study Identifier	Char		Identifier	Unique identifier for a study.	Req	SDTMIG 2.2.4
DOMAIN	Domain Abbreviation	Char	TU	Identifier	Two-character abbreviation for the domain.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.2 SDTMIG App.C2
USUBJID	Unique Subject Identifier	Char		Identifier	Identifier used to uniquely identify a subject across all studies for all applications or submissions involving the product.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.3
TUSEQ	Sequence Number	Num		Identifier	Sequence number given to ensure uniqueness within a dataset for a subject. May be any valid number.	Req	SDTMIG 2.2.4
TUGRPID	Group ID	Char		Identifier	Used to link together a block of related records within a subject in a domain.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TUREFID	Reference ID	Char		Identifier	Internal or external identifier. Example:	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TUSPID	Sponsor ID	Char		Identifier	Sponsor-defined identifier.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TULINKID	Link ID	Char		Identifier	Identifier used to link identified tumors to the assessment results over the course of the study.	Exp	
TUTESTCD	Tumor Identification Short Name	Char	*	Topic	Short name of the TEST in TUTEST. TUTESTCD cannot contain characters other than letters, numbers, or underscores. Examples: TUMIDENT, NEWTUMOR. See Assumption 2	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1
TUTEST	Tumor Identification Test Name	Char	*	Synonym Qualifier	Verbatim name of the test for the tumor/lesion identification. The value in TUTEST cannot be longer than 40 characters. Examples: Tumor Identification, New Tumor Identified. See Assumption 2	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1 SDTMIG 4.1.2.4
TUCAT	Category for Tumor Identification	Char		Grouping Qualifier	Used to categorize tumors.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6
TUSCAT	Sub-Category for Tumor Identification	Char		Grouping Qualifier	A further classification of the TUTEST.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TUORRES	Tumor Identification Result	Char	*	Result Qualifier	<p>Result of the Tumor identification. Examples: When TUTESTCD=TUMIDENT (Tumor Identification), values of TUORRES might be: TARGET or NON-TARGET.</p> <p>When TUTESTCD=NEWTUMOR the value of TUORRES might be: Y</p> <p>When TUTESTCD=BENIGNAB the value of TUORRES might be: BENIGN RENAL LESIONS</p>	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TUSTRESC	Tumor Identification Result Std. Format	Char	*	Record Qualifier	Contains the result value for all findings copied from TUORRES.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TUNAM	Vendor Name	Char		Record Qualifier	The name or identifier of the vendor that performed the Tumor Identification.	Perm	SDTM 2.2.3
TULOC	Location of the Tumor	CHAR	(LOC)	Record Qualifier	<p>Used to specify the anatomical location of the identified tumor. Example: Gastrointestinal Tract.</p> <p>Note: When anatomical location is broken down and collected as distinct pieces of data that when combined provide the overall location information (e.g. organ / laterality /location / sub-location) then the additional information should added as supplemental qualifiers. See Assumption 3</p>	Exp	SDTMIG 2.2.3
TUMETHOD	Method of Identification		*	Record Qualifier	Method used to identify the tumor. Examples: X-ray, MRI, CT-Scan.	Exp	SDTMIG 2.2.3
TUEVAL	Evaluator	Char	(EVAL)	Record Qualifier	<p>Role of the person who provided the evaluation. Examples: INVESTIGATOR, RADIOLOGIST, ONCOLOGIST</p> <p>This column can be left <i>Null</i> when the Investigator provides the complete set of data in the domain. However the column should contain no <i>Null</i> values when data from one or more independent assessors is included meaning that the rows attributed to the Investigator rows should contain a value of INVESTIGATOR</p>	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.4

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TUEVALID	Evaluator Specified	Char		Variable Qualifier	The Evaluator Specified variable is used in conjunction with TUEVAL to provide an additional level of detail. When multiple assessors play the role identified in TUEVAL, values of TUEVALID will attribute a row of data to a particular assessor. TUEVALID should not contain the names of the assessors but should contain values such as RADIOLOGIST 1 or RADIOLOGIST 2.. The TUEVALID variable would not be subject to CDISC Controlled Terminology. See Assumption 5.	Perm	
TUACPTFL	Accepted Record Flag	Char	*	Record Qualifier	In cases where more than one independent assessor (e.g. RADIOLOGIST 1 & RADIOLOGIST 2) provide independent assessments at the same timepoint this flag identifies the record that is considered to be the accepted assessment.	Perm	
VISITNUM	Visit Number	Num		Timing	1. Clinical encounter number. 2. Numeric version of VISIT, used for sorting.	Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISIT	Visit Name	Char		Timing	1. Protocol-defined description of clinical encounter. 2. May be used in addition to VISITNUM and/or VISITDY.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISITDY	Planned Study Day of Visit	Num		Timing		Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
TUDTC	Date/Time of Tumor Identification	Char	ISO 8601	Timing		Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
TUDY	Study Day of Tumor Identification	Num		Timing	1. Study day of the Tumor measurement, measured as integer days. 2. Algorithm for calculations must be relative to the sponsor-defined RFSTDTC variable in Demographics.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.4, SDTMIG 4.1.4.6

1.1.1. ASSUMPTIONS FOR THE TUMOR IDENTIFICATION DOMAIN MODEL

TU Definition: The TU domain represents data that uniquely identifies tumors. The tumors are identified by an investigator and/or independent assessor and in RECIST terms this equates to the identification of Target, Non-Target or New tumors. A record in the TU domain contains the following information: a unique tumor ID value; anatomical location of the tumor; method used to identify the tumor; role of the individual identifying the tumor; and timing information.

1. The organization of data across the TU and TR domains requires a relrec relationship in order to link the data between the 2 domains. A dataset to dataset link would be the most appropriate linking mechanism. Utilizing one of the existing ID variables is not possible in this case because all three of the variables (GRPID, REFID & SPID) are needed (see examples). The --LINKID variable is used for values that support a relrec dataset to dataset relationship and to provide a unique code for each identified tumor.
2. The values of TUTESTCD and TUTEST will be relatively simple and will either represent that the Tumor is identified and categorized at screening or that the Tumor is identified as New (has appeared since the Screening assessment).

Proposed TUTESTCD / TUTEST values for this domain:

TUTESTCD	TUTEST
TUMIDENT	Tumor Identification
NEWTUMOR	New Tumor Identified
BENIGNAB	Benign Abnormality
TUSPLIT	Tumor Split or Divided
TUMERGE	Tumor Merged or Coalesced

During the course of a trial when a new Tumor (or lesion) is identified information about that new tumor may be collected to different levels of detail. The following three scenarios represent the most commonly seen data collection methods employed when a new Tumor (or lesion) is identified. The scenarios set out below are not intended to be exhaustive. The sponsor must decide the appropriate collection method based on their analysis needs or internal processes and it is possible that a sponsor's chosen method is not reflected in the scenarios presented below.

- a. The occurrence of a New Tumor is the sole piece of information that a sponsor collects because this is a sign of disease progression and no further details are required. In such cases a record would be created where TUTEST="New Tumor Identified" and TUORRES="Y".
- b. The occurrence of a New Tumor and the anatomical location of that newly identified Tumor are the only collected pieces of information. In this case it is expected that a record would be created where TUTEST="New Tumor Identified" and TUORRES="Y", and the TULOC variable would be populated with the anatomical location information (the additional location variables may be populated depending on the level of detail collected).
- c. A sponsor might record the occurrence of a New Tumor to the same level of detail as Target and Non-Target Tumors. In this case the occurrence of the new tumor and the anatomical location information, and also measure the New Tumor. In this case it is expected that a record would be created where TUTEST="New Tumor Identified" and TUORRES="Y", and the identifier, TULINKID, would all be populated. The measurement/assessment of the New Tumor would be recorded in the TR domain.

3. TUCAT and TUSCAT have been included as they are standard domain variables however these columns would generally not be needed and so the variables are not included in the accompanying examples.
4. Anatomical Location information might be collected in a number of ways the simplest way is as a long text string and in these cases the text string is captured in the TULOC variable. However, anatomical location might also be collected through a number of distinct and separate variables (that might possibly be subject to controlled terminology) and in such cases the additional information would be recorded in the following Supplemental Qualifiers:

QNAM	QLABEL	Definition
TUSUBLOC	Sub-location of the Tumor	Anatomical location information with more specificity than a gross location
TULOCDET	Detailed Location Information	Detailed anatomical location information that would include details such as: direction (Superior, Posterior); relative direction (Proximal, Distal); axes (Dorsoventral, Mediolateral); planes (Sagittal, Coronal); and any other divisions or sub-anatomy information.
TUORGAN	Organ Affected	Actual Body Organ location of the tumor. This is more specific than Body Organ Class
TULAT	Tumor Location Laterality	Lateral location used to distinguish Right & Left sides. For example if a Tumor was located in the "Right Lung" then the TULOC and QNAM.TULAT values would be TULOC=LUNG; QNAM.TULAT=RIGHT.

5. The Acceptance Flag variable (TUACPTFL) identifies those records that have been determined to be the accepted assessments/measurements by an independent assessor. This flag should not be used by a sponsor for any other data censoring purpose. This would be used in cases where multiple assessors (e.g. RADIOLOGIST 1 & RADIOLOGIST 2) provide assessments or evaluations at the same timepoint or an overall evaluation.
6. The Evaluator Specified variable (TUEVALID) is used in conjunction with TUEVAL to provide additional detail and allows for values that might deviate from the controlled terminology expected in the TUEVAL variable. For example TUEVAL="INDEPENDENT ASSESSOR" and TUEVALID="RADIOLOGIST 1". The TUEVALID variable is not subject to Controlled Terminology. TUEVAL must also be populated when TUEVALID is populated.
7. The following proposed supplemental Qualifiers would be used to represent information regarding previous irradiation of a tumor when that information is known:

QNAM	QLABEL	Definition
PREVIR	Previously Irradiated	Indication of previous irradiation to a tumor.
PREVIRP	Irradiated then Subsequent Progression	Indication of documented progression subsequent to irradiation.

TUMOR RESULTS - TR

tr.xpt, Tumor Results - Findings, Version 3..x.x One record per tumor measurement/assessment per tumor per visit per subject, Tabulation

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
STUDYID	Study Identifier	Char		Identifier	Unique identifier for a study.	Req	SDTMIG 2.2.4
DOMAIN	Domain Abbreviation	Char	TR	Identifier	Two-character abbreviation for the domain.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.2 SDTMIG App, 2
USUBJID	Unique Subject Identifier	Char		Identifier	Identifier used to uniquely identify a subject across all studies for all applications or submissions involving the product.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.3
TRSEQ	Sequence Number	Num		Identifier	Sequence number given to ensure uniqueness within a dataset for a subject. May be any valid number.	Req	SDTMIG 2.2.4
TRGRPID	Group ID	Char		Identifier	Used to link together a block of related records within a subject in a domain.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TRREFID	Reference ID	Char		Identifier	Internal or external identifier.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TRSPID	Sponsor ID	Char		Identifier	Sponsor-defined identifier.	Perm	SDTMIG 2.2.4
TRLINKID	Link ID	Char		Identifier	Identifier used to link the assessment result records to the tumor identification record.	Exp	
TRTESTCD	Tumor Assessment Short Name	Char	*	Topic	Short name of the TEST in TRTEST. TRTESTCD cannot contain characters other than letters, numbers, or underscores. Examples: LDIAM, DIAM. See Assumption 2	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1
TRTEST	Tumor Assessment Test Name	Char	*	Synonym Qualifier	Verbatim name of the test or examination used to obtain the measurement or finding. The value in TRTEST cannot be longer than 40 characters. Examples: LONGEST DIAMETER, LONGEST PERPENDICULAR, AXIAL THICKNESS, VOLUME, AREA. See Assumption 2	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1 SDTMIG 4.1.2.4
TRCAT	Category for Tumor Assessment	Char	*	Grouping Qualifier	Used to categorize assessments. Examples: Measurement Categorical	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6
TRSCAT	Sub-Category for Tumor Assessment	Char		Grouping Qualifier	A further classification of the TRTEST.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TRORRES	Result or Finding in Original Units	Char		Result Qualifier	Result of the Tumor measurement/assessment as originally received or collected.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TRORRESU	Original Units	Char	(UNIT)	Variable Qualifier	Original units in which the data were collected. The unit for TRORRES. Example: mm	Exp	SDTMIG 2.2.3 SDTMIG 4.1.3.2
TRSTRESC	Character Result/Finding in Std Format	Char		Record Qualifier	Contains the result value for all findings, copied or derived from TRORRES in a standard format or standard units. TRSTRESC should store all results or findings in character format; if results are numeric, they should also be stored in numeric format in TRSTRESN	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TRSTRESN	Numeric Result/Finding in Standard Units	Num		Result Qualifier	Used for continuous or numeric results or findings in standard format; copied in numeric format from TRSTRESC. TRSTRESN should store all numeric test results or findings.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TRSTRESU	Standard Units	Char	(UNIT)	Variable Qualifier	Standardized unit used for TRSTRESN.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.3.2 SDTMIG 4.1.5.1
TRSTAT	Tumor Assessment Status	Char	(ND)	Result Qualifier	Used to indicate a measurement was not done, or a tumor measurement was not taken. Should be Null if a result exists in TRORRES.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.1.1
TRREASND	Reason Tumor Measurement Not Performed	Char		Record Qualifier	Describes why a measurement or test was not performed. Examples: BROKEN EQUIPMENT or SUBJECT REFUSED. Used in conjunction with TRSTAT when value is NOT DONE.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.1.1
TRNAM	Vendor Name	Char		Record Qualifier	The name or identifier of the vendor that performed the Tumor measurement or assessment.	Perm	SDTM 2.2.3
TRMETHOD	Method used to identify the Tumor		*	Record Qualifier	Method used to measure the tumor. Examples: X-ray, MRI, CT-Scan.	Exp	SDTMIG 2.2.3

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TREVAL	Evaluator	Char	(EVAL)	Record Qualifier	<p>Role of the person who provided the evaluation. Examples: INVESTIGATOR, RADIOLOGIST, ONCOLOGIST</p> <p>This column can be left <i>Null</i> when the Investigator provides the complete set of data in the domain. However the column should contain no <i>Null</i> values when data from one or more independent assessors is included meaning that the rows attributed to the Investigator rows should contain a value of INVESTIGATOR</p>	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.4
TREVALID	Evaluator Specified	Char		Variable Qualifier	<p>The Evaluator Specified variable is used in conjunction with TREVAL to provide an additional level of detail. When multiple assessors play the role identified in TREVAL, values of TREVALID will attribute a row of data to a particular assessor. TREVALID should not contain the names of the assessors but should contain values such as RADIOLOGIST 1 or RADIOLOGIST 2. The TREVALID variable would not be subject to CDISC Controlled Terminology. Note TREVAL must also be populated when TREVALID is populated. See Assumption 4</p>	Perm	
TRACPTFL	Accepted Record Flag	Char	*	Record Qualifier	<p>In cases where more than one independent assessor (e.g. where TREVALID has values of "RADIOLOGIST 1" & "RADIOLOGIST 2") provide independent assessments at the same timepoint this flag identifies the record that is considered to be the accepted assessment.</p>	Perm	
VISITNUM	Visit Number	Num		Timing	<ol style="list-style-type: none"> 1. Clinical encounter number. 2. Numeric version of VISIT, used for sorting. 	Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISIT	Visit Name	Char		Timing	<ol style="list-style-type: none"> 1. Protocol-defined description of clinical encounter. 2. May be used in addition to VISITNUM and/or VISITDY. 	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISITDY	Planned Study Day of Visit	Num		Timing		Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TRDTC	Date/Time of Tumor Measurement	Char	ISO 8601	Timing		Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
TRDY	Study Day of Tumor Measurement	Num		Timing	1. Study day of the Tumor measurement, measured as integer days. 2. Algorithm for calculations must be relative to the sponsor-defined RFSTDTC variable in Demographics.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.4, SDTMIG 4.1.4.6

1.1.2. ASSUMPTIONS FOR THE TUMOR RESULTS DOMAIN MODEL

TR Definition: The TR domain represents quantitative measurements and/or qualitative assessments of the tumors identified in the TU domain. These measurements are usually taken at baseline and then at each subsequent assessment to support response evaluations. A record in the TR domain contains the following information: a unique tumor ID value; test and result; method used; role of the individual assessing the tumor; and timing information.

- The organization of data across the TU and TR domains requires a relrec relationship in order to link the data between the 2 domains. A dataset to dataset link would be the most appropriate linking mechanism. Utilizing one of the existing ID variables is not possible in this case because all three of the variables (GRPID, REFID & SPID) are needed (see examples). The --LINKID variable is used for values that support a relrec dataset to dataset relationship and to provide a unique code for each identified tumor. TRLINKID is a required variable as the records in the TR domain must relate back to an identification record in TU.
- TRTESTCD / TRTEST values for this domain (this is for illustration purposes these values will be published as Controlled Terminology):

TRTESTCD	TRTEST
AREA	Area
AXTHICK	Axial Thickness
DIAM	Diameter
LDIAM	Longest Diameter
LMAXSP	Major Axis Axial Plane, Long Diameter Target
LPERP	Longest Perpendicular
METVOLNO	Average Metabolic SUV
MJAX3SP	Major Axis 3D (All Planes)

MNAX3SP	Minor Axis 3D
MNAXSP	Minor Axis
MXSUVSSP	Maximum SUV (1 cm Spot)
MXSUVVSP	Maximum SUV (Single Voxel)
PCCHBL	Percent Change From Baseline
PCCHNAD	Percent Change From Nadir
PREVIR	Lesion Previously Irradiated
PREVIRP	Lesion Progressing Since Irradiated
PRODUCT	Product
RADDESP	Radio Density
SAXIS	Short Axis
SUMAREA	Sum of Area
SUMAXTHK	Sum of Axial Thickness
SUMLDIAM	Sum of Longest Diameter
SUMLPERP	Sum of Longest Perpendicular
SUMPDIAM	Sum of the product of the diameters
SUMPROD	Sum of Product
SUMVOL	Sum of Volume
VOLPETSP	Total Tumor Volume
VOLUME	Volume
XPRO3SP	Cross Product 3D
XPRODSP	Cross Product

Note: The sponsor should not derive results for any test indicated in the list above (e.g. "Percent Change From Nadir") if the result was not collected. Tests would be included in the domain only if those data points have been collected on a CRF or have been supplied by an external assessor as part of an electronic data transfer. It is not intended that the sponsor would create derived records to supply those values.

3. The Acceptance Flag variable (TRACPTFL) identifies those records that have been determined to be the accepted assessments/measurements by an independent assessor. This flag should not be used by a sponsor for any other data censoring purpose. This would be used in cases where multiple assessors (e.g. RADIOLOGIST 1 & RADIOLOGIST 2) provide assessments or evaluations at the same timepoint or an overall evaluation.
4. The Evaluator Specified variable (TREVALID) is used in conjunction with TREVAL to provide additional detail and allows for values that might deviate from the controlled terminology expected in the TREVAL variable. For example TREVAL="INDEPENDENT ASSESSOR" and TREVALID="RADIOLOGIST 1". The TREVALID variable is not subject to Controlled Terminology. TREVAL must also be populated when TREVALID is populated.

RESPONSE – RS

rs.xpt, Response - Findings, Version 3..x.x One record per response assessment per visit per subject, Tabulation

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
STUDYID	Study Identifier	Char		Identifier	Unique identifier for a study.	Req	SDTMIG 2.2.4
DOMAIN	Domain Abbreviation	Char	RS	Identifier	Two-character abbreviation for the domain.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.2 SDTMIG App.C2
USUBJID	Unique Subject Identifier	Char		Identifier	Identifier used to uniquely identify a subject across all studies for all applications or submissions involving the product.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.3
RSSEQ	Sequence Number	Num		Identifier	Sequence number given to ensure uniqueness within a dataset for a subject. May be any valid number.	Req	SDTMIG 2.2.4
RSGRPID	Group ID	Char		Identifier	Used to link together a block of related records within a subject in a domain.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
RSREFID	Reference ID	Char		Identifier	Internal or external identifier.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
RSSPID	Sponsor ID	Char		Identifier	Sponsor-defined identifier.	Perm	SDTMIG 2.2.4
RSLINKID	Link ID	Char		Identifier	Used to link the response assessment to the appropriate measurement records (in TR) used to determine the response result.	Perm	
RSTESTCD	Response Assessment Short Name	Char	*	Topic	Short name of the TEST in RSTEST. RSTESTCD cannot contain characters other than letters, numbers, or underscores. Examples: TRGRES, BESTRESP, SYMPTPD	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1
RSTEST	Response Assessment Name	Char	*	Synonym Qualifier	Verbatim name of the response assessment. The value in RSTEST cannot be longer than 40 characters. Examples: Target Response, Best Overall Response, Symptomatic deterioration	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1 SDTMIG 4.1.2.4
RSCAT	Category for Response Assessment	Char		Grouping Qualifier	Used to categorize tumors.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
RSSCAT	Sub-Category for Response Assessment	Char		Grouping Qualifier	A further classification of the RSTEST.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6
RSORRES	Response Assessment Original Result	Char		Result Qualifier	Result of the Response assessment as originally received, collected, or calculated.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
RSSTRESC	Response Assessment Result in Std Format	Char		Record Qualifier	Contains the result value for the response assessment, copied or derived from RSORRES in a standard format or standard units. RSSTRESC should store all results or findings in character format; if results are numeric, they should also be stored in numeric format in RSSTRESN.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
RSSTAT	Response Assessment Status	Char	(ND)	Result Qualifier	Used to indicate the response assessment was not performed. Should be Null if a result exists in RSORRES.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.1.1
RSREASND	Reason Response Assessment Not Performed	Char		Record Qualifier	Describes why a response assessment was not performed. Examples: Subject does not have target lesions. Used in conjunction with TRSTAT when value is NOT DONE.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.1.1
RSNAM	Vendor Name	Char		Record Qualifier	The name or identifier of the vendor that performed the response assessment.	Perm	SDTM 2.2.3
RSEVAL	Evaluator	Char	(EVAL)	Record Qualifier	<p>Role of the person who provided the evaluation. Examples: INVESTIGATOR, RADIOLOGIST, ONCOLOGIST</p> <p>This column can be left <i>Null</i> when the Investigator provides the complete set of data in the domain. However the column should contain no <i>Null</i> values when data from one or more independent assessors is included meaning that the rows attributed to the Investigator rows should contain a value of INVESTIGATOR.</p>	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.4

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
RSEVALID	Evaluator Specified	Char		Variable Qualifier	The Evaluator Specified variable is used in conjunction with RSEVAL to provide an additional level of detail. When multiple assessors play the role identified in RSEVAL, values of RSEVALID will attribute a row of data to a particular assessor. RSEVALID should not contain the names of the assessors but should contain values such as RADIOLOGIST 1 or RADIOLOGIST 2. The RSEVALID variable would not be subject to CDISC Controlled Terminology. See Assumption 5	Perm	
RSACPTFL	Accepted Record Flag	Char		Record Qualifier	In cases where more than one independent assessor (e.g. independent Oncologist) provides an evaluation of response this flag identifies the record that is considered to be the accepted evaluation.	Perm	
VISITNUM	Visit Number	Num		Timing	1. Clinical encounter number. 2. Numeric version of VISIT, used for sorting.	Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISIT	Visit Name	Char		Timing	1. Protocol-defined description of clinical encounter. 2. May be used in addition to VISITNUM and/or VISITDY.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
RSDTC	Date/Time of Response Assessment	Char	ISO 8601	Timing	Date may be derived if based on multiple dates of scans Exception: derived data in RS needed for reviewer	Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
RSDY	Study Day of Response Assessment	Num		Timing	1. Study day of the Tumor measurement, measured as integer days. May be from rand date not first dose date 2. Algorithm for calculations must be relative to the sponsor-defined RFSTDTC variable in Demographics.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.4, SDTMIG 4.1.4.6

1.1.3. ASSUMPTIONS FOR THE TUMOR RESPONSE DOMAIN MODEL

RS Definition: The RS domain represents the response evaluation determined from the data in TR. Data from other sources (in other SDTM domains) might also be used in an assessment of response for example, MacDonald Response Criteria includes a neurological aspect.

1. The RSLINKID variable is used for values that support a relrec dataset to dataset relationship. RSLINKID would be required when a response evaluation relates back to an individual tumor.
2. RSTESTCD / RSTEST values for this domain (this is for illustration purposes these values will be published as Controlled Terminology):

RSTESTCD	RSTEST	Definition
TRGRESP	Target Response	
NTRGRESP	Non-target Response	
OVRLRESP	Overall Response	
BESTRESP	Best Response	
LESNRESP	Lesion Response	
SYMPTPD	Symptomatic Deterioration	

3. When an evaluation of Symptomatic Deterioration is recorded (which is symptomatic of progressive Disease) and additional description of the clinical symptoms is collected then that information would be recorded in the following Supplemental Qualifier:

QNAM	QLABEL	Definition
CLSYMP	Clinical Symptoms of PD	Textual description of clinical symptoms that led to the evaluation of Symptomatic deterioration

4. ***TS – TSPARM/TSVAL needed to represent the Response Criteria used in the clinical trial.***
5. The Evaluator Specified variable (RSEVALID) is used in conjunction with RSEVAL to provide additional detail and allows for values that might deviate from the controlled terminology expected in the RSEVAL variable. For example RSEVAL="INDEPENDENT ASSESSOR" and RSEVALID="RADIOLOGIST 1". The RSEVALID variable is not subject to Controlled Terminology. RSEVAL must also be populated when RSEVALID is populated.

DOP2's End-of-Phase 2 General Advice for Planned Marketing Applications

NDA and BLA applications must comply with all applicable statutes and regulations (e.g. 21 CFR 314, 21 CFR Part 201, and 21 CFR Parts 600 and 601). In addition, FDA has published many guidance documents (available at: www.fda.gov/RegulatoryInformation/Guidances/default.htm) that contain important information necessary for preparing a complete, quality application.

Based on our experience with marketing applications, the following tables focus on specific areas of an application and are intended to help you plan and prepare for submitting a quality application. These comments do not include all issues you need to consider in preparing an application, but highlight areas where we have seen problems and/or issues that can delay our timely review of applications. These are general comments; if you believe some are inapplicable to your planned application we encourage you to provide justification and discuss it with us.

If you will be submitting your application in CDISC format, a separate **Study Data Standards Common Issues Document** can be found at:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

The purpose of the document is to highlight important aspects of CDISC and STDM datasets that should be addressed by the Sponsor/Applicant regarding submission of CDISC data in support of an application for registration. In addition to the information and guidance provided at the above FDA link and CDISC links contained therein, the Division Oncology Products 2 (DOP2) has attached a separate document that details additional Oncology Specific domains and variables that we request be used for all oncology submissions. These domains and variable specifications have been developed by CDISC and will be included in the implementation guidance in the near future. DOP2 is using these domains

GENERAL

Special Protocol Assessment (SPA) Requests

1) It is strongly recommended that you discuss protocols for SPA request at an EOP2 meeting. The SPA protocol should be limited to one indication. Discussions of other indications may warrant another meeting. In addition, the Agency may agree that a specific finding (e.g., a particular p-value on the primary efficacy endpoint) of a study will satisfy a specific objective (e.g., demonstration of efficacy) or support an approval decision. However, final determinations are made after a complete review of a marketing application and are based on the entire data in the application.

SPA Requests for a Single Trial Intended to Support Marketing Approval:
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2) If the protocol for your SPA request is intended to be used as the sole registration trial to support marketing approval, this single trial should be optimally designed and the development program optimally planned. Therefore, you should address the following in your SPA request, and you may also briefly describe these items in your EOP2 meeting briefing document: <ul style="list-style-type: none">• Justification of why a single trial and not multiple trials are appropriate or not possible for drug development and marketing approval for an NME or substantially different indication (e.g., a study is designed to show a clinically meaningful effect on mortality, irreversible morbidity, or prevention of disease with potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible. See 'Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products').• A description of your drug development plan, including each indication that is being or has been studied and a timetable for submission of the planned studies. You should also include

information on where the drug/biologic is marketed outside of the U.S. or indicate if an application for the drug/biologic has been submitted to foreign regulators.

Additional Content for SPA Request Submission:

3) Please submit/address the items below in your SPA request.

- The protocol must be complete, including a FINAL detailed statistical analysis plan for the evaluation of primary and secondary clinical trial endpoints that potential claims will be sought. The cover letter should identify the need for an expert statistical review if the planned trial includes (1) adaptive design, (2) enrichment design, (3) non-inferiority hypotheses, or (4) novel, new or composite endpoints.
- If study is blinded, discuss toxicities of agents (or regimens) that may unmask blinding.
- If radiologic, you should discuss whether an external radiological review will be performed of primary endpoint
- If your trial uses an *in vitro* diagnostic test to identify the treatment population, you should meet with CDRH to discuss the plans for co-development of the diagnostic test prior to the SPA request. Also, you should provide your plans for a commercially available test at the time of proposed approval. The testing procedure used in your clinical trial should be identical (or "bridged") to your proposal for a commercial kit.
- If registration trial is to be primarily completed outside of the U.S., the following issues need to be addressed:
 - How assessment of safety and efficacy of U.S. minorities will be examined (e.g., will another study be conducted?)
 - Applicability of comparator treatment or of disease characteristics to U.S. population
- Any single arm submission should be accompanied by an adequate explanation of the reasons a randomized trial cannot ethically be performed.

Accelerated or Regular Approval:

4) You should include a statement of whether you are seeking approval under 21 CFR 314 Subpart H/21 CFR 601 Subpart E (accelerated approval) or regular approval in your meeting briefing document, SPA request and NDA/BLA submission. If seeking accelerated approval, there should be a description of all protocols for confirmatory trials (including a timetable for expected trial initiation(s), completion of the planned trial(s), submission of final clinical study report(s)), which under § 314.510 and 601.41 would usually be underway at the time of accelerated approval in your SPA request and NDA/BLA submission.

- If surrogate endpoint is being used for accelerated approval, you should justify (i.e., from the literature) why the proposed effect on this surrogate is reasonably likely to predict clinical benefit.

NDA/BLA content and format

CLINICAL

- 1) Original versions of all protocols, statistical analysis plans, Data Safety Monitoring Board (DSMB) and adjudication committee charters, and all amendments.
- 2) Minutes of all DSMB and efficacy endpoint review/adjudication committee meetings.
- 3) Investigator instructions that may have been produced in addition to the protocol and investigator

brochure
4) All randomization lists and, if used, IVRS datasets (in SAS transport format)
5) All datasets used to track adjudications (in SAS transport format)
6) A Reviewers Guide to the data submission that includes, but is not limited to the following: <ul style="list-style-type: none"> a) description of files and documentation b) description of selected analysis datasets c) key variables of interest, including efficacy and safety variables d) SAS codes for sub-setting and combining datasets e) coding dictionary used f) methods of handling missing data g) list of variable contained in every dataset h) listing of raw data definitions i) analysis data definitions j) annotated CRF (the annotated CRF should contain links connecting to the document that defines the variable name and lists the data sets that contain the specific item) k) documentation of programs
7) Clinical study report(s) for all trials (should follow the ICH E3 Structure and Content of Clinical Study Reports guidance (www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129456.pdf)).
8) <u>Pediatric Studies:</u> All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is exempt (i.e. orphan designation), waived or deferred. We request that you submit a pediatric plan that describes development of your product to provide important information on the safe and effective use of in the pediatric population where it may be used. If the product will not be used in pediatric populations your application must include a specific waiver request with the NDA submission, including supporting data. A request for deferral, must include a pediatric plan, certification of the grounds for deferring the assessments, and evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time.
9) <u>Quantitative Safety Analysis Plan (QSAP):</u> The QSAP should state the adverse events of special interest (AESI), the data to be collected to characterize AESIs, and quantitative methods for analysis, summary and data presentation. The QSAP provides the framework to ensure that the necessary data to understand the premarketing safety profile are obtained, analyzed and presented appropriately. When unanticipated safety issues are identified the QSAP may be amended. At a minimum the Safety Analysis Plan should address the following components: <ul style="list-style-type: none"> a) Study design considerations (See: FDA Guidance to Industry: Premarketing Risk Assessment, (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072002.pdf)). b) Safety endpoints for Adverse Events of Special Interest (AERI) c) Definition of Treatment Emergent Adverse Event (TEAE) d) Expert adjudication process (Expert Clinical Committee Charter or Independent Radiology

<p>Review Charter))</p> <p>e) Data/Safety Monitoring Committee (DSMC): (Attach Charter to QSAP)</p> <p>f) Analytical methods (e.g., data pooling or evidence synthesis): statistical principles and sensitivity analyses considered.</p>
<p>10) Integrated summaries of safety and effectiveness (ISS/ISE) as required by 21 CFR 314.50 and in conformance with the following guidance documents:</p> <p>a) Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM136174.pdf)</p> <p>b) Cancer Drug and Biological Products-Clinical Data in Marketing Applications (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071323.pdf)</p>
<p>11) Perform SMQs on the ISS adverse event data that may further inform the safety profile for your investigational agent, and include the results in the ISS report</p>
<p>12) A statement that the manufacturing facilities are ready for inspection upon FDA receipt of the application</p>
<p>13) A chronology of prior substantive communications with FDA and copies of official meeting/telecom minutes.</p>
<p>14) <u>References:</u> There should be active links from lists of references to the referenced article.</p>
<p>Studies, Data And Analyses</p>
<p>15) Provide a table listing all of the manufacturing facilities (e.g. drug product, drug substance, packaging, control/testing), including name of facility, full address including street, city, state, country, FEI number for facility (if previously registered with FDA), full name and title, telephone, fax number and email for on-site contact person, the manufacturing responsibility and function for each facility, and DMF number (if applicable).</p>
<p>16) Provide a table with the following columns for each of the completed Phase 3 clinical trials:</p> <p>a) Site number</p> <p>b) Principle investigator</p> <p>c) Location: City State, Country</p> <p>d) Number of subjects screened</p> <p>e) Number of subjects randomized</p> <p>f) Number of subjects treated who prematurely discontinued (or other characteristic of interest that might be helpful in choosing sites for inspection)</p> <p>g) Number of protocol violations (Major, minor, including definition)</p>
<p>17) Provide an assessment of safety as per the Guidance for Industry: Premarketing Risk Assessment (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072002.pdf).</p>
<p>18) Provide detailed information, including a narrative (data listings are not an acceptable substitute for a narrative), for all patients who died while on study or who terminated study drug or participation in the study prematurely including those categorized as other, lost to follow up, physician decision, or</p>

subject decision. Narrative summaries should contain the following components:

- a) subject age and gender
- b) signs and symptoms related to the adverse event being discussed
- c) an assessment of the relationship of exposure duration to the development of the adverse event
- d) pertinent medical history
- e) concomitant medications with start dates relative to the adverse event
- f) pertinent physical exam findings
- g) pertinent test results (for example: lab data, ECG data, biopsy data)
- h) discussion of the diagnosis as supported by available clinical data
- i) a list of the differential diagnoses, for events without a definitive diagnosis
- j) treatment provided
- k) re-challenge and de-challenge results (if performed)
- l) outcomes and follow-up information
- m) an informed discussion of the case, allowing a better understanding of what the subject experienced.

19) Provide complete case report forms (CRFs) for all patients with serious adverse events, in addition to deaths and discontinuations due to adverse events. You should be prepared to supply any additional CRFs with a rapid turnaround upon request.

20) Provide reports for any autopsies conducted on study.

21) For patients listed as discontinued to due “investigator decision,” “sponsor request,” “withdrew consent,” or “other,” the verbatim reason for discontinuation (as written in the CRF) should be reviewed to ensure that patients did not dropout because of drug-related reasons (lack of efficacy or adverse effects). If discrepancies are found between listed and verbatim reasons for dropout, the appropriate reason for discontinuation should be listed and patient disposition should be re-tabulated. In addition, the verbatim description from the CRF should be included as a variable in the adverse event data set.

22) Regulations require that the safety and effectiveness data be presented for subgroups including “by gender, age, and racial subgroups”. Therefore, as you are gathering your data and compiling your application, we request that you include this data and pertinent analysis

23) The clinical information contained in the NDA/BLA will be reviewed utilizing the CDER Clinical Review Template. Details of the template may be found in the Manual of Policies and Procedures (MAPP) 6010.3

(www.fda.gov/downloads/AboutFDA/ReportsManualsForms/StaffPoliciesandProcedures/ucm080121.pdf). To facilitate the review, we request you provide analyses and discussion, where applicable, that will address the items in the template, including:

- a) Other Relevant Background Information – important regulatory actions in other countries or important information contained in foreign labeling.
- b) Exposure-Response Relationships – important exposure-response assessments.
- c) Less common adverse events (between 0.1% and 1%).
- d) Laboratory Analyses focused on measures of central tendency. Also provide the normal ranges for the laboratory values.
- e) Laboratory Analyses focused on outliers or shifts from normal to abnormal. Also provide the criteria used to identify outliers.
- f) Marked outliers and dropouts for laboratory abnormalities.

- g) Analysis of vital signs focused on measures of central tendencies.
- h) Analysis of vital signs focused on outliers or shifts from normal to abnormal.
- i) Marked outliers for vital signs and dropouts for vital sign abnormalities.
- j) A comprehensive listing of patients with potentially clinically significant laboratory or vital sign abnormalities should be provided. Also, a listing should be provided of patients reporting adverse events involving abnormalities of laboratory values or vital signs, either in the “investigations” SOC or in a SOC pertaining to the specific abnormality. For example, all AEs coded as “hyperglycemia” (SOC metabolic) and “low blood glucose” (SOC investigations) should be tabulated. Analyses of laboratory values should include assessments of changes from baseline to worst value, not simply the last value.
- k) Overview of ECG testing in the development program, including a brief review of the nonclinical results.
- l) Standard analyses and explorations of ECG data.
- m) Overdose experience.
- n) Analysis and summary of the reasons and patterns of discontinuation of the study drug. Identify for each patient the toxicities that result in study discontinuation or dose reduction.
- o) Explorations for:
 - i) Possible factors associated with a higher likelihood of early study termination; include demographic variables, study site, region, and treatment assignment.
 - ii) Dosedependency for adverse findings, which should be supported by summary tables of the incidence of adverse events based on the cumulative dose and the average dose administered.
 - iii) Time dependency for adverse finding, which should be supported by analyses summarizing the length of time subjects experience adverse events and whether recovery occurs during treatment.
 - iv) Drug-demographic interactions
 - v) Drug-disease interactions
- p) Drug-drug interactions
 - i) Dosing considerations for important drug-drug interactions.
 - ii) Special dosing considerations for patients with renal insufficiency, patients with hepatic insufficiency, pregnant patients, and patients who are nursing.

24) Marketing applications must include the clinical evaluation of the potential for QT/QTc interval prolongation (see ICH E14). In oncology, alternative proposals to the "TQT" study may be appropriate. Provide all appropriate data as well as a clinical study report for any study performed to evaluate QT/QTc prolongation.

Financial Disclosure Information

25) Marketing applications must include certain information concerning the compensation to, and financial interests of, any clinical investigator conducting clinical studies, including those at foreign sites, covered by the regulation. This requires that investigators provide information to the sponsor during the course of the study and after completion. See Guidance for Industry - Financial Disclosure by Clinical Investigators (www.fda.gov/RegulatoryInformation/Guidances/ucm126832.htm).

Physician's Labeling Rule
Highlights
1) Type size for all labeling information, headings, and subheadings must be a minimum of 8 points, except for trade labeling. This also applies to Contents and the FPI. [See 21 CFR 201.57(d)(6) and Implementation Guidance]
2) The Highlights must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57(d)(8)]
3) The highlights limitation statement must read as follows: These highlights do not include all the information needed to use [insert name of drug product] safely and effectively. See full prescribing information for [insert name of drug product]. [See 21 CFR 201.57(a)(1)]
4) The drug name must be followed by the drug's dosage form, route of administration, and controlled substance symbol. [See 21 CFR 201.57(a)(2)]
5) The boxed warning is not to exceed a length of 20 lines, requires a heading, must be contained within a box and bolded, and must have the verbatim statement "See full prescribing information for complete boxed warning." Refer to 21 CFR 201.57(a) (4) and to www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm for fictitious examples of labeling in the new format (e.g., Imdicon and Fantom).
6) For recent major changes, the corresponding new or modified text in the Full Prescribing Information (FPI) must be marked with a vertical line ("margin mark") on the left edge. [See 21 CFR 201.57(d) (9) and Implementation Guidance]. Recent major changes apply to only 5 sections (Boxed Warning; Indications and Usage; Dosage and Administration; Contraindications; Warnings and Precautions).
7) The new rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights: (a) "(Drug/Biologic Product) is a (name of class) indicated for (indication(s))."
8) Propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or a rationale for why pharmacologic class should be omitted from the Highlights.
9) Refer to 21 CFR 201.57 (a) (11) regarding what information to include under the Adverse Reactions heading in Highlights. Remember to list the criteria used to determine inclusion (e.g., incidence rate).
10) A general customer service email address or a general link to a company website cannot be used to meet the requirement to have adverse reactions reporting contact information in Highlights. It would not provide a structured format for reporting. [See 21 CFR 201.57 (a) (11)].
11) Do not include the pregnancy category (e.g., A, B, C, D, X) in Highlights
12) The Patient Counseling Information statement must appear in Highlights and must read "See 17 for PATIENT COUNSELING INFORMATION." [See 21 CFR 201.57(a)(14)]
13) A revision date (i.e., Revised: month/year) must appear at the end of Highlights. [See 21 CFR 201.57(a) (15)]. For a new NDA, BLA, or supplement, the revision date should be left blank at the time of submission and will be edited to the month/year of application or supplement approval.
14) A horizontal line must separate the Highlights, Contents, and FPI. [See 21 CFR 201.57(d)(2)]

Table of Contents
15) The headings and subheadings used in the Contents must match the headings and subheadings used in the FPI. [See 21 CFR 201.57(b)]
16) The Contents section headings must be in bold type. The Contents subsection headings must be indented and not bolded. [See 21 CFR 201.57(d)(10)]
17) Create subsection headings that identify the content. Avoid using the word General, Other, or Miscellaneous for a subsection heading.
18) Only section and subsection headings should appear in Contents. Headings within a subsection must not be included in the Contents.
19) When a subsection is omitted, the numbering does not change [see 21 CFR 201.56(d) (1)]. For example, under Use in Specific Populations, subsection 8.2 (Labor and Delivery) is omitted. It must read as follows: 8.1 Pregnancy 8.3 Nursing Mothers (<i>not 8.2</i>) 8.4 Pediatric Use (<i>not 8.3</i>) 8.5 Geriatric Use (<i>not 8.4</i>)
20) When a section or subsection is omitted from the FPI, the section or subsection must also be omitted from the Contents. The heading “Full Prescribing Information: Contents” must be followed by an asterisk and the following statement must appear at the end of the Contents: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”
Full Prescribing Information (FPI)
22) Only section and subsection headings should be numbered. Do not number headings within a subsection (e.g., 12.2.1 Central Nervous System). Use headings without numbering (e.g., Central Nervous System).
23) Other than the required bolding [See 21 CFR 201.57(d) (1), (d) (5), and (d) (10)], use bold print sparingly. Use another method for emphasis such as italics or underline.
24) Do not refer to adverse reactions as “adverse events.” Please refer to the “Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format” (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075057.pdf).
25) The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. For example, [see Use in Specific Populations (8.4)] not See Pediatric Use (8.4). The cross-reference should be in brackets. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use all capital letters or bold print. [See Implementation Guidance, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075082.pdf]
26) Include only references that are important to the prescriber. [See 21 CFR 201.57(c)(16)]
27) Patient Counseling Information must follow after How Supplied/Storage and Handling section. [See 21 CFR 201.56(d)(1)] This section must not be written for the patient but rather for the prescriber so that important information is conveyed to the patient to use the drug safely and effectively. [See 21

CFR 201.57 (c)(18)]

- 28) The Patient Counseling Information section must reference any FDA-approved patient labeling or Medication Guide. [See 21 CFR 201.57(c)(18)] The reference [See FDA- Approved Patient Labeling] or [See Medication Guide] should appear at the beginning of the Patient Counseling Information section to give it more prominence.
- 29) There is no requirement that the Patient Package Insert (PPI) or Medication Guide (MG) be a subsection under the Patient Counseling Information section. If the PPI or MG is reprinted at the end of the labeling, include it as a subsection. However, if the PPI or MG is attached (but intended to be detached) or is a separate document, it does not have to be a subsection, as long as the PPI or MG is referenced in the Patient Counseling Information section.
- 30) The manufacturer information (See 21 CFR 201.1 for drugs and 21 CFR 610 – Subpart G for biologics) should be located after the Patient Counseling Information section, at the end of the labeling.
- 31) If the “Rx only” statement appears at the end of the labeling, delete it. This statement is not required for package insert labeling, only container labels and carton labeling. [See Guidance for Industry: Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 – Elimination of Certain Labeling Requirements]. The same applies to PPI and MG.
- 32) Refer to www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm for fictitious examples of labeling in the new format.
- 33) Refer to the Institute of Safe Medication Practices’ website (<http://www.ismp.org/Tools/abbreviationslist.pdf>) for a list of error-prone abbreviations, symbols, and dose designations.

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

/s/

MELANIE B PIERCE

06/06/2013

LATE-CYCLE COMMUNICATION
DOCUMENTS



NDA 205755

LATE-CYCLE MEETING MINUTES

Novartis Pharmaceuticals Corporation
Attention: Yanina Gutman, Pharm.D.
Senior Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936

Dear Dr. Gutman:

Please refer to your New Drug Application (NDA) dated December 24, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ceritinib, 150 mg capsules.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on March 28, 2014.

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, call Ms. Karen Boyd, Senior Regulatory Project Manager at (301) 796-7032.

Sincerely,

{See appended electronic signature page}

Gideon Blumenthal, M.D.
Clinical Team Leader
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: March 28, 2014, 12:00 PM to 1:30 PM
Meeting Location: Teleconference

Application Number: NDA 205755
Product Name: Zykadia (ceritinib)
Applicant Name: Novartis Pharmaceuticals Corporation

Meeting Chair: Gideon Blumenthal, M.D.
Meeting Recorder: Karen Boyd

FDA ATTENDEES

Richard Pazdur, M.D., Office Director, OHOP
Tamy Kim, Pharm.D., Associate Director of Regulatory Affairs, OHOP
Patricia Keegan, M.D., Division Director, OHOP/DOP2
Gideon Blumenthal, M.D., Clinical Team Leader, OHOP/DOP2
Sean Khozin, M.D., Clinical Reviewer, OHOP/DOP2
Karen Boyd, M.S., Senior Regulatory Project Manager, OHOP/DOP2
Monica Hughes, M.S., Chief, Project Management Staff, OND/OHOP/DOPII
Lijun Zhang, Ph.D., Biostatistics Reviewer, OB
Shenghui Tang, Ph.D., Biostatistics Team Leader, OB
Emily Fox, Ph.D, Nonclinical reviewer, OHOP/DHOT
Alex Putman, Ph.D., Acting Nonclinical Team Leader, OHOP/DHOT
Ruby Leong, Pharm.D., Clinical Pharmacology Reviewer, OCP/DCPV
Hong Zhao, Ph.D., Clinical Pharmacology Team Leader, OCP/DCPV
Pengfei Song, Ph.D., Pharmacometrics reviewer, OCP/DCPV
Nam Atiqur Rahman, Ph.D., Division Director, OCP/DCPV
Jean Tang, Ph.D., Quality Reviewer, OPS/ONDQA/DNDQAI/BRII
Afrouz Nayernama, Ph.D., Health Scientist, OSE/OPE/DPVII
Lauren Iacono-Connors, Clinical Inspection Reviewer, OC/OSI
Sharon Mills, Patient Labeling reviewer, OMP/OMPI/DMPP
Quynh Tran, Regulatory Project Manager, OMP/OPDP/DPDP
Jeannine Best, Lead Clinical Analyst, OND/PMHS
Robert Wittorf, Pharm.D., Manufacturing Inspection Reviewer, OC/OMPQ/DGMPA

EASTERN RESEARCH GROUP ATTENDEES

Patrick Zhou, Independent Assessor

APPLICANT ATTENDEES

Alessandro Riva, MD, President, Novartis Oncology
Gabriela Gruia, MD, Global Head Drug Regulatory Affairs

Margaret Dugan, MD, Senior VP, Global Program Head
Andrea Kay, MD, VP, Senior Global Clinical Program Head
Andrew Joe, MD, Senior Global Clinical Leader
Alicia Rossiter, MD, FCP, Executive Director / Group Head, Integrated Medical Safety
Nassir Habboubi, MD, VP, US Clinical Development and Medical Affairs
Margarida Geraldes, PhD, Director, Biostatistics
Yvonne Lau, PhD, Senior Fellow, Oncology Clinical Pharmacology
Diane Zezza, PhD, Global Head Regulatory CMC
Thomas Gengenbacher, PhD, Franchise Head – Regulatory CMC
Marian Misun, PhD, Technical Project Team Leader
Erika Zannou, PhD, Oncology Franchise Head - TRD
Frank Grande, MS, Regulatory-CMC
Shanthi Ganeshan, PhD, North America Region Head, Drug Regulatory Affairs
Anne Frederick, PhD, Executive Director, Global Program Regulatory Director
Nina Gutman, PharmD, Senior Associate Director, Drug Regulatory Affairs

BACKGROUND

NDA 205755 was submitted on December 24, 2014 for ceritinib.

Proposed indication(s): Treatment of patients with [REDACTED] (b) (4) metastatic non-small cell lung cancer (NSCLC) who have [REDACTED] (b) (4)

PDUFA goal date: August 24, 2014

FDA issued a Background Package in preparation for this meeting on March 27, 2014.

DISCUSSION

1. **Introductory Comments** – 5 minutes: Welcome, Introductions, Ground rules, Objectives of the meeting

Discussion during the meeting: Novartis was welcomed to the late cycle meeting, followed by introductions by FDA and Novartis. Dr. Blumenthal went over the ground rules and objectives of the meeting, specifically that the purpose of the meeting is to give Novartis and the FDA review team the opportunity to discuss the status of the review late in the review cycle. The late cycle meeting is intended to enhance transparency and communication between Novartis and the FDA review team. FDA also communicated that the review is still ongoing, and we will not provide information about the final regulatory action at this meeting.

2. **Discussion of Substantive Review Issues – 10 minutes.**

A. Agreement has not been reached on the design of the post-marketing requirement to conduct a study evaluating of the safety and exposure of ceritinib 450 mg taken with meals.

Discussion during the meeting: Novartis proposed to test 600 mg of ceritinib with a (b) (4) for the postmarketing requirement (PMR). FDA stated that the proposed 600 mg dose with a (b) (4) light meal study would not be able to address the safety concern because taking a 600 mg dose with a meal would result in higher systemic exposure than taking 750 mg in the fasted state, potentially leading to increased toxicity. FDA further stated that a dose of 450 mg taken with a meal is recommended to match the systemic exposure of the dose of 750 mg taken in the fasting state. After further discussion, FDA and Novartis agreed to add an arm to the PMR that tests 450 mg of ceritinib with a meal. So, the final PMR would include a 450 mg arm with a meal, and FDA did not object to a 600 mg arm with a (b) (4), provided appropriate safety measures are instituted. In addition, Novartis did not agree that the labeling (b) (4)

however, more data from the single dose healthy volunteer food effect study will be provided in section 12.3, (b) (4)

Novartis agreed with this compromise.

3. **Additional Applicant Data – Time TBD (Applicant)**

Discussion during the meeting: Novartis did not have additional data to discuss.

4. **Information Requests – 10 minutes**

The following information requests are outstanding as of March 26, 2014: CMC information requests made on February 27 and March 18, 2014 (reproduced below). Novartis should submit the requested information as agreed upon during the teleconferences on March 19, and March 24, 2014.

FDA Information Request sent via email on 2/27/14:

- A. To ensure the batch to batch consistency, add drug substance specification (acceptance criteria) for particle size at (b) (4).
- B. Add a drug substance specification (acceptance criterion) for (b) (4) to confirm that the drug substance (b) (4)

FDA Information Request sent via email on 3/18/14:

- A. Your response provided is not acceptable. Your (b) (4) studies of Ceritinib hard gelatin capsules at 25 °C/60%RH for 6 months did not show any impact on appearance, assay, purity and dissolution. However, (b) (4) may also

impact microbial attributes. Therefore, propose acceptance criteria for (b) (4) (b) (4) in the drug product specification. (b) (4) specification (b) (4) has no impact on the quality of the capsule.

- B. In the Figure 1-1 of your March 12, 2014, response #2, there is an unknown impurity at (b) (4), which is next to the main peak at (b) (4). Please include the Resolution in the system suitability criteria in order to ensure the separation between these two peaks.

Discussion during the meeting: Novartis stated that they officially submitted responses to these information requests. FDA confirmed that we received them.

5. **Postmarketing Requirements/Postmarketing Commitments – 20 minutes**

- A. Subpart H Post-Marketing Requirement: Conduct and submit the results of a multicenter, randomized study establishing the superiority of oral LDK378 over standard chemotherapy in adult patients with ALK-rearranged (ALK-positive) (b) (4) metastatic NSCLC who have been treated previously with one chemotherapy regimen (platinum doublet) and crizotinib.

Novartis—please propose reasonable timelines for Final Protocol submission, Study/Trial Completion, and Final Report submission.

- B. Subpart H Post-Marketing Requirement: Conduct and submit the results of a multicenter, randomized study establishing the superiority of oral LDK378 over standard chemotherapy in previously untreated adult patients with ALK rearranged (ALK-positive), stage IIIB or IV, non-squamous non-small cell lung cancer.

Novartis—please propose reasonable timelines for Final Protocol submission, Study/Trial Completion, and Final Report submission.

- C. Post-Marketing Requirement: Conduct a clinical trial to evaluate the safety and systemic exposure of 450 mg ceritinib taken daily with a meal as compared with that of 750 mg ceritinib taken daily in the fasted state in metastatic ALK-positive NSCLC patients.

Novartis—please propose reasonable timelines for Final Protocol submission, Study/Trial Completion, and Final Report submission

- D. Post-Marketing Requirement: Complete a pharmacokinetic trial to determine the appropriate dose of ceritinib in patients with hepatic impairment in accordance with the FDA Guidance for Industry entitled “Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.”

Final Protocol Submission: submitted;

Study/Trial Completion: 01/31/2016;
Final Report Submission: 06/30/2016.

- E. Post-Marketing Requirement: Conduct a clinical trial to evaluate the effect of repeat doses of ceritinib on the single dose pharmacokinetics of midazolam (a sensitive CYP3A4 substrate) in accordance with the FDA Guidance for Industry entitled “Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations.”

Final Protocol Submission: 09/30/2014;
Study/Trial Completion: 08/31/2016;
Final Report Submission: 02/28/2017.

- F. Post-Marketing Requirement: Conduct a clinical trial to evaluate the effect of repeat doses of ceritinib on the single dose pharmacokinetics of warfarin (a sensitive CYP2C9 substrate) in accordance with the FDA Guidance for Industry entitled “Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations.”

Final Protocol Submission: 09/30/2014;
Study/Trial Completion: 08/31/2016;
Final Report Submission: 02/28/2017.

- G. Post-Marketing Requirement: Conduct a clinical trial to evaluate if proton pump inhibitors, H₂-receptor antagonists, and antacids alter the bioavailability of ceritinib and to determine how to dose ceritinib with regard to concomitant gastric acid reducing agents.

Final Protocol Submission: 01/31/2015;
Study/Trial Completion: 08/31/2015;
Final Report Submission: 02/29/2016.

- H. Post Marketing Commitment: Submit a revised testing monograph (TM) that will include a (b) (4) method and specification for LDK378 drug product (capsule content) as post-approval commitment.

The updated TM will be submitted by 30-April-2014.

- I. Post Marketing Commitment: Submit 9 months stability data for the 3 registration stability batches (batches 1010000660, 1010000958 and 1010001326) and up to 24 months for one batch from supportive stability (batch AEUS/2012-0023).

The updated stability data will be submitted by 16-May-2014.

Discussion during the meeting: FDA clarified that these are draft PMRs and PMCs, and PMR A and B, listed above, will be combined into one PMR. FDA will send draft language for Novartis' consideration after the late cycle meeting, and Novartis will need to propose timelines and milestones. Novartis clarified if they would be required to demonstrate the superiority of ceritinib over standard therapy in both study 2301 and 2303 to convert from accelerated to regular approval. FDA replied that it would depend on the magnitude of the effect, but likely would only need to demonstrate superiority in one of the studies. Regarding PMR F listed above, Novartis asked if they could substitute (b) (4) for warfarin. FDA did not agree with this substitution, as (b) (4) is not a sensitive CYP2C9 substrate according to the FDA Guidance for Industry. Regarding PMR G listed above, Novartis asked if (b) (4) would be acceptable. FDA agreed, stating that a proton pump inhibitor (PPI) could be evaluated as the worst case scenario. In the event that concomitant administration of a PPI has a large impact on ceritinib exposure, an H₂-receptor antagonist and an antacid should be subsequently evaluated.

6. **Major labeling issues – 30 minutes**

Discussion during the meeting: The following sections of the label were discussed at the meeting; 1, 2.1, 2.2, 5.1, 5.2, 5.3, 5.5, 6, 6.1, and 14.

7. **Status of inspections- 2 minutes**

Discussion during the meeting: FDA communicated that all clinical inspections were complete. Determination of the classification for each inspection is pending receipt and complete review of each Establishment Inspection Report. FDA also communicated that the manufacturing and facility inspections were ongoing and there are no issues to report as of today. FDA plans to complete all inspections prior to the action date.

8. **Review Plans – 1 minute**

Discussion during the meeting: FDA communicated that reviews are ongoing and FDA plans to hold a wrap up meeting on April 8, 2014.

9. **Wrap-up and Action Items – 2 minutes**

Discussion during the meeting: FDA wanted to communicate to Novartis that there are ongoing discussions regarding the expiration date of ceritinib. FDA will communicate the results of these discussions mid- to late- next week.

Action items:

- a. FDA will send the latest label to Novartis (with changes made during the late cycle meeting).
- b. FDA and Novartis will schedule a meeting the week of March 31-April 4 to discuss the remaining sections of the label.

- c. FDA will send Novartis updated PMR for subpart H requirements, and Novartis will send FDA associated milestones and timelines.
- d. Novartis will send FDA updated language and associated milestones and timeline for PMR 5C (listed above).

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

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/s/

GIDEON M BLUMENTHAL
04/15/2014



NDA 205755

**LATE CYCLE MEETING
BACKGROUND PACKAGE**

Novartis Pharmaceuticals Corporation
Attention: Yanina Gutman, Pharm.D.
Senior Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936

Dear Dr. Gutman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ceritinib capsules, 150 mg.

We also refer to the Late-Cycle Meeting (LCM) scheduled for March 28, 2014. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Ms. Karen Boyd, Senior Regulatory Project Manager, at (301) 796-7032.

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
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: March 28, 2014, 12:00pm to 1:30pm

Meeting Location: Teleconference

Application Number: NDA 205755

Product Name: Ceritinib

Indication: Treatment of patients with (b) (4) metastatic non-small cell lung cancer (NSCLC) who have (b) (4)

Sponsor/Applicant Name: Novartis Pharmaceuticals Corporation

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, we may not be prepared to discuss that new information at this meeting.

DISCIPLINE REVIEW LETTERS

No Discipline Review letters have been issued.

CURRENT SUBSTANTIVE REVIEW ISSUES

The following substantive review issues have been identified to date:

Clinical/Clinical Pharmacology

1. Final agreement on the post marketing study of the safety and exposure of ceritinib 450 mg with meals has not been reached. FDA needs the applicant's final agreement to this study and milestone timelines.

POST-MARKETING REQUIREMENTS AND COMMITMENTS

Novartis has been informed of the following post-marketing requirements and comments –

1. Subpart H Post-Marketing Requirement: Conduct and submit the results of a multicenter, randomized study establishing the superiority of oral LDK378 over standard chemotherapy in adult patients with ALK-rearranged (ALK-positive) (b) (4) metastatic NSCLC who have been treated previously with one chemotherapy regimen (platinum doublet) and crizotinib.

Novartis—please propose reasonable timelines for Final Protocol submission, Study/Trial Completion, and Final Report submission.

2. Subpart H Post-Marketing Requirement: Conduct and submit the results of a multicenter, randomized study establishing the superiority of oral LDK378 over standard chemotherapy in previously untreated adult patients with ALK rearranged (ALK-positive), stage IIIB or IV, non-squamous non-small cell lung cancer.

Novartis—please propose reasonable timelines for Final Protocol submission, Study/Trial Completion, and Final Report submission.

3. Post-Marketing Requirement: Conduct a clinical trial to evaluate the safety and systemic exposure of 450 mg ceritinib taken daily with a meal as compared with that of 750 mg ceritinib taken daily in the fasted state in metastatic ALK-positive NSCLC patients.

Novartis—please propose reasonable timelines for Final Protocol submission, Study/Trial Completion, and Final Report submission.

4. Post-Marketing Requirement: Complete a pharmacokinetic trial to determine the appropriate dose of ceritinib in patients with hepatic impairment in accordance with the FDA Guidance for Industry entitled “Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.”

Final Protocol Submission: submitted;
Study/Trial Completion: 01/31/2016;
Final Report Submission: 06/30/2016.

5. Post-Marketing Requirement: Conduct a clinical trial to evaluate the effect of repeat doses of ceritinib on the single dose pharmacokinetics of midazolam (a sensitive CYP3A4 substrate) in accordance with the FDA Guidance for Industry entitled “Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations.”

Final Protocol Submission: 09/30/2014;

Study/Trial Completion: 08/31/2016;
Final Report Submission: 02/28/2017.

6. Post-Marketing Requirement: Conduct a clinical trial to evaluate the effect of repeat doses of ceritinib on the single dose pharmacokinetics of warfarin (a sensitive CYP2C9 substrate) in accordance with the FDA Guidance for Industry entitled “Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations.”

Final Protocol Submission: 09/30/2014;
Study/Trial Completion: 08/31/2016;
Final Report Submission: 02/28/2017.

7. Post-Marketing Requirement: Conduct a clinical trial to evaluate if proton pump inhibitors, H₂-receptor antagonists, and antacids alter the bioavailability of ceritinib and to determine how to dose ceritinib with regard to concomitant gastric acid reducing agents.

Final Protocol Submission: 01/31/2015;
Study/Trial Completion: 08/31/2015;
Final Report Submission: 02/29/2016.

8. Post Marketing Commitment: Submit a revised testing monograph (TM) that will include a (b)(4) method and specification for LDK378 drug product (capsule content) as post-approval commitment.

The updated TM will be submitted by 30-April-2014.

9. Post Marketing Commitment: Submit 9 months stability data for the 3 registration stability batches (batches 1010000660, 1010000958 and 1010001326) and up to 24 months for one batch from supportive stability (batch AEUS/2012-0023).

The updated stability data will be submitted by 16-May-2014.

ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

REMS OR OTHER RISK MANAGEMENT ACTIONS

Based upon review of the NDA, FDA will not require a REMS.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at CFR 201.56(a) and (d) and 201.57. We encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information website including:

- The Final Rule (Physician Labeling Rule) on the content and format of 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.

During our preliminary review of your submitted labeling, we identified labeling issues and communicated our proposed changes via electronic mail (email) on Friday, March 21, 2014.

We requested that you resubmit labeling (in Microsoft Word format) that addresses these issues by 12:00 PM EST on March 27, 2014. The resubmitted labeling will be used for further labeling discussions. At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

LATE CYCLE MEETING AGENDA

1. **Introductory Comments** – 5 minutes: Welcome, Introductions, Ground rules, Objectives of the meeting
2. **Discussion of Substantive Review Issues** – 10 minutes. Please refer to the background information for FDA's assessment of each issue.
 - A. Agreement has not been reached on the design of the post-marketing requirement to conduct a study evaluating of the safety and exposure of ceritinib 450 mg taken with meals.

This issue will be introduced by FDA and followed by a discussion.
3. **Additional Applicant Data** – Time TBD (Applicant)
4. **Information Requests** – 10 minutes

The following information requests are outstanding as of March 26, 2014: CMC information requests made on February 27 and March 18, 2014 (reproduced below). Novartis should submit the requested information as agreed upon during the teleconferences on March 19, and March 24, 2014.

FDA Information Request sent via email on 2/27/14:
 - A. To ensure the batch to batch consistency, add drug substance specification (acceptance criteria) for particle size at [REDACTED]^{(b)(4)}.

- B. Add a drug substance specification (acceptance criterion) for (b) (4) to confirm that the drug substance has (b) (4)

FDA Information Request sent via email on 3/18/14:

- A. Your response provided is not acceptable. Your (b) (4) studies of Ceritinib hard gelatin capsules at 25 °C/60%RH for 6 months did not show any impact on appearance, assay, purity and dissolution. However, (b) (4) may also impact microbial attributes. Therefore, propose acceptance criteria for (b) (4) in the drug product specification. (b) (4) specification (b) (4) has no impact on the quality of the capsule.
- B. In the Figure 1-1 of your March 12, 2014, response #2, there is an unknown impurity at (b) (4), which is next to the main peak at (b) (4). Please include the Resolution in the system suitability criteria in order to ensure the separation between these two peaks.

5. **Postmarketing Requirements/Postmarketing Commitments – 20 minutes**

- A. Subpart H Post-Marketing Requirement: Conduct and submit the results of a multicenter, randomized study establishing the superiority of oral LDK378 over standard chemotherapy in adult patients with ALK-rearranged (ALK-positive) (b) (4) metastatic NSCLC who have been treated previously with one chemotherapy regimen (platinum doublet) and crizotinib.

Novartis—please propose reasonable timelines for Final Protocol submission, Study/Trial Completion, and Final Report submission.

- B. Subpart H Post-Marketing Requirement: Conduct and submit the results of a multicenter, randomized study establishing the superiority of oral LDK378 over standard chemotherapy in previously untreated adult patients with ALK rearranged (ALK-positive), stage IIIB or IV, non-squamous non-small cell lung cancer.

Novartis—please propose reasonable timelines for Final Protocol submission, Study/Trial Completion, and Final Report submission.

- C. Post-Marketing Requirement: Conduct a clinical trial to evaluate the safety and systemic exposure of 450 mg ceritinib taken daily with a meal as compared with that of 750 mg ceritinib taken daily in the fasted state in metastatic ALK-positive NSCLC patients.

Novartis—please propose reasonable timelines for Final Protocol submission, Study/Trial Completion, and Final Report submission

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The updated stability data will be submitted by 16-May-2014.

6. **Major labeling issues** – 30 minutes
7. **Status of inspections**- 2 minutes
8. **Review Plans** – 1 minute
The FDA reviews are ongoing and FDA plans to hold a wrap up meeting on April 8, 2014.
9. **Wrap-up and Action Items** – 2 minutes

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/s/

PATRICIA KEEGAN
03/27/2014