CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205266Orig1s000

ADMINISTRATIVE and CORRESPONDENCE

EXCLUSIVITY SUMMARY

NDA # 205266 SUPPL # HFD # 107

Trade Name Odomzo

Generic Name sonidegib

Applicant Name Novartis Pharmaceuticals Corporation

Approval Date, If Known July 24, 2015

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.

N/A

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:

N/A

Reference ID: 3786176

d) Did the applicant request exclusivity?

YES ☒ NO ☐

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

No time period is specified, applicant referred to CFR 314.108 (b)(2) in exclusivity request contained in the original NDA submission. Novartis notes that sonidegib has not previously been approved under section 505(b) of the Federal Food, Drug and Cosmetic Act. Sonidegib is a new chemical entity as defined under 21 CFR 314.108(a).

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?

N/A

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 ☒

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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."

Reference ID: 3786176

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:

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(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?

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Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

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

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

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

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

Investigation #1

IND # YES ☐ NO ☐
Explain:

Investigation #2

IND # YES ☐ NO ☐
Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not

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identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES ☐ NO ☐
Explain: Explain:

Investigation #2

YES ☐ NO ☐
Explain: Explain:

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

YES ☐ NO ☐

If yes, explain:

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Name of person completing form: Anuja Patel, M.P.H.
Title: Senior Regulatory Health Project Manager
Date: May 26, 2015

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

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

Reference ID: 3786176

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
06/30/2015

PATRICIA KEEGAN
06/30/2015

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 205266 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: N/A *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Odomzo Established/Proper Name: sonidegib Dosage Form: 200 mg oral capsules		Applicant: Novartis Pharmaceuticals Corporation Agent for Applicant (if applicable): N/A
RPM: Anuja Patel		Division: Division of Oncology Products 2

NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☐ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check:

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.

❖ Actions	
• Proposed action • User Fee Goal Date is 9.26.15	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ 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 N/A	☐ Received
❖ 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, 505(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.

Reference ID: 3801773

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): Type 1
(confirm chemical classification at time of approval)

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ 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

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☒ MedGuide w/o REMS
☒ REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☐ No
• Indicate what types (if any) of information were issued	☐ None ☒ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☒ Other: ASCO Burst and ☒ Information Advisory
❖ 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	☒ No ☐ 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.	☒ Verified – form submitted 9/26/14 ☐ 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 *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) Approval 7.24.15
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included -Novartis revised labeling received 7.23.15
• Original applicant-proposed labeling	☒ Included -Revised labeling submitted 1.23.15 (included updated safety data based on cut off of 7.11.14) -Revised labeling submitted 1.6.15 in response to filing communication -Original label submitted 9.26.14
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☒ Medication Guide (MG) -Revised MG submitted with PI 1.23.15 -Revised MG submitted with PI 1.6.15 in response to filing communication -Original MG submitted 9.26.14 ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included Attached to Package Insert
• Original applicant-proposed labeling	☒ Included Attached to Package Insert
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included - revised container labeling for the 30-count bottle, (b) (4) and unit-dose blister, as well as revised unit-dose carton labeling submitted 6.12.15 (b) (4)
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	- Acceptability letter issued 11.26.14 -Proprietary Name Review uploaded 11.25.14

❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☐ None: review uploaded 11.25.14 DMEPA: ☐ None; reviews uploaded 6.15.15; 5.13.15; and 11.21.14 DMPP/PLT (DRISK): ☐ None DMPP review uploaded 5.28.15 OPDP: ☐ None OPDP review uploaded 5.28.15 SEALD: ☒ None CSS: ☒ None Product Quality ☒ None Other: ☒ DPMH review uploaded 4.16.15 ☐ None
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	Completed 11.25.15 ☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP ○ If yes, Center Director's Exception for Review memo *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC Reviewed by PERC January 28, 2015. Memo to file in Action Binder If PeRC review not necessary, explain: N/A	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) *(do not include previous action letters, as these are located elsewhere in package)*	• 7.22.15 FDA modifications to PI in response to 7.21.15 submission • 7.22.15 FDA email in agreement to proposed edits regarding Warning and Precautions (Section 5.2) received via email 7.21.2015 • 7.16.15 FDA modifications to PI in response to 7.13.15 submission and in response to 7.16.15 tcon • 7.16.15 FDA modification to PI in response to 6.13.15 submission • 7.9.15 FDA Email stating no further comments on carton and Container submission received

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

	on 6.12.15 • 7.8.15 FDA proposed modifications to PI following 6.8.15 teleconference • 7.6.15 FDA proposed modifications to PI and MG submitted 6.5.15 • 6.30.15 Nonclinical PMR Communication • 6.29.15 Nonclinical PMR Communication • 6.19.15 Nonclinical PMR Communication • 6.14.15 DPMH Comments on draft protocol for Pregnancy Monitoring received 6.2.15 • 6.2.15 Clinical (Pregnancy Monitoring) and Clinical Pharmacology PMR Communications • 5.29.15 OPDP/OMPP edits to Med Guide • 5.28.15 Late Cycle Meeting (LCM) Agenda • 5.26.15 Information Request (IR) • 5.14.15 FDA Preliminary edits to PI • 5.12.15 Comments Re: Pregnancy PMR • 5.7.15 Confirmation of sponsor tcon • 4.28.15 LCM Meeting Confirmation • 4.28.15- FDA Preliminary edits on carton and container labeling • 4.25.15 Clinical IR • 4.14.15 CMC IR letter • 4.15.15 Clinical IR • 3.26.15 Clinical IR • 3.25.15 CMC IR letter • 3.20.15 Clinical IR • 3.13.15 Midcycle Communication letter • 3.9.15 Statistical IR (follow-up to 3.5.15IR) *uploaded in DARRTS 3.12.15* • 3.5.15 Statistical IR • 3.3.15 Midcycle Agenda (Followup Clarification on Pregnancy PMR) • 3.3.15 Midcycle Agenda • 2.26.15 CMC IR letter • 2.24.15 FDA Drug Trials Snapshot on FDA Website

	(followup to sponsor request for review of tables) • 2.13.15 Clinical and Clinical Pharmacology IR • 2.11.15 Clinical IR *uploaded in DARRTS 2.12.15* • 2.11.15 FDA Drug Trials Snapshot on FDA Website Memo • 2.6.15 Proposed dates for Midcycle • 1.30.15 CMC IR letter • 1.26.15 Clinical IR • 1.26.15 Clinical Pharmacology IR • 1.21.15 Clinical Pharmacology IR • 1.19.15 Clinical IR • 1.12.15 Clinical IR • 1.11.15 Clinical Pharmacology IR (PMR for hepatic impairment) *uploaded in DARRTS 1.12.15* • 1.7.15 Clinical and Clinical Pharmacology (QT-IRT) IR • 12.18.14 Clinical and Clinical Pharmacology IR • 12.9.14 Filing Communication • 12.2.14 Regulatory IR (CRO Contact Information) • 11.16.14 DRISK IR • 11.12.14 Statistical IR • 11.7.14 Clinical Pharmacology IR • 10.27.14 General Advice letter (Granting AO Meeting) • 10.7.14 NDA Acknowledgement letter • 10.2.14 Proposed Proprietary Name (OSE) IR *The following communications were sent under the IND:* • 9.13.14 Clinical Advice Letter • 9.10.14 Clinical IR • 9.8.14 Clinical Advice letter under IND • 8.13.14 Clinical Email (re: 120 day safety update) • 8.1.14 CMC Advice letter under IND • 7.21.14 CMC Advice letter under IND • 2.6.14 Confirmation of Agreed iPSP letter • 12.9.13 Agreed iPSP letter

	• 3.6.13 Meeting Denied letter • 7.8.13 Advice Letter
❖ 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)	• 7.21.15 Sponsor Tcon Summary to discuss labeling • 7.16.15 Sponsor Tcon Summary to discuss labeling • 7.8.15 Sponsor Tcon to discuss labeling • 5.28.15 SGE Tcon Summary with Dr. John Digiovanna *uploaded in DARRTS 5.20.15* • 5.14.15 Weekly Sponsor Tcon (discussion of Pregnancy PMR and 2 Clinical Pharmacology PMRs) *uploaded in DARRTS 5.20.15* • 5.13.15 SGE Tcon Summary with patient Rep. Ms. Kristi Burr *uploaded in DARRTS 6.15.15* • 5.13.15 SGE Tcon Summary with Dr. June Robinson *uploaded in DARRTS 5.29.15* • 4.16.15 Weekly Sponsor Tcon (Discuss Clinical and Bioequivalence IRs) *uploaded in DARRTS 5.8.15* • 4.14.15 Internal Labeling Meeting *uploaded in DARRTS 5.8.15* • 4.8.15 Internal Labeling Meeting *uploaded in DARRTS 5.8.15* • 3.25.15 Internal Labeling Meeting *uploaded in DARRTS 5.8.15* • 3.23.15 Internal Labeling Meeting *uploaded in DARRTS 5.8.15* • 3.18.15 Internal Labeling Meeting *uploaded in DARRTS 5.8.15* • 3.12.15 Internal Labeling Meeting *uploaded in DARRTS 5.8.15* • 2.19.15 Internal Midcycle Meeting Summary *uploaded in DARRTS 3.9.15* • 1.16.15 Internal Monthly Meeting *uploaded in DARRTS 2.6.15* • 10.21.15 Internal Planning Meeting Summary *uploaded in DARRTS 2.27.15* • 10.17.14 Division Director's

	Standard Review Designation Memorandum IND Internal Meeting Minutes: • 8.8.13 Informal Tcon to discuss Protocol CLDE225A2201 uploaded in DARRTS 8.15.13
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☐ N/A or no mtg Internal Wrap Up Meeting : 6.15.2015 *Uploaded in DARRTS* 7.29.15
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg Pre-NDA Meeting Held April 15, 2014 *uploaded in DARRTS 5.14.14*
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg Type B EOP 1 Meeting Held June 9, 2011 *uploaded in DARRTS 7.13.11*
• Mid-cycle Communication *(indicate date of mtg)*	☐ N/A Meeting Held March 5, 201; Midcycle Communication *uploaded in DARRTS 3.13.15*
• Late-cycle Meeting *(indicate date of mtg)*	☐ N/A Sponsor F2F Late Cycle Meeting: June 9, 2015; *Issued 7.9.15*
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	N/A
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None *signed 7.24.15*
Division Director Summary Review *(indicate date for each review)*	☐ None *signed 7.22.15*
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None *review uploaded in DARRTS 6.12.15*
PMR/PMC Development Templates *(indicate total number)*	☐ None - 2 Clinical Pharmacology PMRs *uploaded in DARRTS 6.11.15* - 1 Clinical PMR *uploaded in DARRTS 6.24.15* - 2 Nonclinical PMRs *uploaded in DARRTS 7.9.15 (2)*
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Clinical review(s) *(indicate date for each review)*	Addendum to Clinical Review *signed 7.23.15* Review 5.29.15 *Signed* 6.1.15; Review 12.3.14 of SDN 4 and 5 that includes applicant's response to 11.12.14 IR

	Filing Review uploaded in DARRTS 11.19.14
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	On page 26 of 6.1.15 Clinical review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • 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)*	Risk Management Plan submitted 9.26.14 (SDN 1); Amended Risk Management Plan submitted 1.23.15(SDN 18) ☐ None Review 6.4.15 *Uploaded in DARRTS 6.5.15*
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☐ None requested • 2.29.15 (2) • 4.29.15 • 4.30.15 • 5.20.15 • 5.29.15
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Review(s) *(indicate date for each review)*	☐ None Uploaded 5.28.15; Filing Review Uploaded 11.24.14
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None Uploaded 5.27.15; Filing Review Uploaded 11.12.14; QT-IRT Review uploaded 3.9.15
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ 5.29.15 (Memo in DARRTS)
• Supervisory Review(s) *(indicate date for each review)*	☒ 5.28.15 Uploaded in DARRTS 5.28.15
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☒ labeling review *uploaded 7.21.15, signed 7.22.15*; 5.28.15; Filing review uploaded 11.13.14
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• Tertiary review (*indicate date for each review*)	☐ None
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	☐ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	☐ None uploaded in Panorama ; signed by discipline
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	☒ Microbiology Review uploaded 3.12.15
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	See CMC Review
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ Facilities inspections (*action must be taken prior to the re-evaluation date*) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	☒ Acceptable Re-evaluation date: ☐ Withhold recommendation ☐ Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☐ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☐ Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☐ Done *(Send email to CDER OND IO)*
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☒ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☒ Done
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

Internal Wrap Up Meeting Summary
NDA 205266
ODOMZO (sonidegib)
June 15, 2015

NDA: 205266- Type 1 New Molecular Entity
Submission Date: September 26, 2014
Received Date: September 26, 2014
Sponsor: **Novartis Pharmaceuticals Corporation**

Proposed Indication: for the treatment of patients with locally advanced basal cell carcinoma (BCC) who are not amenable to curative surgery or radiation therapy (b) (4) .

Attendees: Patricia Keegan, Anuja Patel, Suzanne Demko, Denise Casey, Sarah Peddicord, Hong Zhao, Stacy Shord, Tamara Johnson, Shaily Arora, Antonia Dow, Jeffrey Summers, Otto Townshend, Ethan Hausman, Naomi Redd, Lauren Iaconno-Connor, Olen Stephens, William Adams, Huanyu Chen, Kun He, Whitney Helms

1. Timeline Discussion

Milestone	10-month Planned Review Cycle for 12 month Standard PDUFA	Comments
Pending Reviews:		
CDTL Review Due	**Friday, June 12, 2015**	**Completed and in DARRTS**
Division Director Review Due	**Friday, July 3, 2015**	***Pending***
Office Director Review Due/Sign-Off	**Friday, July 24, 2015**	***Pending***
Compile and circulate Action Letter and Action Package	**Friday, June 12, 2015**	***Circulating***
FINAL Action Letter Due	**Friday, July 24, 2015**	***Circulating***

12 Month PDUFA GOAL: Saturday, September 26, 2015

Discussion During Meeting:

1. Discipline Update on Status of Reviews

a. **CMC**: OPQ ATL Liang Zhou*: Review is in Panorama; RPM reminded reviewer that OPQ review of 6.12.15 submission of revised carton and container is pending. CMC to draft a memo and upload in Panorama. No further discussion occurred.*

Reference ID: 3799911

b. Non-Clinical: Alex Putman: *Review completed and in DARRTs 5.28.15; PMR templates for 2 carcinogenicity studies pending receipt of milestone dates from Novartis. No additional discussion occurred.*

c. Clinical Pharmacology: Stacy Shord: *Review completed and in DARRTs 5.27.15; PMR/PMC template in DARRTS 6.11.15 No discussion occurred.*

d. Clinical: Denise Casey: *Review completed and in DARRTs 6.1.15; CDTL review completed and in DARRTs 6.12.15; PMR template on pregnancy monitoring program pending in DARRTs. No additional discussion occurred.*

e. Statistics: Huanyu Chen: *Review completed and in DARRTs 5.28.15; No discussion occurred.*

f. OSI (OSI inspection update): Lauren Iacono-Connor: *Review completed and in DARRTs 4.30.15*

OSI provided the following update during the meeting:
FDA conducted 4 BIMO inspections; 2 clinical sites, one of which has compliance issues identified, in particular a large number of PDs relative to other clinical sites, and some missed laboratory assessments and ECGs. A detailed review of these inspectional observations determined that they did not affect study outcome or subject safety, the other clinical study site had no major issues. OSI also inspected 2 CROs, (b) (4) *and* (b) (4) *for their role in determination of efficacy endpoints. There were no major issues found in the CRO inspections.OSI stated that the site-specific subject data listings that Novartis provided in the application were extremely helpful in preparing and conducting these clinical inspections. No discussion occurred.*

2. Status of Consults

a. Pediatric and Maternal Health:
- *Ethan Hausman (Pediatric): Review complete and in DARRTs 4.16.15. No discussion occurred.*
- *Carol Kasten: review completed and in DARRTs 6.11.15; Reviewer stated that revised language was added to Section 8.4 of the PI. No discussion occurred.*

b. DRISK: *Amarilys Vega: Review complete and in DARRTs 6.5.15. No discussion occurred.*

c. Patient Labeling Team: *Morgan Walker: Review complete and in DARRTs 5.28.1. No discussion occurred.*

d. OPDP: *Nickolas Senior: Review complete and in DARRTs 5.28.1. No discussion occurred.*

Reference ID: 3799911

e. DMEPA: *Otto Townsend: Review complete and in DARRTs 5.13.15; Review of 6.12.15 submission of revised carton and container was pending. No discussion occurred.*

f. PERC: *Review complete and PERC meeting minutes in DARRTS 2.9.15. No discussion occurred.*

3. **Discussion of SGE Teleconference:** *Clinical provided update team on discussions with SGEs.*

4. **Labeling Discussion**
   a. *Discussion on status of labeling review of Novartis labeling received 6.5.15 (SDN 53)*
   b. *Labeling meeting scheduled following wrap up meeting; labeling planned to be sent to applicant with our counterproposal week of June 22 and teleconference to be scheduled July 8, 2015 (if needed). No additional discussion occurred.*

5. **Discussion of Postmarketing Requirements**
   - *2 PMRs Pharm/Tox carcinogenicity: PMR negotiations are ongoing; pending receipt of milestone dates*
   - *1 Clinical PMR: Comments on the Draft Protocol for Pregnancy Monitoring Protocol sent 6.14.15; IR to go out informing Novartis to submit final protocol early July and also request for anticipated date of product launch.*
   - *2 Clinical Pharmacology PMRs*

   No discussion occurred.

6. **Discussion of Late Cycle Meeting**
   RPM informed the review team that minutes are being drafted. No further discussion.

7. **Other activities under NDA:**
   - *Draft Press Release received from Sarah Peddicord and forwarded to clinical team DOP 2 edits due to OMA 6.17.15 (this Wednesday)*
   - *Draft ASCO Burst pending receipt from OHOP*
   - *Information Advisory planned- CDER Exec Sec determined. IR is under OC clearance and will be sent t DOP 2 for final review prior to action.*

Reference ID: 3799911

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/s/

ANUJA PATEL
07/30/2015

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

Memorandum

Date: July 21, 2015

From: Anuja Patel, MPH, Sr. Regulatory Health Project Manager DOP2/OHOP

Subject: NDA 205266: Sponsor Tcon to discuss Novartis revised labeling received July 20, 2015 in response to FDA July 16, 2015 modifications to the PI

Novartis Attendees:

Neil Gallagher, MD, PhD, Global Program Head, Oncology Clinical Development
Dalila Sellami, MD, Global Clinical Program Head, Oncology Clinical Development
Judith Prestifilippo, MD, US Medical Director, Oncology
Lily Zhao, PhD, Director, Biostatistics, Oncology
Renata Kisa, MD, US Medical Director, Immunology and Dermatology
Michael Levine, MD, Brand Safety Leader, Integrated Medical Safety, Oncology
Shanthi Ganeshan, PhD, Vice President, NA Region Head, Oncology Drug Regulatory Affairs
Michael Buska, MS, Global Program Regulatory Director, Drug Regulatory Affairs
Lisa Krueger, PharmD, Regulatory Manager, Drug Regulatory Affairs
Jessica Wang, PharmD, Senior Associate Director, Drug Regulatory Affairs

FDA Attendees:

Anuja Patel, Patricia Keegan, Suzanne Demko, Denise Casey, Monica Hughes

Discussion:

During this teleconference, FDA and Novartis discussed Novartis labeling that was received via email July 18, 2015 and formally submitted on July 20, 2015, in response to FDA modified labeling sent on July 16, 2015.

Section 2.2 Dose Modifications
Section 5.2 Musculoskeletal Adverse Reactions
Section 6.1 Clinical Trial Experience (Table 2)

During the teleconference, Novartis agreed to harmonize formatting and spacing per the labeling guidance.

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/s/

ANUJA PATEL
07/29/2015

Patel, Anuja

From: Patel, Anuja
Sent: Friday, July 24, 2015 10:33 AM
To: 'Wang, Jessica-1'
Subject: FDA Action Letter- NDA 205266 Odomzo (sonidegib)
Attachments: Approval Rx ONLY Sonidegib NDA 205266 for Sponsor.pdf

Importance: High

Dear Dr. Wang,

Please find attached a courtesy copy of FDA Action letter that issued today in response to your NDA submission dated and received on September 26, 2014, for Odomzo(sonidegib). The formal letter will be sent to you via postal mail.

Please acknowledge receipt of this email communication and have a wonderful weekend!

Kindest Regards,
Anuja

Anuja Patel, MPH
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
'White Oak Complex, Bldg. 22, Room 2365
.0903 New Hampshire Avenue
Silver Spring, MD 20993
☎301.796.9022 (phone)
301.796.9849 (fax)
anuja.patel@fda.hhs.gov (email)

Patel, Anuja

'rom:	Patel, Anuja
Sent:	Friday, July 24, 2015 7:48 AM
To:	'Wang, Jessica-1'
Subject:	FDA Response: Odomzo NDA 205-266: Final draft labeling submitted 23-Jul-2015 (Seq. No. 0062)
Importance:	High

Dear Dr. Wang,

We refer to your July 23, 2015 amendment to NDA 205266 containing your final draft labeling for Odomzo (sonidegib). We have no additional comments or questions with regards to your submission.

Please acknowledge receipt.

Regards,
Anuja.

Anuja Patel, MPH
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
White Oak Complex, Bldg. 22, Room 2365
10903 New Hampshire Avenue
ilver Spring, MD 20993
☎301.796.9022 (phone)
301.796.9849 (fax)
anuja.patel@fda.hhs.gov (email)

From: Wang, Jessica-1 [mailto:jessica-1.wang@novartis.com]
Sent: Thursday, July 23, 2015 5:33 PM
To: Patel, Anuja
Subject: Odomzo NDA 205-266: Final draft labeling submitted 23-Jul-2015 (Seq. No. 0062)

Dear Anuja,

Reference is made to NDA 205-266 for Odomzo (sonidegib) and our telephone conversation earlier today to discuss final outstanding edits to the draft labeling. Based on the discussion, please note that the final draft Odomzo USPI and Medication Guide has been submitted through the gateway today, 23-Jul-2015, under Seq. No. 0062.

Additionally, reference is made to the email correspondence where I outlined the proposed changes as discussed over the phone as well as another editorial change to the Highlights section in accordance with the CFR. I also updated the "Month Year" to "July 2015" at the end of the USPI. Please let me know if you have any additional comments or questions. I am available tonight and you can reach me on my mobile if needed: (b) (6).

For your reference, I've attached the cover letter and the final draft labeling (clean version in pdf and word format).

Most sincerely,
Jess

Jessica Wang, PharmD
Senior Associate Director
Drug Regulatory Affairs, Oncology
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080
USA

Phone +1 862 7789507
Mobile (b) (6)
jessica-1.wang@novartis.com

Patel, Anuja

·om: Patel, Anuja
Sent: Thursday, July 23, 2015 7:27 AM
To: 'Wang, Jessica-1'
Subject: RE: Odomzo NDA 205-266 Re: Tentative Weekly Thurs TCs

Dear Dr. Wang,

We propose cancelling all weekly tcons for your NDA 205266.

Please confirm receipt.

Regards,
Anuja

Anuja Patel, MPH
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
White Oak Complex, Bldg. 22, Room 2365
10903 New Hampshire Avenue
Silver Spring, MD 20993
☎301.796.9022 (phone)
301.796.9849 (fax)
anuja.patel@fda.hhs.gov (email)

From: Wang, Jessica-1 [mailto:jessica-1.wang@novartis.com]
Sent: Thursday, July 23, 2015 7:26 AM
To: Patel, Anuja
Subject: Odomzo NDA 205-266 Re: Tentative Weekly Thurs TCs

Hi Anuja,

Good morning! For the pending Odomzo NDA 205-266, I wanted to check with you regarding the tentative weekly Thursday TC today and moving forward, are there any discussion topics still outstanding?

Thank you!
Jess

Jessica Wang, PharmD
Senior Associate Director
Drug Regulatory Affairs, Oncology
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080
USA

·one +1 862 7789507
·obile (b) (6)
jessica-1.wang@novartis.com

Patel, Anuja

From: Patel, Anuja
Sent: Tuesday, July 21, 2015 2:11 PM
To: 'Wang, Jessica-1'
Subject: FDA Response: Odomzo NDA 205-266: Post-TC- Quick question on W&P language - Additional Novartis Edits to Section 5.2

Importance: High

Dear Dr. Wang,

We refer to the July 21, 2015, teleconference held at 7:30 AM, EST., between FDA and representatives of Novartis to discuss your labeling revisions received formally on July 20, 2015. We also refer your email sent July 21, 2015, containing additional proposed edit to the package insert and have the following response:

We have reviewed your proposed edits with regards to the Warnings and Precautions Section 5.2, and agree with your proposed edits.

Please confirm receipt.

Thank you,
Anuja

Anuja Patel, MPH
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
White Oak Complex, Bldg. 22, Room 2365
10903 New Hampshire Avenue
Silver Spring, MD 20993
☎301.796.9022 (phone)
301.796.9849 (fax)
anuja.patel@fda.hhs.gov (email)

From: Wang, Jessica-1 [mailto:jessica-1.wang@novartis.com]
Sent: Tuesday, July 21, 2015 11:43 AM
To: Patel, Anuja
Subject: Odomzo NDA 205-266: Post-TC- Quick question on W&P language

Dear Anuja,

Thank you again for taking the time to align with us on the final proposed labeling for Odomzo. Following the TC, I had one minor proposed edit that I would like confirmation on prior to submitting the labeling response.

With regards to the Warnings and Precautions Section 5.2, for consistency with the terminology in this section, we propose the following edit ("musculoskeletal adverse reactions" rather than "(b) (4)"). Please confirm if the Agency would be agreeable to this change (insertion in bold italics, deletion in strikethrough):

Reference ID: 3795371

"***The incidence of musculoskeletal adverse reactions*** [redacted] (b) (4) ***requiring medical intervention*** (magnesium supplementation, muscle relaxants, and analgesics or narcotics) [redacted] (b) (4) 29%, including four patients (5%) who received intravenous hydration or were hospitalized."

Please note that I am planning to send the Odomzo label through the gateway today and hope to get your feedback soon. Many thanks!

Best regards,
Jess

Jessica Wang, PharmD
Senior Associate Director
Drug Regulatory Affairs, Oncology
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080
USA

Phone +1 862 7789507
Mobile [redacted] (b) (6)
jessica-1.wang@novartis.com

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/s/

ANUJA PATEL
07/22/2015

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

Memorandum

Date: July 22, 2015

From: Anuja Patel M.P.H., Sr. Regulatory Health Project Manager DOP2/OHOP

Subject: NDA 205266/ Type 1 NME/ sonidegib (ODOMZO)/ Novartis Pharmaceuticals Corporation- Final FDA Proposed labeling in response to July 21, 2015 submission

Novartis Pharmaceuticals Corporation Attention: Jessica Wang, Pharm. D. Senior Associate Director, Drug Regulatory Affairs, Oncology One Health Plaza East Hanover, NJ 07936-1080

Dear Dr. Wang:

Please find attached FDA's final proposed labeling, inclusive of the package insert (PI) and Medication Guide in response to your amendment submitted on July 21, 2015.

If you are in final agreement with the draft labeling then formally submit a response by close of business today, July 22, 2015. In addition to submitting your response to the NDA, please email me a copy of your submission.

Please let me know if you have any questions.

Regards,

Anuja Patel, M.P.H. Senior Regulatory Health Project Manager Division of Oncology Products 2 Office of Hematology and Oncology Products Center for Drug Evaluation and Research Phone: 301-796-9022, Fax: 301-796-9849

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

Attachment: FDA final proposed labeling edits to Novartis July 21, 2015, Amendment

Patel, Anuja

From: Patel, Anuja
Sent: Thursday, July 16, 2015 11:30 AM
To: 'Wang, Jessica-1'
Subject: FDA Proposed Modification for Noon tcon July 16 2015- NDA 205266
Attachments: Novartis proposed SD 61 tracked to Novartis pre tcon 7 16 15.docx

Importance: High

Hi Dr. Wang,

Please find attached FDA proposed modifications to your labeling submitted on July 13, 2015 for NDA 205266 which is currently under review. I have added line numbers to the label to help facilitate the discussion for the teleconference at Noon. Please note that we will be dialing in about 1 minutes late for a quick internal discussion.

Please acknowledge receipt.

Thank you!
Anuja

Anuja Patel, MPH
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
White Oak Complex, Bldg. 22, Room 2365
10903 New Hampshire Avenue
Silver Spring, MD 20993
☎301.796.9022 (phone)
301.796.9849 (fax)
anuja.patel@fda.hhs.gov (email)

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Reference ID: 3793653

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/s/

ANUJA PATEL
07/16/2015

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

Memorandum

Date: July 16, 2015

From: Anuja Patel, MPH, Sr. Regulatory Health Project Manager DOP2/OHOP

Subject: NDA 205266: Sponsor Tcon to discuss FDA Modification sent July 16, 2015 in response to July 13, 2015 amendment

---

Novartis Attendees:

Neil Gallagher, MD, PhD, Global Program Head, Oncology Clinical Development
Dalila Sellami, MD, Global Clinical Program Head, Oncology Clinical Development
Patrick Burnett, MD, Global Program Medical Director
Judith Prestifilippo, MD, US Medical Director, Oncology
Lily Zhao, PhD, Director, Biostatistics, Oncology
Renata Kisa, MD, US Medical Director, Immunology and Dermatology
Jocelyn Zhou, PhD, Senior Scientist, Oncology Clinical Pharmacology
Michael Levine, MD, Brand Safety Leader, Integrated Medical Safety, Oncology
Shanthi Ganeshan, PhD, Vice President, NA Region Head, Oncology Drug Regulatory Affairs
Paula Rinaldi, RPh, MPH, US Head, Drug Regulatory Affairs, General Medicines
Michael Buska, MS, Global Program Regulatory Director, Drug Regulatory Affairs
Lisa Krueger, PharmD, Regulatory Manager, Drug Regulatory Affairs
Jessica Wang, PharmD, Senior Associate Director, Drug Regulatory Affairs

FDA Attendees:

Anuja Patel, Patricia Keegan, Suzanne Demko, Denise Casey, Whitney Helms, Alex Putman, Monica Hughes

Discussion:

During this teleconference, FDA and Novartis discussed FDA modified labeling to the Package Insert (PI) and Medication Guide (MG) that was sent July 16, 2015, in response to Novartis proposed revisions submitted formally on July 13, 2015. Prior to the teleconference, FDA stated that the labeling that was sent prior to the teleconference was to help facilitate the discussion and that the label had not been reviewed by the Division Director. Hence, FDA may make additional revisions during the teleconference that may have been previously accepted and/or deleted by the review team. Novartis acknowledged the FDA statement.

The following sections were discussed during the July 16, 2015 teleconference:

- Highlights- Boxed Warning
- Section 2 Dosage and Administration
- Section 5 Warnings and Precautions
- Section 6 Adverse Reactions
- Section 14 Clinical Studies
- Medication Guide

Following the teleconference, FDA sent Novartis modified labeling revisions on July 16, 2015, in response to the teleconference and in response to Novartis July 13, 2015, amendment. FDA accepted the edits which Novartis agreed to during the teleconference prior to sending the labeling. Novartis response is due 8 AM, EST, Monday, July 20, 2015

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/s/

ANUJA PATEL
07/16/2015

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

Memorandum

Date: July 8, 2015

From: Anuja Patel, MPH, Sr. Regulatory Health Project Manager DOP2/OHOP

Subject: NDA 205266: Sponsor Tcon to discuss FDA Modification sent July 6, 2015 in response to June 5, 2015 amendment

---

Novartis Attendees:

Neil Gallagher, MD, PhD, Global Program Head, Oncology Clinical Development
Dalila Sellami, MD, Global Clinical Program Head, Oncology Clinical Development
Patrick Burnett, MD, Global Program Medical Director
Judith Prestifilippo, MD, US Medical Director, Oncology
Lily Zhao, PhD, Director, Biostatistics, Oncology
Jocelyn Zhou, PhD, Senior Scientist, Oncology Clinical Pharmacology
Michael Levine, MD, Brand Safety Leader, Integrated Medical Safety, Oncology
Shanthi Ganeshan, PhD, Vice President, NA Region Head, Oncology Drug Regulatory Affairs
Paula Rinaldi, RPh, MPH, US Head, Drug Regulatory Affairs, General Medicines
Matthias Jauslin, PhD, Global Program Regulatory Director, Drug Regulatory Affairs
Michael Buska, MS, Global Program Regulatory Director, Drug Regulatory Affairs
Lisa Krueger, PharmD, Regulatory Manager, Drug Regulatory Affairs
Jessica Wang, PharmD, Senior Associate Director, Drug Regulatory Affairs

FDA Attendees:

Anuja Patel, Patricia Keegan, Suzanne Demko, Denise Casey, Whitney Helms, Latonia Ford, Lori Gorski, Tamara Johnson, Ethan Hausman, Liang Zhou, Stacy Shord, Carol Kasten, Amarilys Vega, Morgan Walker, Tracy Salaam, Nicholas Senior

Discussion:

During this teleconference, FDA and Novartis discussed FDA modified labeling to the Package Insert (PI) and Medication Guide (MG) that was sent July 6, 2015, in response to Novartis' proposed revisions submitted formally on June 5, 2015. Due to audio difficulty in understanding Novartis, FDA advised Novartis that the time allotted for the teleconference be used to identify which sections of the PI and Medication Guide that Novartis agrees to and a separate teleconference will be scheduled for those sections which further discussion is needed.

Novartis acknowledged and agreed with FDA's proposal.

During the teleconference Bayer and FDA discussed the following sections of the package insert:

- Section 1 Indications and Usage
  - (b) (4)
- Section 2 Dosage and Administration
  - Novartis requested that they discuss this section internally and discuss with the FDA at the next teleconference.
- Section 5 Warnings and Precautions
  - Novartis requested that they discuss this section internally and discuss with the FDA at the next teleconference.
  - Novartis agreed to FDA edits in the first paragraph of Section 5.2.
- Section 6 Adverse Reactions
  - Novartis requested that they discuss this section internally and discuss with the FDA at the next teleconference.
  - Novartis agreed to deleting (b) (4) (b) (4) providing the data by reinserting the Table for Laboratory Abnormalities Occurring in ≥ 10% of Patients in Study.
- Section 7 Drug Interactions
  - Novartis agreed to administrative edits made by FDA.
- Section 8 Use in Specific Populations
  - Novartis agreed to edits made under Section 8.1
  - Novartis requested additional time to review Section 8.3
- Section 10 Overdosage
- Section 12 Clinical Pharmacology
  - Novartis agreed to FDA administrative edits under Section 12.3 Pharmacokinetics (Age, Sex, Weight and Race).
- Section 14 Clinical Studies
- Medication Guide
  - Novartis requested that they discuss this section internally and discuss with the FDA at the next teleconference..

Following the teleconference, FDA sent Novartis modified labeling revisions on July 8, 2015 in response to the teleconference and in response to Novartis June 5, 2015 amendment. FDA accepted the edits which Novartis agreed to during the teleconference prior to sending the labeling. Novartis response is due July 13, 2015.

Post Tcon Followup:

FDA scheduled 2 additional teleconferences with Novartis to discuss labeling sections that were not discussed on July 8, 2015 due to audio issues:

- Thursday, July 16, from 10:30 AM to 11:00 AM: Discuss Clinical Pharmacology and Non Clinical sections of USPI based on forthcoming Novartis labeling response due July 13, 2015.
- Thursday, July 16, from 12:00 Noon to 1:00 PM: Discuss other pending sections of the USPI as needed based on forthcoming Novartis labeling response due July 13, 2105.

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/s/

ANUJA PATEL
07/16/2015

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

Memorandum

Date: July 16, 2015

From: Anuja Patel M.P.H., Sr. Regulatory Health Project Manager DOP2/OHOP

Subject: NDA 205266/ Type 1 NME/ sonidegib (ODOMZO)/ Novartis Pharmaceuticals Corporation- FDA's proposed modifications to Novartis proposed labeling submitted July 13, 2015 and following teleconference held July 16, 2015

Novartis Pharmaceuticals Corporation
Attention: Jessica Wang, Pharm.D.
Associate Director, Drug Regulatory Affairs, Oncology
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Wang:

Please find attached FDA's proposed modifications to the package insert (PI) and Medication Guide contained in your amendment submitted on July 13, 2015, in response to our July 8, 2015, e-mail communication containing modifications to the PI and Medication Guide.

Please note that these modifications are in response to the teleconference held July 16, 2015, and include the agreed changes to sections of the PI as discussed with Novartis during the teleconference.

Your response to the attached labeling is requested via e-mail by 8:00 AM, EST, Monday, July 20, 2015, followed with a formal submission. Please remove line numbers prior to formally submitting to your NDA on July 20, 2015.

Please let me know if you have any questions.

Regards,

Anuja Patel, M.P.H.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-9022, Fax: 301-796-9849

Attachment: FDA Additional Modification to Novartis July 13, 2015 Amendment following teleconference held July 16, 2015

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/s/

ANUJA PATEL
07/16/2015

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

Memorandum

Date: July 8, 2015

From: Anuja Patel, MPH, Sr. Regulatory Health Project Manager DOP2/OHOP

Subject: NDA 205266: Sponsor Tcon to discuss FDA Modification sent July 6, 2015 in response to June 5, 2015 amendment

---

Novartis Attendees:

Neil Gallagher, MD, PhD, Global Program Head, Oncology Clinical Development
Dalila Sellami, MD, Global Clinical Program Head, Oncology Clinical Development
Patrick Burnett, MD, Global Program Medical Director
Judith Prestifilippo, MD, US Medical Director, Oncology
Lily Zhao, PhD, Director, Biostatistics, Oncology
Jocelyn Zhou, PhD, Senior Scientist, Oncology Clinical Pharmacology
Michael Levine, MD, Brand Safety Leader, Integrated Medical Safety, Oncology
Shanthi Ganeshan, PhD, Vice President, NA Region Head, Oncology Drug Regulatory Affairs
Paula Rinaldi, RPh, MPH, US Head, Drug Regulatory Affairs, General Medicines
Matthias Jauslin, PhD, Global Program Regulatory Director, Drug Regulatory Affairs
Michael Buska, MS, Global Program Regulatory Director, Drug Regulatory Affairs
Lisa Krueger, PharmD, Regulatory Manager, Drug Regulatory Affairs
Jessica Wang, PharmD, Senior Associate Director, Drug Regulatory Affairs

FDA Attendees:

Anuja Patel, Patricia Keegan, Suzanne Demko, Denise Casey, Whitney Helms, Latonia Ford, Lori Gorski, Tamara Johnson, Ethan Hausman, Liang Zhou, Stacy Shord, Carol Kasten, Amarilys Vega, Morgan Walker, Tracy Salaam, Nicholas Senior

Discussion:

During this teleconference, FDA and Novartis discussed FDA modified labeling to the Package Insert (PI) and Medication Guide (MG) that was sent July 6, 2015, in response to Bayer's proposed revisions submitted formally on June 5, 2015. Due to audio difficulty in understanding Novartis, FDA advised Novartis that the time allotted for the teleconference be used to identify which sections of the PI and Medication Guide that Novartis agrees to and a separate teleconference will be scheduled for those sections which further discussion is needed.

Novartis acknowledged and agreed with FDA's proposal.

During the teleconference Bayer and FDA discussed the following sections of the package insert:

- Section 1 Indications and Usage
  - (b) (4)
- Section 2 Dosage and Administration
  - Novartis requested that they discuss this section internally and discuss with the FDA at the next teleconference.
- Section 5 Warnings and Precautions
  - Novartis requested that they discuss this section internally and discuss with the FDA at the next teleconference.
  - Novartis agreed to FDA edits in the first paragraph of Section 5.2.
- Section 6 Adverse Reactions
  - Novartis requested that they discuss this section internally and discuss with the FDA at the next teleconference.
  - Novartis agreed to deleting (b) (4) (b) (4) providing the data by reinserting the Table for Laboratory Abnormalities Occurring in ≥ 10% of Patients in Study.
- Section 7 Drug Interactions
  - Novartis agreed to administrative edits made by FDA.
- Section 8 Use in Specific Populations
  - Novartis agreed to edits made under Section 8.1
  - Novartis requested additional time to review Section 8.3
- Section 10 Overdosage
- Section 12 Clinical Pharmacology
  - Novartis agreed to FDA administrative edits under Section 12.3 Pharmacokinetics (Age, Sex, Weight and Race).
- Section 14 Clinical Studies
- Medication Guide
  - Novartis requested that they discuss this section internally and discuss with the FDA at the next teleconference..

Following the teleconference, FDA sent Novartis modified labeling revisions on July 8, 2015 in response to the teleconference and in response to Novartis June 5, 2015 amendment. FDA accepted the edits which Novatis agreed to during the teleconference prior to sending the labeling. Novartis response is due July 13, 2015.

Post Tcon Followup:

FDA scheduled 2 additional teleconferences with Novartis to discuss labeling sections that were not discussed on July 8, 2015 due to audio issues:

- Thursday, July 16, from 10:30 AM to 11:00 AM: Discuss Clinical Pharmacology and Non Clinical sections of USPI based on forthcoming Novartis labeling response due July 13, 2015.
- Thursday, July 16, from 12:00 Noon to 1:00 PM: Discuss other pending sections of the USPI as needed based on forthcoming Novartis labeling response due July 13, 2105.

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/s/

ANUJA PATEL
07/14/2015

Patel, Anuja

From: Patel, Anuja
Sent: Thursday, July 09, 2015 9:25 AM
To: 'Wang, Jessica-1'
Subject: RE: Proposed Tcon Date: FDA Proposed Modifications to Label following July 8 2015 T-Con- NDA 205266 sonidegib

Hi Dr. Wang,

We have no comments regarding your carton and container labeling submitted June 12, 2015.

Regards,
Anuja

Anuja Patel, MPH
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
White Oak Complex, Bldg. 22, Room 2365
10903 New Hampshire Avenue
Silver Spring, MD 20993
☎301.796.9022 (phone)
301.796.9849 (fax)
anuja.patel@fda.hhs.gov (email)

From: Wang, Jessica-1 [mailto:jessica-1.wang@novartis.com]
Sent: Thursday, July 09, 2015 9:21 AM
To: Patel, Anuja
Subject: RE: Proposed Tcon Date: FDA Proposed Modifications to Label following July 8 2015 T-Con- NDA 205266 sonidegib

Ok great. Thank you. Confirming date and times of the TCs:

Thurs, July 16, from 10:30 AM to 11:00 AM: Discuss Clin Pharm and Non Clin sections of USPI based on forthcoming Novartis labeling response due July 13.
Thurs, July 16, from 12:00 Noon to 1:00 PM: Discuss other pending sections of the USPI as needed based on forthcoming Novartis labeling response due July 13.

Additionally, when we last spoke over the phone, you had mentioned there may be comments to the container and carton labeling (submitted June 12, 2015). Will this be provided in writing or verbally during a TC?

Thank you!
-Jess

Jessica Wang, PharmD
Senior Associate Director
Drug Regulatory Affairs, Oncology
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080
USA

Reference ID: 3789645

Phone +1 862 7789507
Mobile (b) (6)
jessica-1.wang@novartis.com

From: Patel, Anuja [mailto:Anuja.Patel@fda.hhs.gov]
Sent: Thursday, July 09, 2015 9:15 AM
To: Wang, Jessica-1
Subject: RE: Proposed Tcon Date: FDA Proposed Modifications to Label following July 8 2015 T-Con- NDA 205266 sonidegib

Hi Jessica,

The tcon at Noon will be for 1 hour.

Anuja

From: Wang, Jessica-1 [mailto:jessica-1.wang@novartis.com]
Sent: Thursday, July 09, 2015 9:14 AM
To: Patel, Anuja
Subject: RE: Proposed Tcon Date: FDA Proposed Modifications to Label following July 8 2015 T-Con- NDA 205266 sonidegib

Hi Anuja,

I confirm receipt and acknowledge the dates and times of our scheduled TCs. Can you confirm the proposed duration of the tcon at Noon?

The dial-in information is provided below.

Dial in information (FDA TC):

US/Canada Toll Free: (b) (4)
Switzerland (freephone): (b) (4)

Participant Passcode: (b) (4)

Global Access Dial-In-Numbers **View a List**

Thanks and best regards,
Jess

Jessica Wang, PharmD
Senior Associate Director
Drug Regulatory Affairs, Oncology
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080
USA

Phone +1 862 7789507
Mobile (b) (6)
jessica-1.wang@novartis.com

From: Patel, Anuja [mailto:Anuja.Patel@fda.hhs.gov]
Sent: Thursday, July 09, 2015 8:47 AM
To: Wang, Jessica-1
Subject: Proposed Tcon Date: FDA Proposed Modifications to Label following July 8 2015 T-Con- NDA 205266 sonidegib
Importance: High

Reference ID: 3789645

Dear Dr. Wang,

For the next tcon, we propose keeping the 10:30 weekly tcon time slot for July 16, 2015 at 10:30 AM, EST to discuss clinical pharmacology and nonclinical sections of your forthcoming Package Insert due Monday, July 13, 2015.

In addition, we propose having a tcon at 12 Noon on July 16, 2015 to go over and pending sections of the Package Insert and the Medication Guide as needed based on your response to our July 8, 2015 teleconference and e-mail communication containing the revised labeling.

To ensure that there is no audio issues from our end I have reserved a different room.

Please acknowledge receipt and confirm the proposed date and time. Please provide a dial in number in your response. Thank you.

Regards,
Anuja

Anuja Patel, MPH
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
White Oak Complex, Bldg. 22, Room 2365
10903 New Hampshire Avenue
Silver Spring, MD 20993
☎301.796.9022 (phone)
301.796.9849 (fax)
anuja.patel@fda.hhs.gov (email)

From: Wang, Jessica-1 [mailto:jessica-1.wang@novartis.com]
Sent: Wednesday, July 08, 2015 2:28 PM
To: Patel, Anuja
Subject: RE: FDA Proposed Modifications to Label following July 8 2015 T-Con- NDA 205266 sonidegib

Dear Anuja,

Thank you for sharing the labeling following the teleconference today. I apologize that we were having such difficulty hearing you. Hopefully, our next teleconference will be more clear.

With regards to the labeling, I propose to remove the comments on the side if both Novartis and FDA has agreed to the edit. For example, the first comment regarding [redacted] (b) (4) I was planning to remove the comment to clean up the label.

Please let me know if you are okay with this approach or would you rather I acknowledge each of these comments with “From Novartis”.

We will target to submit the labeling response to you by Monday and follow with a formal submission to the NDA as requested. Please let me know the next TC date and time and we can use the same dial-in information as today.

Thanks and best regards,
Jess

Jessica Wang, PharmD

Reference ID: 3789645

Senior Associate Director
Drug Regulatory Affairs, Oncology
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080
USA

Phone +1 862 7789507
Mobile (b) (6)
jessica-1.wang@novartis.com

From: Patel, Anuja [mailto:Anuja.Patel@fda.hhs.gov]
Sent: Wednesday, July 08, 2015 12:28 PM
To: Wang, Jessica-1
Subject: FDA Proposed Modifications to Label following July 8 2015 T-Con- NDA 205266 sonidegib
Importance: High

Hi Dr. Wang,

Please find attached labeling following the tcon today. As discussed I am including the word version with the line numbers to help facilitate our next tcon which I anticipate scheduling end of next week (depending on calendar/room availability). A response to the attached labeling communication is requested by close of business Monday, July 13, 2015, in order for the review team to review your response and prepare for the next teleconference. When you submit your response via email to me you may leave in the line numbers; however please remove prior to formally submitting to your NDA.

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

Regards
Anuja

Anuja Patel, MPH
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
White Oak Complex, Bldg. 22, Room 2365
10903 New Hampshire Avenue
Silver Spring, MD 20993
☎301.796.9022 (phone)
301.796.9849 (fax)
anuja.patel@fda.hhs.gov (email)

Reference ID: 3789645

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/s/

ANUJA PATEL
07/09/2015

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

Memorandum

Date: July 8, 2015

From: Anuja Patel M.P.H., Sr. Regulatory Health Project Manager DOP2/OHOP

Subject: NDA 205266/ Type 1 NME/ sonidegib (ODOMZO)/ Novartis Pharmaceuticals Corporation- FDA's proposed modifications to Novartis proposed labeling submitted June 5, 2015 following teleconference held July 8, 2015

Novartis Pharmaceuticals Corporation
Attention: Jessica Wang, Pharm.D.
Associate Director, Drug Regulatory Affairs, Oncology
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Wang:

Please find attached FDA's proposed modifications to the package insert (PI) and Medication Guide contained in your amendment submitted on June 5, 2015, containing your responses to our May 14 and 29, 2015, preliminary comments on the PI and Medication Guide, respectively.

Please note that these modifications are in response to the teleconference held July 8, 2015, and include the agreed changes to sections of the PI as discussed with Novartis during the teleconference.

Your response to the attached labeling is requested via e-mail by close of business Monday, July 13, 2015. Please remove line numbers prior to formally submitting to your NDA on July 13, 2015.

Please let me know if you have any questions.

Regards,

Anuja Patel, M.P.H.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-9022, Fax: 301-796-9849

Attachment: FDA Additional edits to Novartis June 5, 2015 Amendment following July 8, 2015 Teleconference

Reference ID: 3789223

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/s/

ANUJA PATEL
07/08/2015

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

Memorandum

Date: June 6, 2015

From: Anuja Patel M.P.H., Sr. Regulatory Health Project Manager DOP2/OHOP

Subject: NDA 205266/ Type 1 NME/ sonidegib (ODOMZO)/ Novartis Pharmaceuticals Corporation- FDA's proposed modifications to Novartis proposed labeling submitted June 5, 2015

Novartis Pharmaceuticals Corporation
Attention: Jessica Wang, Pharm.D.
Associate Director, Drug Regulatory Affairs, Oncology
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Wang:

Please find attached FDA's proposed modifications to on the package insert (PI) and Medication Guide contained in your amendment submitted on June 5, 2015, containing your responses to our May 14 and 29, 2015, preliminary comments on the PI and Medication Guide, respectively.

In addition, we confirm the teleconference tentatively scheduled for Wednesday, July 8, 2015 from 9:00 a.m. to 10:00 a.m., EST to discuss your forthcoming response to this communication. We acknowledge receipt of your June 23, 2015, email confirmation confirming the teleconference and your dial-in number provided below:

Dial in information:

US/Canada Toll Free: (b) (4)
Switzerland (freephone): (b) (4)

Participant Passcode: (b) (4)

We look forward to discussing the attached labeling revisions during the teleconference. During the teleconference we will also discuss the due date for your response to this communication.

Please let me know if you have any questions.

Regards,

Anuja Patel, M.P.H.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-9022, Fax: 301-796-9849

Attachment: FDA Additional edits to Novartis June 5, 2015 Amendment

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/s/

ANUJA PATEL
07/06/2015

Boyd, Karen

From: Boyd, Karen
Sent: Tuesday, June 30, 2015 3:02 PM
To: 'Wang, Jessica-1'
Cc: Patel, Anuja; Myers, Claire
Subject: NDA 205266- sonidegib: Nonclinical PMR dates
Attachments: NDA_205266_nonclinical_PMR_6_29_15.pdf

Importance: High

Hi Jessica,

As a follow up to my email from yesterday regarding the carcinogeneity study (also attached), please provide the requested scheduled milestone dates via email by **2pm on Thursday, July 2nd**.

Please send them via email to me (karen.boyd@fda.hhs.gov), Anuja (Anuja.patel@fda.hhs.gov) and Claire Myers (claire.myers@fda.hhs.gov), followed by a formal submission to your NDA.

Please confirm receipt.

Thanks,
Karen

From: Boyd, Karen
Sent: Monday, June 29, 2015 4:48 PM
To: 'Wang, Jessica-1'
Cc: Patel, Anuja
Subject: RE: Alternate FDA contact June 25 through July 3 for NDA 205266- sonidegib

Hi Jessica,

Please see attached for our response to your nonclinical PMR proposal.

Also, I did not receive clearance to send you the label yet today. I am hopeful for tomorrow.

Please confirm receipt.

Thanks,
Karen

Karen Boyd, M.S., PMP
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

Reference ID: 3786231

Phone: 301-796-7032
Fax: 301-796-9849

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

Memorandum

Date: June 29, 2015

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

Subject: NDA 205266: PMR Milestones Discussion

Novartis Pharmaceuticals Corporation
Attention: Jessica Wang, Pharm.D.
Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Wang,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for "Odomzo (sonidegib), 200 mg capsules."

Please also refer to your June 22, 2015 submission containing your response to the FDA proposed non-clinical PMRs, including the PMR language and proposed scheduled milestone dates.

Here is our response to your June 22, 2015 submission:

> Your proposal (b) (4) is not acceptable. Submit your scheduled milestone dates for a 2-year rat carcinogenicity study and a 6-month transgenic mouse carcinogenicity study. Scheduled milestones should include dates for SPA submission, final protocol submission, study completion, and final report submission.

If you have any questions, please contact me until June 30th or Ms. Anuja Patel afterwards.

Best,
Karen

Karen C. Boyd, M.S., PMP
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
06/29/2015

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/s/

KAREN C BOYD
06/30/2015

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

Memorandum

Date: June 29, 2015

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

Subject: NDA 205266: PMR Milestones Discussion

Novartis Pharmaceuticals Corporation
Attention: Jessica Wang, Pharm.D.
Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Wang,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for "Odomzo (sonidegib), 200 mg capsules."

Please also refer to your June 22, 2015 submission containing your response to the FDA proposed non-clinical PMRs, including the PMR language and proposed scheduled milestone dates.

Here is our response to your June 22, 2015 submission:

> Your proposal (b) (4) is not acceptable. Submit your scheduled milestone dates for a 2-year rat carcinogenicity study and a 6-month transgenic mouse carcinogenicity study. Scheduled milestones should include dates for SPA submission, final protocol submission, study completion, and final report submission.

If you have any questions, please contact me until June 30th or Ms. Anuja Patel afterwards.

Best,
Karen

Karen C. Boyd, M.S., PMP
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
06/29/2015

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

Memorandum

Date: June 19, 2015

From: Anuja Patel, M.P.H., Sr. Regulatory Health Project Manager DOP2/OHOP

Subject: NDA 205266 (sonidegib), Novartis Pharmaceuticals Corporation: Proposed PMC/PMR Language (Nonclinical)

Novartis Pharmaceuticals Corporation
Attention: Jessica Wang, Pharm.D.
Associate Director, Drug Regulatory Affairs, Oncology
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Wang,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for "Odomzo (sonidegib), 200 mg capsules."

We refer to our June 2, 2015, electronic mail communication containing clinical and clinical pharmacology post-marketing requirement (PMR) and post-marketing commitment (PMC) proposals and to our June 9, 2015, late cycle meeting between FDA representatives and Novartis Pharmaceuticals Corporation. As noted in our June 2 and 9, 2015, communications, we have the following additional nonclinical PMRs.

Please note that additional post-marketing requirement (PMR) and post-marketing commitment (PMC) proposals may be forthcoming while your application is under review.

PMRs Subject to the Reporting Requirements Under Section 505(o)

For the following two postmarketing studies/trials you are required to conduct please provide the following milestone dates that you will be required to meet. These dates should be derived from careful assessment of the feasibility of the trial/study to include items such as resource acquisition, accrual rate, drop-out rate, and various required institutional approvals. Allow yourself reasonable additional buffer time for possible contingencies.

NONCLINICAL

1. To evaluate the potential for a serious risk of carcinogenicity, conduct a rodent carcinogenicity study in the mouse. Submit the carcinogenicity protocol for a Special Protocol Assessment (SPA) prior to initiating the study.

SPA Submission	MONTH/YEAR (Applicant to Provide)
Final Protocol Submission:	MONTH/YEAR (Applicant to Provide)
Study Completion:	MONTH/YEAR (Applicant to Provide)
Final Report:	MONTH/YEAR (Applicant to Provide)

2. To evaluate the potential for a serious risk of carcinogenicity, conduct a long-term (2 year) rodent carcinogenicity study in the rat. Submit the carcinogenicity protocol for a Special Protocol Assessment (SPA) prior to initiating the study.

SPA Submission	MONTH/YEAR (Applicant to Provide)
Final Protocol Submission:	MONTH/YEAR (Applicant to Provide)
Study Completion:	MONTH/YEAR (Applicant to Provide)
Final Report:	MONTH/YEAR (Applicant to Provide)

In addition, please note that final language will be included in the action letter. We are requesting that you respond to our proposal by close of business on **Tuesday, June 23, 2015**, or sooner.

Please let me know if you have any questions.

Regards,

Anuja Patel, M.P.H.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-9022
Fax: 301-796-9849

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/s/

ANUJA PATEL
06/19/2015

MEMORANDUM OF INTERNAL MEETING MINUTES

MEETING DATE:	May 13, 2015
TIME:	1:00 PM -1:30 PM, ET
LOCATION:	Teleconference, WO 22, RM 2201
APPLICATION:	NDA 205266
DRUG NAME:	sonidegib
TYPE OF MEETING:	Teleconference with Special Government Employee (SGE), Ms. Kristi Burr, cleared for participation by CDER's Division of Advisory Committee and Consultant Management (DACCM).

FDA ATTENDEES:

Patricia Keegan- Division Director, Division of Oncology Products 2
Denise Casey-Medical Officer
Anuja Patel- Senior Regulatory Health Project Manager
Suzanne Demko- Clinical Disciplinary Team Leader

EXTERNAL CONSTITUENT ATTENDEES:

Ms. Kristi Burr (Patient Representative)

BACKGROUND: Ms. Burr agreed to serve and was cleared as an SGE for this new molecular entity (NME) application. Prior to this teleconference, background materials and draft product labeling were provided to Ms. Burr, along with five specific division questions for Ms. Burr to address during this teleconference. Those materials are attached to this document.

DISCUSSION POINTS:

In this application, Novartis seeks the approval of ODOMZO (sonidegib), for the treatment of patients with locally advanced basal cell carcinoma (laBCC) who are not amenable to curative surgery or radiation therapy [redacted] (b) (4)

Discussion:

Prior to discussing the questions, Ms. Burr requested clarification on (INSERT)

FDA Questions for Discussion During Teleconference:

1. In your practice, how do you evaluate tumor response to treatment in patients with laBCC? Please describe an algorithm if you have one. Comment on the Applicant's assessment of response using modified RECIST which integrates three measures (i.e., MRI, photography, biopsy) for a composite overall response rate endpoint.

   DISCUSSION DURING TELECONFERENCE: Ms. Burr stated that she is not a provider so cannot comment on this question. Ms. Burr commented that the briefing package was written more for physicians who treat BCC and that she does not favor the term 'cosmetic improvement' when describing the changes in disfiguring disease.

2. [redacted] (b) (4)

   DISCUSSION DURING TELECONFERENCE: [redacted] (b) (4)

3. Is the risk: benefit profile of sonidegib favorable for the treatment of patients with advanced BCC? Please comment specifically on the long-term use of this drug in a potentially indolent disease and the risk for muscle-related adverse reactions including rhabdomyolysis.

   DISCUSSION DURING TELECONFERENCE: Ms. Burr stated that she is not a provider so cannot comment on this question.

4. Sonidegib is a hedgehog inhibitor with teratogenic effects in animals. Do you expect that these risks will influence prescribers in the management of patients with laBCC who are of child-bearing age?

   DISCUSSION DURING TELECONFERENCE: Ms. Burr stated that she is not a provider so cannot comment on this question.

5. Does the attached draft label adequately reflect the risks and benefits of sonidegib for the treatment of patients with laBCC not amenable to local therapies?

   DISCUSSION DURING TELECONFERENCE: Ms. Burr agreed that the draft label adequately reflect the risks and benefits of sonidegib for the treatment of patients with laBCC not amenable to local therapies. Ms. Burr expressed concern over the language used to describe the risks of seminal transmission in the label. FDA stated that consideration would be given to an adequate description of this risk in the label.

ATTACHMENTS: Background information provided to Ms. Burr via a password protected file, secure email communication on May 6, 2015.

36 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this

Patel, Anuja

From: Patel, Anuja
Sent: Wednesday, May 13, 2015 11:35 AM
To: 'BCCNS Life Support Network'
Subject: RE: SGE Briefing Document (Password Protected) for Teleconference Scheduled for May 13, 2015 at 1PM, EST
Attachments: proposed amended PI labeling received 1_23_2015 with PK edits 5 13 15 clean for SGE.pdf

Dear Ms. Burr,

Thank you for your email.

Our Division made additional edits today to the proposed package insert for this application. Please find attached a more current label that we will discuss during today teleconference. This label replaces the one that was included in the briefing document.

Please acknowledge receipt.

Regards,
Anuja

From: BCCNS Life Support Network [mailto:kristi@bccns.org]
Sent: Wednesday, May 13, 2015 11:06 AM
To: Patel, Anuja
Subject: RE: SGE Briefing Document (Password Protected) for Teleconference Scheduled for May 13, 2015 at 1PM, EST

Hi, I called and left a message, but I was able to find the call in number, after I read past the line that indicated it would be sent later. Sorry for the confusion. Thank you.

Kristi
Kristi Schmitt Burr, Executive Director
BCCNS Life Support Network
P.O. Box 321; Burton, OHIO 44021
Office: (440) 834-0011; Fax: (440) 834-0132
www.bccns.org / www.gorlinsyndrome.org

From: Patel, Anuja [mailto:Anuja.Patel@fda.hhs.gov]
Sent: Wednesday, May 13, 2015 9:26 AM
To: Kristi@bccns.org
Cc: Miller, Deborah
Subject: RE: SGE Briefing Document (Password Protected) for Teleconference Scheduled for May 13, 2015 at 1PM, EST
Importance: High

Hi Ms. Burr,

In the briefing document we reference vismodegib data. I wanted to provide a copy of the approved package insert as reference during today's teleconference. The link to the PI (found on Drugs at FDA website) is below:
http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/203388lbl.pdf

We look forward to speaking with you later today.

Reference ID: 3779049

Regards,
Anuja

Anuja Patel, MPH
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
White Oak Complex, Bldg. 22, Room 2365
10903 New Hampshire Avenue
Silver Spring, MD 20993
S301.796.9022 (phone)
301.796.9849 (fax)
anuja.patel@fda.hhs.gov (email)

From: Patel, Anuja
Sent: Wednesday, May 06, 2015 1:35 PM
To: 'Kristi@bccns.org'
Subject: FDA: SGE Briefing Document (Password Protected) for Teleconference Scheduled for May 13, 2015 at 1PM, EST
Importance: High

Hello Ms. Burr,

Attached is a password protected briefing document for your review prior to the teleconference scheduled for **May 13, 2015 at 1:00 PM, EST**. I will be emailing you the password to open this document in a separate e-mail momentarily. Kindly confirm receipt of this email and the attachment.

Please let me know if you have any issues opening the file after you receive the password.

The dial in number for the teleconference is below:
Step 1: Participant Dial In: 1 855 828 1770 (toll free)
Step 2: Enter Meeting ID: (b) (4)
Step 3: State your Name following Prompt

Feel free to contact me if you have any questions. The Agency appreciates your time and patience in reviewing this application and assisting us in protecting the nation's public health.

Regards,
Anuja

Anuja Patel, MPH
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
White Oak Complex, Bldg. 22, Room 2365
10903 New Hampshire Avenue
Silver Spring, MD 20993
☎301.796.9022 (phone)
301.796.9849 (fax)
anuja.patel@fda.hhs.gov (email)

Reference ID: 3779049

From: Patel, Anuja
Sent: Friday, April 17, 2015 7:15 AM
To: 'Kristi@bccns.org'
Subject: SGE Availability for Teleconference with FDA/ DOP 2 Divisional Assignment for New Molecular Entity (sonidegib)
Importance: High

Dear Ms. Burr,

Allow me to introduce myself as the Senior Regulatory Project Manager with Division of Oncology Products 2 (DOP 2), Office of Hematology and Oncology Products (OHOP).

At our request, you were contacted and screened for conflict of interest by the Division of Advisory Committee and Consultants Management to participate in a divisional assignment for us for a New Drug Application (NDA), New molecular Entity (NME) we are currently reviewing. You have been cleared by DACCM. DOP 2 is preparing the briefing package for the following product which will be sent to you soon (password protected). Please note that contents of the briefing package are **CONFIDENTIAL and not publicly releasable**.

Product: sonidegib
Proposed Indication: for treatment of patients with locally advanced basal cell carcinoma (BCC) who are not amenable to curative surgery or radiation therapy (b) (4)

In the meantime, I wanted to see if we could get a teleconference (tcon) scheduled sometime the week of May 11th, preferably May 13th or May 14th. Please let me know if either of the proposed dates works for you and if not please feel free to provide alternate dates for a 30 minute tcon. I don't anticipate the tcon to last more than 30 minutes.

In addition, secure email between CDER and you will need to be established since confidential information may be included in the message (for example, trade secrets). 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. Once your email is secured, we will send out the briefing package prior to the teleconference, please let me know how much time is spent during your review as I will need to complete a time sheet for your assignment.

Thank you in advance in helping us protecting the public's health. Feel free to contact me if you have any questions, my contact information is below. If you could acknowledge receipt of this email that would be greatly appreciated!

Kindest Regards,
Anuja

Anuja Patel, MPH
Sr. Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
White Oak Complex, Bldg. 22, Room 2365
10903 New Hampshire Avenue
Silver Spring, MD 20993
☎301.796.9022 (phone)
301.796.9849 (fax)
anuja.patel@fda.hhs.gov (email)

Reference ID: 3779049

This email has been checked for viruses by Avast antivirus software.
www.avast.com

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

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/s/

ANUJA PATEL
06/15/2015

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

Memorandum

Date: June 14, 2015

From: Anuja Patel, M.P.H., Sr. Regulatory Health Project Manager DOP2/OHOP

Subject: NDA 205266 (sonidegib), Novartis Pharmaceuticals Corporation: Proposed PMC/PMR Language

---

Novartis Pharmaceuticals Corporation
Attention: Jessica Wang, Pharm.D.
Associate Director, Drug Regulatory Affairs, Oncology
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Wang,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for "Odomzo (sonidegib), 200 mg capsules."

We also refer to our June 2, 2015, electronic mail (e-mail) communication containing proposed Post-marketing Requirements (PMRs) subject to the reporting requirements under Section 506B.

We also refer to your June 2, 2015 submission to your NDA containing your proposed draft non-interventional study protocol entitled, "Sonidegib (LDE225) Pregnancy Monitoring Program" and to your June 8, 2015, submission with proposed milestone dates in response to our June 2, 2015, communication.

We have the following comments regarding your draft protocol:

- We have reviewed the submitted draft protocol for the pregnancy monitoring program. Your responses to our preliminary comments are acceptable and the draft protocol appears adequate to proceed. We remind you that the intent of this postmarketing requirement is to capture all pregnancies with potential sonidegib exposure. The Agency emphasizes the importance of prospective data collection in this program. Given the small estimated sample size over the ten-year duration, every effort should be taken to maximize enrollment into the program, to retain enrollees, and to reduce loss to follow-up. This may include a plan to review retention and follow-up practices after the start of the program. It is anticipated that outcomes of all pregnancies reported from the pharmacovigilance database should be accounted for in this program. If a pregnancy is not captured for prospective monitoring, the pregnancy data must be accounted for retrospectively.

Please let me know if you have any questions.

Regards,

Anuja Patel, M.P.H.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-9022
Fax: 301-796-9849

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

/s/

ANUJA PATEL
06/14/2015

MEMORANDUM OF INTERNAL MEETING MINUTES

MEETING DATE:	May 28, 2015
TIME:	1:15 PM - 2:15 PM
LOCATION:	Teleconference, WO 22, RM 2365
APPLICATION:	NDA 205266
DRUG NAME:	sonidegib
TYPE OF MEETING:	Teleconference with Special Government Employee (SGE/FED), Dr. John Digiovanna, cleared for participation by CDER's Division of Advisory Committee and Consultant Management (DACCM).

FDA ATTENDEES:

Denise Casey-Medical Officer, DOP 2
Anuja Patel- Senior Regulatory Health Project Manager, DOP 2

EXTERNAL CONSTITUENT ATTENDEES:

Dr. John Digiovanna, NIH

BACKGROUND: Dr. Digiovanna agreed to serve and was cleared as an SGE for this new molecular entity (NME) application. Prior to this teleconference, background materials and draft product labeling were provided to Dr. Digiovanna, along with five specific division questions for Dr. Digiovanna to address during this teleconference. Those materials are attached to this document.

DISCUSSION POINTS:

In this application, Novartis seeks the approval of ODOMZO (sonidegib), for the treatment of patients with locally advanced basal cell carcinoma (laBCC) who are not amenable to curative surgery or radiation therapy [redacted] (b) (4)

Discussion:

Dr. Digiovanna provided written response via electronic mail (e-mail) on May 28, 2015, in response to the FDA questions that were included in the SGE briefing materials.

FDA Questions for Discussion During Teleconference:

1. In your practice, how do you evaluate tumor response to treatment in patients with laBCC? Please describe an algorithm if you have one. Comment on the Applicant's assessment of response using modified RECIST which integrates three measures (i.e., MRI, photography, biopsy) for a composite overall response rate endpoint.

   DISCUSSION DURING TELECONFERENCE: Dr. Digiovanna stated that it is difficult to standardize evaluation of a heterogenous population. Dr. Digiovanna expressed concern over following response in neurotropic lesions due to development of skipped lesions (i.e. auditory and facial lesions along nerves) and in lesions that are complicated by infection. Dr. Digiovanna further discussed certain histologic variants, including pleoform BCC which are more invasive than others and mentioned that nodular lesions are easier to assess for response. He further emphasized that photography is not helpful if it does not take into account tumors that are palpated and expressed concern over how many biopsies were being obtained and from what areas of the tumor and suggested that the assessment be conducted by a dermatopathologist.

   FDA acknowledged Dr. Digiovanna's concerns and provided details of the response assessment summarized in Table 2 (page 10) of the SGE background materials. Following FDA clarification, Dr. Digiovanna considered the response assessment criteria to be reasonable upon hearing further details from the FDA, but emphasized the heterogenous population

   Please refer to Dr. Digiovanna's written response attached for additional details.

2. [redacted] (b) (4)

(b) (4)

DISCUSSION DURING TELECONFERENCE: (b) (4)

3. Is the risk:benefit profile of sonidegib favorable for the treatment of patients with advanced BCC? Please comment specifically on the long-term use of this drug in a potentially indolent disease and the risk for muscle-related adverse reactions including rhabdomyolysis.

   DISCUSSION DURING TELECONFERENCE: Overall, Dr. Giovanna found the risk benefit to be favorable and requested that additional information on the reversibility of some of the toxicities be provided in the package insert so that providers could properly inform patients of the expected toxicities when deciding to take this drug or have surgery as alternative. Dr. Giovanna provided examples of alopecia and taste disturbance as factors for patients stopping vismodegib treatment. He stated that in an indolent disease, it may be difficult to tolerate some toxicities with longterm use.

4. Sonidegib is a hedgehog inhibitor with teratogenic effects in animals. Do you expect that these risks will influence prescribers in the management of patients with laBCC who are of child-bearing age?

   DISCUSSION DURING TELECONFERENCE: Dr. Digiovanna stated that there are no non-teratogenic alternative efficacious treatments and expressed concern regarding the risk for teratogenicity. FDA provided information regarding the proposed pregnancy registry and after the discussion, Dr. Digiovanna found that the post marketing requirement for pregnancy registry and the Medication Guide included in the package insert (PI) would be adequate.

5. Does the attached draft label adequately reflect the risks and benefits of sonidegib for the treatment of patients with laBCC not amenable to local therapies?

DISCUSSION DURING TELECONFERENCE: Dr. Digiovanna stated that the draft label sufficiently reflects the risks and benefits of sonidegib for the treatment of patients with laBCC not amenable to local therapies;however, under section 6.1 Clinical Trial Experience, Dr. Digiovanna expressed concern regarding the text: (b) (4)

He further stated that the labeling does not address (b) (4)

Additional SGE Comments:

There were no other SGE comments.

ATTACHMENTS: Background information provided to Dr. Robinson via a password protected file, secure email communication on May 7, 2015.

18 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

Patel, Anuja

From: Patel, Anuja
Sent: Wednesday, May 13, 2015 11:40 AM
To: Digiovanna, John J (NIH) (jdigiova@mail.nih.gov)
Cc: Casey, Denise (CDER)
Subject: Revised Draft PI (updated 5.13.15): SGE Availability for Teleconference with FDA/ DOP 2 Divisional Assignment for New Molecular Entity (sonidegib)
Attachments: proposed amended PI labeling received 1_23_2015 with PK edits 5 13 15 clean for SGE.pdf

Dear Dr. Digiovanna,

Our Division made additional edits today to the proposed package insert for this application. Please find attached a more current label that we will discuss during the forthcoming teleconference. This draft label replaces the one that was included in the briefing document.

Please acknowledge receipt.

Regards,
Anuja

From: Patel, Anuja
Sent: Wednesday, May 13, 2015 9:23 AM
To: Digiovanna, John J (NIH) (jdigiova@mail.nih.gov)
Subject: RE: SGE Availability for Teleconference with FDA/ DOP 2 Divisional Assignment for New Molecular Entity (sonidegib)
Importance: High

Hi Dr. Digiovanna,

In the briefing document, we reference vismodegib data that is from the package insert (PI). I wanted to provide you a copy of the approved package insert for vismodegib so that you have it available to you during the teleconference and while you review the materials. The link to the PI (found on Drugs at FDA website) is below:
http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/203388lbl.pdf

We look forward to speaking with you on May 28, 2015. Thank you for your time.

Regards,
Anuja

Anuja Patel, MPH
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
White Oak Complex, Bldg. 22, Room 2365
10903 New Hampshire Avenue
Silver Spring, MD 20993

Reference ID: 3778989

S301.796.9022 (phone)
301.796.9849 (fax)
anuja.patel@fda.hhs.gov (email)

From: Patel, Anuja
Sent: Monday, May 11, 2015 4:36 PM
To: Digiovanna, John J (NIH)
Subject: RE: SGE Availability for Teleconference with FDA/ DOP 2 Divisional Assignment for New Molecular Entity (sonidegib)

Hi Dr. Digiovanna,

I have you confirmed for May 28, 2015 from 11:30 AM to Noon.

Anuja

From: Digiovanna, John (NIH/NCI) [E] [mailto:jdigiova@mail.nih.gov]
Sent: Monday, May 11, 2015 3:18 PM
To: Patel, Anuja
Subject: RE: SGE Availability for Teleconference with FDA/ DOP 2 Divisional Assignment for New Molecular Entity (sonidegib)

Yes,
I can do Thursday May 28, 11:30-noon.
Thank you.

From: Patel, Anuja (FDA/CDER)
Sent: Monday, May 11, 2015 1:50 PM
To: Digiovanna, John (NIH/NCI) [E]
Subject: RE: SGE Availability for Teleconference with FDA/ DOP 2 Divisional Assignment for New Molecular Entity (sonidegib)
Importance: High

Hello Dr. Digiovanna,

I apologize for the delay in receipt. The clinical team needed to get some additional information from the Applicant. We would be happy to reschedule the teleconference to give you more time to review. Would you be free on any of the following dates?

May 27, 2015

- 8:30-9 AM, EST
- 10-10:30 AM, EST

May 28, 2015

- 11-11:30 AM
- 11:30- 12 Noon

Take care,
Anuja

From: Digiovanna, John (NIH/NCI) [E] [mailto:jdigiova@mail.nih.gov]
Sent: Monday, May 11, 2015 1:18 PM
To: Patel, Anuja

Subject: RE: SGE Availability for Teleconference with FDA/ DOP 2 Divisional Assignment for New Molecular Entity (sonidegib)

Hi Anuja,
As I wrote below, I need some advanced warning to properly do this evaluation. I am just returning from out of town for the skin biology meeting, the Society for Investigative Dermatology, and I am clinical attending this week. I just opened an email with the documents you sent. This is insufficient time for me to properly review this by Thursday. Can you please reschedule.
John DiGiovanna

From: Digiovanna, John (NIH/NCI) [E]
Sent: Wednesday, April 08, 2015 11:12 AM
To: Patel, Anuja (FDA/CDER)
Subject: RE: SGE Availability for Teleconference with FDA/ DOP 2 Divisional Assignment for New Molecular Entity (sonidegib)

I can do May 14: 12:30 PM - 1:00 PM

Please send your information a few weeks in advance to permit time for me to review appropriately.

Thanks.

John Digiovanna

From: Patel, Anuja (FDA/CDER)
Sent: Wednesday, April 08, 2015 7:14 AM
To: Digiovanna, John (NIH/NCI) [E]
Subject: RE: SGE Availability for Teleconference with FDA/ DOP 2 Divisional Assignment for New Molecular Entity (sonidegib)
Importance: High

Hello Dr. Digiovanna,

We are a bit behind on our review so I will need to reschedule our teleconference from April 22, 2015 to mid May to allow for the review team to prepare a briefing document for your review prior to the meeting. Would you be available any of the following dates/times (EST)?

May 11: 12 Noon -12:30 PM, EST or 2:00 PM - 2:30 PM
May 13: Noon - 12:30 PM or 12:30 PM - 1:00 PM or 1:00 PM - 1:30 PM
May 14: 12:30 PM - 1:00 PM

Please note that or phone provider is changing in May so I will be providing you a different dial in number. If you could respond at your earliest convenience that would be greatly appreciated!

We apologize for any inconvenience.

Thank you!
Anuja

Anuja Patel, MPH
Sr. Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
White Oak Complex, Bldg. 22, Room 2365

Reference ID: 3778989

10903 New Hampshire Avenue
Silver Spring, MD 20993
☎301.796.9022 (phone)
301.796.9849 (fax)
anuja.patel@fda.hhs.gov (email)

From: Patel, Anuja
Sent: Tuesday, March 24, 2015 1:34 PM
To: Digiovanna, John J (NIH)
Subject: RE: SGE Availability for Teleconference with FDA/ DOP 2 Divisional Assignment for New Molecular Entity (sonidegib)

Hello!

Thank you for the prompt response. We have you confirmed for April 22, 2015 from 12:30 PM to 1:00 PM, EST. The dial in number is provided below:

DIAL IN NUMBER:
866-715-9310
Participant Code: (b) (4)

Let me check with the Division of Advisory Committee and Consultant Management Staff regarding whether you need to complete the time sheet and I will get back to you.

Take care,
Anuja

From: Digiovanna, John (NIH/NCI) [E] [mailto:jdigiova@mail.nih.gov]
Sent: Tuesday, March 24, 2015 1:30 PM
To: Patel, Anuja
Subject: RE: SGE Availability for Teleconference with FDA/ DOP 2 Divisional Assignment for New Molecular Entity (sonidegib)

Hi Anuja,

I can make the teleconference at either time. Do you need a timesheet even if I am an NIH employee and not compensated by FDA??
John DiGiovanna

John J. DiGiovanna, MD
DNA Repair Section
Dermatology Branch
National Cancer Institute
NIH, BLDG 37 RM 4002
Bethesda, MD 20892
TEL 301-402-1607
FAX 301-594-3409

From: Patel, Anuja (FDA/CDER)
Sent: Tuesday, March 24, 2015 1:27 PM
To: Digiovanna, John (NIH/NCI) [E]
Subject: SGE Availability for Teleconference with FDA/ DOP 2 Divisional Assignment for New Molecular Entity (sonidegib)
Importance: High

Dear Dr. Digiovanna,

Allow me to introduce myself as the Senior Regulatory Project Manager with Division of Oncology Products 2 (DOP 2), Office of Hematology and Oncology Products (OHOP).

At our request, you were contacted and screened for conflict of interest by the Division of Advisory Committee and Consultants Management to participate in a divisional assignment for us for a New Drug Application (NDA), New molecular Entity (NME) we are currently reviewing. You have been cleared by DACCM. DOP 2 is preparing the briefing package for the following product which will be sent to you soon (password protected). Please note that contents of the briefing package are CONFIDENTIAL and not publicly releasable.

Product: sonidegib
Proposed Indication: for treatment of patients with locally advanced basal cell carcinoma (BCC) who are not amenable to curative surgery or radiation therapy (b) (4)

In the meantime, I wanted to see if we could get a 30 minute teleconference scheduled **April 22, 2015 between 11:30 and 12 Noon or between 12:30 PM and 1:00 PM**, **EST**. Please let me know if this date and times works for you. I don't anticipate the tcon to last more than 30 minutes. If you are available another date/time please let me know and I will see what opens up on our end.

In addition, once you receive the briefing package, please let me know how much time is spent during your review as I will need to complete a time sheet for your assignment.

Thank you in advance in helping us protecting the public's health. Feel free to contact me if you have any questions, my contact information is below. If you could acknowledge receipt of this email that would be greatly appreciated!

Kindest Regards,
Anuja

Anuja Patel, MPH
Sr. Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
White Oak Complex, Bldg. 22, Room 2365
10903 New Hampshire Avenue
Silver Spring, MD 20993
•301.796.9022 (phone)
301.796.9849 (fax)
anuja.patel@fda.hhs.gov (email)

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

Reference ID: 3778989

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/s/

ANUJA PATEL
06/14/2015

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

Memorandum

Date: June 2, 2015

From: Anuja Patel, M.P.H., Sr. Regulatory Health Project Manager DOP2/OHOP

Subject: NDA 205266 (sonidegib), Novartis Pharmaceuticals Corporation: Proposed PMC/PMR Language

---

Novartis Pharmaceuticals Corporation
Attention: Jessica Wang, Pharm.D.
Associate Director, Drug Regulatory Affairs, Oncology
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Wang,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for "Odomzo (sonidegib), 200 mg capsules."

Please note that additional post-marketing requirement (PMR) and post-marketing commitment (PMC) proposals may be forthcoming while your application is under review. Provide your agreement and your proposed scheduled milestone dates to the below proposals. We remind you to use due diligence in proposing timelines for completion of these trials.

In addition, please note that final language will be included in the action letter. We are requesting that you respond to our proposal by close of business on Monday, June 8, 2015.

PMRs Subject to the Reporting Requirements Under Section 506B

CLINICAL

1. Conduct a Pregnancy Pharmacovigilance Study to evaluate pregnancy outcomes and infant outcomes following exposure to sonidegib. This study will include a mechanism to collect, classify, and analyze data on direct exposures (women exposed to sonidegib as treatment) and indirect exposures (women exposed to sonidegib through the seminal fluid of a male partner). The Pregnancy Pharmacovigilance Study will be initiated and functioning at the time of product launch. There will be interim annual reporting of the data collected from the study. The study, at a minimum, will include the following key elements (see the Guidance for Industry Establishing Pregnancy Exposure Registries for a detailed description of these elements):

    - Data collection of prospective and retrospective data points, adequate to produce informative, reliable data outcomes.

- Data analysis utilizing descriptive statistics for summarizing data that will fully capture outcomes of concern. Data collected prospectively analyzed separate from data collected retrospectively.

- Description of procedures including the patient recruitment, along with healthcare provider awareness of potential safety risk and existence of this study, and the monitoring of pregnancy and infant outcomes.

Each annual interim and final report should constitute a stand-alone report of cumulative pregnancy and infant outcomes data.

Final Protocol Submission:	MONTH 2015
Study/Trial Completion:	Applicant to provide date
Final Report Submission:	Applicant to provide date (Month 2025)

Other:

Annual Interim Report Submission for nine years:	MONTH 2016
	MONTH 2017
	MONTH 2018
	MONTH 2019
	MONTH 2020
	MONTH 2021
	MONTH 2022
	MONTH 2023
	MONTH 2024

CLINICAL PHARMACOLOGY

2. Complete the ongoing pharmacokinetic trial to determine an appropriate dose of sonidegib in patients with moderate to severe 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."

Study/Trial Completion:	30 September 2015
Final Report Submission:	31 July 2016

3. Submit the final study report for the completed clinical pharmacokinetic (drug interaction) trial to determine how to dose a gastric acid-reducing agent with sonidegib.

Final Report Submission:	31 July 2015

To assist you in organizing the submission of final study reports, we refer you to the following resources:

- Guidance for Industry entitled, *Structure and Content of Clinical Reports* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073113.pdf

- Guidance for Industry, entitled, *Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072974.pdf

- Guidance for Industry, entitled, *Reports on the Status of Postmarketing Study Commitments – Implementation of Section 130 of the Food and Drug Administration Modernization of 1997* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM080569.pdf.

- Guidance for Industry, entitled, *Postmarketing Studies and Clinical Trials — Implementation of Section 505(o) of the Food, Drug, and Cosmetic Act* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM172001.pdf

Please note for any multi-study PMC/PMR, results from each study are to be submitted as an individual clinical study report (CSR) to the NDA or BLA as soon as possible after study completion. The cover letter for these individual CSRs should identify the submission as PMC/PMR CORRESPONDENCE – PARTIAL RESPONSE in bold, capital letters at the top of the letter and should identify the commitment being addressed by referring to the commitment wording and number, if any, used in the approval letter, as well as the date of the approval letter.

The PMC/PMR final study report (FSR) submission intended to fulfill the PMC/PMR should include submission of the last remaining CSR and all previously submitted individual CSRs. The FSR should also contain an integrated analysis and thoughtful discussion across all studies regarding how these data support the fulfillment of the PMC/PMR. The cover letter should state the contents of the submission.

Furthermore, if a PMC/PMR requests, as a milestone, the submission of individual study reports as interim components of a multi-study PMC/PMR, the cover letter should identify the submission as PMC/PMR CORRESPONDENCE – INTERIM STUDY REPORT in bold, capital letters at the top of the letter and should identify the commitment being addressed by referring to the commitment wording and number, if any, used in the final action letter, as well as the date of the final action letter.

Please let me know if you have any questions.

Regards,

Anuja Patel, M.P.H.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-9022
Fax: 301-796-9849

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

/s/

ANUJA PATEL
06/02/2015

MEMORANDUM OF INTERNAL MEETING MINUTES

MEETING DATE:	May 13, 2015
TIME:	1:30 PM -2:30 PM, ET
LOCATION:	Teleconference, WO 22, RM 2201
APPLICATION:	NDA 205266
DRUG NAME:	sonidegib
TYPE OF MEETING:	Teleconference with Special Government Employee (SGE), Dr. June Robinson, cleared for participation by CDER's Division of Advisory Committee and Consultant Management (DACCM).

FDA ATTENDEES:

Patricia Keegan- Division Director, Division of Oncology Products 2 (DOP 2)
Denise Casey-Medical Officer, DOP 2
Anuja Patel- Senior Regulatory Health Project Manager, DOP 2
Suzanne Demko- Clinical Team Leader, DOP 2

EXTERNAL CONSTITUENT ATTENDEES:

Dr. June Robinson

BACKGROUND: Dr. Robinson agreed to serve and was cleared as an SGE for this new molecular entity (NME) application. Prior to this teleconference, background materials and draft product labeling were provided to Dr. Robinson, along with five specific Division questions for Dr. Robinson to address during this teleconference. Those materials are attached to this document.

DISCUSSION POINTS:

In this application, Novartis seeks the approval of ODOMZO (sonidegib), for the treatment of patients with locally advanced basal cell carcinoma (laBCC) who are not amenable to curative surgery or radiation therapy [redacted] (b) (4)

Discussion:

FDA Questions for Discussion During Teleconference:

1. In your practice, how do you evaluate tumor response to treatment in patients with laBCC? Please describe an algorithm if you have one. Comment on the Applicant's assessment of response using modified RECIST which integrates three measures (i.e., MRI, photography, biopsy) for a composite overall response rate endpoint.

   DISCUSSION DURING TELECONFERENCE: Dr. Robinson stated that many of the locally advanced tumors have excess scar tissue, and expressed concern regarding the response criteria not taking into account the full area of tumor. Dr. Robinson also questioned the ability of the punch biopsy to adequately assess tumor presence. FDA clarified that the applicant submitted a protocol amendment that ensured that patients had annotated photography such that investigators outlined areas of the tumor that were palpable, and that patients had multiple biopsies depending on the surface area of the lesion. After receiving this additional information, Dr. Robinson considered the overall response criteria to be adequate and had no further questions or concerns.

2. [redacted] (b) (4)

   DISCUSSION DURING TELECONFERENCE: [redacted] (b) (4)

   [redacted] (b) (4)

3. Is the risk:benefit profile of sonidegib favorable for the treatment of patients with advanced BCC? Please comment specifically on the long-term use of this drug in a potentially indolent disease and the risk for muscle-related adverse reactions including rhabdomyolysis.

   DISCUSSION DURING TELECONFERENCE: Dr. Robinson stated agreement that despite the toxicities, the benefits of sonidegib outweigh the risks for patients with inoperable laBCC. Dr. Robinson was concerned about toxicities with long term use of sonidegib and asked about the duration of treatment. FDA clarified that there was no specific duration of treatment for patients who maintained their response to sonidegib. In addition, FDA also stated that the study population was too small to adequately estimate the optimal length of treatment, and commented on the prolonged half-life of the drug. FDA stated that in a few patients who discontinued sonidegib due to adverse reactions, there was evidence of durability of response.

   With regards to the risk for muscle-related adverse reactions including rhabdomyolysis, Dr. Robinson inquired about concurrent renal insufficiency and expressed concern about this risk in the elderly and vulnerable population. FDA clarified that renal impairment was not commonly associated with serum CK elevation; however a large number of patients also received intravenous hydration which may have prevented impending renal insufficiency or rhabdomyolysis.

   Dr. Robinson stated that the proposed label with FDA revisions adequately addresses the risk for muscle toxicity.

4. Sonidegib is a hedgehog inhibitor with teratogenic effects in animals. Do you expect that these risks will influence prescribers in the management of patients with laBCC who are of child-bearing age?

   DISCUSSION DURING TELECONFERENCE: Dr. Robinson expressed concern regarding the risk for teratogenicity but considered the black box to be adequate in addressing this risk.

   In addition, Dr. Robinson commented that vismodegib is currently being used off-label by some practitioners to prevent the development of BCC in patients with Gorlin syndrome. She expressed concern that sonidegib would similarly be used off label in the community. FDA acknowledged Dr. Robinson's concerns regarding potential risks and different risk-benefit assessment for this off-label use.

5. Does the attached draft label adequately reflect the risks and benefits of sonidegib for the treatment of patients with laBCC not amenable to local therapies?

DISCUSSION DURING TELECONFERENCE: Dr. Robinson stated that the draft label sufficiently reflects the risks and benefits of sonidegib for the treatment of patients with laBCC not amenable to local therapies.

Additional SGE Comments:

- Dr. Robinson questioned the benefit of long term exposure in patients who do not have clear evidence of response to sonidegib as compared to the patient who has a relatively rapid response to treatment and can tolerate the toxicity for a defined treatment period.

- Dr. Robinson stated that overall, although BCC may be a relatively indolent disease, it can cause additional suffering in terms of frequent infections and spontaneous bleeding leading to increased emergency room visits. She further stated that considering this, a drug that could potentially decrease tumor burden may decrease these additional disease-related complications.

ATTACHMENTS: Background information provided to Dr. Robinson via a password protected file, secure email communication on May 7, 2015.

36 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

Patel, Anuja

From:	Patel, Anuja
Sent:	Wednesday, May 13, 2015 11:38 AM
To:	'June K Robinson'
Cc:	Casey, Denise (CDER)
Subject:	RE: SGE Revised Package Insert -for Teleconference Scheduled for May 13, 2015 at 1:30 PM, EST
Attachments:	proposed amended PI labeling received 1_23_2015 with PK edits 5 13 15 clean for SGE.pdf
Importance:	High

Tracking:

Recipient	Read
'June K Robinson'	
Casey, Denise (CDER)	Read: 5/13/2015 12:06 PM

Dear Dr. Robinson,

Our Division made additional edits today to the proposed package insert for this application. Please find attached a more current draft label that we will discuss during today teleconference. This label replaces the one that was included in the briefing document.

Please acknowledge receipt and thank you for your time.

Regards,
Anuja

Anuja Patel, MPH
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
White Oak Complex, Bldg. 22, Room 2365
10903 New Hampshire Avenue
Silver Spring, MD 20993
S301.796.9022 (phone)
301.796.9849 (fax)
anuja.patel@fda.hhs.gov (email)

-----Original Message-----
From: Patel, Anuja
Sent: Wednesday, May 13, 2015 9:18 AM
To: 'June K Robinson'
Cc: Casey, Denise (CDER)

Reference ID: 3769632

Subject: RE: SGE Briefing Document (Password Protected) for Teleconference Scheduled for May 13, 2015 at 1:30 PM, EST
Importance: High

Hi Dr. Robinson,

In the briefing document we reference vismodegib data. I wanted to provide a copy of the approved package insert as reference during today's teleconference. The link to the PI (found on Drags at FDA website) is below:
http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/203388lbl.pdf

We look forward to speaking with you later today.

Regards,
Anuja

Anuja Patel, MPH
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
White Oak Complex, Bldg. 22, Room 2365
10903 New Hampshire Avenue
Silver Spring, MD 20993
S301.796.9022 (phone)
301.796.9849 (fax)
anuja.patel@fda.hhs.gov (email)

-----Original Message-----
From: June K Robinson [mailto:june-robinson@northwestern.edu]
Sent: Saturday, May 09, 2015 8:35 AM
To: Patel, Anuja
Subject: RE: SGE Briefing Document (Password Protected) for Teleconference Scheduled for May 13, 2015 at 1:30 PM, EST

I have the document and opened it.

June K. Robinson, MD
Research Professor of Dermatology
Northwestern University Feinberg School of Medicine
Department of Dermatology
676 St. Clair St, Room 1265
Chicago, IL 60611
Telephone 312-926-7449

_____
From: Patel, Anuja [Anuja.Patel@fda.hhs.gov]
Sent: Thursday, May 7, 2015 6:57 AM
To: June K Robinson
Subject: SGE Briefing Document (Password Protected) for Teleconference Scheduled for May 13, 2015 at 1:30 PM, EST

Reference ID: 3769632

Dear Dr. Robinson,

Attached is a password protected briefing document for your review prior to the 30 minute teleconference scheduled for May 13, 2015 at 1:30 PM, EST. I will be emailing you the password to open this document in a separate e-mail momentarily.
Please let me know if you have any issues opening the file after you receive the password.

The dial in number for the teleconference has been changed since we are now using a different provider. Please see instructions below for joining the teleconference:
Step 1: Participant Dial In: 1 855 828 1770 (toll free)
Step 2: Enter Meeting ID: (b) (4)
Step 3: State your Name following Prompt (you will be placed on hold until FDA activates the call)

Feel free to contact me if you have any questions. The Agency appreciates your time and patience in reviewing this application and assisting us in protecting the nation's public health.

Kindly confirm receipt of this email and the attachment.

Regards,
Anuja

Anuja Patel, MPH
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
White Oak Complex, Bldg. 22, Room 2365
10903 New Hampshire Avenue
Silver Spring, MD 20993
•301.796.9022 (phone)
301.796.9849 (fax)
anuja.patel@fda.hhs.gov<mailto:anuja.patel@fda.hhs.gov> (email)

From: June K Robinson [mailto:june-robinson@northwestern.edu]
Sent: Sunday, March 22, 2015 1:07 PM
To: Patel, Anuja
Subject: Re: (DIAL IN): SGE Availability for Teleconference with FDA/ DOP 2 Divisional Assignment for New Molecular Entity (sonidegib)

Thank you.
June

Sent from my iPhone

On Mar 20, 2015, at 2:19 PM, Patel, Anuja <Anuja.Patel@fda.hhs.gov<mailto:Anuja.Patel@fda.hhs.gov>> wrote:
Hello Dr. Robinson,

We have our teleconference confirmed for Wednesday, April 22,2 015, Noon, EST. The dial in number for the teleconference is below:

Reference ID: 3769632

DIAL IN NUMBER:
866-715-9310
Participant Code: (b) (4)

We will be providing you a password protected background package prior to the meeting. Please let me know if you will be on vacation or unable to access email so that we can plan accordingly. We look forward to speaking with you soon.

Please acknowledge receipt of this email.

Regards,
Anuja

-----Original Message-----
From: June K Robinson [mailto:june-robinson@northwestern.edu]
Sent: Wednesday, March 18, 2015 9:38 PM
To: Patel, Anuja
Subject: RE: SGE Availability for Teleconference with FDA/ DOP 2 Divisional Assignment for New Molecular Entity (sonidegib)

Thank you for giving me advance notice. I am available for a teleconference call on April 22 (Wed) and April 24 (Friday).

I would prefer to limit the conference call to usually working hours.

June

June K. Robinson, MD
Research Professor of Dermatology
Northwestern University Feinberg School of Medicine
Department of Dermatology
676 St. Clair St, Room 1265
Chicago, IL 60611
Telephone 312-926-7449

_____
From: Patel, Anuja [Anuja.Patel@fda.hhs.gov<mailto:Anuja.Patel@fda.hhs.gov>]
Sent: Wednesday, March 18, 2015 10:07 AM
To: June K Robinson
Subject: SGE Availability for Teleconference with FDA/ DOP 2 Divisional Assignment for New Molecular Entity (sonidegib)

Dear Dr Robinson,

Allow me to introduce myself as the Senior Regulatory Project Manager with Division of Oncology Products 2 (DOP 2), Office of Hematology and Oncology Products (OHOP).

At our request, you were contacted and screened for conflict of interest by the Division of Advisory Committee and Consultants Management to participate in a divisional assignment for us for a New Drug Application (NDA), New molecular Entity (NME) we are currently reviewing. You have been cleared by DACCM. DOP 2 is preparing the briefing package for the following product which will be sent to you soon (password protected). Please note that contents of the briefing package are CONFIDENTIAL and not publicly releasable.

Reference ID: 3769632

Product: sonidegib
Proposed Indication: for treatment of patients with locally advanced basal cell carcinoma (BCC) who are not amenable to curative surgery or radiation therapy (b) (4)

In the meantime, I wanted to see if we could get a teleconference scheduled sometime the week of November 4. Please let me know what dates and times (EST) you are available week of April 20th for a 30 minute tcon. I don't anticipate the tcon to last more than 30 minutes. In addition, once you receive the briefing package, please let me know how much time is spent during your review as I will need to complete a time sheet for your assignment.

Thank you in advance in helping us protecting the public's health. Feel free to contact me if you have any questions, my contact information is below. If you could acknowledge receipt of this email that would be greatly appreciated!

Kindest Regards,
Anuja

Anuja Patel, MPH
Sr. Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
White Oak Complex, Bldg. 22, Room 2365
10903 New Hampshire Avenue
Silver Spring, MD 20993
•301.796.9022 (phone)
301.796.9849 (fax)

anuja.patel@fda.hhs.gov<mailto:anuja.patel@fda.hhs.gov<mailto:anuja.patel@fda.hhs.gov%3cmailto:anuja.patel@fda.hhs.gov>> (email)

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

Reference ID: 3769632

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/s/

ANUJA PATEL
05/29/2015

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

Memorandum

Date: May 29, 2015

From: Anuja Patel M.P.H., Sr. Regulatory Health Project Manager DOP2/OHOP

Subject: NDA 205266/ Type 1 NME/ sonidegib (ODOMZO)/ Novartis Pharmaceuticals Corporation

---

Novartis Pharmaceuticals Corporation
Attention: Jessica Wang, Pharm.D.
Associate Director, Drug Regulatory Affairs, Oncology
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Wang:

Please find attached FDA's additional edits and comments from the Office of Prescription Drug Promotion (OPDP) and our patient labeling (PL) team in the Division of Medical Policy Programs (DMPP) in response to your Medication Guide submitted on January 23, 2015.

In areas of the Medication Guide that you agree with FDA's proposed edits, please accept the tracked change to aid in reviewability. Please include a comment (cite "From Novartis" in the comment field) stating your agreement.

For those edits which you do not agree, provide a comment (cite "From Novartis" in the comment field) and include justification for your counterproposal.

Please provide a response to FDA's proposed changes by 12:00 PM, EST on June 5, 2015. In addition to submitting your response to the NDA, please email me a copy of your responses as well as a clean and redlined version of the Medication Guide.

Please let me know if you have any questions.

Regards,

Anuja Patel, M.P.H.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-9022, Fax: 301-796-9849

Attachment: FDA Additional edits to Medication Guide

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Reference ID: 3770282

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/s/

ANUJA PATEL
05/29/2015

Patel, Anuja

From: Patel, Anuja
Sent: Tuesday, May 26, 2015 10:23 AM
To: 'Wang, Jessica-1'
Cc: Ganeshan, Shanthi
Subject: RE: FDA preliminary Edits to PI/ NDA 205266/ sonidegib/ Novartis

Importance: High

Dear Dr. Wang,

We refer to your email sent May 22, 2015 requesting an extension for the due date of your response to our May 14, 2015, email communication containing our preliminary edits to the package insert.

We have the following response to your email:

- **In order to have an informed and productive conversation about the label at the late cycle meeting (LCM), we will need to have the label submitted formally to us by 12 noon, EST on Friday, June 5, 2015. We will grant you an extension until this date and time. This new extended due date is so we have time to review the label in advance of the LCM. In addition, please note that we are aware that additional back and forth on the label will be needed.**

Kindly acknowledge receipt and email me a courtesy copy of your response once it is formally submitted through the gateway.

Regards,
Anuja

Anuja Patel, MPH
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
White Oak Complex, Bldg. 22, Room 2365
10903 New Hampshire Avenue
Silver Spring, MD 20993
☎301.796.9022 (phone)
301.796.9849 (fax)
anuja.patel@fda.hhs.gov (email)

From: Wang, Jessica-1 [mailto:jessica-1.wang@novartis.com]
Sent: Friday, May 22, 2015 2:49 PM
To: Patel, Anuja
Cc: Ganeshan, Shanthi
Subject: RE: FDA preliminary Edits to PI/ NDA 205266/ sonidegib/ Novartis

Dear Anuja,

Reference ID: 3764326

Novartis has reviewed the FDA's revisions/edits to the proposed Odomzo USPI and would like to request additional time to respond:

- [redacted] (b) (4) Novartis would like to further evaluate the data (already submitted in the NDA) to determine if additional information in the laBCC population can be included in the USPI to help prescribers
- Discuss these additional information and class labeling with FDA during the late-cycle meeting prior to submitting a response (revised proposed label).

We would really appreciate your consideration to this request. Please let us know if this is acceptable to the review team.

Although I will be out of the office next week, Shanthi (cc'ed) will be happy to further discuss; feel free to give her a call at (862) 684-6317.

Best regards,
Jessica

Jessica Wang, PharmD
Senior Associate Director
Drug Regulatory Affairs, Oncology
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080
USA

Phone +1 862 7789507
Mobile [redacted] (b) (6)
jessica-1.wang@novartis.com

From: Patel, Anuja [mailto:Anuja.Patel@fda.hhs.gov]
Sent: Thursday, May 14, 2015 4:50 PM
To: Wang, Jessica-1
Subject: FDA preliminary Edits to PI/ NDA 205266/ sonidegib/ Novartis
Importance: High

Dear Dr. Wang,

Please find attached FDA's preliminary edits and comments to your revised package insert (PI) labeling submitted on January 23, 2015.

In areas of the label that you agree with FDA's proposed edits, please accept the tracked change to aid in reviewability. Please include a comment (cite "From Novartis" in the comment field) stating your agreement. For those edits which you do not agree, provide a comment (cite "From Novartis" in the comment field) and include justification for your counterproposal.

Please provide a response to FDA's proposed changes by **12:00 PM, EST on May 29, 2015**. In addition to submitting your response to the NDA, please email me a copy of your responses as well as a clean and redlined version of the labeling.

I am attaching a word version (tracked) to assist in your review.

Please acknowledge receipt.

Regards,

Reference ID: 3764326

Anuja

Anuja Patel, MPH
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
White Oak Complex, Bldg. 22, Room 2365
10903 New Hampshire Avenue
Silver Spring, MD 20993
☎301.796.9022 (phone)
301.796.9849 (fax)
anuja.patel@fda.hhs.gov (email)

Reference ID: 3764326

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/s/

ANUJA PATEL
05/26/2015

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

Memorandum

Date: May 14, 2015

From: Anuja Patel, MPH, Sr. Regulatory Health Project Manager DOP2/OHOP

Subject: NDA 205266 Sonidegib- 30 minute Weekly Teleconference- Discussion of Pregnancy PMR and 2 Clinical Pharmacology PMRs

---

Novartis Attendees

Dalila Sellami, MD, Global Clinical Program Head, Oncology Clinical Development
Henry Castro, MD, Senior Global Clinical Leader, Oncology Clinical Development
Stacey Kalambakas, MD, Senior Global Clinical Leader, Oncology Clinical Development
Jocelyn Zhou, PhD, Senior Scientist, Oncology Clinical Pharmacology
Shefali Kakar, PhD, Senior Director, Oncology Clinical Pharmacology
Klaus Kucher, MD, Executive Director, Head TM Profiling ATI
June Ke, PhD, Senior Investigator, DMPK
Michael Levine, MD, Brand Safety Leader, Integrated Medical Safety, Oncology
Lily Zhao, PhD, Director, Biostatistics
Michelle Quinlan, Associate Director, Biostatistics
Shanthi Ganeshan, PhD, Vice President, NA Region Head, Oncology Drug Regulatory Affairs
Michael Buska, MS, Global Program Regulatory Director, Drug Regulatory Affairs
Lisa Krueger, PharmD, Regulatory Manager, Drug Regulatory Affairs
Jessica Wang, PharmD, Senior Associate Director, Drug Regulatory Affairs

FDA Attendees:
Dr. Jeff Summers, Deputy Director, Safety
Denise Casey, Clinical Reviewer
Stacy Shord, Clinical Pharmacology Reviewer
Hong Zhao, Clinical Pharmacology Team Leader (TL)
Tamara Johnson, Acting TL, Pediatric and Maternal Health
Norma Griffin, Acting TL, Project Management

On the phone:
Suzanne Demko, Clinical TL
Anuja Patel, Sr. RPM
Carol Kasten, Maternal Health Reviewer

Regulatory Background:

- **May 13, 2015-** Novartis acknowledged FDA comments sent via electron mail (e-mail) on May 12, 2015, regarding Pregnancy PMR and stated that they do not have any specific questions for clarification at this time related to the pregnancy PMR. Novartis stated that they intend to address all comments in the draft protocol which we are targeting for a submission in approximately 4-6 weeks.

- **May 12, 2015**: FDA issued the following comments via e-mail in response to Novartis April 17, 2015 submission containing their proposed Pregnancy Monitoring Program:

    1. A plan for assessing infant outcomes should be included to follow up infants at birth, at 12 months, and at a time point in between. (b) (4)

    2. You have not specified the duration for which the program will run. We recommend a ten-year time period.

    3. We will provide additional comments upon submission of the full protocol.

- **May 7, 2015:** FDA sent e-mail confirmation for the weekly tcon scheduled for May 14, 2015, and informed Novartis that FDA would like to discuss clinical pharmacology PMRs.

Purpose: The purpose of this 30 minute teleconference is to discuss FDA expectations regarding the hepatic impairment trial and to get an update on the studies for the following PMRs:

- **Pregnancy PMR**

  To conduct a Pregnancy Pharmacovigilance Study to collect data to evaluate pregnancy outcomes and infant outcomes following exposure to sonidegib.

  Discussion During Meeting: FDA acknowledged Novartis response sent via e-mail on May 13, 2015 and stated that the draft protocol to be submitted should include specific information on enrollment, including total sample size, and supporting documentation and justification for the proposed population size.

- **Clinical Pharmacology PMRs**
  - A PMR clinical study to evaluate the effect of acid-reducing agents on the pharmacokinetics of sonidegib and how to dose sonidegib for patients concurrently taking acid-reducing agents.

    Discussion During Meeting: FDA requested an update on the ongoing trial. (b) (4)

- A PMR clinical study to evaluate the effect of moderate and severe hepatic impairment on the pharmacokinetics of sonidegib and determine an appropriate dose for patients with hepatic impairment

  Discussion During Meeting: FDA requested an update on the ongoing hepatic impairment trial. (b) (4)

  FDA further advised Novartis that when providing timeline due dates to FDA for the PMRs, Novartis should add additional 3-6 months for any unforeseen circumstances that may delay the timeline for meeting the due dates.

Post-Meeting follow-up: *Novartis informed FDA during the teleconference that they will e-mail a summary of the study status for the clinical studies discussed above to the RPM.*

From: Wang, Jessica-1 [mailto:jessica-1.wang@novartis.com]
Sent: Thursday, May 14, 2015 2:26 PM
To: Patel, Anuja
Subject: Follow-up to FDA/NVS TC 5/14: Details regarding Clin Pharm PMRs- status of studies

Dear Anuja,

Reference is made to Odomzo (sonidegib) NDA 205-266 and the FDA/NVS weekly TC held today (14-May-2015) to discuss the two Clinical Pharmacology post-marketing requirements (PMRs) and the pregnancy PMR which were originally communicated during the Mid-Cycle Meeting.

As discussed, below is a brief summary of the study status for the two Clinical Pharmacology PMRs communicated during the TC. Apologies if there was any difficulty in hearing.

- (b) (4)

  Note: Novartis acknowledges FDA's recommendation to add 6 months to the proposed PMR commitment date as a buffer.
- **Study CLDE225A2113 – Hepatic impairment study:**
  - The study was initiated in Mar 2013 and enrollment has been completed.
  - Final CSR would be available 4Q2015.

(b) (4)

Thank you again for the opportunity to discuss these PMRs with the Agency and we greatly appreciate your feedback.

Take care and best regards,
Jess

Jessica Wang, PharmD
Senior Associate Director
Drug Regulatory Affairs, Oncology
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080
USA

Phone +1 862 7789507
Mobile (b) (6)
jessica-1.wang@novartis.com

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/s/

ANUJA PATEL
05/20/2015

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

Memorandum

Date: May 14, 2015

From: Anuja Patel M.P.H., Sr. Regulatory Health Project Manager DOP2/OHOP

Subject: NDA 205266/ Type 1 NME/ sonidegib (ODOMZO)/ Novartis Pharmaceuticals Corporation

---

Novartis Pharmaceuticals Corporation
Attention: Jessica Wang, Pharm.D.
Associate Director, Drug Regulatory Affairs, Oncology
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Wang:

Please find attached FDA's preliminary edits and comments to your revised package insert (PI) labeling submitted on January 23, 2015, with the 120-day safety update. Your labeling submitted January 23, 2015, included additional safety data from the pivotal Study CLDE225A2201 and is based on a data cut-off of July 11, 2014, which is 78 weeks after last patient was randomized (also referred to as the 18-month analysis).

We have the following general comment:

- In addition to these proposed edits, please update the Table of Contents, update table and figure numbers if needed, and correct formatting as needed. You are responsible for submitting prescribing information that meets the Selected Requirements of Prescribing Information (SRPI) requirements. Please refer to the SRPI checklist on the *PLR Requirements for Prescribing Information* website found at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm

In areas of the label that you agree with FDA's proposed edits, please accept the tracked change to aid in reviewability. Please include a comment (cite "From Novartis" in the comment field) stating your agreement.

For those edits which you do not agree, provide a comment (cite "From Novartis" in the comment field) and include justification for your counterproposal.

Please provide a response to FDA's proposed changes by 12:00 PM, EST on May 29, 2015. In addition to submitting your response to the NDA, please email me a copy of your responses as well as a clean and redlined version of the labeling.

Please note these are our preliminary comments, this labeling is currently being reviewed by our counterparts in Office of Prescription Drug Promotion (OPDP) and the Patient Labeling Team (PLT) and additional comments will follow.

Please let me know if you have any questions.

Regards,

Anuja Patel, M.P.H.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-9022, Fax: 301-796-9849

Attachment: FDA Preliminary edits to Package Insert

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

Reference ID: 3756011

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/s/

ANUJA PATEL
05/14/2015

From:	Biable, Missiratch (Mimi)
To:	"Wang, Jessica-1"
Cc:	Patel, Anuja
Subject:	NDA 205266: Pregnancy PMR for sonidegib
Date:	Tuesday, May 12, 2015 2:33:00 PM
Importance:	High

Dear Dr. Wang,

I am sending you these comments on behalf of Ms. Anuja Patel who is currently out of the office.

Any concerns or clarifications you may have can be addressed during the tcon scheduled for Thursday's, May 14, 2015.

Review of your submitted pregnancy monitoring concept sheet finds that the proposed program appears to meet the majority of elements that we require; however, we have the following comments.

1) A plan for assessing infant outcomes should be included to follow up infants at birth, at 12 months, and at a time point in between. (b) (4)

2) You have not specified the duration for which the program will run. We recommend a ten-year time period.

3) We will provide additional comments upon submission of the full protocol.

Regards,

Missiratch (Mimi) Biable, M.S., R.A.C (US)
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Email: Missiratch.biable@fda.hhs.gov
Phone: 301-796-0154

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/s/

MISSIRATCH BIABLE
05/12/2015

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

Memorandum

Date: April 16, 2015

From: Anuja Patel, MPH, Sr. Regulatory Health Project Manager DOP2/OHOP

Subject: NDA 205266 Sonidegib- 30 minute Weekly Teleconference

---

Novartis Attendees
Neil Gallagher, MD, PhD, Global Program Head, Oncology Clinical Development
Dalila Sellami, MD, Global Clinical Program Head, Oncology Clinical Development
Henry Castro, MD, Senior Global Clinical Lead, Oncology Clinical Development
Stacey Kalambakas, MD, Senior Global Clinical Lead, Oncology Clinical Development
Michael Levine, MD, Brand Safety Leader, Integrated Medical Safety, Oncology
Lily Zhao, PhD, Director, Biostatistics
Tingting Yi, PhD, Associate Director, Biostatistics
Feng Tai, PhD, Associate Director, Biostatistics
Matthias Jauslin, PhD, Global Program Regulatory Director, Drug Regulatory Affairs
Shanthi Ganeshan, PhD, Vice President, NA Region Head, Oncology Drug Regulatory Affairs
JoyceAnn Sinno, PhD, Director, Senior Regulatory Expert Global Regulatory CMC Oncology
Lisa Krueger, PharmD, Drug Regulatory Affairs
Jessica Wang, PharmD, Senior Associate Director, Drug Regulatory Affairs

FDA Attendees:
Anuja Patel, Regulatory Project Manager
Suzanne Demko, Clinical Team Leader
Denise Casey, Medical Officer
Okpo Eradiri, Biopharmaceutics Reviewer
Liang Zhou, Application Team Leader, OPQ

Purpose: The purpose of this 30 minute teleconference is to discuss the following clinical and the Biopharmaceutics information request that was issued via email to the Applicant on April 15, 2015.

Biopharmaceutics:

1. In the April 14, 2015 response to the Biopharmaceutics Information Request, the dissolution acceptance criteria are incorrectly updated. Update the dissolution acceptance criteria in the Specifications Table as follows:

   30 min: (b) (4) %
   90 min: %

<u>Discussion During Meeting</u>: FDA clarified that the Specifications table submitted to the NDA on 4/14/2015 should be updated by deleting (b) (4); Novartis acknowledged FDA's request. The dissolution acceptance criteria agreed to now reads:

Q = (b) (4) % in 30 min
Q = (b) (4) % in 90 min

<u>Clinical:</u>

2. We have received and are reviewing your Response to FDA Information Request 23 (IR23) which includes an analysis of pooled safety data for the 571 patients treated across twelve clinical studies in the sonidegib development program with regard to musculoskeletal adverse events. Please provide the following additional items:

   A. The dataset for this pooled safety population.

   B. An analysis of the demographics, baseline disease characteristics, extent of exposure, and adverse events that occurred in this pooled safety population.

   C. A separate analysis of lipase elevation and an assessment of the clinical impact of lipase elevation (including the development of pancreatitis) across the pooled population.

   D. Narratives of all serious adverse events and adverse events of special interest that occurred during these studies. (FDA acknowledges that there may be some information in your response that overlaps with that of the Summary of Clinical Safety Addendum 2-Appendix 2 which includes SAE reports from five studies covering the period from September 1, 2014 to December 26, 2014; however, we are now requesting SAE reports and narratives from the twelve studies pooled for your response to IR23 from study start through final database lock or for ongoing studies, the latest data cut-off date with cleaned data on adverse events.)

Discussion During Meeting: To facilitate the discussion, Novartis provided their response to the propose content for the response to the April 15, 2015, clinical Information request sent via e-mail prior to the teleconference. FDA generally agreed to the proposed content.

FDA clarified that the purpose of the request for additional information on exposure and adverse events was for labeling. FDA stated that our intent is to specifically review the clinical impact of musculoskeletal adverse drug reactions and lipase elevation across a larger safety population. FDA acknowledged that the inclusion of some patients and studies in this safety analysis ((b) (4) would confound a review of sonidegib-related lipase elevation and pancreatitis and advised that Novartis exclude such patients and provide additional commentary justifying the exclusion. FDA also stated that narratives of serious adverse events and adverse events of pancreatitis and lipase elevation would satisfy request 2D.

Post Tcon Action Item:

A complete response to the Biopharmaceutics Information Request was formally submitted and received April 16, 2015 and was forwarded to the review team. A complete response to the clinical Information Request was received on April 23, 2015.

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/s/

ANUJA PATEL
05/08/2015

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

Memorandum

Date: April 14, 2015

From: Anuja Patel, MPH, Sr. Regulatory Health Project Manager DOP2/OHOP

Subject: NDA 205266 (sonidegib): Internal Labeling Meeting #4 (Part 2)

FDA reviewed and discussed Novartis's proposed labeling revisions, submitted January 23, 2015 with the 120-day safety update. The proposed labeling included in this submission incorporates the additional 6 months of safety data from the pivotal study CLDE225A2201.

Attendees: Anuja Patel, Suzanne Demko, Patricia Keegan, Stacy Shord, Denise Casey, Nam Atiqur Rahman

Discussion: The purpose of this meeting was to go over any remaining clinical sections but specifically to gain agreement on the following sections with clinical pharmacology:

2 DOSAGE AND ADMINSTRATION
7 DRUG INTERACTIONS

In addition the following section were discussed as they were not discussed during March 25, 2015 meeting (Labeling Meeting #4).

6 ADVERSE REACTIONS

There was discussion on muscle toxicity with clinical pharmacology and the team agreed to no post-marketing requirement for muscle toxicity.

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/s/

ANUJA PATEL
05/08/2015

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

Memorandum

Date: April 8, 2015

From: Anuja Patel, MPH, Sr. Regulatory Health Project Manager DOP2/OHOP

Subject: NDA 205266 (sonidegib): Internal Labeling Meeting #5

FDA reviewed and discussed Novartis's proposed labeling revisions, submitted January 23, 2015 with the 120-day safety update. The proposed labeling included in this submission incorporates the additional 6 months of safety data from the pivotal study CLDE225A2201.

Attendees: Anuja Patel, Suzanne Demko, Patricia Keegan, Whitney Helms, Alexander Putman, Ethan Hausman, Jeanine Best, Karen Boyd, Jeanne Fourie Zirkelbach, Jennie Chang, Amarilys Vega, Denise Casey

Discussion: The following sections were discussed:

Section 5.1: Embryo-fetal Death and Severe Birth Defects
Section 8.1: Pregnancy
Section 8.3: Nursing Mothers
Section 8.4: Pediatric Use
Section 12.1: Mechanism of Action
Section 13: Nonclinical Toxicology
Boxed Warning
Section 17

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/s/

ANUJA PATEL
05/08/2015

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

Memorandum

Date: March 25, 2015

From: Anuja Patel, MPH, Sr. Regulatory Health Project Manager DOP2/OHOP

Subject: NDA 205266 (sonidegib): Internal Labeling Meeting #4

FDA reviewed and discussed Novartis's proposed labeling revisions, submitted January 23, 2015 with the 120-day safety update. The proposed labeling included in this submission incorporates the additional 6 months of safety data from the pivotal study CLDE225A2201.

Attendees: Anuja Patel, Suzanne Demko, Patricia Keegan, Denise Casey, Nick Senior, Tamara Johnson

Discussion: The following sections of the PI were discussed:

4 CONTRAINDICATIONS
- Discussion to (b) (4) state "None".

5 WARNINGS AND PRECAUTIONS
- Section 5.1 was moved to the next meeting.

6 ADVERSE REACTIONS

17 PATIENT COUNSELING

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/s/

ANUJA PATEL
05/08/2015

Patel, Anuja

From: Patel, Anuja
Sent: Thursday, May 07, 2015 10:23 AM
To: 'Wang, Jessica-1'
Subject: FDA Weekly Teleconference Next Week- May 14, 2015- sonidegib/ NDA 205266

Importance: High

Hello Dr. Wang,

We would like to confirm the teleconference for next Thursday, May 14, 2015 to discuss the proposed clinical pharmacology post marketing requirements (PMR). For the teleconference, please include the responsible parties that will be managing the orphan impairment trials as well as your regulatory team as participants.

Please confirm receipt of this email and next week's teleconference.

Feel free to contact me if you have additional questions.

Regards,
Anuja

Anuja Patel, MPH
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
White Oak Complex, Bldg. 22, Room 2365
10903 New Hampshire Avenue
Silver Spring, MD 20993
☎301.796.9022 (phone)
301.796.9849 (fax)
anuja.patel@fda.hhs.gov (email)

Reference ID: 3749647

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/s/

ANUJA PATEL
05/07/2015

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

Memorandum

Date: March 18, 2015

From: Anuja Patel, MPH, Sr. Regulatory Health Project Manager DOP2/OHOP

Subject: NDA 205266 (sonidegib): Internal Labeling Meeting #2

FDA reviewed and discussed Novartis's proposed labeling revisions, submitted January 23, 2015 with the 120-day safety update. The proposed labeling included in this submission incorporates the additional 6 months of safety data from the pivotal study CLDE225A2201.

Attendees: Anuja Patel, Suzanne Demko, Patricia Keegan, Stacy Shord, Denise Casey, Hong Zhao, Ethan Hausman

Discussion: The team discussed the following sections:

- **2 DOSAGE AND ADMINISTRATION**
- **7 DRUG INTERACTION**
- **8.5 GERIATRIC USE**
- **8.6 HEPATIC IMPAIRMENT**
- **8.7 RENAL IMPAIRMENT**
- **12.2 PHARMACODYNAMICS**
- **12.3 PHARMACOKINETICS**

In addition, it was noted that DMEPA will need to be invited to future discussions for Section 2. The Pediatric and Maternal Health Reviewers confirmed that they will review section 8.1 for conformity to the Pregnancy and Lactation Labeling Final Rule.

Action Item- Clinical to work on (b) (4)

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/s/

ANUJA PATEL
05/08/2015

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

Memorandum

Date: March 23, 2015

From: Anuja Patel, MPH, Sr. Regulatory Health Project Manager DOP2/OHOP

Subject: NDA 205266 (sonidegib): Internal Labeling Meeting #3

FDA reviewed and discussed Novartis's proposed labeling revisions, submitted January 23, 2015 with the 120-day safety update. The proposed labeling included in this submission incorporates the additional 6 months of safety data from the pivotal study CLDE225A2201.

Attendees: Anuja Patel, Suzanne Demko, Denise Casey. Patricia Keegan, Liang Zhou, William Adams, Benjamin Stevens, Amarilys Vega, Ethan Hausman, Carol Kasten, Latonia Ford, Okpo Eradiri

Discussion: The team discussed the following sections:

- **3 DOSAGE FORMS AND STRENGTHS**
- **11 DESCRIPTION**
- **16 HOW SUPPLIED/STORAGE AND HANDLING**
- **CARTON AND CONTAINER LABELING: Bottle of 30 capsules; (b) (4) Unit Dose (blister pack of 30 capsules**

➢ OPQ discussion of (b) (4) . OPQ agreed to (b) (4) . OPQ/DOP 2 looked for guidance regarding dissolution but could not find anything on FDA website.

➢ The bottle labels and unit dose carton include the statement "Product of Switzerland". (b) (4) . OPQ discussed internally and agreed to leave "Product of Switzerland" in the label.

Post Meeting Follow-up: During the Office of Product Quality (OPQ) teleconference with Novartis on Friday, April 24, 2015, FDA communicated to the applicant that (b) (4)

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/s/

ANUJA PATEL
05/08/2015

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

Memorandum

Date: March 12, 2015

From: Anuja Patel, MPH, Sr. Regulatory Health Project Manager DOP2/OHOP

Subject: NDA 205266 (sonidegib): Internal Labeling Meeting #1

FDA reviewed and discussed Novartis's proposed labeling revisions, submitted January 23, 2015 with the 120-day safety update. The proposed labeling included in this submission incorporates the additional 6 months of safety data from the pivotal study CLDE225A2201.

Attendees: Anuja Patel, Suzanne Demko, Denise Casey, Kun He, Huanyu Chen, Carol Kasten, Ethan Hausman

Discussion: The team discussed the following sections:

- **1 INDICATIONS AND USAGE**
- **14 CLINICAL STUDIES, REFERENCES**

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/s/

ANUJA PATEL
05/08/2015

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

Memorandum

Date: April 28, 2015

From: Anuja Patel M.P.H., Sr. Regulatory Health Project Manager DOP2/OHOP

Subject: NDA 205266/ Type 1 NME/ sonidegib (ODOMZO)/ Novartis Pharmaceuticals Corporation

---

Novartis Pharmaceuticals Corporation
Attention: Jessica Wang, Pharm.D.
Associate Director, Drug Regulatory Affairs, Oncology
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Wang:

Please find attached FDA's preliminary comments to your carton and container labeling submitted on September 26, 2014.

In addition, we also refer to the April 23, 2015, product quality information request letter and to the April 24, 2015, teleconference between representatives of Office of Product Quality and representatives from Novartis Pharmaceuticals Corporation.

Attached is our preliminary comments on your proposed carton and container labeling.

Provide a response to FDA's proposed changes by close of business on May 12, 2015. In addition to formally submitting your response to the NDA, please email me a copy of your responses to our comments and questions below as well as the revised carton and container labeling.

FDA comments regarding the Unit-dose Blister, 30-count Bottle, (b) (4), and Unit-dose Carton container labeling:

Container Labels (Unit-dose Blister):

1. Revise the presentation of the proprietary name so only the first letter in the proprietary name is capitalized. Words written in all-capital letters are less legible than words written in mixed case letters.

Container Label (Unit-dose blister):

(b) (4)

Reference ID: 3741505

Container Labels (30-count (b) (4) *Bottles):*

(b) (4)

2. Revise the presentation of the proprietary name so only the first letter in the proprietary name is capitalized. Words written in all-capital letters are less legible than words written in mixed case letters.

3. The net quantity statement competes in prominence with the strength and Medication Guide statements. We recommend decreasing the font size of the net quantity statement and relocating the net quantity statement to the lower right hand corner of the Principal Display Panel (PDP).

<u>Container Label (30-count bottle)</u>:

(b) (4)

Reference ID: 3741505

(b) (4)

[redacted]

Unite-Dose Carton Labeling

1. Revise the presentation of the proprietary name so only the first letter in the proprietary name is capitalized. Words written in all-capital letters are less legible than words written in mixed case letters.

2. The net quantity statement competes in prominence with the Medication Guide statement. We recommend increasing the font size of the Medication Guide statement, decreasing the font size of the net quantity statement, and relocating the net quantity statement to the lower left or right hand corner of the PDP.

Reference ID: 3741505

Carton Labeling (Unit-Dose):

(b) (4)

Please let me know if you have any questions.

Regards,

Anuja Patel, M.P.H.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-9022, Fax: 301-796-9849

Reference ID: 3741505

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/s/

ANUJA PATEL
04/28/2015

Patel, Anuja

From: Patel, Anuja
Sent: Tuesday, April 28, 2015 12:33 PM
To: 'Wang, Jessica-1'
Subject: (Response Requested by April 29, 2015) New Date for Late Cycle Meeting/ Foreign Visitor Forms: Sonidegib NDA 205-266
Attachments: Foreign Visitor Form.doc

Importance: High

Dear Dr. Wang,

We refer to my email communication sent April 22, 2015 informing you that I would be contacting you with regards to new proposed dates for the Late Cycle Meeting.

- The new date of the Late Cycle Meeting is Tuesday, June 9, 2015 from 11:00 AM, EST to 12 Noon, EST. We will grant you a Face to Face meeting however due to meeting logistics of the room, space is limited. We encourage you to bring no more than 10 representatives from Novartis. Please provide a list of your attendees by May 25, 2015. Should you need to have additional attendees join via teleconference please let me know so that I can incorporate into the meeting logistics.

- In addition, please find attached the foreign visitor forms for your review and completion. Please submit the completed forms to me via email no later than May 25, 2015.

Kindly acknowledge receipt and confirm the proposed new date and time, including the meeting format, for the teleconference. Please note that you do have the option of converting the Face to Face meeting to a teleconference. If you wish to convert this meeting to a teleconference please let me know.

Regards,
Anuja

Anuja Patel, MPH
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
White Oak Complex, Bldg. 22, Room 2365
10903 New Hampshire Avenue
Silver Spring, MD 20993
☎301.796.9022 (phone)
301.796.9849 (fax)
anuja.patel@fda.hhs.gov (email)

From: Patel, Anuja
Sent: Wednesday, April 22, 2015 3:23 PM
To: 'Wang, Jessica-1'
Cc: Agosto, Teicher
Subject: RE: Sonidegib NDA 205-266: touch base- late-cycle meeting and 4/23 FDA/NVS TC
Importance: High

Reference ID: 3742073

Dear Dr. Wang,

We refer to your email communication sent today (April 22, 2015) and have the following response to your items:

1) Were you able to confirm the Late-cycle meeting (teleconference) for 19-May-2015 at 8:00AM?

   FDA Response: Due to scheduling conflict among the required attendees, I am unable to confirm the Late Cycle meeting (teleconference) for May 19, 2015. We will be looking into dates availability for the following months. I will be contacting you in the future with regards to new proposed dates for the Late Cycle Meeting. Thank you for your understanding.

2) We are targeting to submit a response to the FDA Clinical Information Request (IR 27) received on 15-Apr-2015 prior to tomorrow's tentative TC; however, we may only be able to finalize it later in the day and dispatched through the gateway by end of the day tomorrow. If in the case, we are unable to provide a response for your team to review prior to the TC, did you still want to have the teleconference (perhaps to discuss other issues/questions)? I will also provide you with an update on the status of our response tomorrow via email.

   FDA Response: We acknowledge your response and propose canceling the teleconference for tomorrow, April 23, 2015. We look forward to receiving you response to April 15, 2015 clinical information request. Please note that Teicher Agosto will be sending Novartis a CMC Information Request in the future.

Please acknowledge receipt.

Regards,
Anuja

Anuja Patel, MPH
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
White Oak Complex, Bldg. 22, Room 2365
10903 New Hampshire Avenue
Silver Spring, MD 20993
☎301.796.9022 (phone)
301.796.9849 (fax)
anuja.patel@fda.hhs.gov (email)

From: Wang, Jessica-1 [mailto:jessica-1.wang@novartis.com]
Sent: Wednesday, April 22, 2015 2:12 PM
To: Patel, Anuja
Subject: Sonidegib NDA 205-266: touch base- late-cycle meeting and 4/23 FDA/NVS TC

Hi Anuja,

For Sonidegib NDA 205-266, I just wanted to touch base with you regarding a couple items:

1) Were you able to confirm the Late-cycle meeting (teleconference) for 19-May-2015 at 8:00AM?
2) We are targeting to submit a response to the FDA Clinical Information Request (IR 27) received on 15-Apr-2015 prior to tomorrow's tentative TC; however, we may only be able to finalize it later in the day and dispatched through the gateway by end of the day tomorrow. If in the case, we are unable to provide a response for your team to review prior to the TC, did you still want to have the teleconference

Reference ID: 3742073

(perhaps to discuss other issues/questions)? I will also provide you with an update on the status of our response tomorrow via email.

Thanks so much and talk to you soon,
Jess

Jessica Wang, PharmD
Senior Associate Director
Drug Regulatory Affairs, Oncology
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080
USA

Phone +1 862 7789507
Mobile (b) (6)
jessica-1.wang@novartis.com

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/s/

ANUJA PATEL
04/28/2015

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

Memorandum

Date: April 24, 2015

From: Anuja Patel, M.P.H., Sr. Regulatory Health Project Manager DOP2/OHOP

Subject: NDA 205266/ Type 1 (NME): Clinical Request for Information

---

Novartis Pharmaceuticals Corporation
Attention: Jessica Wang, Pharm.D.
Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Wang:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for "Odomzo (sonidegib), 200 mg capsules."

FDA requests responses to the following information requests by Wednesday, April 29, 2015.

- The Study A2201 Clinical Study Report (page 112) states: "Prior chemotherapy was administered to 1 patient with mBCC for adjuvant and palliative measures; no patient with laBCC received systemic chemotherapy."

  Please clarify the indication for the administration of carboplatin and paclitaxel to patients 1532-001, 1504-011, and 1512-002 in the 200 mg treatment group. The case report forms do not reflect that these regimens were administered for the treatment of BCC (i.e., the box "Mark if treatment was for BCC" was not checked by the investigator); however, the medical histories of these patients do not indicate that any had prior malignancies other than BCC or medical problems that would call for treatment with systemic chemotherapy. Additionally provide a list of patients treated with systemic chemotherapy on the 800 mg arm with the indication for each treatment. This information will impact the product label in providing an accurate description of the treatments patients had for BCC prior to study entry.

Please submit a formal amendment to NDA with your responses **by Wednesday, April 29, 2015**. Please email me a courtesy copy of the cover letter once your submission has been formally submitted.

If you have any questions, please feel free to call me.

Regards,

Anuja Patel, M.P.H.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-9022
Email: Anuja.Patel@fda.hhs.gov

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/s/

ANUJA PATEL
04/24/2015

Patel, Anuja

From: Patel, Anuja
Sent: Wednesday, April 15, 2015 7:32 AM
To: 'Wang, Jessica-1'
Subject: Addendum: FDA Clinical Information Request/Confirmation of Teleconference for April 16, 2015: NDA 205266/ Novartis/ sonidegib

Importance: High

Dear Dr. Wang,

We refer to your NDA 205266 application under our review and to our April 15, 2015, email communication containing our clinical information request and confirmation of the teleconference scheduled for April 16, 2015. I have the following additional comment regarding the information request:

- **We request a formal response to the clinical information request no later than close of business, Thursday, April 23, 2015.**

Please acknowledge receipt.

Thank you!
Anuja

Anuja Patel, MPH
Sr. Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
White Oak Complex, Bldg. 22, Room 2365
10903 New Hampshire Avenue
Silver Spring, MD 20993
☎301.796.9022 (phone)
301.796.9849 (fax)
anuja.patel@fda.hhs.gov (email)

From: Patel, Anuja
Sent: Wednesday, April 15, 2015 7:23 AM
To: 'Wang, Jessica-1'
Subject: FDA Clinical Information Request/Confirmation of Teleconference for April 16, 2015: NDA 205266/ Novartis/ sonidegib
Importance: High

Dear Dr. Wang,

We refer to your NDA application (NDA 205266) which is currently under our review. Our clinical team has the following information request and requests to confirm the 30 minute teleconference for tomorrow, April 16, 2015 at 10:30 AM. The purpose of the teleconference will be to agree upon the content of your submission in response to our information request.

Reference ID: 3732067

We have received and are reviewing your Response to FDA Information Request 23 (IR23) which includes an analysis of pooled safety data for the 571 patients treated across twelve clinical studies in the sonidegib development program with regard to musculoskeletal adverse events. Please provide the following additional items:

A. **The dataset for this pooled safety population.**

B. **An analysis of the demographics, baseline disease characteristics, extent of exposure, and adverse events that occurred in this pooled safety population.**

C. **A separate analysis of lipase elevation and an assessment of the clinical impact of lipase elevation (including the development of pancreatitis) across the pooled population.**

D. **Narratives of all serious adverse events and adverse events of special interest that occurred during these studies. (FDA acknowledges that there may be some information in your response that overlaps with that of the Summary of Clinical Safety Addendum 2-Appendix 2 which includes SAE reports from five studies covering the period from September 1, 2014 to December 26, 2014; however, we are now requesting SAE reports and narratives from the twelve studies pooled for your response to IR23 from study start through final database lock or for ongoing studies, the latest data cut-off date with cleaned data on adverse events.)**

Please confirm the time and the dial in number for tomorrow's teleconference. Please feel free to contact me if you have any questions.

Regards,
Anuja

Anuja Patel, MPH
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
White Oak Complex, Bldg. 22, Room 2365
10903 New Hampshire Avenue
Silver Spring, MD 20993
☎301.796.9022 (phone)
301.796.9849 (fax)
anuja.patel@fda.hhs.gov (email)

Reference ID: 3732067

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/s/

ANUJA PATEL
04/15/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205266

INFORMATION REQUEST

Novartis Pharmaceuticals Corporation
Attention: Joyce Ann Sino, PhD
Director, Global Regulatory CMC- Oncology
One Health Plaza, Bldg. 339 Rm 1151
East Hanover, NJ 07936

Dear Dr. Sinno:

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

We are requesting the following information. We request a prompt written response by Friday, April 17, 2015, in order to continue our evaluation of your NDA.

In reference to your Amendments dated 03/24 (SDN 28) and 04/07 (SDN 34), we have the following *Information Request*.

1. The updated Section 3.2.P.3.3 in response to the Agency's comment 1 is not adequate as it does not provide a complete description of the manufacturing process. For example, [redacted] (b) (4) Please revise Section 3.2.P.3.3 with complete description for ALL manufacturing process steps.

2. For the response to Comment 3, [redacted] (b) (4) Clarify the discrepancy and update. To avoid confusion, please consider using the standard terminology (e.g. ASTM).

3. In updated Section 3.2.P.2.3.3 responding to the Agency's comment 5.a, it is stated that [redacted] (b) (4) However, this is not represented in Table 3-4. Please clarify and update the section.

4. It appears that there are some typos in Table 6-1 in Section 1.11.1 of Amendment 04/07. For example, some mass individual weights in the second column are shown as "[redacted] (b) (4) Make appropriate corrections and update the table.

To avoid further delay for the review, we ask that **you carefully review all your documents before submission.**

If you have any questions, call Teicher Agosto, Regulatory Business Process Manager, at (240) 402-3777.

Sincerely,

Olen Stephens, Ph.D.
Acting Branch 2 Chief
Office of New Drug Products
Office of Pharmaceutical Quality

Olen Stephens - S

Digitally signed by Olen Stephens -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Olen Stephens -S, 0.9.2342.19200300.100.1.1=2000558826
Date: 2015.04.14 09:53:25 -04'00'

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205266

INFORMATION REQUEST

Novartis Pharmaceuticals Corporation
Attention: Joyce Ann Sino, PhD
Director, Global Regulatory CMC- Oncology
One Health Plaza, Bldg. 339 Rm 1151
East Hanover, NJ 07936

Dear Dr. Sinno:

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

We are requesting the following information. We request a prompt written response by Monday, April 13, 2015, in order to continue our evaluation of your NDA.

Based on the provided dissolution data for the clinical batches used in Study CLDE225A2201, the dissolution acceptance criteria for Sonidegib Capsules, 200 mg, the FDA-recommended dissolution acceptance criteria during Tier-1 and Tier 2 testing are:

30 min: NLT (b) (4) %
90 min: NLT %

Implement the recommended dissolution acceptance criteria and submit an updated Specifications Table to the NDA by 4/13/2015.

If you have any questions, call Teicher Agosto, Regulatory Business Process Manager, at (240) 402-3777.

Sincerely,

Liang Zhou -A

Digitally signed by Liang Zhou -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Liang Zhou -A, 0.9.2342.19200300.100.1.1=1300085729
Date: 2015.04.07 14:30:46 -04'00'

Liang Zhou, Ph.D.
Quality Assessment Lead
Office of New Drug Products
Office of Pharmaceutical Quality

Face to Face Mid-Cycle Internal Meeting
Meeting Summary
February 19, 2015

NDA:	205266- Type 1 New Molecular Entity
Product:	sonidegib (LDE 225), capsule, 200 mg, oral
Proposed Proprietary Name:	ODOMZO
Submission Date:	September 26, 2014
Received Date:	September 26, 2014
Sponsor:	Novartis Pharmaceuticals Corporation

Proposed Indication: for the treatment of patients with locally advanced basal cell carcinoma (BCC) who are not amenable to curative surgery or radiation therapy (b) (4)

Attendees Present: Richard Pazdur, Patricia Keegan, Monica Hughes, Anuja Patel, Suzanne Demko, Denise Casey, Kun He, Huanyu (Jade) Chen, Hong Zhao, Stacy Shord, Whitney Helms, Alexander Putman, Liang Zhou, Liang Zhao, Ben Stevens, Amarilys Vega, Naomi Redd, Brian Booth, Tamara Johnson, Tracy Salaam, Shaily Arora, Otto Townsend, Yubing Tang, Teicher Agosto, Tamy Kim, Erik Laughner, William Adams, Amy Barone.

Discussion During Meeting:

1. **Slides were presented by the following disciplines (in order):**
   - Regulatory Intro- Anuja Patel
   - Clinical and Statistical, Efficacy & Safety- Denise Casey
   - Clinical Pharmacology- Stacy Shord
   - Pharm/Tox Review- Alex Putman
   - Chemistry, Manufacturing and Control- Liang Zhou and Ben Stevens
   - DRISK- Amarilys Vega

2. **Benefit-Risk Overview (summarized from Clinical):**
   - The risk-benefit for the use of sonidegib at a dose of 200 mg daily for the treatment of laBCC not amenable to surgery or radiation is favorable based on the primary (6 month) and updated (12 month) safety and activity results of Study A2201.
   - (b) (4)
   - Muscle toxicity in the setting of CK elevation is treatment-related and dose-dependent. This toxicity needs to be addressed in product labeling.
   - *Action Item for Stats*: Check the 95 % CI for vismodegib (see slide 20) and compare to sonidegib for ORR/activity in BCC.

Reference ID: 3712924

(b) (4)

- *Action Item for Clinical*: Check incidence of rhabdomyolosis observed with statin drug products

3. CMC

- No Drug Product or Drug Substance Issues to date
- Manufacturing Process Issue: (b) (4)

(b) (4)

4. Discussion of PMR/PMCs

- **Clinical**
  - A PMR to conduct a pregnancy pharmacovigilance study to collect pregnancy registry data to evaluate pregnancy outcomes and infant outcomes following exposure to sonidegib.
  - A PMR to further study CK elevation and muscle toxicity associated with sonidegib treatment may be considered.

- **Clinical Pharmacology**- 2 potential PMRs
  - Conduct a clinical pharmacokinetic trial to determine an appropriate dose for patients with moderate and severe hepatic impairment.
  - Conduct a clinical pharmacokinetic trial to determine how to dose sonidegib for patients concurrently taking acid-reducing agents.

Reference ID: 3712924

- **Nonclinical**- 1 PMR likely, similar to that of vismodegib, for carcinogenesis
- **CMC**- No PMRs/PMCs

Post Meeting Follow Up:

- *On 2/19/15 during the midcycle meeting for sonidegib (a Hedgehog pathway inhibitor), the risk of rhabdomyolysis was discussed as part of the drug safety profile. This discussion raised concerns about vismodegib (another Hedgehog inhibitor, approved in 2012), which only lists muscle spasms (no mention of myopathy or rhabdomyolysis) in the product labeling. DPV will review the post-marketing cases in FAERS and the literatures to assess the risk of rhabdomyolysis associated with vismodegib and provide recommendations for DOP 2 consideration. DPV anticipates needing to reach out to the reporters and applicant for additional case details. Therefore, DPV proposed a due date of 03/31/2015.*
- *OSE/DOP 2 Meeting scheduled for March 2, 2015 to discuss next steps in developing PMR for sonidegib, similar to vismodegib that is a hybrid of an enhanced PV and prospective registry. This is in preparation for the OND Mid-cycle meeting on March 5, 2015.*
- *Statistics review team provided the following update via e-mail on February 24, 2015 regarding slide 20 of the midcycle: [* (b) (4)
- *Clinical reviewer provided update to CDTL and Division Director on incidence of rhabdomyolisis and muscle toxicity with statin drugs via email on March 2, 2015*

Reference ID: 3712924

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/s/

ANUJA PATEL
03/09/2015

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

Memorandum

Date: March 26, 2015

From: Anuja Patel, M.P.H., Sr. Regulatory Health Project Manager DOP2/OHOP

Subject: NDA 205266/ Type 1 (NME): Clinical Request for Information

---

Novartis Pharmaceuticals Corporation
Attention: Jessica Wang, Pharm.D.
Associate Director, Drug Regulatory Affairs, Oncology
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Wang:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for "Odomzo (sonidegib), 200 mg capsules."

Our clinical team has the following information request:

1. Provide a pooled safety analysis of patients treated with sonidegib **across all studies** in the sonidegib clinical development program (do not include healthy volunteer studies) who required a medical intervention (e.g., administration of intravenous hydration, administration of narcotics for pain control, hospitalization, etc.) for musculoskeletal adverse reactions that occurred during treatment with sonidegib. State the search criteria that will be used for this analysis. (The search criteria used by Novartis for identification of muscular events to be reviewed by the Independent Adjudication Committee (IAC) described in Section 4, page 21 of the final IAC Muscular Events Report would be acceptable). Include in the analysis:
   a. A table displaying the following information: study number, patient's age and gender, dose of sonidegib received, adverse reaction(s), medical intervention, and commentary on if there was resolution of the adverse reaction, if treatment was resumed and if there was recurrence of the adverse reaction with retreatment.
   b. A separate similar table that displays this information for the patients receiving sonidegib 200 mg daily in Study A2201.

Please submit a formal amendment to the NDA with your response **by close of business, Thursday, April 2, 2015.** Please email me and CC: Mimi Biable, who is covering for me between April 1, 2015 and April 3, 2015, a courtesy copy of the cover letter once your submission has been formally submitted.

If you have any questions, please feel free to contact me.

Regards,

Anuja Patel, M.P.H.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-9022
Email: Anuja.Patel@fda.hhs.gov

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/s/

ANUJA PATEL
03/26/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205266

INFORMATION REQUEST

Novartis Pharmaceuticals Corporation
Attention: Joyce Ann Sino, PhD
Director, Global Regulatory CMC- Oncology
One Health Plaza, Bldg. 339 Rm 1151
East Hanover, NJ 07936

Dear Dr. Sinno:

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

We are requesting the following information. We request a prompt written response by Monday, March 30, 2015, in order to continue our evaluation of your NDA.

Provide the dissolution profile data at release for the clinical batches of Sonidegib Capsules, 200 mg, used in the Phase II safety and efficacy study (# A2201). For each clinical batch, state the duration of use in the study. In addition, submit the stability dissolution profile data generated for the four clinical batches in support of their use in Study A2201. In order to facilitate review of the requested data, provide the overall mean of percent sonidegib dissolved at each time point and the associated overall range across all clinical batches. Please use the following Table to provide the dissolution data.

% Sonidegib Dissolved
Mean(n), [range], %CV

Batch Number	15 min	30 min	45 min	60 min	90 min
X280 1110					
X076 0211					
X193 0711					
X278 0613					
Grand Mean **Overall Range**					

If you have any questions, call Teicher Agosto, Regulatory Business Process Manager, at (240) 402-3777.

Sincerely,

Liang Zhou -A

Digitally signed by Liang Zhou -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Liang Zhou -A, 0.9.2342.19200300.100.1.1=1300085729
Date: 2015.03.25 11:44:57 -04'00'

Liang Zhou, Ph.D.
Quality Assessment Lead
Office of New Drug Products
Office of Pharmaceutical Quality

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

Memorandum

Date: March 20, 2015

From: Anuja Patel, M.P.H., Sr. Regulatory Health Project Manager DOP2/OHOP

Subject: NDA 205266/ Type 1 (NME): Clinical Request for Information

---

Novartis Pharmaceuticals Corporation
Attention: Jessica Wang, Pharm.D.
Associate Director, Drug Regulatory Affairs, Oncology
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Wang:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for "Odomzo (sonidegib), 200 mg capsules."

Our clinical team has the following information request:

1. Regarding the safety and effectiveness profile of sonidegib in older patients, please provide the following:

   a. A summary table derived from the 18 month safety dataset comparing the incidence of adverse events (by System Organ Class and Preferred Term), at both the 200 and 800 mg doses, in patients less than sixty-five years of age, patients greater than 65 years, and patients greater than 75 years treated with sonidegib on Study A2201. Include the incidence of all events, grade 3-4 events, serious adverse events and events that led to dose adjustment, interruption or discontinuation in both age groups.

   b. A summary table derived from the 12 month dataset that shows the observed objective response rate and duration of response in patients above and below the age of sixty-five years treated with sonidegib on Study A2201.

2. We are further evaluating the risk for musculoskeletal adverse reactions that may be associated with sonidegib treatment. Provide a summary table of patients who had sonidegib interrupted, reduced, or discontinued secondary to asymptomatic serum creatine kinase (CK) elevation during Study A2201. Include the starting dose, the reduced dose, the severity of the CK elevation, the number of days until recovery and whether the toxicity recurred upon resuming treatment with sonidegib. Provide a similar table of patients who had sonidegib dosing interrupted, reduced, or discontinued

secondary to musculoskeletal adverse reactions in the setting of normal/baseline serum CK. Comment on whether the toxicity recurred with resuming treatment with sonidegib and if the patient had subsequent CK elevation associated with the musculoskeletal adverse reactions.

Please submit a formal amendment to the NDA with your response **by close of business, Tuesday, March 24, 2015**. Please email me a courtesy copy of the cover letter once your submission has been formally submitted.

If you have any questions, please feel free to contact me.

Regards,

Anuja Patel, M.P.H.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-9022
Email: Anuja.Patel@fda.hhs.gov

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/s/

ANUJA PATEL
03/20/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205266

MID-CYCLE COMMUNICATION

Novartis Pharmaceuticals Corporation
Attention: Jessica Wang, Pharm.D.
Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Wang:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Odomzo (sonidegib), 200 mg capsules.

We also refer to the teleconference between representatives of your firm and the FDA on March 5, 2015. 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) 796-9022.

Sincerely,

{See appended electronic signature page}

Anuja Patel, M.P.H.
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: Thursday, March 5, 2015
1:00 P.M. to 2:00 P.M., EST

Application Number: 205266
Product Name: sonidegib
Proposed Indication: for the treatment of patients with locally advanced basal cell carcinoma (BCC) who are not amenable to curative surgery or radiation therapy (b) (4)

Applicant Name: Novartis Pharmaceuticals Corporation

Meeting Chair: Suzanne Demko
Meeting Recorder: Anuja Patel

FDA ATTENDEES

Patricia Keegan, Director, Division of Oncology Products 2 (DOP2)
Monica Hughes, Chief, Project Management Staff, DOP2
Anuja Patel, Senior Regulatory Health Project Manager (SRPM)
Claire Myers, RPM
Suzanne Demko, Clinical Team Leader (CDTL)
Denise Casey, Medical Officer, DOP 2
Huanyu (Jade) Chen, Statistics Reviewer
Brian Booth, Deputy Director, Clinical Pharmacology
Whitney Helms, Non-Clinical (TL)
Alexander Putman, Non-Clinical Reviewer
Liang Zhou, Application Team Lead (ATL), Office of Product Quality (OPQ)
Ben Stevens, Drug Substance (DS) Quality Reviewer, OPQ
Teicher Agosto, Regulatory Business Process Manager (RBPM), OPQ
Latonia Ford, Safety RPM, Office of Surveillance and Epidemiology (OSE)
Nick Senior, Labeling Reviewer, Office of Prescription Drug Promotion (OPDP)
Amarilys Vega, Reviewer, Division of Risk Management (DRISK)
Naomi Redd, DRISK Reviewer (TL)
Carol Casten, Maternal Health Medical Officer, Division of Pediatric and Maternal Health,
Tamara Johnson, Pediatric Maternal Health (Acting TL)
Lori Gorski, SRPM, Division of Pediatric and Maternal Health
Morgan Walker, Patient Labeling Reviewer, Office of Medical Policy (OMP)
Barbara Fuller, Patient Labeling (TL), OMP
Tracy Salaam, Safety Evaluator (TL), Division of Pharmacovigilance II (DPV II)
Shaily Arora, Safety Evaluator, DPV II

EASTERN RESEARCH GROUP ATTENDEES
Patrick Zhou

APPLICANT ATTENDEES
Neil Gallagher, MD, PhD, Global Program Head, Oncology Clinical Development
Dalila Sellami, MD, Global Clinical Program Head, Oncology Clinical Development
Michael Levine, MD, Brand Safety Leader, Integrated Medical Safety, Oncology
Lily Zhao, PhD, Director, Biostatistics
Tingting Yi, PhD, Associate Director, Biostatistics
Jocelyn Zhou, PhD, Senior Scientist, Oncology Clinical Pharmacology
Diane Zezza, PhD, Global Head, Regulatory Affairs CMC
JoyceAnn Sinno, PhD, Director, Senior Regulatory Expert Global Regulatory CMC Oncology
Nancy Turner, PhD, Director, Preclinical Safety
Heidi Einolf, PhD, Director, Drug Metabolism and Pharmacokinetics
Gabriela Gruia, MD, Senior Vice President, Global Head, Oncology Drug Regulatory Affairs
Shanthi Ganeshan, PhD, Vice President, NA Region Head, Oncology Drug Regulatory Affairs
Matthias Jauslin, PhD, Global Program Regulatory Director, Drug Regulatory Affairs
Michael Buska, MS, Global Program Regulatory Director, Drug Regulatory Affairs
Lisa Krueger, PharmD, Drug Regulatory Affairs
Jessica Wang, PharmD, Associate Director, Drug Regulatory Affairs

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:

a. (b) (4)

Reference ID: 3715439

***Discussion During Meeting*: Novartis acknowledged FDA's comment and asked if they could submit an statement from an outside expert to address this issue. FDA agreed to the submission of such a statement insofar as no new information or data are included.**

b. FDA acknowledges the definition of rhabdomyolysis utilized by the Independent Adjudication Committee and that none of the investigator-reported cases of rhabdomyolysis in Study A2201met this definition according to the committee. The narratives of these patients and others with muscle-related serious adverse events suggest that there is risk for serious muscle toxicity and development of rhabdomyolysis if patients do not discontinue sonidegib treatment and/or are not provided with appropriate supportive care (intravenous fluids, pain medications) in a timely manner. FDA acknowledges that this toxicity is dose-related and less prevalent at the intended dose of 200 mg daily and is unlikely to change the overall risk:benefit profile of sonidegib in patients with laBCC (b) (4); however, this drug class effect will need to be well-described in the label, including appropriate dose modification/management guidelines for clinicians. See the clinical pharmacology information requests below.

***Discussion During Meeting*: Novartis agreed with FDA's comment and stated that they will be prepared to discuss this safety aspect further during the labeling negotiations.**

Nonclinical:

c. PMRs for carcinogenicity are likely to be requested.

***Discussion During Meeting*: Novartis acknowledged FDA's comment. No additional discussion occurred.**

Clinical Pharmacology:

d. (b) (4)

***Discussion During Meeting*: Novartis acknowledged FDA's comment. No additional discussion occurred.**

Reference ID: 3715439

e. FDA acknowledges Novartis' proposed labeling recommendations with strong CYP3A inhibitors and inducers. FDA is requesting additional simulations to determine the potential effect of a moderate CYP3A inhibitor and a moderate CYP3A inducer on sonidegib exposure. See clinical pharmacology information request **c** below.

Discussion During Meeting: ***Novartis acknowledged FDA's comment. No additional discussion occurred.***

3.0 INFORMATION REQUESTS

a. Provide the confirmed best overall response (BORR), time of the confirmed best overall response rate and the duration of the confirmed response (DOR) for the 10 patients administered a sonidegib dose of 200 mg who experienced muscle toxicity. Consider providing this data as additional columns of Table 2-3 (listed below) that summarized the muscle toxicity observed with a 200 mg dose that was submitted to the NDA in Response to FDA Information Request 7 (dated 18-Dec-2014) on 19-Jan-2015.

Table 2-3 Summary details for patients with BCC who developed muscle toxicity requiring dose reduction, interruption, and/or discontinuation of study drug (6-month analysis) - Study A2201 (Sonidegib 200mg group) (Safety Set)

Patient ID	Preferred term (CTC grade)	Creatine phosphokinase level (U/L)[a]	Sonidegib PK level (ng/mL)[b]	Time of onset (days)	Action taken	Supportive care	Time to resolution (days)	Recurrence of event on restarting treatment
1150-007	Blood creatine phosphokinase increased (G3)	1019	1530	170	Drug interrupted	No	6	No
1197-008	Muscle spasms (G3)	272	553	141	Drug withdrawn	Thiocolchicoside, tramadol, hexaquine	Ongoing	-
1237-003	Muscular weakness (G1)	273	827	224	Dose adjusted	No	Ongoing	-
1238-001	Muscle spasms (G3)	109	1350	140	Drug withdrawn	No	104	-
1350-003	Blood creatine phosphokinase increased (G2)	706	570	72	Drug interrupted	No	9	No
1512-002	Blood creatine phosphokinase increased (G4)	1977, 2145[c]	1550	107	Drug interrupted	No	2	No
	Blood creatine phosphokinase increased (G2)	953	1550	109	Drug withdrawn	No	25	-
	Myalgia (G2)	645	670	120	Drug interrupted	No	3	No
1513-005	Muscle spasms (G2)	110	1690	108	Drug withdrawn	No	34	-
1515-004	Blood creatine phosphokinase increased (G4)[d]	2107	1610	85	Drug interrupted	No	Ongoing	-
1532-001	Blood creatine phosphokinase increased (G3)	1698, 2162[c]	875	335	Drug interrupted	No	4	No
	Rhabdomyolysis (G3)	1698, 2162[c]	875	335	Drug interrupted	No	4	No
1536-001	Blood creatinine increased (G2)	18	522	141	Drug interrupted	No	8	No

[a] Creatine phosphokinase levels at the closest available time point to the AE start date.
[b] Sonidegib PK levels (trough) at the closest available time point on the same day or prior to the event are provided.
[c] Two assessments on the same day.
[d] On the same day of CK increase, the patient also experienced a grade 4 CKMB increase, which caused the study drug to be withdrawn. Of note, no ECG abnormalities were reported at the same time point.
Source: [Study A2201-Listing 16.2.5-1.1], [Study A2201-Listing 16.2.5-1.5], [Study A2201-Listing 16.2.7-1.1], [Study A2201-Listing 16.2.6-3], and [Study A2201-Listing 16.2.8-1.6]

Reference ID: 3715439

An example of a table is provided here.

Patient ID	Preferred Term (CTC grade)	CK Level	Sonidegib Level	Time of Onset	Action Taken	Time to Resolution	Confirmed BORR	Time of BORR	DOR
ABC									

***Discussion During Meeting*: Novartis acknowledged FDA's comment and committed to submit the requested information formally to the NDA by March13, 2015, as FDA requested. No additional discussion occurred.**

b. Provide a tabular summary of muscle toxicity for patients administered a sonidegib dose of 800 mg. In the tabular summary, include the patient ID, preferred term, CTC grade, creatine phosphokinase level, sonidegib level, sonidegib dose at the time of the event, time of onset, action taken (including dose interruption followed by dose reduction), and time to resolution (similar to Table 2-3 above). The summary should list each muscle toxicity event for each individual patient listed in the table (such that the table clearly identifies which patients had recurrence of the muscle toxicity despite dose interruption and dose reduction).

An example of a table is provided here.

Patient ID	Preferred Term (CTC grade)	CK Level	Sonidegib Dose	Sonidegib Level	Time of Onset	Action Taken	Time to Resolution	Time to Recurrence
ABC	Event 1 Event 2 Event 3		Level 1 Level 2 Level 3			Interruption/Reduction Interruption/Reduction Withdraw		

***Discussion During Meeting*: Novartis acknowledged FDA's comment and committed to submit the requested information formally to the NDA. Novartis requested an extension of one week to submit the requested information and FDA agreed to extend the due date for this information request. The formal response is due March 20, 2015.**

c. Submit the following simulations, including the study report or summary, model files and other related excel files as listed below, formally to the NDA. 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

Reference ID: 3715439

FDA using Simcyp. Software specific excel files such as parameter estimation data files and simulation outputs should be submitted as MS Excel files. Study reports should be provided as PDF files (screenshots can be incorporated if required).

i. Simulate the effect of a moderate CYP3A inhibitor (such as aprepitant or erythromycin) on sonidegib exposure following a single dose and at steady state in cancer patients administered a 200 mg dose. Effects of both chronic use and short term use of a moderate inhibitor on steady state sonidegib pharmacokinetics should be simulated. Novartis can apply the strategy for the effect of ketoconazole presented in your response to FDA's information request (Response to FDA Information Request 1 (Clinical Pharmacology) received 07-Nov-2014).

ii. Simulate the effect of a strong CYP3A inducer (such as rifampin) on sonidegib exposure following a single dose and at steady state in cancer patients administered a 200 mg dose. Use both the library rifampin model and a modified rifampin model according to Simcyp's recent update on the drug's induction potency. Update your simulation in Study 1400133 using the modified rifampin model.

iii. Simulate the effect of a moderate CYP3A inducer (such as efavirenz) on sonidegib exposure following a single dose and at steady state in cancer patients administered a 200 mg dose.

***Discussion During Meeting*: Novartis acknowledged FDA's request for information and will submit formally by March 13, 2015as FDA requested.**

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

a. A PMR clinical study to evaluate the effect of moderate and severe hepatic impairment on the pharmacokinetics of sonidegib and determine an appropriate dose for patients with hepatic impairment.

***Discussion During Meeting*: Novartis acknowledged FDA's comment and there were no further questions. No additional discussion occurred.**

b. A PMR clinical study to evaluate the effect of acid-reducing agents on the pharmacokinetics of sonidegib and how to dose sonidegib for patients concurrently taking acid-reducing agents.

***Discussion During Meeting*: Novartis acknowledged FDA's comment and there were no further questions. No additional discussion occurred.**

c. A PMR to conduct a pregnancy pharmacovigilance study to collect pregnancy registry data to evaluate pregnancy outcomes and infant outcomes following exposure to sonidegib.

Reference ID: 3715439

Description of FDA proposed requirement:

This study will include a mechanism to collect, classify, and analyze data on direct exposures (women exposed to sonidegib as treatment) and indirect exposures (women exposed to sonidegib through the seminal fluid of a male partner). The Pregnancy Pharmacovigilance Study will be initiated and functioning at the time of product launch. The registry and study, at minimum, will include the following key elements (see the Guidance for Industry Establishing Pregnancy Exposure Registries for a detailed description of these elements):

- Data collection of prospective and retrospective data points, adequate to produce informative, reliable data outcomes.
- Data analysis utilizing descriptive statistics for summarizing data that will fully capture outcomes of concern. Data collected prospectively analyzed separate from data collected retrospectively.
- Description of registry procedures including the patient recruitment, along with healthcare provider awareness of potential safety risk and existence of pregnancy registry, and the monitoring of pregnancy and infant outcomes.

Each interim and final report should constitute a stand-alone report of cumulative registry outcomes data.

***Discussion During Meeting*: Novartis acknowledged FDA's comment and stated that Novartis' primary focus is safety and that Novartis believes that the Risk Mitigation Program they have put in place and proposed labeling will adequately address this issue. FDA stated that the purpose of this PMR is to address the issue as a class effect and require a study that can provide additional data to inform labeling. Novartis acknowledged FDA's explanation and asked to continue talks on this topic in a separate forum. FDA stated that the Regulatory Project Manager for this NDA will follow-up with Novartis after the Midcycle Communication to discuss any additional communication on this issue that may be deemed necessary.**

5.0 ADVISORY COMMITTEE MEETING

There are no plans for an Advisory Committee Meeting at this time.

***Discussion During Meeting*: It was again noted by FDA that a Special Government Employee (SGE) with expertise in the clinical management of basal cell carcinoma will perform an additional review of specific aspects of the sonidegib application. No additional discussion took place.**

Reference ID: 3715439

6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

- Late-Cycle Meeting with Applicant: Tuesday, May 19, 2015
- Background for Late Cycle to Applicant: planned for May 8, 2015
- Proposed labeling and any post marketing commitment requests to Novartis: planned for June 5, 2015

***Discussion During Meeting*: The dates were acknowledged and no additional discussion took place.**

Reference ID: 3715439

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/s/

ANUJA PATEL
03/13/2015

Patel, Anuja

From: Wang, Jessica-1 <jessica-1.wang@novartis.com>
Sent: Monday, March 09, 2015 10:38 AM
To: Patel, Anuja
Subject: RE: FDA Statistical Information Request- NDA 205266 (sonidegib)

Dear Anuja,

Many thanks for checking with the statistical review team and getting back to me so soon.

I am acknowledging receipt.

Best regards,
Jess

Jessica Wang, PharmD
Associate Director
Drug Regulatory Affairs, Oncology
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080
USA

Phone +1 862 7789507
Mobile (b) (6)
jessica-1.wang@novartis.com

From: Patel, Anuja [mailto:Anuja.Patel@fda.hhs.gov]
Sent: Monday, March 09, 2015 10:34 AM
To: Wang, Jessica-1
Subject: RE: FDA Statistical Information Request- NDA 205266 (sonidegib)
Importance: High

Dear Dr. Wang,

We refer to your email below sent March 6, 2015, containing Novartis proposed approach in response to our statistical information request sent March 5, 2015.

The statistical review team has reviewed your response and finds your approach acceptable. Please formally submit to the NDA by the requested due date or sooner if available. Please email me a courtesy copy of your submission once it has been submitted thru the gateway.

Please ACK receipt.

Regards,
Anuja

Anuja Patel, MPH
Sr. Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
White Oak Complex, Bldg. 22, Room 2365
10903 New Hampshire Avenue
Silver Spring, MD 20993

Reference ID: 3714963

☎301.796.9022 (phone)
301.796.9849 (fax)
anuja.patel@fda.hhs.gov (email)

From: Wang, Jessica-1 [mailto:jessica-1.wang@novartis.com]
Sent: Friday, March 06, 2015 1:58 PM
To: Patel, Anuja
Subject: RE: FDA Statistical Information Request- NDA 205266 (sonidegib)

Dear Anuja,

Hope all is well and thank you again for the nice discussion at the mid-cycle meeting yesterday.

Reference is made to the Odomzo (sonidegib) NDA 205-266 and the FDA Statistical Information Request received on 05-Mar-2015. Novartis has reviewed the request to resubmit select CSR and SCE Addendum tables for the FAS population using a table template provided by FDA. We have the following points of clarification for the Agency to consider.

Please indicate whether the Agency agrees to the proposed approach for the response for the following tables:

- CSR Table 10-2 entitled Protocol deviations leading to exclusion from the per-protocol set (pEAS)
  - Note that the per-protocol set (PPS) is defined using pEAS as the basis, and major protocol deviations would exclude some pEAS patients from being included in PPS. Therefore, Novartis proposes to generate this table using pEAS, rather than FAS (as indicated in the request). For reasons that excluded patients from being included in pEAS, please refer to CSR Table 11-2 and SCE Addendum Table 2-5, for which FAS was used as the analysis set.
- CSR Table 11-2 and SCE Addendum Table 2-5 entitled Patients with laBCC included and excluded from the Primary Efficacy Analysis Set
  - Note as per the pEAS definition, all mBCC patients are included in pEAS. The reasons for inclusion and exclusion in pEAS presented in CSR Table 11-2 and SCE Addendum Table 2-5 are only applicable for the laBCC patients. Therefore, this table is not applicable for the mBCC patients and thus will not be provided within the response.
- SCE Addendum Table 2-11 entitled Duration of exposure to study drug (Safety Set)
  - Note the exposure information is generated for patients who took at least one dose of sonidegib, i.e. based on the safety set. There is one laBCC patient in 800 mg FAS who did not take any study medication and therefore will not be included in this table.

We are requesting confirmation and/or feedback from your team as soon as possible in order address the information request to by the due date.

Thanks and best regards,
Jess

Jessica Wang, PharmD
Associate Director
Drug Regulatory Affairs, Oncology
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080
USA

Phone +1 862 7789507
Mobile (b) (6)
jessica-1.wang@novartis.com

Reference ID: 3714963

From: Patel, Anuja [mailto:Anuja.Patel@fda.hhs.gov]
Sent: Thursday, March 05, 2015 8:41 AM
To: Wang, Jessica-1
Subject: FDA Statistical Information Request- NDA 205266 (sonidegib)
Importance: High

Dear Dr. Wang,

Please find attached statistical information request with a response requested March 10, 2015.

Please acknowledge receipt.

Thank you!
Anuja

Anuja Patel, MPH
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
White Oak Complex, Bldg. 22, Room 2365
10903 New Hampshire Avenue
Silver Spring, MD 20993
☎301.796.9022 (phone)
301.796.9849 (fax)
anuja.patel@fda.hhs.gov (email)

Reference ID: 3714963

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/s/

ANUJA PATEL
03/12/2015

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

Memorandum

Date: March 5, 2015

From: Anuja Patel, M.P.H., Sr. Regulatory Health Project Manager DOP2/OHOP

Subject: NDA 205266/ Type 1 (NME): Statistical Request for Information

---

Novartis Pharmaceuticals Corporation
Attention: Jessica Wang, Pharm.D.
Associate Director, Drug Regulatory Affairs, Oncology
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Wang:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for "Odomzo (sonidegib), 200 mg capsules."

Our statistical team has the following information request:

1. Please resubmit the clinical study report (CSR) Tables 10-1 10-2, 11-1, 11-2, 11-3, 11-3, 11-4, 11-5, 11-6, 11-7 for the FAS population using table template below.

2. Please resubmit the clinical efficacy addendum (12 -month update) Tables 2-2, 2-4, 2-5, 2-6, 2-7, 2-8, 2-9, 2-10, 2-11 for the FAS population using table template below.

Table Template

(b) (4)

	LaBCC	
	Sonidegib 200 mg (N=XX)	**Sonidegib 800 mg (N=XX)**

Please submit a formal amendment to the NDA with your response **by 3:00 PM, EST, Tuesday, March 10, 2015**. Please email me a courtesy copy of the cover letter once your submission has been formally submitted.

If you have any questions, please feel free to contact me.

Regards,

Anuja Patel, M.P.H.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-9022
Email: Anuja.Patel@fda.hhs.gov

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/s/

ANUJA PATEL
03/05/2015

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

Memorandum

Date : March 3, 2015

From: Anuja Patel, M.P.H., Sr. Regulatory Health Project Manager DOP2/OHOP

Subject: NDA 205266/ Type 1 (NME): Midcycle Communication Meeting (Teleconference) Agenda

---

Novartis Pharmaceuticals Corporation
Attention: Jessica Wang, Pharm.D.
Associate Director, Drug Regulatory Affairs, Oncology
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Wang:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for "Odomzo (sonidegib), 200 mg capsules."

Please find attached our agenda for the Midcycle Communication Meeting, via teleconference, scheduled for Thursday, March 5, 2015 from 1:00 P.M. to 2:00 P.M., EST. We are confirming the following sponsor dial in number:

US/Canada Toll Free: (b) (4)

Participant Passcode: (b) (4)

As we may get snow on Thursday, we are requesting that you provide 10-15 lines for the FDA in case we have FDA review team members that will be dialing in off-site.

If you have any questions, please feel free to call me.

Regards,

Anuja Patel, M.P.H.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Midcycle Communication Meeting- Agenda

Sponsor Mid-Cycle Communication Meeting Agenda
March 5, 2015
NDA 205266

Application: NDA 205266- Type 1 New Molecular Entity

Product:	sonidegib (LDE 225), capsule, 200 mg, oral
Proposed Proprietary Name:	ODOMZO
Sponsor:	Novartis Pharmaceuticals Corporation
Proposed Indication:	for the treatment of patients with locally advanced basal cell carcinoma (BCC) who are not amenable to curative surgery or radiation therapy (b) (4)
Date:	Thursday, March 5, 2015
Time:	1:00 PM – 2:00 PM, EST
Location:	Teleconference

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.

Topics for Discussion:

1. Introductions

2. Significant Review Issues Identified by FDA:

Clinical:

a. (b) (4)

Reference ID: 3710456

b. FDA acknowledges the definition of rhabdomyolysis utilized by the Independent Adjudication Committee and that none of the investigator-reported cases of rhabdomyolysis in Study A2201met this definition according to the committee. The narratives of these patients and others with muscle-related serious adverse events suggest that there is risk for serious muscle toxicity and development of rhabdomyolysis if patients do not discontinue sonidegib treatment and/or are not provided with appropriate supportive care (intravenous fluids, pain medications) in a timely manner. FDA acknowledges that this toxicity is dose-related and less prevalent at the intended dose of 200 mg daily and is unlikely to change the overall risk:benefit profile of sonidegib in patients with laBCC (b) (4); however, this drug class effect will need to be well-described in the label, including appropriate dose modification/management guidelines for clinicians. See the clinical pharmacology information requests below.

Nonclinical:

c. PMRs for carcinogenicity are likely to be requested.

Clinical Pharmacology:

d. (b) (4)

e. FDA acknowledges Novartis' proposed labeling recommendations with strong CYP3A inhibitors and inducers. FDA is requesting additional simulations to determine the potential effect of a moderate CYP3A inhibitor and a moderate CYP3A inducer on sonidegib exposure. See clinical pharmacology information request **c** below.

3. New or Pending Information Requests

Clinical Pharmacology:

Submit a response to the following information requests formally to your NDA by March 13, 2015:

a. Provide the confirmed best overall response (BORR), time of the confirmed best overall response rate and the duration of the confirmed response (DOR)

Reference ID: 3710456

for the 10 patients administered a sonidegib dose of 200 mg who experienced muscle toxicity. Consider providing this data as additional columns of Table 2-3 (listed below) that summarized the muscle toxicity observed with a 200 mg dose that was submitted to the NDA in Response to FDA Information Request 7 (dated 18-Dec-2014) on 19-Jan- 2015.

Table 2-3 Summary details for patients with BCC who developed muscle toxicity requiring dose reduction, interruption, and/or discontinuation of study drug (6-month analysis) - Study A2201 (Sonidegib 200mg group) (Safety Set)

Patient ID	Preferred term (CTC grade)	Creatine phosphokinase level (U/L)[a]	Sonidegib PK level (ng/mL)[b]	Time of onset (days)	Action taken	Supportive care	Time to resolution (days)	Recurrence of event on restarting treatment
1150-007	Blood creatine phosphokinase increased (G3)	1019	1530	170	Drug interrupted	No	6	No
1197-008	Muscle spasms (G3)	272	553	141	Drug withdrawn	Thiocolchicoside, tramadol, hexaquine	Ongoing	-
1237-003	Muscular weakness (G1)	273	827	224	Dose adjusted	No	Ongoing	-
1238-001	Muscle spasms (G3)	109	1350	140	Drug withdrawn	No	104	-
1350-003	Blood creatine phosphokinase increased (G2)	706	570	72	Drug interrupted	No	9	No
1512-002	Blood creatine phosphokinase increased (G4)	1977, 2145[c]	1550	107	Drug interrupted	No	2	No
	Blood creatine phosphokinase increased (G2)	953	1550	109	Drug withdrawn	No	25	-
	Myalgia (G2)	645	670	120	Drug interrupted	No	3	No
1513-005	Muscle spasms (G2)	110	1690	108	Drug withdrawn	No	34	-
1515-004	Blood creatine phosphokinase increased (G4)[d]	2107	1610	85	Drug interrupted	No	Ongoing	-
1532-001	Blood creatine phosphokinase increased (G3)	1698, 2162[c]	875	335	Drug interrupted	No	4	No
	Rhabdomyolysis (G3)	1698, 2162[c]	875	335	Drug interrupted	No	4	No
1536-001	Blood creatinine increased (G2)	18	522	141	Drug interrupted	No	8	No

[a] Creatine phosphokinase levels at the closest available time point to the AE start date.
[b] Sonidegib PK levels (trough) at the closest available time point on the same day or prior to the event are provided.
[c] Two assessments on the same day.
[d] On the same day of CK increase, the patient also experienced a grade 4 CKMB increase, which caused the study drug to be withdrawn. Of note, no ECG abnormalities were reported at the same time point.
Source: [Study A2201-Listing 16.2.5-1.1], [Study A2201-Listing 16.2.5-1.5], [Study A2201-Listing 16.2.7-1.1], [Study A2201-Listing 16.2.6-3], and [Study A2201-Listing 16.2.8-1.6]

An example of a table is provided here.

Patient ID	Preferred Term (CTC grade)	CK Level	Sonidegib Level	Time of Onset	Action Taken	Time to Resolution	Confirmed BORR	Time of BORR	DOR
ABC									

b. Provide a tabular summary of muscle toxicity for patients administered a sonidegib dose of 800 mg. In the tabular summary, include the patient ID, preferred term, CTC grade, creatine phosphokinase level, sonidegib level, sonidegib dose at the time of the event, time of onset, action taken (including dose interruption followed by dose reduction), and time to resolution (similar to Table 2-3 above). The summary should list each muscle toxicity event for each individual patient listed in the table (such that the table clearly identifies which patients had recurrence of the muscle toxicity despite dose interruption and dose reduction).

Reference ID: 3710456

An example of a table is provided here.

Patient ID	Preferred Term (CTC grade)	CK Level	Sonidegib Dose	Sonidegib Level	Time of Onset	Action Taken	Time to Resolution	Time to Recurrence
ABC	Event 1 Event 2 Event 3		Level 1 Level 2 Level 3			Interruption/Reduction Interruption/Reduction Withdraw		

c. Submit the following simulations, including the study report or summary, model files and other related excel files as listed below, formally to the NDA. 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 FDA using Simcyp. Software specific excel files such as parameter estimation data files and simulation outputs should be submitted as MS Excel files. Study reports should be provided as PDF files (screenshots can be incorporated if required).

   i. Simulate the effect of a moderate CYP3A inhibitor (such as aprepitant or erythromycin) on sonidegib exposure following a single dose and at steady state in cancer patients administered a 200 mg dose. Effects of both chronic use and short term use of a moderate inhibitor on steady state sonidegib pharmacokinetics should be simulated. Novartis can apply the strategy for the effect of ketoconazole presented in your response to FDA's information request (Response to FDA Information Request 1 (Clinical Pharmacology) received 07-Nov-2014).

   ii. Simulate the effect of a strong CYP3A inducer (such as rifampin) on sonidegib exposure following a single dose and at steady state in cancer patients administered a 200 mg dose. Use both the library rifampin model and a modified rifampin model according to Simcyp's recent update on the drug's induction potency. Update your simulation in Study 1400133 using the modified rifampin model.

   iii. Simulate the effect of a moderate CYP3A inducer (such as efavirenz) on sonidegib exposure following a single dose and at steady state in cancer patients administered a 200 mg dose.

Reference ID: 3710456

4. Major Safety Concerns/ Risk Management Update

a. A PMR clinical study to evaluate the effect of moderate and severe hepatic impairment on the pharmacokinetics of sonidegib and determine an appropriate dose for patients with hepatic impairment.

b. A PMR clinical study to evaluate the effect of acid-reducing agents on the pharmacokinetics of sonidegib and how to dose sonidegib for patients concurrently taking acid-reducing agents.

c. A PMR to conduct a pregnancy pharmacovigilance study to collect pregnancy registry data to evaluate pregnancy outcomes and infant outcomes following exposure to sonidegib.

5. Advisory Committee Meeting Plans

a. No AC meeting planned; however, as noted above, SGEs with an expertise in basal cell carcinoma will be consulted with regard to aspects of the sonidegib application.

6. Proposed Date and Format for Late-Cycle Meeting/Other Projected Milestones

- Late-Cycle Meeting with Applicant: Tuesday, May 19, 2015
- Background for Late Cycle to Applicant: planned for May 8, 2015
- Proposed labeling and any post marketing commitment requests to Novartis: planned for June 5, 2015

Reference ID: 3710456

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/s/

ANUJA PATEL
03/03/2015

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

Memorandum

Date : March 3, 2015

From: Anuja Patel, M.P.H., Sr. Regulatory Health Project Manager DOP2/OHOP

Subject: NDA 205266/ Type 1 (NME): Additional Details Re: Pregnancy PMR for Midcycle Communication Meeting (Teleconference) scheduled for March 5, 2015

Novartis Pharmaceuticals Corporation
Attention: Jessica Wang, Pharm.D.
Associate Director, Drug Regulatory Affairs, Oncology
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Wang:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for "Odomzo (sonidegib), 200 mg capsules."

Please also refer to my e-mail communication sent today, March 3, 2015 with our proposed agenda for the Midcycle Communication Meeting (Teleconference), scheduled for Thursday, March 5, 2015 from 1:00 P.M. to 2:00 P.M., EST.

We have the following additional information to inform the discussion under Item 4c *Major Safety Concerns/Risk Management Update* of the agenda:

- A PMR to conduct a pregnancy pharmacovigilance study to collect pregnancy registry data to evaluate pregnancy outcomes and infant outcomes following exposure to sonidegib.

  Description of FDA proposed requirement:
  To conduct a Pregnancy Pharmacovigilance Study to collect pregnancy registry data to evaluate pregnancy outcomes and infant outcomes following exposure to sonidegib. This study will include a mechanism to collect, classify, and analyze data on direct exposures (women exposed to sonidegib as treatment) and indirect exposures (women exposed to sonidegib through the seminal fluid of a male partner). The Pregnancy Pharmacovigilance Study will be initiated and functioning at the time of product launch. The registry and study, at minimum, will include the following key elements (see the Guidance for Industry Establishing Pregnancy Exposure Registries for a detailed description of these elements):

- Data collection of prospective and retrospective data points, adequate to produce informative, reliable data outcomes.

- Data analysis utilizing descriptive statistics for summarizing data that will fully capture outcomes of concern. Data collected prospectively analyzed separate from data collected retrospectively.

- Description of registry procedures including the patient recruitment, along with healthcare provider awareness of potential safety risk and existence of pregnancy registry, and the monitoring of pregnancy and infant outcomes.

Each interim and final report should constitute a stand-alone report of cumulative registry outcomes data.

If you have any questions, please feel free to call me.

Regards,

Anuja Patel, M.P.H.
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/

ANUJA PATEL
03/03/2015

Initial Planning Meeting
Meeting Summary
October 21, 2014

NDA: 205266- Type 1 New Molecular Entity
eCTD submission: SDN 001

Product: sonidegib (LDE 225), capsule, 200 mg, oral
Proposed Proprietary Name: ODOMZO
Submission Date: September 26, 2014
Received Date: September 26, 2014
Sponsor: Novartis Pharmaceuticals Corporation

Proposed Indication: for the treatment of patients with locally advanced basal cell carcinoma (BCC) who are not amenable to curative surgery or radiation therapy (b) (4)

Current Review Team for NDA 205266:
Denotes attendee
*Patricia Keegan, M.D., Director DOP2
*Monica Hughes, M.S., CPMS, DOP2
*Anuja Patel, M.P.H., Senior Regulatory Health Project Manager
*Suzanne Demko, PA-C., Clinical Team Leader (CDTL)
*Denise Casey, M.D., Medical Officer (DOP 2)
*Kun He, Ph.D., Statistics (TL)
Huanyu (Jade) Chen, Ph.D., Statistics
Hong Zhao, Ph.D., Clinical Pharmacology (TL)
*Stacy Shord, Pharm, D., Clinical Pharmacology
*Liang Zhao, Ph.D., Clinical Pharmacology
*Whitney Helms, Ph.D., Non-Clinical (TL)
Alexander Putman, Non-Clinical
Jennie Chang, Pharm. D. Acting Associate Director for Labeling
Liang Zhou, Ph.D., ONDQA Application Team Lead (ATL)
*Ali Al Hakim, Ph.D., ONDQA Branch Chief
William Adams, Ph.D., Drug Product (DP) Product Quality Reviewer, ONDQA
*Ben Stevens, Ph.D., Drug Substance (DS) Quality Reviewer, ONDQA
Yubing Tang, Process Reviewer, ONDQA
Steve Langille, Micro Reviewer, ONDQA
*Teicher Agosto, ONDQA, Regulatory Business Process Manager (RBPM)
Catherine Tran-Zwanetz, ONDQA, RBPM (TL)
*Okpo Eradiri, Biopharmaceutics Reviewer
Angelica Dorantes, Biopharmaceutics Reviewer (TL)
Robert Wittorf, OMPQ Reviewer, CMC Manufacturing Inspections
Janice Pohlman, OSI TL
Lauren Iacono-Connor, OSI Reviewer, OSI Inspections
Susan Thompson, OSI
Frances Fahnbulleh, OSE, Safety RPM
*Karen Hennessy, DOP 2, Safety RPM
Pending- QT Reviewer
*Amarilys Vega, DRISK Reviewer

Reference ID: 3708769

*Otto Townshend, DMEPA Safety Reviewer
Alice Chi-Ming Tu, DMEPA Safety Reviewer (TL)
*Mona Patel, DRISK Reviewer
*Naomi Redd, DRISK Reviewer (TL)

Regulatory Background

Sonidegib is a Hedgehog (Hh) pathway inhibitor, has been investigated in basal cell carcinoma (BCC) under IND 102,961. Novartis stated in their application that sonidegib has not yet received marketing approval by any health authority.

A pre-NDA (Type B) clinical meeting was held April 15, 2014, between FDA and Novartis under IND 102961 to discuss and reach agreement that the data provided from Study CLDE225A2201, entitled "A phase II, randomized, double-blind study of efficacy and safety of two dose levels of LDE225, 200 mg and 800 mg, in patients with locally advanced basal cell carcinoma (laBCC) or metastatic basal cell carcinoma (mBCC)," is sufficient to support a new drug application (NDA) for sonidegib for the proposed indication for the treatment of patients with locally advanced basal cell carcinoma (laBCC) (b) (4) Meeting minutes from this meeting issued on May 14, 2014. A separate CMC pre-NDA meeting was held June 18, 2014 and meeting minutes were issued July 17, 2014.

The following summary of Regulatory History was provided to the team prior to the meeting:

EOP 1 Type B Meeting held June 9, 2011	Meeting Minutes Issued July 13, 2011	To discuss specific aspects of the development plan of LDE 225 in patients with locally advanced (b) (4) that is not amendable to radiation therapy or curative surgery
Type C Meeting Request submitted February 13, 2013	Meeting Denied letter issued March 6, 2013	To discuss the planned analyses from the LDE225 development program in preparation for a planned NDA submission. Meeting Request was considered premature and FDA requested Novartis resubmit as EOP 2/Pre-NDA when high level data is available.
Meeting WRO Only and Briefing Materials submitted April 3, 2013	Advice Letter issued July 8, 2013	Novartis requested written feedback from FDA in lieu of the March 6, 2013 Meeting Denied letter. The purpose was to obtain

Reference ID: 3708769

		written comment from the FDA on the planned analyses from the sonidegib development program in preparation for a possible NDA submission
Clinical Type B pre-NDA Meeting held April 15, 2014	Meeting Minutes Issued May 14, 2014	To discuss and reach agreement that the data provided from Study CLDE225A2201 is sufficient to support NDA submission; captured PDUFA V Agreements
CMC Type B pre-NDA Meeting held June 18, 2014	Meeting Minutes issued July 17, 2014	To discuss the adequacy of the proposed content of CMC information for the NDA submission
June 18, 2014 CMC Amendment	CMC General Advice Letter issued July 21, 2014	CMC information submitted following n June 18, 2014 CMC Meeting
June 30, 2014 CMC Amendment	CMC General Advice Letter issued August 1, 2014	Purpose was to respond to June 30, 2014 submission that was submitted in response to June 18, 2014 meeting and to clearly state agreement under PDUFA 5
August 15, 2014 Clinical Amendment	Advice letter issued September 8, 2014 stating FDA will not amend the meeting minutes and will not issue new agreements under the PDUFA V program. FDA provided responses regarding the acceptability of the proposals to submit additional information in the planned NDA.	Novartis requested FDA's Agreement with inclusion of 1) the BOLT 50-week updated safety and efficacy data with the NDA at the end of September 2014 and 2) a new BOLT clinical database cut-off for the 120 day safety update.
September 9, 2014 Clinical Amendment / Request for FDA Response	Advice letter issued September 13, 2014 restating the comments from the September 8, 2014 letter	Novartis requested clarification and requested that FDA address a typographical error to the September 8, 2014 Advice letter.

Reference ID: 3708769

*A standard **reminder** that all team members should notify the RPM, the CDTL, their team leader and other team members as soon as issues arise during the review process, instead of waiting until the next scheduled meeting to discuss.

Discussion Items:

1. **Review Status:**
   - Priority Review was requested by Novartis, however the team discussed and agreed to granting a standard review
   - Exclusivity Request: Novartis requested exclusivity for this NME for the treatment of patients with locally advanced basal cell carcinoma (BCC) who are not amenable to curative surgery or radiation therapy (b) (4)
   - Orphan Drug Designation – no orphan drug designation requested
   - Environmental Assessments; Categorical Exclusion requested in this New Molecular Entity (NME) application. OPQ RBPM will review request.
   - A request for full waiver of pediatric studies was included in this NME.
   - (b) (4)
   - Proprietary Name Review- conditional acceptance granted August 19, 2013
   - Risk Management Plan included in this NME application

   ***DISCUSSION DURING MEETING**: The team discussed the submission and determined that based on the data submitted a priority review designation would not be granted and therefore agreed to grant 12 month priority review (PDUFA Goal Date: September 26, 2015). In addition, the team discussed expediting the review clock and agreed to completing the reviews on a 10 month clock; therefore, the Division planned an early action date July 24, 2015.*

2. **Review and Discussion of Milestone Dates:**
   - **Filing Action Date:** Tuesday, November 25, 2014
   - **Deficiencies Identified Letter (Day 74 Letter):** Tuesday, December 9, 2014
   - **Hold Midcycle Communication with Sponsor:** Scheduled for Thursday, March 5, 2015
   - **Late Cycle Meeting with Applicant:** Scheduled for Tuesday, May 19, 2015
   - **Send proposed labeling with PMR/ PMCs / REMs to sponsor (with 1 week response):** August 26, 2015 (Planned: Friday June 12, 2015)
   - **Primary Reviews due:** Friday, May 29, 2015
   - **Secondary Reviews due:** Friday, June 5, 2015
   - **Issue Disciplinary Review letters (as needed) by June 14, 2015**
   - **PDUFA Goal Date:** September 26, 2015
   - **Division's Planned Action Goal Date:** Friday, July 24, 2015

3. **Review and determination of consult and additional reviewers needed for application.**

   ***DISCUSSION DURING MEETING:** The following update was provided by the RPM:*

   - *Medication Guide included with application therefore a Patient Labeling Consult to be uploaded in DARRTs – uploaded November 10, 2014*

Reference ID: 3708769

- *OPDP (former DDMAC) consult to be uploaded in DARRTs - consult uploaded November 10, 2014*
- *OSE Consult for DMEPA/DRISK to be uploaded in DARRTs- consult uploaded November 10, 2014*
- *OSI Inspections Consult to be uploaded in DARRTs: uploaded in DARRTs December 2, 2014*
- *QT-IRT Consult to be submitted- uploaded in DARRTS November 12, 2014*
- *The Pediatric Page was prepared and sent via email communication to George Greely on November 19, 2015*
- *Micro Consult and Facility Consults to be uploaded by Teicher Agosto*
- *Patient Representative and Special Government Employees (SGE) were determined to be needed to assist with this application review, therefore a request for Divisional Assignments will be requested in order to review product labeling and respond to specific questions from the Division. RPM and Medical Officer will contact OHCA for suitable Patient Representative.*

4. Internal Team Meetings:

- **Filing Meeting:** Scheduled for Wednesday, November 12, 2014 (* Note, Tuesday, November 11, 2014 is a holiday)
- **Mid-Cycle Meeting:** Anticipated for week of February 23
  (Target Planner Date: Thursday, February 26, 2015)
- **Wrap- Up Meeting**: Per 10-month clock, anticipated for week of May 25, 2015 (Target Planner Date: Sunday, May 31, 2015)

DISCUSSION DURING MEETING: *The review team discussed and identified that Clinical, Statistics, and Clinical Pharmacology disciplines will present at the Midcycle Meeting. OPQ RPBM (Teicher Agosto) will consolidate their slides and send to OND RPM to forward to CDTL for review.*

Slides will be sent to CDTL no later than 1 week prior to Internal Midcycle

Both a Press Release and Burst are planned. Press Release to be sent to Press Office 2 months prior to action.

- **Labeling Meetings & Labeling submitted in the application included:**
  - Draft PI Labeling (tracked changes in Word);
  - Carton/Container: Unit dose (200 mg) blister packs of 30 capsules, bottle of 30 capsules, (b) (4);
  - Med Guide

DISCUSSION DURING MEETING: *The review team discussed and agreed to begin scheduling labeling 2-3 weeks after the Internal Midcycle meeting. The team agreed to scheduling 5 labeling meetings for this application. CDTL prepared the following table with the breakdown of labeling sections by discipline and in discussion order for each meeting.*

Reference ID: 3708769

Meeting Date	Discipline	Label Section
TBD	Clinical, Statistics	1, 14
TBD	Clinical Pharmacology, Clinical	2, 7, 8.5, 8.6, 8.7, 12.2, 12.3
TBD	CMC, DMEPA, Clinical	3, 11, 16
TBD	Clinical	4, 5, 6, 17
TBD	Clinical, Maternal Health Team, Nonclinical	5.1, 8.1, 8.3, 8.4, 12.1, 13
When PI is significantly complete, send label to applicant, OPDP and Patient Labeling Team. Schedule a meeting two to three weeks later to review applicant, OPDP and Patient Labeling Team edits		

- **Team Meetings and PMR/PMC Working Meetings**:

DISCUSSION DURING MEETING: *The team agreed to scheduling monthly team meetings and a separate PMR/PMC meeting will be scheduled ad hoc as soon as safety issues are identified. OPQ will be setting up OPQ internal meetings and will invite OND RPM as fyi.*

5. **Applicant Orientation Presentation:** scheduled for November 17, 2014

DISCUSSION DURING MEETING: *No further discussion occurred.*

6. **ODAC Not Needed:**

DISCUSSION DURING MEETING: *The review team discussed and determined that ODAC will not be needed for the following reasons:*

- *This drug/biologic is not first in its class;*
- *The clinical study design was acceptable;*
- *The application did not raise significant safety or efficacy issues; and*
- *The application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease*

7. **ONDQA Discussion**

DISCUSSION DURING MEETING: *This NDA will be Pilot for new ONDQA Reorg; OPQ RBPM, Teicher Agosto, will assist with the following consults via Panorama:*

- *Establishment (EES)/ Coordinate Inspections- Teicher working on issues with Panorama team*
- *Microbiology- already assigned to Steve Langille in Panorama*
- *Biopharmaceuticals- already assigned to Okpo Eradiri in Panorama*

Reference ID: 3708769

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/s/

ANUJA PATEL
02/27/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205266

INFORMATION REQUEST

Novartis Pharmaceuticals Corporation
Attention: Joyce Ann Sino, PhD
Director, Global Regulatory CMC- Oncology
One Health Plaza, Bldg. 339 Rm 1151
East Hanover, NJ 07936

Dear Dr. Sinno:

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

We are requesting the following information. We request a prompt written response by March 25, 2015, in order to continue our evaluation of your NDA.

1. In compliance with 21 CFR 314.50 (d) (1) (ii) (c) a complete description of the commercial scale manufacturing process is required. Current description in 3.2. P.3.3 is in complete (e.g., [redacted] (b) (4)). In reference to your amendment dated January 09, 2015, update Section P.3.3 with all the operating parameters and the ranges including those described in response to the Agency's comment 9 and 10 under Section 1.11.1 of 01/09/2015 Amendment. You can either revise the manufacturing process description in section 3.2.P.3.3 to include requisite information or submit proposed commercial scale Master Batch Records to Section 3.2.R.

2. It is the Agency's understanding that the [redacted] (b) (4)

3. Clarify if [redacted] (b) (4) .

4. For each of the equipment in Table 4-1 in P.3.3, provide the following information: (a) size/ capacity of the equipment and (b) percent occupancy or fill level at the proposed commercial scale. Clarify whether the percent occupancy/fill level at lab scale and pilot scale (Table 3-1 in P.2.1) are comparable to what is proposed for commercial scale.

5. With regard to Table 1-1 of Section 3.2.P.3.4.,
   a. Provide available data in section 3.2.P.2.3 to support proposed ranges for critical process parameters at commercial process. Include summary result of the studies.
   b. Clarify the discrepancy in the ranges shown for [redacted] (b) (4) Table 3-1 in section 3.2.P.2.3 shows the ranges as [redacted] (b) (4), whereas Table 1.1, in section 3.2.P.3.4 the range is shown as [redacted] (b) (4).

6. Provide all [redacted] (b) (4) test results for all the validation and the registration stability batches. If inconsistences in test results are observed, provide explanations.

If you have any questions, call Teicher Agosto, Regulatory Business Process Manager, at (240) 402-3777.

Sincerely,

Liang Zhou -A

Digitally signed by Liang Zhou -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Liang Zhou -A, 0.9.2342.19200300.100.1.1=1300086739
Date: 2015.02.26 14:17:52 -05'00'

Liang Zhou, Ph.D.
Quality Assessment Lead
Office of New Drug Products
Office of Pharmaceutical Quality

Patel, Anuja

From: Patel, Anuja
Sent: Tuesday, February 24, 2015 11:22 AM
To: 'Wang, Jessica-1'
Subject: RE: FDA Request for Information: Drug Trials Snapshot on FDA Website- NDA 205266- Novartis (sonidegib)

Importance: High

Dear Dr. Wang,

We refer to our February 11, 2015 information request regarding data intended for posting to the FDA Drug Trials Snapshot web page and to your email received February 17, 2015, with proposed revised tables and a request for FDA to respond as to the adequacy of the tables. We have the following response:

- The tables as proposed are acceptable; please submit them formally to the NDA. Please also note that the data you submit may be posted on the FDA website in the format outlined in the February 11, 2015 communication.

Kindly ACK receipt.

Regards,
Anuja

Anuja Patel, MPH
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
White Oak Complex, Bldg. 22, Room 2365
10903 New Hampshire Avenue
Silver Spring, MD 20993
☎301.796.9022 (phone)
301.796.9849 (fax)
anuja.patel@fda.hhs.gov (email)

From: Wang, Jessica-1 [mailto:jessica-1.wang@novartis.com]
Sent: Monday, February 23, 2015 1:24 PM
To: Patel, Anuja
Subject: RE: FDA Request for Information: Drug Trials Snapshot on FDA Website- NDA 205266- Novartis (sonidegib)

Dear Anuja,

Do you know when we could expect the feedback regarding the FDA information request for Drug Trials Snapshot information for the FDA website (see email below)?

I would like to give sufficient time for my team to review the FDA feedback and provide a robust response. Given the requested deadline of 25-Feb-2015 and depending on scope of work based on the feedback to be received, we may need to request an extension for the due date of the response.

Apologies for any inconvenience.

Reference ID: 3706602

Regards,
Jess

Jessica Wang, PharmD
Associate Director
Drug Regulatory Affairs, Oncology
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080
USA

Phone +1 862 7789507
Mobile (b) (6)
jessica-1.wang@novartis.com

From: Patel, Anuja [mailto:Anuja.Patel@fda.hhs.gov]
Sent: Thursday, February 19, 2015 8:06 AM
To: Wang, Jessica-1
Subject: RE: FDA Request for Information: Drug Trials Snapshot on FDA Website- NDA 205266- Novartis (sonidegib)

Hello Dr. Wang,

I am confirming receipt. Your email was forwarded to the team and we will followup with you soon.

Anuja

From: Wang, Jessica-1 [mailto:jessica-1.wang@novartis.com]
Sent: Thursday, February 19, 2015 7:28 AM
To: Patel, Anuja
Subject: RE: FDA Request for Information: Drug Trials Snapshot on FDA Website- NDA 205266- Novartis (sonidegib)

Hi Anuja,

I wanted to follow-up and check that you received my email below sent on Tues regarding the FDA information request for the Drug Trials Snapshot information.

Your feedback is much appreciated!

Thanks and best regards,
Jess

Jessica Wang, PharmD
Associate Director
Drug Regulatory Affairs, Oncology
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080
USA

Phone +1 862 7789507
Mobile (b) (6)
jessica-1.wang@novartis.com

From: Wang, Jessica-1
Sent: Tuesday, February 17, 2015 2:47 PM
To: 'Anuja.Patel@fda.hhs.gov'
Subject: RE: FDA Request for Information: Drug Trials Snapshot on FDA Website- NDA 205266- Novartis (sonidegib)

Reference ID: 3706602

Dear Anuja,

With regards to the FDA Information Request pertaining to the Drug Trials Snapshot website received on 11-Feb-2015, my team has reviewed the FDA sample shell tables included in the request and propose to make adaptations to the tables to provide more relevant and meaningful information for the public regarding the pivotal Study A2201. Please kindly refer to the Novartis-proposed shell tables attached, including a description of our approach for the response.

We are requesting confirmation and/or feedback from your team as soon as possible in order to proceed with addressing the information request by the due date of 25-Feb-2015.

Many thanks and best regards,
Jess

Jessica Wang, PharmD
Associate Director
Drug Regulatory Affairs, Oncology
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080
USA

Phone +1 862 7789507
Mobile (b) (6)
jessica-1.wang@novartis.com

From: Patel, Anuja [mailto:Anuja.Patel@fda.hhs.gov]
Sent: Wednesday, February 11, 2015 8:22 AM
To: Wang, Jessica-1
Subject: FDA Request for Information: Drug Trials Snapshot on FDA Website- NDA 205266- Novartis (sonidegib)
Importance: High

Dear Dr. Wang,

Please find attached a request for information that we are sending out for your New Molecular entity, sonidegib, currently under review in the Division of Oncology Products 2.

Please acknowledge receipt and feel free to contact me if you have any questions.

Regards,
Anuja

Anuja Patel, MPH
Sr. Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
White Oak Complex, Bldg. 22, Room 2365
10903 New Hampshire Avenue
Silver Spring, MD 20993
☎301.796.9022 (phone)
301.796.9849 (fax)
anuja.patel@fda.hhs.gov (email)

Reference ID: 3706602

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/s/

ANUJA PATEL
02/24/2015

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

Memorandum

Date: February 13, 2015

From: Anuja Patel, M.P.H., Sr. Regulatory Health Project Manager DOP2/OHOP

Subject: NDA 205266/ Type 1 (NME): Clinical and Clinical Pharmacology Request for Information

---

Novartis Pharmaceuticals Corporation
Attention: Jessica Wang, Pharm.D.
Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Wang:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for "Odomzo (sonidegib), 200 mg capsules."

We also refer to our information request sent via e-mail on December 18, 2014 and acknowledge receipt of your formal response received on January 20, 2015.

Our clinical and clinical pharmacology review team has the following request for additional information:

1. [redacted] (b) (4)

2. In Table 2-3 provided in your Response to FDA Information Request 7, received December 18, 2014 and attached, please clarify which patients listed with the action "drug interrupted" or "dose adjusted" restarted sonidegib treatment at the 200 mg dose and which patients restarted sonidegib treatment at a reduced dose and did not have a recurrent muscle-related toxicity. [redacted] (b) (4)

Please provide a response (via e-mail) to the above requests for information by 2 PM, EST. **Wednesday, February 18, 2015** and follow with a formal submission to your NDA by close of business, February 18, 2015.

If you have any questions, please feel free to call me.

Regards,

Anuja Patel, M.P.H.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Email: Anuja.Patel@fda.hhs.gov

Attachment:
Table 2-3 as provided by Novartis in Novartis' January 20, 2015 amendment in response to FDA Information Request issued on December 18, 2014.

Table 2-3 Summary details for patients with BCC who developed muscle toxicity requiring dose reduction, interruption, and/or discontinuation of study drug (6-month analysis) - Study A2201 (Sonidegib 200mg group) (Safety Set)

Patient ID	Preferred term (CTC grade)	Creatine phosphokinase level (U/L)[a]	Sonidegib PK level (ng/mL)[b]	Time of onset (days)	Action taken	Supportive care	Time to resolution (days)	Recurrence of event on restarting treatment
1150-007	Blood creatine phosphokinase increased (G3)	1019	1530	170	Drug interrupted	No	6	No
1197-008	Muscle spasms (G3)	272	553	141	Drug withdrawn	Thiocolchicoside, tramadol, hexaquine	Ongoing	-
1237-003	Muscular weakness (G1)	273	827	224	Dose adjusted	No	Ongoing	-
1238-001	Muscle spasms (G3)	109	1350	140	Drug withdrawn	No	104	-
1350-003	Blood creatine phosphokinase increased (G2)	706	570	72	Drug interrupted	No	9	No
1512-002	Blood creatine phosphokinase increased (G4)	1977, 2145[c]	1550	107	Drug interrupted	No	2	No
	Blood creatine phosphokinase increased (G2)	953	1550	109	Drug withdrawn	No	25	-
	Myalgia (G2)	645	670	120	Drug interrupted	No	3	No
1513-005	Muscle spasms (G2)	110	1690	108	Drug withdrawn	No	34	-
1515-004	Blood creatine phosphokinase increased (G4)[d]	2107	1610	85	Drug interrupted	No	Ongoing	-
1532-001	Blood creatine phosphokinase increased (G3)	1698, 2162[c]	875	335	Drug interrupted	No	4	No
	Rhabdomyolysis (G3)	1698, 2162[c]	875	335	Drug interrupted	No	4	No
1536-001	Blood creatinine increased (G2)	18	522	141	Drug interrupted	No	8	No

[a] Creatine phosphokinase levels at the closest available time point to the AE start date.
[b] Sonidegib PK levels (trough) at the closest available time point on the same day or prior to the event are provided.
[c] Two assessments on the same day.
[d] On the same day of CK increase, the patient also experienced a grade 4 CKMB increase, which caused the study drug to be withdrawn. Of note, no ECG abnormalities were reported at the same time point.
Source: [Study A2201-Listing 16.2.5-1.1], [Study A2201-Listing 16.2.5-1.5], [Study A2201-Listing 16.2.7-1.1], [Study A2201-Listing 16.2.6-3], and [Study A2201-Listing 16.2.8-1.6]

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/s/

ANUJA PATEL
02/13/2015

Patel, Anuja

From: Patel, Anuja
Sent: Wednesday, February 11, 2015 2:42 PM
To: 'Wang, Jessica-1'
Subject: Clinical Information Request: February 12, 2015 Teleconference- Novartis (sonidegib) NDA 205266

Importance: High

Dear Dr. Wang,

We are confirming the 30 minute teleconference for tomorrow, February 12, 2015 at 10:30 AM, EST.

We have the following request for information from the clinical team:

1. **Provide the location of the collected data on reasons why individual patients were considered not amenable to local therapies and therefore eligible for enrollment in Study A2201 (i.e. are there specific patient listings by patient ID or is this information only captured in the CRFs)?.**

2. **Please provide a table listing all patients in the 200 mg treatment arm of Study A2201 that shows a side-by-side comparison of centrally and investigator-determined best confirmed objective response. Sort the table by agreement between the response assessments. In cases where there was non agreement, provide comments on why there was discordance in the individual response assessment (if this data is available).**

Please provide a response to Item #1 above by tomorrow 10:00 AM, EST and provide a response via email to Item 2 no later than February 25, 2015. Please follow with a formal amendment to the NDA with your responses.

Please note, we may have additional statistical comments prior to the meeting however those comments will not be available until tomorrow morning.

Please acknowledge receipt of this email. Thank you!

Regards,
Anuja

Anuja Patel, MPH
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
White Oak Complex, Bldg. 22, Room 2365
10903 New Hampshire Avenue
Silver Spring, MD 20993
☎301.796.9022 (phone)
301.796.9849 (fax)
anuja.patel@fda.hhs.gov (email)

Reference ID: 3701540

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/s/

ANUJA PATEL
02/12/2015

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

Memorandum

Date: February 11 2015

From: Anuja Patel, RPM, DOP2/OHOP/CDER/FDA

Subject: Request for Information Intended to Populate the FDA Drug Trials Snapshot Website for: NDA 205266 sonidegib

---

Novartis Pharmaceuticals Corporation
Attention: Jessica Wang, Pharm.D.
Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Wang,

We are requesting your assistance in populating the attached tables for your New Molecular Entity, sonidegib, currently under review in the Division. If the application is approved, this information will be posted publically at the FDA drug snapshot website: http://www.fda.gov/Drugs/InformationOnDrugs/ucm412998.htm

We are asking for this information and making it public to allow for greater transparency into participation in clinical trials for newly-approved drugs and biologics.

The website will include information on study design, results of efficacy and safety studies, and whether there were any differences in efficacy and side effects within sex, race, and age subgroups. The website is not intended to replace or replicate the package insert (PI), which is intended for health care practitioners, and will contain the following:

- Information written in consumer-friendly language
- Information that focuses on subgroup data and analyses
- Links to the PI for the product and to the FDA reviews at Drugs@FDA

Information will be published approximately 30 days after drug/biologic approval

Therefore, we are requesting that you provide your data and complete the attached tables as well as provide descriptions of the analyses used to generate the data and any programs used to generate or analyze the data, if these are not already in the NDA 205266 submission.

We are requesting you submit this information no later than February 25, 2015.

Thank you in advance for your cooperation.

Please let me know if you have any questions.

Regards,

Anuja Patel, M.P.H.
Senior Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products

Attachments: Proposed Shell Tables for Completion

Reference ID: 3700784

PROPOSED SHELL TABLES

Table 1. Listing of Clinical Trials for the Efficacy Analysis

Study ID	No. of patients enrolled in the Drug X Arm	No. of patients enrolled in the Comparator Arm

Reference ID: 3700784

Table 2.1 Baseline Demographics, Single or Pooled Pivotal Efficacy Trials

Demographic Parameters	Comparator/ Control (n=) n (%)	Treatment Group(s) (n=)		Total (n=) n (%)
		Treatment arm #1 (n=) n (%)	Treatment arm #2 (n=) n (%)	
Sex				
Male				
Female				
Age				
Mean years (SD)				
Median (years)				
Min, max (years)				
Age Group				
<17 years				
≥17 - <65 years				
≥65 years				
≥75 years				
Race				
White				
Black or African American				
Asian				
American Indian or Alaska Native				
Native Hawaiian or Other Pacific Islander				
Other				
Ethnicity				
Hispanic or Latino				
Not Hispanic or Latino				
Region				
United States				
Rest of the World				
Canada				
South America				
Europe				
Asia				
Africa				

Source: list datasets or other sources of information

Reference ID: 3700784

Table 2.2 Baseline Demographics, Multiple Pivotal Efficacy Trials

Demographic Parameters	Trial #1 (N=)		Trial #2 (N=)		Total (n=) n (%)
	Comparator/ Control (n=) n (%)	Treatment arm (n=) n (%)	Comparator/ Control (n=) n (%)	Treatment arm (n=) n (%)	
Sex					
Male					
Female					
Age					
Mean years (SD)					
Median (years)					
Min, max (years)					
Age Group					
<17 years					
≥17 - <65 years					
≥65 years					
≥75 years					
Race					
White					
Black or African American					
Asian					
American Indian or Alaska Native					
Native Hawaiian or Other Pacific Islander					
Other					
Ethnicity					
Hispanic or Latino					
Not Hispanic or Latino					
Region					
United States					
Rest of the World					
Canada					
South America					
Europe					
Asia					
Africa					

Source: list datasets or other sources of information

Reference ID: 3700784

Table 3 Subgroup Analysis of Primary Endpoint, Pivotal Efficacy Trials

Demographic Subgroup	Trial #1 (N=)			Trial #2 (N=)		
	Comparator/control (n=) n (%)	**Treatment arm** (n=) n (%)	Difference (95% CI)	**Comparator/control** (n=) n (%)	**Treatment arm** (n=) n (%)	Difference (95% CI)
Overall Response/All patients						
Sex						
Male						
Female						
Age Group						
<17 years						
≥17 - <65 years						
≥65 years						
≥75 years						
Race						
White						
Black or African American						
Asian						
American Indian or Alaska Native						
Native Hawaiian or Other Pacific Islander						
Other						
Ethnicity						
Hispanic or Latino						
Not Hispanic or Latino						
Region						
United States						
Rest of the World						
Canada						
South America						
Europe						
Asia						
Africa						

Source: list datasets or other sources of information

Reference ID: 3700784

Table 4 Safety Population, Size and Denominators

Safety Database for the Study Drug[1] Individuals exposed to the study drug in this development program for the indication under review N= (N is the sum of all available numbers from the columns below)			
Clinical Trial Groups	New Drug (n=)	Active Control (n=)	Placebo (n=)
Normal Volunteers			
Controlled trials conducted for this indication[2]			
All other than controlled trials conducted for this indication[3]			
Controlled trials conducted for other indications[4]			

[1] *study drug* means the drug being considered for approval; do not include comparator arm drugs, placebo, or vehicle control in this table

[2] to be used in product's labeling

[3] if placebo arm patients switch to study drug in open label extension, the n should include their number; do not count twice patients who go into extension from randomized study drug arm

[4] include n in this column only if patients exposed to the study drug for indication(s) other than that in the marketing application have been included in the safety database under review. Consider n=0 in this column if no patients treated for other indication(s) were included in this safety database.

Reference ID: 3700784

Table 5.1 Baseline Demographics, Safety Population, Single or Pooled Trials (If efficacy population = safety population, refer to Table 2.1 or 2.2)

Demographic Parameters	Comparator/ Control (n=) n (%)	Treatment Group(s) (n=)		Total (n=) n (%)
		Treatment arm #1 (n=) n (%)	Treatment arm #2 (n=) n (%)	
Sex				
Male				
Female				
Age				
Mean years (SD)				
Median (years)				
Min, max (years)				
Age Group				
<17 years				
≥17 - <65 years				
≥65 years				
≥75 years				
Race				
White				
Black or African American				
Asian				
American Indian or Alaska Native				
Native Hawaiian or Other Pacific Islander				
Other				
Ethnicity				
Hispanic or Latino				
Not Hispanic or Latino				
Region				
United States				
Rest of the World				
Canada				
South America				
Europe				
Asia				
Africa				

Source: list datasets or other sources of information

Reference ID: 3700784

Table 5.2 Baseline Demographics, Safety Population, Multiple Trials

Demographic Parameters	Trial #1 (N=)		Trial #2 (N=)		Total (n=) n (%)
	Comparator/ Control (n=) n (%)	Treatment arm (n=) n (%)	Comparator/ Control (n=) n (%)	Treatment arm (n=) n (%)	
Sex					
Male					
Female					
Age					
Mean years (SD)					
Median (years)					
Min, max (years)					
Age Group					
<17 years					
≥17 - <65 years					
≥65 years					
≥75 years					
Race					
White					
Black or African American					
Asian					
American Indian or Alaska Native					
Native Hawaiian or Other Pacific Islander					
Other					
Ethnicity					
Hispanic or Latino					
Not Hispanic or Latino					
Region					
United States					
Rest of the World					
Canada					
South America					
Europe					
Asia					
Africa					

Source: list datasets or other sources of information

Reference ID: 3700784

Table 6.1 Subgroup Analysis of TEAEs, Safety Population

Demographic Subgroup	Comparator/Control		Treatment		Relative Risk	95% CI	
	n (%)	Total, N	n (%)	Total, N		LL	UL
Any TEAEs							
Sex							
Male							
Female							
Age Group							
<17 years							
≥17 - <65 years							
≥65 years							
≥75 years							
Race							
White							
Black or African American							
Asian							
American Indian or Alaska Native							
Native Hawaiian or Other Pacific Islander							
Other							
Ethnicity							
Hispanic or Latino							
Not Hispanic or Latino							
Region							
United States							
Rest of the World							
Canada							
South America							
Europe							
Asia							
Africa							

Source: list datasets or other sources of information

Reference ID: 3700784

Table 6.2 Subgroup Analysis by Sex of Common AEs, Safety Population (Events ≥ 2% of drug-treated subjects and more frequent than placebo)[1]

	Male (N=)		**Female** (N=)	
MedDRA System Organ Class Preferred Term	**Comparator/Control** (n=) n (%)	**Total Drug X** (n=) n (%)	**Comparator/Control** (n=) n (%)	**Total Drug X** (n=) n (%)
Gastrointestinal disorders				
Nausea				
Vomiting				
Diarrhea				
Abdominal pain				
General disorders/administration site conditions				
Fatigue				
Edema peripheral				
Infections and Infestations				
Influenza				
Urinary tract infection				
Injury, poisoning and procedural complications				
Fall				
Contusion				
Investigations				
Weight increased				
Blood CPK increased				
Musculoskeletal & connective tissue disorders				
Arthralgia				
Nervous system disorders				
Dizziness				
Headache				
Psychiatric disorders				
Depression				
Insomnia				
Respiratory, thoracic & mediastinal disorders				
Cough				
Skin & subcutaneous tissue disorders				
Rash				
Pruritus				

Source: list datasets or other sources of information

Reference ID: 3700784

Example of an application-specific adverse event

Table 6.3 Subgroup Analysis by Age of Dizziness/Gait Disturbance Adverse Events, Safety Population*

	Age ≥17-<65 years (N=)		**Age ≥65 years** (N=)	
MedDRA Preferred Term	**Comparator/Control** (n=) n (%)	**Total Drug X** (n=) n (%)	**Comparator/Control** (n=) n (%)	**Total Drug X** (n=) n (%)
Dizziness				
Ataxia				
Vertigo				
Balance disorder				
Gait disturbance				
Coordination abnormal				
Cerebellar syndrome				
Cerebellar ataxia				
Vestibular ataxia				
Vestibular disorder				
Total				

*Pediatric subjects were not included in the safety population
Source: list datasets or other sources of information

Reference ID: 3700784

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/s/

ANUJA PATEL
02/11/2015

Patel, Anuja

From: Patel, Anuja
Sent: Friday, February 06, 2015 8:03 AM
To: Wang, Jessica-1 (jessica-1.wang@novartis.com)
Subject: FDA Proposed Dates for Mid-cycle Communication with Novartis and Late Cycle Meeting with Novartis- NDA 205266 (sonidegib)

Importance: High

Dear Dr. Wang,

I refer to our phone call yesterday during which I informed you of the tentatively scheduled dates for the mid cycle communication and late cycle meeting with Novartis for your new drug application (NDA) NDA 205266 for sonidegib (proposed proprietary name: ODOMZO) for treatment of patients with locally advanced basal cell carcinoma (BCC) who are not amenable to curative surgery or radiation therapy (b) (4)

The proposed dates are below:

Mid-cycle Communication to Sponsor:
Thursday, March 5, 2015
1:00 PM to 2:00 PM, EST
Proposed Meeting Format: Teleconference

Late Cycle Meeting
Tuesday, May 19, 2015
1:00 PM to 2:00 PM, EST
Proposed Meeting Format: Teleconference

For additional information on what to expect prior to and during these meetings, please refer to page 30 and pages 39 through 41 of the ***CDER 21st Century Review Process- Desk Reference Guide*** which can be found at http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/UCM218757.htm

Please acknowledge receipt and feel free to contact me if you have any questions.

Regards,
Anuja

Anuja Patel, MPH
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
White Oak Complex, Bldg. 22, Room 2365
10903 New Hampshire Avenue
Silver Spring, MD 20993
☎301.796.9022 (phone)
301.796.9849 (fax)
anuja.patel@fda.hhs.gov (email)

Reference ID: 3698320

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/s/

ANUJA PATEL
02/06/2015

Internal Meeting
Meeting Summary
January 16, 2015

NDA: 205266- Type 1 New Molecular Entity
eCTD submission: SDN 001

Product: sonidegib (LDE 225), capsule, 200 mg, oral
Proposed Proprietary Name: ODOMZO
Submission Date: September 26, 2014
Received Date: September 26, 2014
Sponsor: Novartis Pharmaceuticals Corporation

Proposed Indication: for the treatment of patients with locally advanced basal cell carcinoma (BCC) who are not amenable to curative surgery or radiation therapy (b) (4)

Current Review Team for NDA 205266
*Attendees marked with **

Patricia Keegan
Monica Hughes
*Anuja Patel
*Suzanne Demko
*Denise Casey
*Kun He
*Huanyu (Jade) Chen
Hong Zhao
*Stacy Shord
*Liang Zhao,
*Whitney Helms
Alexander Putman
Jennie Chang
*Liang Zhou
*William Adams
*Ben Stevens
Donna Christner
Yubing Tang
Steve Langille
*Teicher Agosto
Catherine Tran-Zwanetz
Okpo Eradiri
Angelica Dorantes
Robert Wittorf
Janice Pohlman
*Lauren Iacono-Connor, OSI Reviewer
Susan Thompson
Frances Fahnbulleh, OSE, Safety RPM
(changed to Latonia Ford- effective 1.15.15)
Nick Senior, OPDP Reviewer
*Otto Townshend, DMEPA
Alice Chi-Ming Tu, DMEPA
*Amarylis Vega, DRISK Reviewer
Naomi Redd, DRISK TL

Discussion Items:

1. Discuss status of Information Requests and responses received

   Discussion During Meeting: No pending information requests (please refer to table). Office of Pharmaceuticals Products (OPQ) informed the team that all CMC comments in the Day 74 letter for drug product (DP) process have been received an are adequate at this time. The DP reviewer informed the RPM that they may have some information requests in mid-cycle review but will not be major, if any.

2. Weekly Sponsor Teleconferences Scheduled for Thursdays

Reference ID: 3698694

Discussion During Meeting: RPM confirmed that weekly tcons with the Applicant have been scheduled starting January 22, 2015 for every Thursday. The team agreed to sending the RPM 48 hrs prior to scheduled teleconference any discussion points for the teleconference. The purpose of the teleconference is to get any clarification on responses to information requests as needed.

If no comments/questions received 48 hours prior, then RPM will contact Applicant cancel the teleconferences for that week.

3. OPQ Update regarding Inspections

Discussion During Meeting- site inspections have been processed. Additional updates will be provided via OPQ RPBM and OPQ Application Team Lead during midcycle meeting.

4. OSI Update

Discussion During Meeting: Inspection assignments were issued in early December 2014. Earliest start dates anticipated to be mid Jan 2015.

5. Dates Milestone Letters Must Issue
(Anticipated Goal Date (AGD): July 24, 2015; PDUFA Goal: September 25, 2015)

Milestone	10-month Planned Review Cycle for 12 month Standard	Comments
Hold Mid-Cycle Communication to Sponsor	Planner Target Date: Thursday, February 26, 2015	Scheduled for Thursday, March 5, 2015
Send proposed labeling/PMR/PMC/REMS to applicant (with 1 week response)	Planner Target Date: Sunday, June 7, 2015	Actual Due Date: Friday, June 5, 2015
Late Cycle Meeting	3 months prior to planned action goal date	Scheduled for Tuesday, May 19, 2015
Week after the proposed labeling has been sent, discuss the Labeling/PRM/PMC with Applicant	Planner Target Date: Sunday, June 14, 2015	Actual Due Date: Friday, June 12, 2015
Review Target Due Dates:	Planner Target Dates:	Actual Due Dates:
Primary Review Due	Sunday, May 31, 2015	Friday, May 29, 2015
Secondary Review Due	Sunday, June 7, 2015	Friday, June 5, 2015 ** Issue Disciplinary Review letters (as needed) by June 14, 2015
CDTL Review Due	Sunday, June 14, 2014	Friday, June 12, 2015
Division Director Review Due	Sunday, July 5, 2014	Friday, July 3, 2015

Reference ID: 3698694

Milestone	10-month Planned Review Cycle for 12 month Standard	Comments
Office Director Review Due/Sign-Off	Sunday, July 26, 2015	Friday, July 24, 2015
Compile and circulate Action Letter and Action Package	Planner Target Date: Sunday, June 14, 2015	Actual Due Date: Friday, June 12, 2015
FINAL Action Letter Due	Planner Target Date: Sunday, July 26, 2015 PDUFA GOAL: Saturday, September 26, 2015	Planned Action Due Date: Friday, July 24, 2015

4. Upcoming Meetings:

a. Internal Meeting to Prepare for Mid-Cycle: Tuesday, February 10, 2015

Discussion During Meeting: The team discussed and agreed that this meeting was not needed therefore meeting will be cancelled. The team agreed to providing the slides to CDTL 1 week prior to the Midcycle meeting.

b. Mid-Cycle Meeting: Thursday, February 19, 2015

c. Mid-Cycle Communication with Applicant: Thursday, March 5, 2015
(to be confirmed with Applicant)

d. Internal Labeling Meetings:
- Labeling Meeting # 1: Thursday, March 12, 2015
- Labeling Meeting #2: Wednesday, March 18, 2015
- Labeling meeting #3: Monday, March 23, 2015
- Labeling Meeting #4: Wednesday, March 25, 2015
- Labeling Meeting #5: Thursday, March 26, 2015
  (Label to Applicant/ SCL to OPDP following Labeling mtg #5)
- Labeling Meeting #6: Monday, April 27, 2015
  (Discuss Applicant's edits and OPDP edits to labeling)

e. Internal Pre-Meeting for Late-Cycle: Thursday, April 23, 2015
- Background for Late Cycle due May 8, 2015

f. Late-Cycle Meeting with Applicant: Tuesday, May 19, 2015
(to be confirmed with Applicant)

g. Internal Wrap Up Meeting: Thursday, May 28, 2014

Discussion During Meeting: The team agreed to the scheduled labeling meeting dates, Mid-Cycle Meeting, Mid-Cycle Communication with Applicant, Internal pre-Meeting for late-Cycle and Late Cycle Meeting. No further discussion.

Reference ID: 3698694

8. Miscellaneous Items or Issues:

- Special Government Employee (SGE) Update

  Discussion During Meeting: RPM updated the team and informed them that the competing products list was sent to DACCM and the following SGEs will be screened once the list has been finalized:
  - *Dr. June Robinson- Dr. Robinson's SGE Appointment expires April 24, 2015. In an email from DFO Laura Tesh, Dr. Robinson declined to be reappointed as an SGE.*
  - *Dr. John DiGiovanna*
  - *Kristi Burr Schmitt- Patient Rep*

- PMR/PMC Discussion

Discussion During Meeting: The following PMR/PMC are anticipated but may change as review of the application is ongoing.
- ***Clinical- possible PMC to further evaluate muscle toxicity – still under review***
- ***Pharm/Tox Review- 1 PMC possibly for carcinogenicity- still reviewing***
- ***CMC- no PMR/PMC***

Reference ID: 3698694

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/s/

ANUJA PATEL
02/06/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205266

INFORMATION REQUEST

Novartis Pharmaceuticals Corporation
Attention: Joyce Ann Sino, PhD
Director, Global Regulatory CMC- Oncology
One Health Plaza, Bldg. 339 Rm 1151
East Hanover, NJ 07936

Dear Dr. Sinno:

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

We are requesting the following information. We request a prompt written response by February 6, 2015, in order to continue our evaluation of your NDA.

1. On page 11 of section 2.3.S.2.2 of the quality overall summary (QOS) and in sections 3.2.S.2.2 and 3.2.S.2.6, [redacted] (b) (4) .

2. On page 2 of section 3.2.S.2.1, the firm reports manufacturing sites and functions. It is not clear which testing procedures are carried out at the Novartis Pharma Schweizerhalle AG and [redacted] (b) (4) sites (*i.e.*, as currently written, overlap in testing functions is implied). Please precisely note the tests that will be carried out at each of the listed sites.

3. The specification for sonidegib reports the limits for [redacted] (b) (4) to one decimal place. Please list these limits to 2 decimal places per ICH Q3A.

4. Throughout section 3.2.S.2.2, the term "approximately" is used to describe the manufacturing process. In general, descriptive qualifiers are not sufficiently specific to describe a manufacturing process. Please remove "approximately" and other

descriptive qualifiers from the text describing the manufacturing process and use specific descriptors.

5. Process details are missing from Section 3.2.S.2.2. Please provide:

(b) (4)

6. On page 6 of section 3.2.S.2.2, the firm provides a synthetic narrative describing the preparation of (b) (4)

7. On page 8 of section 3.2.S.2.3, the firm provides specifications for (b) (4)

8. On page 6 of section 3.2.S.2.3, the firm provides a specification for (b) (4) . An acceptance criterion for the impurity (b) (4) is included at NMT (b) (4) %. (b) (4) Please explain the rationale for controlling (b) (4) at this level and provide any data regarding the capability of the manufacturing route to eliminate this impurity. This (b) (4) impurity should also be included in the potential impurity listing under section 3.2.S.3.2 either as a specified impurity or an unspecified impurity, depending on what levels, if any, have be measured to date.

9. On page 7 of section 3.2.S.2.3, the firm provides a specification for (b) (4) The acceptance criterion for assay is listed as (b) (4) %. Please clarify if this is an aqueous solution.

10. Please provide representative CoAs for each of the materials used in the manufacture of sonidegib [redacted] (b) (4) [redacted]

11. On page 12 of section 3.2.S.2.3, the firm provides a specification for the starting material [redacted] (b) (4) [redacted].

12. On page 4 of section 3.2.S.2.4, the firm provides specifications and controls for [redacted] (b) (4) The acceptance criterion for appearance is [redacted] (b) (4) [redacted]" Please explain the origin of the observed color and whether there is any time dependency for color formation. Impurity [redacted] (b) (4) is also specified at NMT [redacted] (b) (4) %. Please explain the origin of this impurity including its mechanism of formation and provide details regarding any related critical process parameters that affect levels observed in [redacted] (b) (4)

13. In section 3.2.S.2.4, the firm provides methods for controlling the key mutagenic/toxic impurities [redacted] (b) (4) [redacted] While specificity is demonstrated for several of these methods against a subset of related substances [redacted] (b) (4), [redacted] it is not clear if the included methods are sufficiently capable of differentiating amongst these key impurities. Please provide data that supports the capability of each of these methods to resolve the aforementioned impurities.

14. In section 3.2.S.2.6, the firm presents a summary of changes to the manufacturing process. [redacted] (b) (4), [redacted] Please explain the original purpose of these steps and provide rationale for this change.

15. Given the strong association between [redacted] (b) (4), it is recommended that the firm provide [redacted] (b) (4) final DS specification and provide a strict acceptance criterion for [redacted] (b) (4). This acceptance criterion should be supported by data that would ensure [redacted] (b) (4). [redacted] (b) (4) [redacted] is not demonstrated in the data provided to date.

16. On page 8 of section 3.2.S.3.2, the firm provides details regarding [redacted] (b) (4) [redacted] for sonidegib. As described in section 3.2.S.7.3, [redacted] (b) (4) [redacted]

(b) (4)

17. On page 13 of section 3.2.S.3.2, the firm provides details for potential (b) (4) impurities (b) (4) Please explain if any test has been carried out for this potential impurity (b) (4)

18. The proposed drug substance acceptance criterion for (b) (4) (NMT (b) (4) %) is not justified by the levels observed in the batch analysis data ((b) (4) %). It is recommended that these acceptance criteria be tightened to be more in line with the observed data or data provided to address the safety of (b) (4) at the proposed limits.

19. On page 36 of section 3.2.S.4.3, the firm provides a (b) (4) as part of the HPLC method validation. It is not clear from which sample mixture or spectrum this data is obtained. Please clarify.

20. On page 7 under the HSGC validation contained in section 3.2.S.4.3, the firm provides an analysis of the repeatability of the response factors for several solvent standard solutions (b) (4) . Please provide this information. (b) (4) Please explain.

21. On page 4 in section 3.2.S.4.3, the firm establishes the LOQ for the (b) (4) analysis method. (b) (4) Please explain how this method sufficiently establishes LOQ or LOD per ICH Q2A.

22. On page 6 of section 3.2.S.4.5, the firm provides justification for the specified levels of impurity (b) (4)). The firm states " (b) (4) " Referring to table 3-19 of section 3.2.S.7.3, it is not apparent that levels of (b) (4) increase during the included

photostability testing for batch 1284037. Please provide any experimental data indicating [redacted] (b) (4).

23. On page 8 of section 3.2.S.4.5, the firm provides a rationale for [redacted] (b) (4) Accompanying toxicology data is provided in order to establish a PDE level for [redacted] (b) (4). The firm should provide any data pertaining to the [redacted] (b) (4) should also be included in the potential impurity listing under section 3.2.S.3.2.

24. On page 47 of section 3.2.S.7.3 under "interpretation of data," the sponsor provides a statistical evaluation for the assay results from long term stability to support a proposed [redacted] (b) (4) month retest period. [redacted] (b) (4) The sponsor should reevaluate the data for [redacted] (b) (4) support of the [redacted] (b) (4) month retest period and provide further updated stability data for [redacted] (b) (4).

25. Please provide the proposed label for the bulk drug substance.

If you have any questions, call Teicher Agosto, Regulatory Project Manager, at (240) 402-3777.

Sincerely,

Liang Zhou -A Digitally signed by Liang Zhou -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Liang Zhou -A, 0.9.2342.19200300.100.1.1=1300085729
Date: 2015.11.30 16:12:00 -05'00'

Liang Zhou, Ph.D.
Quality Assessment Lead
Office of New Drug Products
Office of Pharmaceutical Quality

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

Memorandum

Date: January 28, 2015

From: Anuja Patel, M.P.H., Sr. Regulatory Health Project Manager DOP2/OHOP

Subject: NDA 205266: PeRC Meeting

On January 28, 2015, PeRC meeting was held and the committee discussed NDA 205266 and agreed to granting a full pediatric waiver for Odomzo (sonidegib) for patients with locally advanced basal cell carcinoma who are not amenable to curative surgery or radiation therapy. Meeting minutes have been uploaded in DARRS on February 9, 2015.

Patel, Anuja

From: Patel, Anuja
Sent: Monday, January 26, 2015 8:21 AM
To: 'Wang, Jessica-1'
Subject: RE: FDA Clinical Pharmacology Information Request:NDA 205266 (sonidegib)- Response Required by Friday, February 6, 2015

Importance: High

Dear Dr. Wang,

The clinical pharmacology review team has reviewed your proposal sent via email on January 23, 2015 and agree with Novartis.

Please reference your email and this email response in the formal submission of your response to our information request sent January 21, 2015.

Please acknowledge receipt.

Thank you!
Anuja

Anuja Patel, MPH
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
White Oak Complex, Bldg. 22, Room 2365
10903 New Hampshire Avenue
Silver Spring, MD 20993
☎301.796.9022 (phone)
301.796.9849 (fax)
anuja.patel@fda.hhs.gov (email)

From: Wang, Jessica-1 [mailto:jessica-1.wang@novartis.com]
Sent: Friday, January 23, 2015 1:38 PM
To: Patel, Anuja
Subject: RE: FDA Clinical Pharmacology Information Request:NDA 205266 (sonidegib)- Response Required by Friday, February 6, 2015

Dear Anuja,

Reference is made to the FDA Clinical Pharmacology Information Request received on 21-Jan-2015. With regards to Question 3, my team is requesting confirmation on the following approach to address the FDA reviewer's request.

FDA IR Question 3:

3. You have provided an exposure-response analysis (logistic regression model) of sonidegib in patients with advanced basal cell carcinoma for probability of best overall response (CR or PR) using sonidegib minimal concentrations (Cmin) measured at week 5. Provide similar analyses for probability of best overall response using Cmin at week 17 and

Reference ID: 3692019

simulated average AUC adjusted by dose intensity before the event of best overall response (dose intensity: total dose up to an event divided by time).

Novartis proposal:

Novartis intends to use the 6-month primary analysis for Study A2201 (data cut-off date: 28-Jun-2013) for this response based on the rationale that pharmacokinetic (PK) data reconciliation was conducted in the 6-month primary analysis, but not for the 12-month analysis.

Novartis proposes the following steps of calculation and analysis. Does the Agency agree?

1. For "simulated average AUC", we will use the dose intensity (DI) divided by the individual post-hoc Clearance from the PopPK model.
2. DI is defined as cumulative dose divided by duration of exposure.
3. The period to consider for DI is:
    - For responders and their first CR/PR assessed while on treatment, from first dose to the first CR/PR;
    - For responders and their first CR/PR assessed after treatment discontinuation and for non-responders, from first dose to the min (cutoff date, last dose date), i.e. the entire duration while they are on treatment.
4. Then we will use "simulated average AUC" to correlate with best overall response by logistic regression modeling.

We would appreciate a response as early as possible so that we may proceed with addressing the Information Request according to the requested timeframe.

Thanks and best regards,
Jess

Jessica Wang, PharmD
Associate Director
Drug Regulatory Affairs, Oncology
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080
USA

Phone +1 862 7789507
Mobile (b) (6)
jessica-1.wang@novartis.com

From: Patel, Anuja [mailto:Anuja.Patel@fda.hhs.gov]
Sent: Wednesday, January 21, 2015 3:45 PM
To: Wang, Jessica-1
Subject: FDA Clinical Pharmacology Information Request:NDA 205266 (sonidegib)- Response Required by Friday, February 6, 2015
Importance: High

Dear Dr. Wang,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for "Odomzo (sonidegib), 200 mg capsules."

Kindly find attached information request from our clinical pharmacology team. A formal response is requested by Friday, February 6, 2015. Please acknowledge receipt.

Thank you!

Reference ID: 3692019

Anuja

Anuja Patel, MPH
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
White Oak Complex, Bldg. 22, Room 2365
10903 New Hampshire Avenue
Silver Spring, MD 20993
☎301.796.9022 (phone)
301.796.9849 (fax)
anuja.patel@fda.hhs.gov (email)

Reference ID: 3692019

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/s/

ANUJA PATEL
01/26/2015

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

Memorandum

Date: January 26, 2015

From: Anuja Patel, M.P.H., Sr. Regulatory Health Project Manager DOP2/OHOP

Subject: NDA 205266/ Type 1 (NME): Clinical Request for Information

---

Novartis Pharmaceuticals Corporation
Attention: Jessica Wang, Pharm.D.
Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Wang:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for "Odomzo (sonidegib), 200 mg capsules."

Our clinical review team has the following request for information:

1. The number of protocol deviations that occurred during Study A2201 is large. FDA acknowledges the large number of clinical assessments required per the protocol and that many of the deviations resulted from required assessments being performed outside of the protocol-specified timepoints; however, the protocol deviation dataset and the corresponding line listings (Table 14.1-1.6) and case report forms do not categorize the deviations as major or minor and do not always provide details (e.g. "tumor evaluation criteria not met" or "biopsy not performed" or "MRI not performed") that allow for a reasonable conclusion regarding the impact of the protocol deviations on the study data.

    a. Please clarify if Novartis considers the five patients who reported major protocol deviations which led to exclusion from the per-protocol set (summarized in Table 10.2 in the Clinical Study Report for A2201) to be the only major protocol deviations during Study A2201. If there are other major deviations/violations, provide a summary table similar to Table 10.2.

    b. Has Novartis performed an analysis to determine if any of the deviations that pertained to a missed/delayed MRI or tumor biopsy or photography session during study A2201 had an impact on the objective response and duration of response data?

c. Did any of the surgical resections that occurred during the study and were considered protocol deviations in the dv.xpt database impact measurement of response or duration of response in individual patients?

Please submit your response to the above requests for information formally to your NDA by Noon, EST, **Friday, January 30, 2015**. Please email me when your response has been formally submitted.

If you have any questions, please feel free to call me.

Regards,

Anuja Patel, M.P.H.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Email: Anuja.Patel@fda.hhs.gov

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/s/

ANUJA PATEL
01/26/2015

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

Memorandum

Date: January 21, 2015

From: Anuja Patel, M.P.H., Sr. Regulatory Health Project Manager DOP2/OHOP

Subject: NDA 205266/ Type 1 (NME): Clinical Pharmacology Request for Information

---

Novartis Pharmaceuticals Corporation
Attention: Jessica Wang, Pharm.D.
Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Wang:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for "Odomzo (sonidegib), 200 mg capsules."

FDA requests responses to the following information requests by Friday, February 6, 2015.

1. Submit the drug product's dissolution profiles in simulated fed and fasted intestinal fluids to the NDA and provide a hyperlink to this report in the response to this information request. The proposed labeling states, "(b) (4) , suggesting that this information is available for sonidegib.

2. Reference is made to your population Pharmacokinetics (PK) analysis report. FDA finds that the full population PK model (run3.mod) in the report to be over-parameterized and did not successfully converge. You need to provide a population PK model of successful convergence, which can be potentially achieved by using a simplified error structure, for the assessment of covariate effects on drug exposure. Alternatively, you can use a stepwise approach including procedures of forward selection and backward elimination for the development of a final population PK model. Submit a population analysis report for the associated analysis. NONMEM dataset, NONMEM control streams, and scripts used to generate analyses should be provided for the analyses requested. Data files should be submitted as SAS transport files (eg, Data1.xpt) and other files submitted as ASCII text files (eg, myfile_ctl.txt, myfile_out.txt). Please refer to the following pharmacometric data and models submission guidelines for details:

http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm).

3. You have provided an exposure-response analysis (logistic regression model) of sonidegib in patients with advanced basal cell carcinoma for probability of best overall response (CR or PR) using sonidegib minimal concentrations (Cmin) measured at week 5. Provide similar analyses for probability of best overall response using Cmin at week 17 and simulated average AUC adjusted by dose intensity before the event of best overall response (dose intensity: total dose up to an event divided by time).

Please submit a formal amendment to NDA with your responses **by Friday, February 6, 2015**. Please email me a courtesy copy of the cover letter once your submission has been formally submitted.

If you have any questions, please feel free to call me.

Regards,

Anuja Patel, M.P.H.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-9022
Email: Anuja.Patel@fda.hhs.gov

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/s/

ANUJA PATEL
01/21/2015

Patel, Anuja

From: Patel, Anuja
Sent: Monday, January 19, 2015 9:48 PM
To: 'Wang, Jessica-1'
Subject: FDA Clinical Information Request:NDA 205266 (sonidegib)- Response Required by Friday, January 23, 2015
Attachments: NovartisIRforsonidegibNDA1-13-14.pdf

Importance: High

Dear Dr. Wang,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for "Odomzo (sonidegib), 200 mg capsules."

Kindly find attached another information request from our clinical team. A formal response is requested by Friday, January 23, 2015. Please acknowledge receipt.

Thank you!

Anuja

Anuja Patel, MPH
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
White Oak Complex, Bldg. 22, Room 2365
10903 New Hampshire Avenue
Silver Spring, MD 20993
☎301.796.9022 (phone)
301.796.9849 (fax)
anuja.patel@fda.hhs.gov (email)

Reference ID: 3688931

1. There appear to be discrepancies among the adverse event analysis performed by the FDA clinical reviewer using the 12 month AE dataset (ADAE.xpt), Table 2.3 on page 30 of the Addendum to Summary of Clinical Safety: 12 month Analysis, (b) (4) Please see Table 2.3 copied from the addendum to the Summary of Clinical Safety, (b) (4) , and the reviewer's draft adverse event incidence table derived from ADAE.xpt in module 5.3.5.3, for your reference. The highlighted terms are adverse events where the incidence rate between the sponsor's Table 2.3 and the reviewer's draft table are different. We have also highlighted adverse events (b) (4) that are not consistent with the reviewer's analysis and/or Table 2.3 in the addendum to SCS. Please re-run your analysis or provide an explanation for these discrepancies.

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/s/

ANUJA PATEL
01/19/2015

Patel, Anuja

From: Wang, Jessica-1 <jessica-1.wang@novartis.com>
Sent: Sunday, January 11, 2015 6:10 PM
To: Patel, Anuja
Subject: RE: FDA Response: NDA 205266 Odomzo (sonidegib): Question re: (b) (4)

Dear Anuja,

Thank you for your email. I confirm receipt of this FDA response.

Best regards,
Jessica

Jessica Wang, PharmD
Associate Director
Drug Regulatory Affairs, Oncology
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080
USA

Phone +1 862 7789507
Mobile (b) (6)
jessica-1.wang@novartis.com

From: Patel, Anuja [mailto:Anuja.Patel@fda.hhs.gov]
Sent: Sunday, January 11, 2015 6:02 PM
To: Wang, Jessica-1
Subject: FDA Response: NDA 205266 Odomzo (sonidegib): Question re: (b) (4)
Importance: High

Dear Dr. Wang,

We refer to your email sent January 5, 2015. We have the following comment:

- Submit a complete/final study report as a post marketing requirement as discussed during the pre NDA meeting under the related IND. (b) (4)

Please acknowledge receipt.

Regards,
Anuja

Anuja Patel, MPH
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
White Oak Complex, Bldg. 22, Room 2365
10903 New Hampshire Avenue
Silver Spring, MD 20993
☎301.796.9022 (phone)

Reference ID: 3685429

301.796.9849 (fax)
anuja.patel@fda.hhs.gov (email)

From: Wang, Jessica-1 [mailto:jessica-1.wang@novartis.com]
Sent: Monday, January 05, 2015 2:47 PM
To: Patel, Anuja
Subject: NDA 205266 Odomzo (sonidegib): Question re: (b) (4)

Dear Anuja,

Reference is made to NDA 205-266 for ODOMZO (sonidegib) and the Novartis response to FDA Clinical Pharmacology information request submitted on 19-Nov-2014 (Seq. No. 0003) (attached for your reference).

Please note that within the response document ('clinical-response-fda-20141119'), Novartis provided an additional comment to Question 1 with regards to the hepatic impairment study A2113, as shown below.

(b) (4)

(b) (4)

We would appreciate if the Agency could confirm that this proposal is acceptable. Thanks so much.

Best regards,
Jessica

Jessica Wang, PharmD
Associate Director
Drug Regulatory Affairs, Oncology
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080
USA

Phone +1 862 7789507
Mobile (b) (6)
jessica-1.wang@novartis.com

Reference ID: 3685429

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/s/

ANUJA PATEL
01/12/2015

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

Memorandum

Date: January 12, 2015

From: Anuja Patel, M.P.H., Sr. Regulatory Health Project Manager DOP2/OHOP

Subject: NDA 205266/ Type 1 (NME): Clinical Request for Information

---

Novartis Pharmaceuticals Corporation
Attention: Jessica Wang, Pharm.D.
Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Wang:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for "Odomzo (sonidegib), 200 mg capsules."

We also refer to our email communication sent January 7, 2015 containing the following clinical comment:

- Specify the location in the NDA of the meeting minutes from the independent adjudication committee that analyzed the events of muscle toxicity/rhabdomyolysis that occurred during Study A2201. If these are not within the NDA submission already, please submit the minutes **by January 15, 2015 or sooner**.

Our clinical review team has the following request for additional information in reference to the comment above:

1. Page 23 of the INDEPENDENT SAFETY REVIEW & ADJUDICATION COMMITTEE FOR MUSCULAR EVENTS REPORT (Section 5.3.5.3) states:

   "The Adjudication Committee will complete and provide to Novartis a unified Adjudication Committee Assessment form and a final report content based on unified agreement from the committee."

   a. Please clarify if the "final report" from the adjudication committee is the content within pages 7 through 11 of adjudication report. If there are additional reports written by the Adjudication Committee (e.g. discussion/rationale for individual patient adjudication decisions), submit these to the NDA.

b. Provide copies of the adjudication committee's individual patient assessment forms and a copy of the meeting minutes. Note that Appendix 7.1 and 7.2 of the adjudication report are labeled "Adjudication Committee Assessment Form" and "Muscular Event Assessment Form (Novartis output)" respectively; however, the links are not functional and it is not clear if these links will contain one template form or the individualized assessment forms for each patient case.

Please submit your response to the above requests for information formally to your NDA by **Monday, January 19, 2015**. Please email me when your response has been formally submitted.

If you have any questions, please feel free to call me.

Regards,

Anuja Patel, M.P.H.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Email: Anuja.Patel@fda.hhs.gov

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/s/

ANUJA PATEL
01/12/2015

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

Memorandum

Date: January 7, 2015

From: Anuja Patel, M.P.H., Sr. Regulatory Health Project Manager DOP2/OHOP

Subject: NDA 205266/ Type 1 (NME): Clinical and Clinical Pharmacology Request for Information

---

Novartis Pharmaceuticals Corporation
Attention: Jessica Wang, Pharm.D.
Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Wang:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for "Odomzo (sonidegib), 200 mg capsules."

Our QT-IRT review team has the following request for additional information:

1. Please submit a subject ID map file between adpkeg.xpt and those in ECG Warehouse for Study CLDE225X1101.

2. Please upload ECG waveform files to ECG Warehouse for Study CLDE225B2209 if available.

3. Please include PR interval, QRS interval, HR into adpkeg.xpt and adeg.xpt.

Please submit Items 1-3 above **by January 15, 2015**. Please email me when your response has been formally submitted.

In addition, we have the following request for information from our clinical team:

4. Specify the location in the NDA of the meeting minutes from the independent adjudication committee that analyzed the events of muscle toxicity/rhabdomyolysis that occurred during Study A2201. If these are not within the NDA submission already, please submit the minutes **by January 15, 2015 or sooner**.

If you have any questions, please feel free to call me.

Regards,

Anuja Patel, M.P.H.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Email: Anuja.Patel@fda.hhs.gov

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/s/

ANUJA PATEL
01/07/2015

From:	Biable, Missiratch (Mimi)
To:	"jessica-1.wang@novartis.com"
Cc:	Patel, Anuja
Subject:	NDA 205266--Clinical and Clinical Pharmacology Information Request- Response Required
Date:	Thursday, December 18, 2014 5:39:34 PM
Importance:	High

Dear Dr. Wang,

I am sending this email on behalf of your Regulatory Project Manager, Anuja Patel, who is currently out of the office.

The Clinical and Clinical Pharmacology team have the following information request. Please submit your response to your NDA by **COB, Friday January 2, 2015**, with a courtesy copy to me and Ms. Patel via email.

1. (b) (4)

2. We are reviewing the pharmacokinetic and safety data on muscle toxicity associated with sonidegib. Please provide a summary analysis (table or graph is acceptable) of all patients with basal cell carcinoma treated with sonidegib 200 mg daily on studies A2201 and X2101 who developed any muscle toxicity requiring dose reduction, interruption and/or discontinuation of study drug. Include the toxicity (e.g, CK elevation, spasm, myalgia, rhabdomyolisis etc.), the corresponding creatinine kinase levels and the sonidegib PK levels, time of onset, action taken in terms of interrupting or dose-reducing sonidegib, any supportive care treatment administered (e.g., IV hydration), time to resolution and whether or not there was a recurrence of muscle toxicity upon restarting sonidegib.

3. We are attempting to verify information presented in the patient narratives. Clarify if laboratory values and investigator assessments are included in the case report forms (CRFs) or solely in datasets. If the information is included in the CRFs, provide an example of a stepwise search of a CRF for information surrounding a specific patient, adverse event and date.

Regards,

Missiratch (Mimi) Biable, M.S., R.A.C (US)
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Email: Missiratch.biable@fda.hhs.gov
Phone: 301-796-0154

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/s/

MISSIRATCH BIABLE
12/18/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205266

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

Novartis Pharmaceuticals Corporation
Attention: Jessica Wang, Pharm. D.
Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Wang:

Please refer to your New Drug Application (NDA) dated September 26, 2014, received September 26, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Odomzo (sonidegib) capsules, 200 mg.

We also refer to your amendments dated October 8 and 23, 2014; November 14, 17, 19, 20 (2), 24, 2014, and December 2, 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 **Standard**. 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 September 26, 2015.

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 commitment requests by August 26, 2015

In addition, the planned date for our internal mid-cycle review meeting is **February 19, 2015.** We are not currently planning to hold an advisory committee meeting to discuss this application.

At this time, we are notifying you that we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We have the following comments and request that you submit the following information formally to your NDA no later than **Friday, January 9, 2015**:

Microbiology Quality Assessment:

1. Submit the results microbial limits testing performed through [insert date] on long-term stability batches according to the schedule provided in ICH Q1A section 2.2.6, since the NDA lacks historical data for this product. The microbial limits testing schedule may be modified after a sufficient amount of consistent and satisfactory microbial limits test results has been established.

Biopharmaceutics:

2. The dissolution stability data were reported at only the proposed specification-sampling time points, 30 minutes and 90 minutes. Submit in SAS transport file format, the complete multi-point dissolution profiles obtained at release and in the stability program for every batch, under all storage conditions and packaging configurations.

   If multiple time point profiling data were not collected, perform a full profiling (n=12) of the clinical and registration batches at the current stability time point using the following sampling times: 10, 15, 20, 30, 45, 60 & 90 minutes and submit these data as an amendment to the NDA no later than February 20, 2015.

3. Similar to the release and stability data, provide the individual vessel dissolution data in SAS transport file format to support the suitability of the dissolution method for your proposed drug product. It is noted that data from the dissolution method development experiments are summarized in Module 3, section 3.2.P.2 but are only presented graphically with no individual vessel data tabulations.

4. The discriminating capability of your proposed dissolution method has not been adequately investigated. The testing conducted to demonstrate the discriminating ability of a dissolution method should compare the dissolution profiles of the proposed target product and variant formulations that are intentionally manufactured with meaningful variations for the most relevant critical manufacturing variables (i.e., ± 10-20% change to the specification-ranges of these variables). Provide data from appropriate experiments to demonstrate the discriminating power of the proposed dissolution test method. In addition, if available, submit data showing the capability of the selected dissolution method to reject batches that are not bioequivalent.

5. Provide a list of the Critical Material Attributes (CMA) and Critical Process Parameters (CPP) affecting dissolution with supporting data (graphical and tabular form) using the proposed dissolution method.

Drug Substance:

6. Clarify and explain the several instances where sponsor or vendor ID numbers are cited without an identifying structure or chemical name. For example:

(b) (4)

Furthermore, structures are frequently referred to by alternate names and/or ID numbers throughout the document. This leads to confusion during review between sections of the CTD. Please correct and/or revise accordingly.

Please provide a summary table including: 1.) all of the chemical structures included in the application; 2.) their chemical names; and 3.) a listing of all of their identifiers as used throughout the application (*i.e.*, sponsor numbers, vendor numbers, and common names as used in the application).

7. In the quality overall summary (QOS) 2.3.S.2, (b) (4) . Please explain.

8. In the QOS 2.3.S.2, (b) (4)

(b) (4)

Manufacturing Process for Drug Product:

9. [redacted] (b) (4)

10. For the following process steps, provide appropriate justification to support the selection of critical process parameters and the proposed control range for various process parameters. Currently, the information presented in 3.2.P.2. is not adequate as there is no supporting data to justify the proposed ranges:

[redacted] (b) (4)

11. Based on your justification for the above item, provide a complete description of your drug product manufacturing process that includes equipment type for each process step, and ranges or set points for process parameters. You can either revise section 3.2.P.3.3 or submit a master batch record (MBR) in 3.2R.

12. Executed Batch Records submitted in 3.2.R. only contains information for the [redacted] (b) (4) Provide batch record for all steps included in a representative batch.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. 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.

Labeling issues and comments identified during our preliminary review of your submitted labeling are provided in the attached labeling. In addition, we have the following labeling comment:

13. The heading for DRUG INTERACTIONS does not appear centered. All headings in HL must be bolded and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Please resubmit revised labeling (in both clean and redlined (track changes shown) Microsoft Word format) that addresses our comments and issues by January 6, 2015. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and Medication Guide. 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 Medication Guide 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.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call Ms. Anuja Patel, Senior Regulatory Project Manager, at (301) 796-9022.

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

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/s/

PATRICIA KEEGAN
12/09/2014

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

Memorandum

Date: December 2, 2014

From: Anuja Patel, M.P.H., Sr. Regulatory Health Project Manager DOP2/OHOP

Subject: NDA 205266/ Type 1 (NME): Request for Information – CRO Contact Information

---

Novartis Pharmaceuticals Corporation
Attention: John A. Robinson, Ph.D.
Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Robinson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for "Odomzo (sonidegib), 200 mg capsules."

Please provide the full name, title, and contact information for the authorized point of contact(s) for the following Contract Research Organizations which were identified in your NDA application:

(b) (4)

Please respond via e-mail by 2:00 PM, EST today, December 2, 2014, and follow with a formal submission to the NDA.

If you have any questions, please feel free to call me.

Regards,

Anuja Patel, M.P.H.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-9022
Email: Anuja.Patel@fda.hhs.gov

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/s/

ANUJA PATEL
12/02/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 205266

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080

ATTENTION: John A. Robinson, PhD
Director

Dear Dr. Robinson:

Please refer to your New Drug Application (NDA) dated September 26, 2014, received September 26, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sonidegib Capsules, 200 mg.

We also refer to:

- your September 26, 2014, correspondence, received September 26, 2014, requesting review of your proposed proprietary name, Odomzo
- your October 8, 2014, amendment received October 8, 2014, to your request for name review

We have completed our review of the proposed proprietary name, Odomzo and have concluded that it is acceptable.

If any of the proposed product characteristics as stated in your September 26, 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 Frances Fahnbulleh, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0942. For any other information regarding this application, contact Anuja Patel, Regulatory Project Manager in the Office of New Drugs, at (301) 796-9022.

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
11/26/2014

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

Memorandum

Date: November 16, 2014

From: Anuja Patel, M.P.H., Sr. Regulatory Health Project Manager DOP2/OHOP

Subject: NDA 205266/ Type 1 (NME): Division of Risk Management (DRISK) Comment regarding your proposal for additional risk mitigating activities

---

Novartis Pharmaceuticals Corporation
Attention: John A. Robinson, Ph.D.
Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Robinson:

Please refer to your New Drug Application (NDA) submitted on September 26, 2014, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for "Odomzo (sonidegib), 200 mg capsules."

The Division of Risk Management (DRISK), Center for Drug Evaluation and Research, has the following comments and request for response by close of business Thursday, November 20, 2014:

- Your submission from September 26, 2014 includes a proposal for additional risk mitigating activities (i.e., (b) (4) addressing the risks of myopathy/rhabdomyolysis and reproductive toxicity and fertility. (b) (4)

- FDA advises Novartis Pharmaceuticals Corporation that the additional risk mitigation materials you propose are considered promotional in nature and should be submitted to FDA for review separately with other promotional materials.

If you have any questions, please feel free to contact me.

Regards,

Anuja Patel, M.P.H.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-9022
Email: Anuja.Patel@fda.hhs.gov

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/s/

ANUJA PATEL
11/16/2014

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

Memorandum

Date: November 12, 2014

From: Anuja Patel, M.P.H., Sr. Regulatory Health Project Manager DOP2/OHOP

Subject: NDA 205266/ Type 1 (NME): Statistical Request for Information

---

Novartis Pharmaceuticals Corporation
Attention: John A. Robinson, Ph.D.
Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Robinson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for "Odomzo (sonidegib), 200 mg capsules."

We also refer to our November 12, 2014, e-mail communication requesting a 30 minute teleconference on Thursday, November 13, 2014 at 1:30 PM, EST. We have the following statistical comments and requests for response.

For pivotal study CLDE225C2201, please provide the following information as soon as possible.

1. The primary efficacy data should also be submitted at patient level (one observation per patient) including (b) (4) locally advanced basal cell carcinoma (BCC) (b) (4) patients in the full analysis set (FAS) population.

2. Provide the executive programs and case report form (CRF) source data used to generate key analysis data sets for primary and key secondary efficacy endpoints. We acknowledge that the CRF source data with traceability variables are not CDISC-compliant.

3. Provide the executive SAS programs with adequate documentation to reproduce the results in clinical study report (CSR) Tables 10-1 10-2, 11-1, 11-2, 11-3, 11-5, 11-6, 11-7, 11-12, 11-14, 11-17, 11-8, and 11-21.

4. Provide the executive SAS programs with adequate documentation to reproduce the figures 11-1, 11-2, 11-3, and 11-4 in the CSR

5. In the define.pdf please provide adequate comment for variable label, data format decode of categorical and numerical variable(s), meaning of missing value, and algorithm(s) to derive new variable from raw data to derived data. Bookmarks/hyperlinks should be adequately linked for the contents of data files, derivations of the variables, coding of the variables.

6. Provide the data monitoring committee (DMC) meeting minutes for the planned interim analyses of overall response rate, progression-free survival, and overall survival.

7. Provide the executive SAS programs with adequate documentation to reproduce safety analysis.

Please confirm the proposed date and time for the teleconference and provide a dial in number. Please submit a formal amendment to NDA with your responses **by close of business, Friday, November 14, 2014**. Please email me a courtesy copy of the cover letter once your submission has been formally submitted.

If you have any questions, please feel free to contact me.

Regards,

Anuja Patel, M.P.H.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-9022
Email: Anuja.Patel@fda.hhs.gov

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/s/

ANUJA PATEL
11/12/2014

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

Memorandum

Date: November 7, 2014

From: Anuja Patel, M.P.H., Sr. Regulatory Health Project Manager DOP2/OHOP

Subject: NDA 205266/ Type 1 (NME): Clinical Pharmacology Request for Information

---

Novartis Pharmaceuticals Corporation
Attention: John A. Robinson, Ph.D.
Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Robinson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for "Odomzo (sonidegib), 200 mg capsules."

We also refer to our May 14, 2014 meeting minutes of the April 15, 2014 pre-NDA meeting, and to your electronic submission of September 26, 2014, which consisted of a Type 1 (NME) new drug application (NDA). We are currently reviewing your submission and our Clinical Pharmacology Reviewer has the following comments requests for additional information:

1. Submit to the NDA a description of the proposed post marketing studies, including your proposed timelines for completion of these studies and submission of the final study reports, for the hepatic impairment study and two drug interaction studies with appropriate cytochrome P450 probe substrates and a proton pump inhibitor as requested during the pre-NDA meeting held on April 15, 2014.
2. We conducted an initial review of the physiologically based pharmacokinetic (PBPK) study report (Study 1400133) entitled "Simcyp predictions of the interaction of LDE225 with ketoconazole or rifampin". It appears that sonidegib exposure is generally higher in cancer patients as compared to healthy subjects and that the sonidegib PBPK model has been developed primarily using pharmacokinetic (PK) data of healthy subjects. Figures 7-2 and 7-4 found in this study report show that the model is not able to describe sonidegib PK profiles in cancer patients on day 15.
    a. Submit your justification formally to the NDA whether the current data and the PBPK model allow prediction of the magnitude of sonidegib exposure change by concomitant use of strong CYP3A modulators in cancer patients, especially if higher sonidegib exposure observed in cancer patients is primarily due to lower hepatic metabolism.

b. Submit the following simulations, including the study reports, model files and other related excel files as listed below, formally to the NDA.

Simulate the effect of strong CYP3A inhibitor ketoconazole administered at a dose of 200 mg twice daily (b.i.d.) on steady state sonidegib PK (C_{max} and AUC within dosing interval) when sonidegib is administered at a dose of

i. 200 mg once daily (q.d.)
ii. 200 mg once every other day (q.o.d.)

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).

Please submit a formal amendment to NDA with your responses **by November 19, 2014**. Please email me a courtesy copy of the cover letter once your submission has been formally submitted.

If you have any questions, please feel free to call me.

Regards,

Anuja Patel, M.P.H.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-9022
Email: Anuja.Patel@fda.hhs.gov

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/s/

ANUJA PATEL
11/07/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205266

Novartis Pharmaceuticals Corporation
Attention: John A. Robinson, Ph.D.
Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Robinson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for "Odomzo (sonidegib), 200 mg capsules."

We also refer to your September 26, 2014, correspondence requesting an application orientation meeting to discuss Odomzo (sonidegib). Based on the statement of purpose, objectives, and proposed agenda, we will consider this an informal type C meeting. Meeting minutes will not be issued.

The meeting is scheduled as follows:

Date: Tuesday, November 18, 2014
Time: 12 Noon – 1:00 PM, EST
Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1415
Silver Spring, Maryland 20903

Please e-mail Anuja Patel a list of your meeting participants so that their names can be entered into our LobbyGuard system.

Please submit desk copies and/or slides to Anuja Patel at the following address:

Anuja Patel
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 1415
10903 New Hampshire Avenue
Silver Spring, Maryland
Use zip code **20903** *if shipping via United States Postal Service (USPS).*
Use zip code **20993** *if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

If you have any questions, please call me at (301) 796-9022.

Sincerely,

{See appended electronic signature page}

Anuja Patel, M.P.H.
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/

ANUJA PATEL
10/27/2014

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

Memorandum

DATE: October 17, 2014

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

SUBJECT: Designation of NDA application review status

Sponsor: Novartis Pharmaceuticals Corporation
Product: sonidegib
Proposed Indications:
Treatment of patients with locally advanced basal cell carcinoma (BCC) who are not amenable to curative surgery or radiation therapy
[redacted] (b) (4)

TO: NDA 205266

The review status of this file submitted as an original NDA is designated to be:

☒ Standard (10 Months) ☐ Priority (6 Months)

Novartis' Request
Novartis requested priority review "[redacted] (b) (4) thereby justifying a request for priority review as described in the 2013 FDA guidance *Expedited Programs for Serious conditions - Drugs and Biologics*."

[redacted] (b) (4)

(b) (4)

Review Designation
I am designating this as a standard review based on the absence of summary data supporting a conclusion that sonidegib would provide a significant improvement in safety or effectiveness over vismodegib.

Vismodegib received FDA approval (b) (4) The approval of vismodegib was based on demonstration of clinically important tumor shrinkage as evidenced by durable overall response rates (ORR) in patients with locally advanced (ORR 43%, median duration 7.6 months) or metastatic (ORR 30%, median duration of response 7.6 months) BCC. While all responses were partial responses in patients with metastatic BCC, there were 13 (20.6%) patients with complete responses and 14 (22.2%) patients with partial responses among those with locally advanced BCC. Vismodegib labeling identifies two items in Warnings and Precautions: embryofetal toxicity and avoidance of blood donation.

As described in FDA Guidance for Industry:Expedited Programs for Serious Conditions – Drugs and Biologics,[1] "an application for a drug will receive priority review designation if it is for a drug that treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness."

As stated in the Guidance, "significant improvement may be illustrated by the following examples:

- Evidence of increased effectiveness in treatment, prevention, or diagnosis of a condition
- Elimination or substantial reduction of a treatment-limiting adverse reaction
- Documented enhancement of patient compliance that is expected to lead to an improvement in serious outcomes

---

1 http://www fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf

- Evidence of safety and effectiveness in a new subpopulation

Generally, if there is an available therapy, sponsors should compare their investigational drug to the available therapy in clinical testing with an attempt to show superiority relating to either safety or effectiveness. Alternatively, sponsors could show the drug's ability to effectively treat patients who are unable to tolerate, or whose disease failed to respond to, available therapy or show that the drug can be used effectively with other critical agents that cannot be combined with available therapy."

While this application meets the first requirement, i.e., sonidegib treats a serious condition, the NDA does not meet the second requirement. Specifically, the efficacy of sonidegib was not directly compared with vismodegib so that minor differences in response rate or durability may be reflect differences between the two study populations rather than differences in efficacy. In addition, Novartis did not study sonidegib in a population that was intolerant of vismodegib nor does the application provide evidence of elimination or substantial reduction of a treatment-limiting adverse reaction of vismodegib. The Warnings and Precautions listed in the vismodegib labeling are also the same as proposed for the sonidegib label by Novartis.

{See appended electronic signature page}

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/s/

PATRICIA KEEGAN
10/17/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205266

NDA ACKNOWLEDGMENT

Novartis Pharmaceuticals Corporation
Attention: John A. Robinson, Ph.D.
Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Robinson:

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: Odomzo (sonidegib), 200 mg capsules

Date of Application: September 26, 2014

Date of Receipt: September 26, 2014

Our Reference Number: NDA 205266

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 November 25, 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) 796-9022.

Sincerely,

{See appended electronic signature page}

Anuja Patel, M.P.H.
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/

ANUJA PATEL
10/07/2014

Fahnbulleh, Frances

From: Fahnbulleh, Frances
Sent: Thursday, October 02, 2014 4:54 PM
To: 'john.robinson@novartis.com'
Subject: NDA 205266 sonidegib, Proposed Proprietary Name-Odomzo

Dear Mr. Robinson,
Reference is made to your NDA submission dated and received on September 26, 2014. Further reference is made to your request for Proprietary Name Review also included in the submission.

We note a discrepancy in the recommended dosage of sonidegib (proposed proprietary name, Odomzo) listed in the Request for Proprietary Name Review (PNR) [Module 1.12.4] and the proposed Prescribing Information (PI) [Module 1.14.1.3] that were included in your NDA submission on September 26, 2014.

According to the PNR request, the usual dose is [redacted] (b) (4); however, the proposed PI states, "The recommended dosage of ODOMZO is 200 mg taken orally once daily, [redacted] (b) (4)

Please clarify this discrepancy. What is the intended usual dose of sonidegib?

Kindly respond to this request by Monday, October 6, 2014.

Respectfully,

Frances Fahnbulleh, RPh, PharmD
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
CDER/FDA/WO22 , Rm#3471
Ph: 301-796-0942/ Fax 301-796-9906
email: Frances.Fahnbulleh@fda.hhs.gov

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Reference ID: 3638868

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/s/

FRANCES G FAHNBULLEH
10/02/2014
IR sent electronically via email.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 102961

ADVICE/INFORMATION REQUEST

Novartis Pharmaceutical Corporation
Attention: John Robinson, Ph.D.
Director, Drug Regulatory Affairs Oncology
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Robinson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Sonidegib (LDE225), 200mg capsules.

We refer to the April 15, 2014, pre-NDA meeting (under the Program) between representatives of Novartis and the FDA, and our May 14, 2014, meeting minutes for that meeting. We also refer to our September 8, 2014 Advice letter in response to your August 15, 2014, amendment containing a request for FDA's agreement to inclusion of 1) the BOLT 50-week updated safety and efficacy data with the NDA at the end of September 2014 and 2) a new BOLT clinical database cut-off for the 120 day safety update.

In addition, we refer to your September 9, 2014 amendment to your IND requesting clarification and addressing a typographical error to our September 8, 2014 letter.

Clarification regarding CLDE225A2201 Clinical Study Report (CSR)

1. Can the FDA please clarify/confirm that the 24 week CSR is acceptable for the NDA filing with the 50 week data presented as addendums to SCE and SCS but we will add an addendum to the CSR containing links to the SCS and SCE addendums?

   FDA Response: FDA confirms that it is acceptable that the BOLT A2201 clinical study report (CSR) include the primary analysis of 24 week data (data cut-off date June 28, 2013) and that the 50 week updated data (with complete datasets encompassing information through the latest data cut-off) will be provided as addenda to the Summary of Clinical Efficacy (SCE) and Summary of Clinical Safety (SCS). FDA confirms that Novartis' proposal to provide an addendum to the CSR containing functional hyperlinks to the relevant SCS and SCE addenda, rather than to provide all information within the CSR addendum, is acceptable.

Correction on page 3 typographical errors regarding 120 day safety update

2. Novartis believes there were two typographical errors on page 3 of the FDA response dated September 8, 2014 which are bolded and underlined below:

   Novartis September 10, 2014, submission states: "Listings of new serious adverse events (SAEs), deaths on study, and adverse events of special interest (e.g., rhabdomyolysis) occurring from **December 13, 2014**, through July 11, 2014 (BOLT study) **or** since August 31, 2014 through December 2014 (approximately 3 months after planned submission of the NDA) for all other ongoing studies"

   Novartis believes the date in these two paragraphs should be **"December 31, 2013"** through July 11, 2014 and the **"or"** should be **"and"** because the safety data i.e. listings of new serious adverse events (SAEs), deaths on study, and adverse events of special interest (e.g., rhabdomyolysis) from December 31, 2013 through July 11, 2014 will be based on the BOLT pivotal study clinical database, while the safety data from August 31, 2014 through December 2014 will include SAEs and deaths (and adverse events of special interest only if reported as SAEs) and will be obtained from only the Novartis SAE ARGUS database (for all ongoing studies) and would be the most current safety data.

   Please confirm if you agree with these corrections?

   FDA Response: FDA acknowledges the typographical errors for the dates that are bolded above. FDA intended to use the word "or" to differentiate the cut off dates for the BOLT study versus other studies. FDA confirms that new information from all studies should be provided in the proposed safety update. FDA reiterates that this updated safety information should include a revised risk assessment based on this new information.

If you have any questions, contact Anuja Patel, Senior Regulatory Project Manager, at (301) 796-9022.

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

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/s/

PATRICIA KEEGAN
09/13/2014

Patel, Anuja

From: Patel, Anuja
Sent: Wednesday, September 10, 2014 1:16 PM
To: 'Robinson, John'
Subject: FDA Request for Formal Submission: LDE225 IND102961 Novartis revised proposal for submitting updated safety and efficacy data with the NDA and the composition of the 120 day safety update

Importance: High

Dear Dr. Robinson,

We refer to our September 8, 2014 Advice letter and to your September 9, 2014 email communication requesting clarification on our letter. In addition, I am acknowledging receipt of your voice message from this morning and am writing to you in follow-up to my voice message which I left today at approximately 1:10 PM, EST.

We are currently reviewing your September 9, 2014 email communication however we request that you formally your September 9, 2014 e-mail communication to your IND by close of business today, September 10, 2014.

Please notify me when you have formally submitted to your IND and acknowledge receipt of this email.

Regards,
Anuja

Anuja Patel, MPH
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
White Oak Complex, Bldg. 22, Room 2365
10903 New Hampshire Avenue
Silver Spring, MD 20993
☎301.796.9022 (phone)
301.796.9849 (fax)
anuja.patel@fda.hhs.gov (email)

From: Robinson, John [mailto:john.robinson@novartis.com]
Sent: Tuesday, September 09, 2014 4:04 PM
To: Patel, Anuja
Subject: RE: FDA Advice Letter: LDE225 IND102961 Novartis revised proposal for submitting updated safety and efficacy data with the NDA and the composition of the 120 day safety update

Hello Anuja,

Thank you for the Agency's response.

I would ask for one point of clarification on page 2 of the response, the FDA makes the statement:

"In addition, please submit (or provide functioning hyperlinks to) the relevant

Reference ID: 3625182

sections of the addenda as an addendum to the final Clinical Study Report (CSR) for the BOLT trial [Protocol CLDE225A2201 (2201)] to ensure that the CSR for the BOLT trial contains all the relevant information"

It is not clear whether the FDA is expecting that the CSR will also be updated to include this 50 week data. As discussed at the Pre-NDA meeting Novartis's intent was to provide the BOLT A2201 pivotal CSR with the primary analysis of 24 week data and the 50 week updated data will be provided only as addendums to the SCE and SCS (with datasets). The SCE and SCS addendums are written such that there is a side by side comparison between the 24 week and 50 week results, however Novartis can provide an addendum to the CSR containing links to the SCS and SCE addendums to easily direct the reviewer to those results.

Can the FDA please clarify/confirm that the 24 week CSR is acceptable for the NDA filing with the 50 week data presented as addendums to SCE and SCS but we will add an addendum to the CSR containing links to the SCS and SCE addendums ?

Also I believe there is some typos on page 3 which I have highlighted in yellow below:

"Listings of new serious adverse events (SAEs), deaths on study, and adverse events of special interest (e.g., rhabdomyolysis) occurring from December 13, 2014, through July 11, 2014 (BOLT study) or since August 31, 2014 through December 2014 (approximately 3 months after planned submission of the NDA) for all other ongoing studies"

"A narrative summary of the updated safety information occurring from December 13, 2014, through July 11, 2014 (BOLT study) or through December 2014 (approximately 3 months after the planned NDA submission date) for all other ongoing studies. FDA notes that this updated safety information should include a revised risk assessment based on this new information."

I believe this date should be "**December 31, 2013"** through July 11, 2014 and the "or" should be "and" because the safety data i.e. listings of new serious adverse events (SAEs), deaths on study, and adverse events of special interest (e.g., rhabdomyolysis) from December 31, 2013 through July 11, 2014 will be based on the BOLT pivotal study clinical database, while the safety data from August 31, 2014 through December 2014 will include SAEs and deaths (and adverse events of special interest only if reported as SAEs) and will be obtained from only the Novartis SAE ARGUS database (for all ongoing studies) and would be the most current safety data. **Please confirm these corrections for that information highlighted in yellow?**

Best Regards,
John

John Robinson, PhD
Director Reg Affairs Oncology
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080
USA

Phone +1 862 7788786
Fax +1 9737818265
john.robinson@novartis.com
www.novartis.com

Reference ID: 3625182

From: Patel, Anuja [mailto:Anuja.Patel@fda.hhs.gov]
Sent: Monday, September 08, 2014 9:06 PM
To: Robinson, John
Subject: FDA Advice Letter: LDE225 IND102961 Novartis revised proposal for submitting updated safety and efficacy data with the NDA and the composition of the 120 day safety update
Importance: High

Dear Dr. Robinson,

We refer to the April 15, 2014, pre-NDA meeting (under the Program) between representatives of Novartis and the FDA, and our May 14, 2014, meeting minutes for that meeting.

We also refer to your August 15, 2014, amendment containing a request for FDA's agreement with inclusion of 1) the BOLT 50-week updated safety and efficacy data with the NDA at the end of September 2014 and 2) a new BOLT clinical database cut-off for the 120 day safety update.

Attached is a courtesy copy of our letter in response to your submission. A formal copy of this letter will be sent to you via postal mail.

Please confirm receipt and provide an update this week as to when you anticipate submitting your NDA application for sonidegib.

Thank you!
Anuja

Anuja Patel, MPH
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
White Oak Complex, Bldg. 22, Room 2365
10903 New Hampshire Avenue
Silver Spring, MD 20993
☎301.796.9022 (phone)
301.796.9849 (fax)
anuja.patel@fda.hhs.gov (email)

Reference ID: 3625182

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/s/

ANUJA PATEL
09/10/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 102961

ADVICE/INFORMATION REQUEST

Novartis Pharmaceutical Corporation
Attention: John Robinson, Ph.D.
Director, Drug Regulatory Affairs Oncology
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Robinson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Sonidegib (LDE225), 200mg capsules.

We refer to the April 15, 2014, pre-NDA meeting (under the Program) between representatives of Novartis and the FDA, and our May 14, 2014, meeting minutes for that meeting.

We also refer to your August 15, 2014, amendment containing a request for FDA's agreement with inclusion of 1) the BOLT 50-week updated safety and efficacy data with the NDA at the end of September 2014 and 2) a new BOLT clinical database cut-off for the 120 day safety update.

We will not amend the meeting minutes and will not issue new agreements under the PDUFA V program. However, we provide the following responses regarding the acceptability of the proposals to submit additional information in the planned NDA.

<u>Submission of 50 week updated safety and efficacy data</u>

Question 1: Novartis is requesting agreement to submit the BOLT 50 week updated safety and efficacy data with the NDA at the end of September instead of at day 120 post NDA filing. The updates would be in the form of addendums to the SCS and SCE (with a single proposed labeling document) as originally agreed to during the April 15, 2014 pre-NDA meeting. Listings of SAEs from the ARGUS SAE database (August 31, 2014 data cut-off) for all other ongoing studies with text summarizing the updated safety information (appendix to the SCS addendum) will also be included. Does the Agency agree?

FDA Response: We agree to your proposal to submit the following additional information in the original NDA submission:

- Addenda to the Summary of Clinical Safety (SCS) and the Summary of Clinical Efficacy (SCE) containing narrative descriptions of the updated summary results for safety and efficacy, respectively, from the BOLT study incorporating new information obtained after the data cut-off date of the SCS and SCE (June 28, 3013) through the data cut-off date of December 31, 2013 (week 50);

- Safety and efficacy datasets that contain **all** data obtained through the data cut-off date of December 31, 2013, that support, and will allow FDA to verify, the updated summary information described in these addenda; and

- An appendix to the SCS addendum containing (1) listings of new serious adverse events and adverse events of interest occurring since the data cut-off date for the SCS through the August 31, 2014 data cut-off for all ongoing studies of sonedigib (other than the BOLT study) and (2) text summarizing this new safety information. FDA notes that this updated safety information should include a revised risk assessment based on this new information.

In addition, please submit (or provide functioning hyperlinks to) the relevant sections of the addenda as an addendum to the final Clinical Study Report (CSR) for the BOLT trial [Protocol CLDE225A2201 (2201)] to ensure that the CSR for the BOLT trial contains all the relevant information.

<u>Composition of Day 120 Safety Update</u>

Question 2: The Day 120 Safety Update would now include safety information from the BOLT clinical database (data cut-off July 11, 2014-78 week updated data) as an addendum to the SCS, and listings of SAEs from the ARGUS SAE database (data cut-off 1 month before the 120 day submission) for all other ongoing studies with text summarizing the updated safety information (appendix to the SCS addendum). Does the Agency agree?

FDA Response: Your proposal to submit the following information in the 120-day Safety Update is acceptable

- Listings of new serious adverse events (SAEs), deaths on study, and adverse events of special interest (e.g., rhabdomyolysis) occurring from December 13, 2014, through July 11, 2014 (BOLT study) or since August 31, 2014 through December 2014 (approximately 3 months after planned submission of the NDA) for all other ongoing studies

- A narrative summary of the updated safety information occurring from December 13, 2014, through July 11, 2014 (BOLT study) or through December 2014 (approximately 3 months after the planned NDA submission date) for all other ongoing studies. FDA notes that this updated safety information should include a revised risk assessment based on this new information.

If you have any questions, contact Anuja Patel, Senior Regulatory Project Manager, at (301) 796-9022.

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

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/s/

PATRICIA KEEGAN
09/08/2014

Patel, Anuja

From: Patel, Anuja
Sent: Wednesday, August 13, 2014 11:12 PM
To: 'Robinson, John'
Subject: FDA Request for Formal Submission: LDE225 IND102961 Novartis revised proposal for submitting updated safety and efficacy data with the NDA and the composition of the 120 day safety update

Importance: High

Dear Dr. Robinson,

We refer to your e-mail communication sent August 13, 2014 informing the FDA that Novartis plans to submit the LDE225 NDA application for advanced Basal Cell Carcinoma at the end of September 2014. In that e-mail communication, you also stated that Novartis would like to reach an agreement with the FDA on a revised proposal for submitting updated safety and efficacy data with the NDA and the composition of the 120 day safety update.

We have the following response to your e-mail communication:

- Submit formally to your IND 102961 no later than close of business, Friday, August 15, 2014, your revised proposal for submitting updated safety and efficacy data with the NDA and the composition of the 120 day safety update.
- Please submit the information requested above as General Correspondence/Clinical Information and Meeting/Other. In your cover letter, please reference our April 15, 2014 p-NDA meeting, your August 13, 2014 e-mail communication, and our August 13, 2014 response to your communication. Upon receipt of your formal submission, we will review your proposal and will follow up with you soon.

Please acknowledge receipt of this e-mail and feel free to contact me if you have any questions.

Thank you,
Anuja

Anuja Patel, MPH
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
White Oak Complex, Bldg. 22, Room 2365
10903 New Hampshire Avenue
Silver Spring, MD 20993
☎301.796.9022 (phone)
301.796.9849 (fax)
anuja.patel@fda.hhs.gov (email)

From: Robinson, John [mailto:john.robinson@novartis.com]
Sent: Wednesday, August 13, 2014 9:29 AM
To: Patel, Anuja
Subject: RE: LDE225 IND102961 response to phone request regarding NDA submission

Hello Anuja,

Reference ID: 3609978

As you stated, Novartis has received the remaining advice from the FDA on Monday August 4th. Based on this information Novartis plans to submit the LDE225 NDA for advanced Basal Cell Carcinoma at the end of September 2014.

In preparation for submitting the NDA, considering there has been a significant delay from the original planned filing date, Novartis would like to reach agreement with the FDA on a revised proposal for submitting updated safety and efficacy data with the NDA and the composition of the 120 day safety update.

Specifically, Novartis had agreed in the April 15th Pre-NDA meeting to provide a safety and efficacy update for the pivotal BOLT study based on a **31-Dec 2013 cut-off (50 week updated data)** and SAEs for all other ongoing studies (with text summarizing the updated safety information) with an ARGUS SAE database cut-off approximately 1 month prior to the 120 day submission. As also agreed to, revised labeling along with an addendum to the SCS and SCE would be provided. (see FDA final meeting minutes attached)

Due to the delay in the filing, the safety and efficacy update from the pivotal BOLT study (**50 wk data; 31- Dec 2013 cut-off**) is now available, therefore we are requesting agreement to submit the BOLT 50 wk updated safety and efficacy data with the NDA at the end of September. The updates would be in the form of addendums to the SCS and SCE as originally agreed to (with a single proposed label document). Then on day 120 the safety update would include safety from the BOLT clinical database (**data cut-off July 11, 2014- 78 week data**) as an addendum to the SCS and safety data for all other ongoing studies from the ARGUS SAE safety database (with a text summary) having a data cut-off approximately 1 month before that submission.

I would kindly ask if you would review this proposal and let me know as soon as possible if the Agency agrees.

Best Regards,
John

John Robinson, PhD
Director Reg Affairs Oncology
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080
USA

Phone +1 862 7788786
Fax +1 9737818265
john.robinson@novartis.com
www.novartis.com

Reference ID: 3609978

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/s/

ANUJA PATEL
08/13/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 102961

GENERAL ADVICE

Novartis Pharmaceuticals Corporation
Attention: Joyce Ann Sino, PhD
Director, Global Regulatory CMC- Oncology
One Health Plaza, Bldg. 339 Rm 1151
East Hanover, NJ 07936

Dear Dr. Sinno:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Sonidegib (LDE225), 200mg Capsules.

We also refer to your June 30, 2014, CMC amendment, that provide the FDA with supportive CMC information based on Type B meeting (CMC meeting) held on June 18, 2014.

We have reviewed the referenced material and have the following comments:

1. ***Question 1***:
   Does the Agency agree that the drug substance stability data package as outlined in Table 1-1 of the attachment is adequate for filing of the NDA and sufficient to support (b) (4) (b) (4) for drug substance manufactured at both (b) (4) and Novartis Pharma Schweizerhalle AG?

   FDA Response to Question 1:
   Under table 1-1, the stability studies to be submitted at the time of NDA filing are not sufficient to support (b) (4) for the proposed drug substance manufactured at the (b) (4). However, the submitted data and information for the (b) (4) site is sufficient for filing the NDA.

2. ***Question 2:***
   Does the Agency agree that additional stability data for drug substance manufactured at (b) (4) and Novartis Pharma Schweizerhalle AG may be submitted prior to midcycle review without an extension of the review period?

   FDA Response to Question 2:
   No, refer to our response in question 1.

3. ***Question 3***:
   Does the Agency agree that the drug product stability data package as outlined in Table 2-1 of the attachment is adequate for filing of the NDA (b) (4)

All drug product batches on registration and supportive stability studies were manufactured at Patheon, Inc. (intended commercial site) using (b) (4) drug substance. Novartis will provide a post-approval commitment to complete stability studies on commercial-scale drug product batches made with drug substance from each commercial manufacturing site.

FDA Response to Question 3:
Refer to our response to Question 1. The stability data packages for (b) (4) manufactured with drug substance manufactured by (b) (4) will be acceptable for filing the NDA. Adequacy of the data will be determined at the time of NDA submission.

4. ***Question 4:***
Does the Agency agree that additional stability data for drug product manufactured with drug substance from (b) (4) and (b) (4) may be submitted prior to mid-cycle review without an extension of the review period?

FDA Response to Question 4:
No, refer to our response to questions 1 and 3.

Additional Comments:

5. This application for sonedigib, a new molecular entity, will be subject to "the Program" under PDUFA V. Therefore, you may reach agreement with the FDA on a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

During the June 18, 2014 meeting, there were no agreements on late submission of any component of the application. However, based on your June 30, 2014 amendment to this IND, you have requested to submit updated stability data on drug product and drug substance as a late submission.

We agree that this information is considered a minor application component that can be submitted within 30 days after the submission of the NDA.

6. With the exception of the inclusion of information on the (b) (4) we confirm our agreement that contents of the NDA as proposed in the meeting briefing package constitute a complete Quality component of the proposed NDA.

7. All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

If you have any questions, call Teicher Agosto, Regulatory Project Manager, at (240) 402-3777.

Sincerely,

{See appended electronic signature page}

Ali Al Hakim, Ph.D.
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
08/01/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 102961

GENERAL ADVICE

Novartis Pharmaceuticals Corporation
Attention: Joyce Ann Sino, PhD
Director, Global Regulatory CMC- Oncology
One Health Plaza, Bldg. 339 Rm 1151
East Hanover, NJ 07936

Dear Dr. Sinno:
Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Sonidegib (LDE225), 200mg Capsules.

We also refer to your June 18, 2014, CMC amendment, that provide the FDA with supportive CMC information based on Type B meeting (CMC meeting) held on June 18, 2014.

We have reviewed the referenced material and have the following comments:

Regarding NDA section 3.2.P.5:
(c) As [redacted] (b) (4) is a known carcinogen, we recommend that the specification [redacted] (b) (4) should include a test and an acceptance criterion for this compound.

Additional FDA comment:
The CMC information in amendments S-132 (dated 05/08/12) and S-330 (dated 04/28/14) indicates that [redacted] (b) (4) is a known carcinogen [redacted] (b) (4) [redacted] Because [redacted] (b) (4) is a known carcinogen, its presence must be controlled. The submitted data showing that, to date, [redacted] (b) (4) has been observed in [redacted] (b) (4) at levels below [redacted] (b) (4) ppm is not sufficient to assure that [redacted] (b) (4) will not be present in future lots [redacted] (b) (4) We see two possible options for the control of [redacted] (b) (4) One option would be [redacted] (b) (4) [redacted] Amendments S-132 and S-330 state that [redacted] (b) (4) ppm is a safe limit for [redacted] (b) (4) This criterion would be evaluated at the time of NDA submission. A second option would be [redacted] (b) (4) [redacted]

If you have any questions, call Teicher Agosto, Regulatory Project Manager, at (240) 402-3777.

Sincerely,

{See appended electronic signature page}

Ali Al Hakim, Ph.D.
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
07/21/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 102961

MEETING MINUTES

Novartis Pharmaceuticals Corporation
Attention: Joyce Ann Sino, PhD
Director, Global Regulatory CMC- Oncology
One Health Plaza, Bldg. 339 Rm 1151
East Hanover, NJ 07936

Dear Dr. Sinno:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Sonidegib (LDE225), 200mg Capsules.

We also refer to the face to face meeting between representatives of your firm and the FDA on June 18, 2014. The purpose of the meeting was to obtain the Agency's advice and agreement on the adequacy of the proposed content of CMC information for the NDA submission.

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 Teicher Agosto, Regulatory Project Manager at (240) 402-3777.

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

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

Meeting Date and Time: Wednesday, June 18, 2014, 12:30 – 1:30 pm EST
Meeting Location: 10903 New Hampshire Avenue
White Oak Building, Conference Room:
Silver Spring, Maryland 20903

Application Number: IND 102961
Product Name: Sonidegib (LDE225)
Indication: treatment of patients with locally advanced basal cell carcinoma (laBCC) (b) (4)

Sponsor/Applicant Name: Novartis Pharmaceuticals Corp.

Meeting Chair: Ali Al Hakim, Branch Chief
Meeting Recorder: Teicher Agosto, Regulatory Project Manager

FDA ATTENDEES
Ali Al Hakim, PhD, Branch Chief, ONDQA
William Adams, Ph.D., CMC Reviewer, ONDQA
Robert Wittorf, PharmD, Compliance Officer CDER/OC/OMPQ/DGMPA,
Norma Griffin, Regulatory Health Project Manager, DOP 2, OHOP
Teicher Agosto, PharmD, RPh, Regulatory Project Manager, ONDQA

SPONSOR ATTENDEES
Neil Gallagher MD, PhD Global Program Head, Oncology Clinical Development
Diane Zezza, PhD, Global Head, Regulatory Affairs - CMC
Shanti Ganeshan, PhD, North America Region Head - Drug Regulatory Affairs
Christoph Bucher, PhD, Project Leader, Chemical and Analytical Development, Technical R &D
Nancy Turner, Director, Preclinical Safety
John Robinson PhD, Director, Oncology Drug Regulatory Affairs
Christopher Ziltener, Project Team Leader, Technical Research and Development
Joyce Ann Sinno PhD, Director, Senior Regulatory Expert Global Regulatory CMC Oncology

1.0 BACKGROUND

Sonidegib (LDE225) is an orally bioavailable small molecule inhibitor of the Hh signaling pathway. Novartis suggests that, sonidegib is a potential systemic treatment option for patients with locally advanced (b) (4) basal cell carcinoma (BCC).

Novartis submitted a Type B meeting request to the FDA on April 16, 2014. The purpose of this meeting is to discuss the adequacy of the proposed content of CMC information for the NDA submission. A Meeting Briefing Package was received on April 28, 2014. A Meeting Granted letter was mailed to Novartis on May 7, 2014. Meeting preliminary comments were sent to Novartis on June 13, 2014. The sponsor sent additional information to be discussed during the meeting on June 18, 2014, see attached.

2.0 DISCUSSION

Question 1:

Does the Agency agree with the content of Quality Module 3 as outlined in the electronic Common Technical Document (eCTD) Table of Contents and therefore constitutes a complete NDA?

FDA Response to Question 1:

The listed eCTD sections are acceptable in that all sections which provide CMC information are included. We have the following comments regarding the description of CMC information to be included in specific sections and the background information:

Regarding the proposed Regulatory Starting Materials
The agency does not agree with your proposal (b) (4) Based on the synthesis, impurity information and proposed controls provided in the meeting package, we recommend that (b) (4) be considered (b) (4) We recommend that you propose (b) (4)

Regarding NDA section 3.2.S.2:
(a) The NDA should specify whether a site for (b) (4) is to be assigned to material from a specific manufacturing site; and specify the tests to be performed at each proposed control site.
(b) The adequacy of the process description including process parameters and in process controls will be addressed during the NDA evaluation.

Regarding NDA section 3.2.S.3:
(a) The NDA should address (b) (4)

Reference ID: 3594671

(b) The test results from the impurity carry-over studies should be sufficient to support the proposed specifications for (b) (4) drug substance. The analytical methods used in these studies should be briefly described, and their sensitivity and selectivity provided.
(c) The submitted genotoxic impurity spiking study information lacks sufficient detail to support a conclusion. Provide the details of these studies in the NDA for evaluation. This study should include a description of the analytical methods; sensitivity and selectivity for the analytical methods should be indicated; and a justification for the proposed acceptance criteria should be included.

Regarding NDA section 3.2.S.4:
(a) The NDA should include method descriptions and validation studies for each of the proposed tests performed at each proposed control site.
(b) The specification for (b) (4) submitted in amendment S-190 (dated 22 Feb 2013) appears to be acceptable in that it includes testing for identity, purity and assay. Final evaluation of the tests, analytical methods and acceptance criteria will be made at the time of NDA review based on supporting data and information in the NDA.
(c) The batch analysis data should include a brief description of the analytical methods used to obtain each data point. Selectivity and sensitivity for each analytical method for purity should be indicated.

Regarding NDA section 3.2.S.7:
(a) Sufficient stability data from each of the proposed manufacturing sites should be provided in the NDA to support a unified storage condition and retest period.
(b) Appropriate retest period for the drug substance will be granted based on the amount and the nature of the stability data that will be provided in the NDA.

Regarding NDA section 3.2.P.5:
(a) Method descriptions and validation studies should be provided for analytical procedures used at each of the proposed control sites.
(b) The NDA should include a detailed description of the differences between the clinical, registration and batches submitted in the NDA.
(c) Test results from batches made at the proposed drug product manufacturing site using the registration formulation; the registration manufacturing process; and drug substance from both of the proposed suppliers will be considered as primary batches. All other data will be evaluated as supportive information.
(c) As (b) (4) is a known carcinogen, we recommend that the specification for (b) (4) should include a test and an acceptance criterion for this compound.
(d) The specification for 200mg hard gelatin capsules submitted in amendment S-268 (dated 25 Nov 2013) appears to be acceptable in that it includes testing for identity, purity, assay, uniformity of dosage units, and drug release. Final evaluation of the tests, analytical methods and acceptance criteria will be made at the time of NDA review based on supporting data and information provided in the NDA.
(e) The batch analysis data should include a brief description of the analytical methods used to obtain each data point with selectivity and sensitivity specified for the purity method(s).

Regarding NDA section 3.2.P.7:
(a) Since the drug product (b) (4) of each of the proposed blister pack and bottle configurations should be provided in the NDA.

Reference ID: 3594671

Regarding NDA section 3.2.P.8:
(a) The primary stability studies should include data from batches made with drug substance from both proposed manufacturers; made at the proposed drug product manufacturing site and using each of the proposed packaging configurations. All other study data will be evaluated as supportive information.
(b) Sufficient stability data should be included in the NDA [redacted] (b) (4) for all the packaging configurations.
(c) Appropriate expiry dating for the drug product will be granted based on the amount and the nature of the stability data that will be provided in the NDA.

Additional Comments

(a) Please provide the pharmaceutical development studies which substantiate the intended commercial manufacturing process parameters for both drug substance and drug product.
(b) Please list manufacturing facilities used to manufacture the drug substance [redacted] (b) (4) Please include drug substance and drug product facilities intended for commercial manufacturing. If the sites are the same for both, please indicate this. Also, please outline any difference in processes pertaining to the drug product and drug substance, if any, between manufacturing facilities.
(c)Please list the sites in which release and stability testing of both the drug substance and drug product will be performed. Please include name, address, establishment number, and contact information.

Meeting Discussion:
Novartis agrees to [redacted] (b) (4) The agency stated that the [redacted] (b) (4) needs to be validated, but that validation does not need to be completed at the time of NDA submission and is not a requirement for pre-approval inspection. and that launch supplies already manufactured using [redacted] (b) (4) are acceptable for commercial use [redacted] (b) (4)

Additional Comments:

- Please list the sites in which release and stability testing of both the drug substance and drug product will be performed. Please include name, address, establishment number, and contact information.

  Meeting Discussion:
  Novartis agreed to summarize the stability data that would be provided at submission and the stability data that could be provided by mid-cycle review, so that agreement can be reached as to the stability data that may be submitted during review.

- Novartis agreed to provide the site and contact information on the suppliers (b) (4) [redacted] before the NDA submission.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There are no specific issues requiring further discussion at this time.

Reference ID: 3594671

4.0 ACTION ITEMS

Novartis request feedback on the drug substance and drug product stability package, in order to finalize the content of Module 3 for submission. The agency agreed to provide feedback as an amendment.

5.0 ATTACHMENTS AND HANDOUTS

Handout provided by Novartis on June 18, 2014, see attached.

18 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this

Reference ID: 3594671

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/s/

ALI H AL HAKIM
07/17/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 102961

MEETING MINUTES

Novartis Pharmaceutical Corporation
Attention: John Robinson, Ph.D.
Director, Drug Regulatory Affairs Oncology
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Robinson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for "sonidegib (LDE225)."

We also refer to the meeting between representatives of your firm and the FDA on April 15, 2014. The purpose of the meeting was to discuss and reach agreement that the data provided from Study CLDE225A2201, entitled "A phase II, randomized, double-blind study of efficacy and safety of two dose levels of LDE225, 200 mg and 800 mg, in patients with locally advanced basal cell carcinoma (laBCC) or metastatic basal cell carcinoma (mBCC)," is sufficient to support a new drug application (NDA) for sonidegib for the proposed indication for the treatment of patients with locally advanced basal cell carcinoma (laBCC) (b) (4)

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-9022.

Sincerely,

{See appended electronic signature page}

Anuja Patel M.P.H.
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:	Tuesday, April 15, 2014 from 10:00 A.M. to 11:30 A.M., EST
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1315 Silver Spring, Maryland 20903
Application Number:	IND 102961
Product Name:	sonidegib (LDE225)
Proposed Indication:	treatment of patients with locally advanced basal cell carcinoma (laBCC) [redacted] (b) (4)
Sponsor/Applicant Name:	Novartis Pharmaceuticals Corporation
Meeting Chair:	Suzanne Demko
Meeting Recorder:	Anuja Patel

FDA ATTENDEES

Patricia Keegan, Director, Division of Oncology Products 2 (DOP 2), OHOP
Jeff Summers, Deputy Division Director, Safety, DOP 2, OHOP
Suzanne Demko, Clinical Team Leader, DOP 2, OHOP
Kaushik Shastri, Clinical Reviewer, DOP 2, OHOP, CDER
Monica Hughes, Chief, Project Manager Staff, DOP 2, OHOP
Anuja Patel, Regulatory Health Project Manager, DOP 2, OHOP
Rajeshwari Sridhara, Director, Division of Biometrics V
Huanyu (Jade) Chen, Statistical Reviewer
Lillian Zhang, Clinical Pharmacology Acting Team Leader, DCPV
Xianhua (Walt) Cao, Clinical Pharmacology Reviewer, DCPV
Whitney Helms, Pharmacology/Toxicology Team Leader, DHOT
Ali Al Hakim, Chemistry Branch Chief, ONDQA
William Adams, Chemistry Team Leader, ONDQA
Naomi Redd, DRISK Reviewer, OSE

EASTERN RESEARCH GROUP ATTENDEES

Patrick J. Zhou, Independent Assessor
Uchechukwu Chimeh, Independent Assessor

SPONSOR ATTENDEES

Neil Gallagher MD, PhD Global Program Head, Oncology Clinical Development
Dalila Sellami MD, Global Clinical Program Head, Oncology Clinical Development
Eunju Hurh PhD, Senior Fellow, Oncology Clinical Pharmacology
Nancy Turner PhD, Director, Preclinical Safety
Kalyanee Appanna PhD, Executive Director Biostatistics, Oncology
Gabriela Gruia SVP & Global Head, Oncology Drug Regulatory Affairs
Sven Gogov MD, Global Clinical Leader, Oncology Clinical Development
Shanthi Ganeshan PhD, NA Region Head, Oncology Drug Regulatory Affairs
Matthias Jauslin PhD, Global Program Regulatory Director, Oncology Drug Regulatory Affairs
John Robinson PhD, Director, Oncology Drug Regulatory Affairs
Mike Levine, MD, Brand Safety Leader, Integrated Medical Safety, Oncology
Lily Zhao, Sr. Associate Director Biostatistics, Oncology
Peter Berry, Sr. Director, Submission Management, Oncology

1.0 BACKGROUND

Sonidegib (LDE225) is an orally bioavailable small molecule inhibitor of the hedgehog (Hh) signaling pathway. Novartis suggests that, sonidegib is a potential systemic treatment option for patients with locally advanced (la BCC) (b) (4)

Purpose

The objective of the pre-NDA meeting identified by Novartis is to obtain agreement between Novartis and the FDA on whether the available data will support the filing of a NDA submission.

As this meeting is considered also to be a pre-submission meeting for a new molecular entity, the forthcoming application will be subject to "the Program" under PDUFA V. Therefore, the purpose of this meeting is also to reach agreement between Novartis and the FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions.

Novartis' Proposed Indication

Sonidegib is indicated for the treatment of patients with:

- Locally advanced basal cell carcinoma (BCC) who are not amenable to curative surgery or radiation therapy

(b) (4)

Reference ID: 3506369

Regulatory Timeline

- On June 9, 2011, an End of Phase 1 (EoP 1) meeting was held with Division of Drug Oncology Products (now DOP 1) to discuss the study design (the choice of a comparator arm, sonidigib dose, patient population, and statistical aspects) of the planned randomized double-blind study intended to support a marketing application for the treatment of basal cell carcinoma, CLDE225A2201 (A2201) entitled, "A Phase II, randomized double-blind study of efficacy and safety of two dose levels of LDE225 in patients with locally advanced or metastatic basal cell carcinoma." In addition, Novartis sought agreement on the proposed clinical pharmacology studies to be conducted to support a future NDA submission for LDE225. .

- (b) (4)

- On June 5, 2012, a Type C teleconference was held between Novartis and Office of New Drug Quality Assessment to discuss the proposed starting materials and control strategy for genotoxic impurities in LDE225 drug substance. FDA's June 15, 2012, final meeting minutes stated that the proposed approaches described in the May 8, 2012, meeting briefing document appeared acceptable. However, the meeting minutes requested that any changes in process be reported to the NDA and that the adequacy of the proposals described would be determined at the time of NDA review.

- On February 13, 2013, Novartis submitted a Type C meeting request to discuss the planned analyses from the LDE225 development program in preparation for a planned NDA submission. FDA denied the meeting on March 6, 2013, as FDA deemed the request to be premature. FDA requested that Novartis resubmit their meeting request as a Type B meeting when the high-level data from the trial intended to support a regulatory application was available.

- On April 3, 2013, Novartis submitted a request for written feedback from FDA on the development program for sonidigib in basal cell carcinoma. On July 8, 2013, FDA issued a written response to the April 3, 2013, submission, informing Novartis that there was insufficient information provided in the April 3, 2013, submission to determine whether Study A2201 had demonstrated substantial evidence of a treatment effect on a surrogate endpoint or of an effect that is a measure of direct clinical benefit, sufficient to support filing of the proposed NDA. In addition, FDA informed Novartis that there was

Reference ID: 3506369

inadequate information to determine whether the safety database was adequate to characterize serious risks and describe the adverse reaction profile in sufficient detail in product labeling for (b) (4) the 200 mg (b) (4) sonidigib daily dosage regimen.

- On June 12, 2013, Novartis submitted a revised Protocol A2201 (version 5). On August 2, 2013, FDA provided clinical comments via electronic mail (e-mail) advising Novartis that the proposed revisions to the response criteria, specifically the revisions regarding (b) (4) were not acceptable and could alter the acceptability of these data to support labeling claims.

- On August 8, 2013, an informal (non-PDUFA) teleconference was held between FDA and Novartis to discuss FDA's comments conveyed on August 2, 2013 regarding Protocol A2201, version 5, submitted June 12, 2013. During the teleconference, FDA informed Novartis that the provision in amendment 5 of the protocol (b) (4) is not acceptable. FDA strongly recommended that Novartis further amend Protocol A2201 to make it clear that response assessments will be harmonized to include evaluation of the same target lesions by each modality included in the composite assessment plan, and that all versions (current and future) of Protocol A2201 ensure that, for patients with locally advanced basal cell carcinoma, a composite overall response assessment for each target lesion incorporates photographic, MRI and histological evaluation

  The following agreements were made during the teleconference:

  - Novartis will revise the protocol to clarify that for patients with laBCC assessed with all modalities (photo, MRI and histology) the same lesion has been evaluated, i.e. surface component (by photo and biopsy), sub-dermal component (by MRI and biopsy, where practicable);
  - Novartis would update Appendix 2, table 3-1 to capture all possible assessment scenarios for tumor response;
  - Rather than withdrawing Protocol version 5, Novartis agreed to submit a revised protocol (version 6) to supersede version 5 for clarity, to address FDA's concerns and to propose a plan for integrated evaluation of lesions using the three modalities; and
  - FDA agreed to review and provide comments on the draft of version 6 of the protocol prior to its official submission to the IND.

- On August 19, 2013, FDA issued a letter informing Novartis that their proposed proprietary name "ODOMZO" was conditionally acceptable.

- On October 1, 2013, Novartis submitted a proposed draft, revised Protocol A2201 (version 6), which provided additional clarifications and a plan for an integrated review of photo, MRI, and histology data by an independent oncologist for patients with laBCC.

Reference ID: 3506369

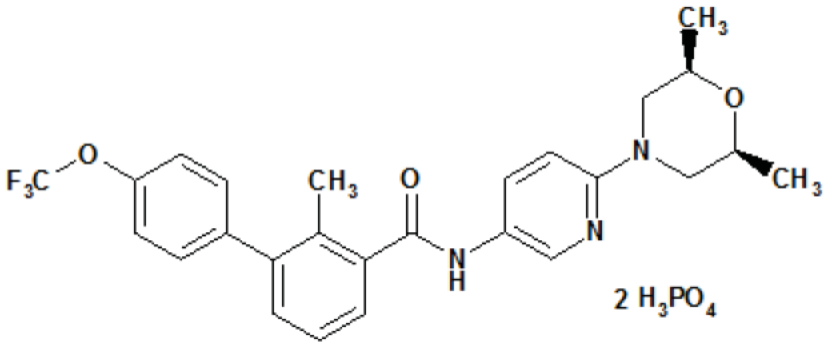
As requested by Novartis, FDA provided written comments on November 7, 2013, in an advice information letter regarding this draft amendment and the Independent Review Charter (IRC) charter. The final version of the revised protocol (version 6) was received on November 25, 2013.

- On October 2, 2013, Novartis submitted an amendment containing a proposed initial Pediatric Study Plan (iPSP). On December 9, 2013, FDA acknowledged Novartis' iPSP plan in a letter (b) (4) On January 8, 2014, Novartis submitted an amendment containing an Agreed Initial Pediatric Study Plan (iPSP) in response to FDA letter of December 9, 2013. On February 6, 2014, FDA confirmed agreement to Novartis' January 8, 2014, Agreed iPSP, in which Novartis stated that Novartis' plan is to request a waiver from all requirements from PREA in a marketing application for all pediatric age groups for the indication of basal cell carcinoma (BCC).

- On December16, 2013, Novartis submitted a Type B, Pre-NDA meeting request that was subsequently withdrawn on December 20, 2013 because the meeting request was premature since the first interpretable results (FIR) of Protocol CLDE225A2201, intended to support an NDA, would not be available until January 21, 2014. The formal request to withdraw the meeting request was received January 6, 2014.

Chemistry, Manufacturing, and Control (CMC)

Chemical Structure



Chemical name

N-[6-(cis-2,6-Dimethylmorpholin-4-yl)pyridine-3-yl]-2-methyl-4'-(trifluoromethoxy) [1,1'-biphenyl]-3-carboxamide diphosphate

Reference ID: 3506369

Molecular formula

- [redacted] (b) (4) $C_{26}H_{26}F_3N_3O_3 \cdot 2H_3PO_4$
- [redacted] (b) (4)

Physical Properties and Drug Substance

Novartis describes the compound as a white to off-white powder [redacted] (b) (4) and almost insoluble, with <10µg/mL solubility across the pH range (pH 1-10). [redacted] (b) (4) The hard gelatin capsules contain LDE225 drug substance at dose strength [redacted] (b) (4) 200 mg, [redacted] (b) (4) (based on free base content) with commonly used compendial grade excipients. [redacted] (b) (4) Hard gelatin capsules containing 200 mg are foreseen as commercial formulation that would be presented within an NDA. For additional CMC information please refer to the Investigator Brochure in appendix 14 of the briefing background.

Nonclinical

According to the March 6, 2014 meeting background materials, Novartis evaluated sonidegib in safety pharmacology, repeat dose toxicity, genotoxicity, reproductive toxicity, and phototoxicity studies in rats and dogs. Repeat dose toxicity studies evaluated the safety of daily, oral sonidegib for up to 6 months in rats and dogs.

In a cardiovascular safety pharmacology study in dogs, single oral doses up to 1000 mg/kg showed no adverse effects on heart rate, core body temperature, systolic and diastolic arterial blood pressure, and ECG interval durations, morphology, and rhythm. Sonidegib decreased hERG channel activity at the highest test concentration achievable of 0.5 µM (0.24 µg/ml) by 20.7 %.

Sonidegib was shown to be fetotoxic as evidenced by abortion and/or complete resorption of fetuses and teratogenic at all doses tested in rabbits. In a fertility study in rats, sonidegib administered to female rats at ≥ 2 mg/kg resulted in a complete lack of fertility.

According to Novartis, sonidegib was not genotoxic in studies conducted in vitro and in vivo, and showed no potential risk for phototoxicity.

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Clinical

Study Design of Protocol CLDE225A2201

Study CLDE225A2201 (A2201) is a randomized (2:1), double-blind study evaluated the anti-tumor activity and safety of two dose levels of sonidegib for the treatment of patients with locally advanced, unresectable or metastatic basal cell carcinoma.

The target patient population in study A2201was comprised of patients with a histologically confirmed diagnosis of locally advanced BCC that were not amenable to surgery or radiation therapy (b) (4). Eligible patients with locally advanced BCC were defined as:

- Patients who had experienced recurrence following prior surgery and/or radiation therapy and were not deemed to be candidates for further curative treatment
- Patients with BCCs in anatomically challenging locations, such as the eye, inner canthus of the nose and ears, for which surgery and/or radiation therapy may have resulted in severe disfigurement or dysfunction
- Patients with locally advanced BCC who were considered to be poor risk for surgery due to co-morbidities or for whom radiation therapy was contraindicated.

Study Objectives

Novartis stated that, based on the final version of the protocol (version 6), their primary objective for this study was to assess the the objective response rate (ORR) to sonedigib, as determined by central review according to modified RECIST (mRECIST) in patients with locally advanced basal cell carcinoma (laBCC) and according to RECIST version 1.1 in patients with metastatic basal cell carcinoma (mBCC).

Novartis' secondary objectives were to assess the duration of overall response (DoR), as determined by central review, according to mRECIST for locally advanced BCC patients and RECIST 1.1 for metastatic BCC patients, and to assess the rate of complete response (CR) as determined by central review, according to mRECIST in patients with locally advanced BCC and RECIST 1.1 in patients with metastatic BCC.

Statistical Analysis of Study Data

As per version 6 of the protocol, the study design allowed accrual of approximately 210 patients in order to obtain 150 patients in the primary efficacy analysis set (pEAS) if both treatment arms continued accrual beyond the interim analysis for futility. Randomization (2:1) to the sonedigib 800 mg dose or 200mg dose was stratified by stage of disease, disease histology for laBCC patients and non-aggressive, and geographic region [Australia vs. Europe vs. North America]. The primary analysis of ORR was to be performed when all patients had been treated for 24 weeks or had discontinued treatment. An additional analysis for safety and to update efficacy information was to be performed 78 weeks following enrollment of the last patient.

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The efficacy data was analyzed based on two analysis sets: the primary efficacy analysis set (pEAS) and the full analysis set (FAS). As per version 6 of the protocol "Treatment with LDE225 will be considered sufficiently efficacious if the observed ORR on any treatment arm at the end of the study is 30% or higher. For example, if a total of 100 patients are enrolled on the high dose arm, observing 30 or more responses (CR+PR) will constitute a positive study outcome. The point estimate of ORR of each arm and its 95% exact CI will be provided. The difference in ORR between the two treatment arms will be summarized."

An interim analysis (IA) to assess the safety and futility of sonidegib was conducted when the first 48 randomized patients had been treated for 16 weeks or discontinued treatment. Either (or both) treatment arms could be terminated for futility for a predictive probability of <0.2 that the ORR was 30% in that arm. As stated in the protocol "If neither of the treatment arms is terminated at IA [interim analysis], then the study will continue and enroll approximately 100 patients eligible for the pEAS in the 800 mg arm and approximately 50 such patients in the 200 mg arm assuming proportional distribution of replacement patients on both arms. If one arm is terminated and the study continues with a single arm e.g. the 200 mg arm, then approximately 100 patients will be enrolled in that arm."

The FAS comprises all patients who were assigned study treatment (regardless of receiving the treatment). Patients were classified according to the treatment they were assigned in accordance with the intent-to-treat (ITT) principle.

The pEAS are a subset of the FAS, defined as patients with tumors that had been adequately assessed by photographs, radiologic scans (MRI or CT), or both. For patients with laBCC, adequate assessment by photograph was defined as those with annotated photographs or those without annotated photographs and documentation of the absence of palpable sub-dermal components outside the margins of the photographed lesion(s).

It is noted that despite FDA's recommendations during July and August 2013, that the primary analysis of objective response rate (ORR) and key secondary analyses of progression-free survival (PFS) and overall survival (OS) be performed in the intent to treat population (FAS), and Novartis' agreement to analyze these endpoints using the FAS, this is not reflected in the final version of the protocol. In their November 25, 2013 submission, containing Protocol 2201 version 6, Novartis argued that it is appropriate to use the Primary Efficacy Analysis Set (pEAS) as the primary analysis set with the FAS as the supportive analysis set. As implemented, pEAS represents all randomized mBCC patients and all laBCC patients adequately assessed according to mRECIST. Both analyses (based on pEAS and FAS) will be provided in the CSR and in the summary of clinical efficacy.

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Results

This study recruited 230 patients between June 2011 and January 2013. Patients were randomized (1:2) to receive sonidegib 200 mg capsule orally, once daily (N=79) or sonidegib 800 mg orally, once daily (N=151). The majority of patients had laBCC (N=194, 84%), aggressive histology (N=112, 49%), and were accrued in European (N=128, 56%) or North American (N=90, 39%) sites. The data cut-off date for the primary analysis was June 28, 2013.

In February 2014, Novartis received the first "interpretable results" of the A2201 study. The median duration of follow-up was 13.9 months (from randomization to data cut-off date) and all patients without evidence of disease progression had been treated for at least 24 weeks. Treatment discontinuations were reported for 40 (51%) patients in the sonidegib 200 mg group and 104 (69%) patients in the sonidegib 800 mg group based on the full analysis set (FAS). The most frequently reported primary reason for discontinuation in the 200 mg dose cohort was adverse events (20%), followed by progressive disease (19%), subject withdrawal (6.3%), and physician decision (3.8%). most frequently reported primary reason for discontinuation in the 800 mg dose cohort was adverse events (32%) followed by withdrawal by subject (18%), physician decision (6.6%) and progressive disease (4%). The median duration of exposure to study treatment was 8.9 months in the sonidegib 200 mg group and 6.5 months in the sonidegib 800 mg group in the safety analysis population.

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The background materials provide the following study results for ORR, CRR and DoR in the table included under in Question 1, which is reformatted from the table in the March 6, 2014 meeting briefing document.

ORR, CRR and DoR Summary Table per Central Review Using mRECIST for laBCC (b) (4) in the Full Analysis (intent-to-treat) Population

Efficacy Endpoints as determined by central independent review according to mRECIST	(b) (4)	laBCC		(b) (4)
		LDE225 200 mg	LDE225 800 mg	
FAS Population**		N=66	N=128	
ORR n (%) 95% CI (%)		31 (47.0) (34.6, 59.7)	45 (35.2) (26.9, 44.1)	
CRR n (%)		2 (3.0)	0 (0.0)	
DoR* No. of PFS events No. censored Median DoR(mo) (95% CI) % EFS probability @ 9 mo (95% CI) % EFS probability@ 12mo (95% CI)		 4 27 NE 82 % (54, 94) 66% (26, 88)	 3 42 NE 83% (54, 94) 83% (54, 94)	

NE = not estimable
* DoR is defined as the time from the first observed response (CR or PR) to the first documented disease progression or death and it is summarized for patients with confirmed responses only.
** Primary Efficacy Population Per July/August 2013 Agreements with FDA

ORR, CRR and DoR Summary Table per Central Review Using mRECIST for laBCC (b) (4) in the Primary Efficacy Analysis Population (pEAS)

Efficacy Endpoints as determined by central independent review according to mRECIST	(b) (4)	laBCC		(b) (4)
		LDE225 200 mg	LDE225 800 mg	
pEAS Population**		N=42	N=93	
ORR n (%) 95% CI(%)a		18 (42.9) (27.7, 59.0)	35 (37.6) (27.8, 48.3)	
CRR n (%)		2 (4.8)	0 (0.0)	
DoR* No. of PFS events No. censored		 3 15	 1 34	

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Efficacy Endpoints as	(b) (4)	laBCC		(b) (4)
Median DoR(mo) (95% CI)		NE	NE	
% EFS probability @ 9 mo (95% CI)		82% (44, 95)	92% (57, 99)	
% EFS probability@ 12mo (95% CI)		NE	92% (57, 99)	

NE = not estimable
* DoR is defined as the time from the first observed response (CR or PR) to the first documented disease progression or death and it is summarized for patients with confirmed responses only.
** Supportive Efficacy Population per July/August 2013 Agreements with FDA

Novartis believes the study met its primary objective defined as the observed objective response rate (ORR) on any treatment arm being 30% or higher in either FAS or pEAS population. In addition, the lower bound of the 95% confidence interval of ORR exceeds 20% which is the pre-specified threshold of clinical relevance as per the study design operating characteristics.

QTc Interval Prolongation and Safety Results

(b) (4)

A total of 4 (1.7%) patients died during the study (up to 30 days after end of treatment). All 4 patients were in the sonidegib 800 mg group; none in the 200 mg group. The reason for death was basal cell carcinoma (Day 16), cardiac failure congestive (Day 17), cardiac death (Day 196), and disease progression (Day 38). Novartis states that the two cardiac-related deaths (congestive heart failure and cardiac death) occurred in patients in >80 years with cardiac medical history and confounding risk factors.

Novartis reports that in this trial, the most common adverse events (>10% in the 200 mg cohort and 800 mg dose cohorts, respectively) were muscle spasms (49%; 67%), dysgeusia (38%; 59%), alopecia (43%; 55%), nausea (33%; 45%), increased blood creatine phosphokinase (CPK) levels (29%; 37%), weight decreased (27%; 38%), fatigue (29%; 36%), deceased appetite (19%; 31%), myalgia (19%; 26%), diarrhea (24%; 22%), vomiting (6.3%; 26%), headache (15%;13%), constipation (7.6%; 13%), arthralgia (12%; 8.0%), and back pain (6.3%; 10%). Novartis reports that the most common serious adverse events in this trial were rhabdomyolysis (2.6%), increased blood CPK levels (1.7%), and vomiting (1.7%).

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Clinical Pharmacology

Studies/data analyses will be completed and final study reports and dataset will be included in the original NDA submission:

- A1102: Phase I dose escalation PK study in healthy Japanese volunteers
- A2108: DDI study with ketoconazole and rifampicin in healthy volunteers
- A2110: Phase I human ADME study in healthy volunteers
- A2114: Food effect in high fat meal for capsule in healthy volunteers.
- PK-QTc analysis: Healthy volunteers (A1102, A2114, A2108 control, A2110) and patients (A2201, X2101, X1101, B2209)
- PK-efficacy analysis: BCC patients (A2201)
- PK-CPK analysis: Cancer patients (A2201, X2101, X1101, B2209)
- Population PK analysis: Healthy volunteers (A1102, A2114) and cancer patients (A2201, X2101, X1101)
- Ethnic sensitivity for PK: Comparison of PK in Japanese vs. Western healthy subjects (A1102, A2114)

Studies are ongoing or will be conducted and final study reports will not be included in the original NDA submission:

(b) (4)

Preliminary meeting comments were issued by FDA and sent to Novartis on April 14, 2014. Novartis was unable to provide a response to FDA Preliminary comments due to network failure therefore FDA and Novartis addressed all of the questions during the April 15, 2014 meeting. Novartis provided slides as handouts during the meeting to facilitate discussion. The slides were formally submitted on April 30, 2014.

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2. DISCUSSION

GENERAL COMMENTS

FDA will not be able to reach agreements with Novartis on the contents of a complete application for an NDA under the PDUFA V program, because the pre-NDA meeting for discussion of Quality components of the NDA has not been held. FDA recommends that Novartis submit a request for a pre-NDA meeting to discuss and reach agreement on the CMC information necessary to allow the NDA to be considered complete and to reach agreement on submission of late components, if any are planned.

Novartis Position to Question 1: Data from pivotal Study A2201 in support of NDA
In February 2014, the Sponsor received the first interpretable results of the pivotal study (A2201). The primary endpoint of this study is ORR (including CR or PR) according to mRECIST in laBCC patients, as determined by central review, and RECIST 1.1 in mBCC patients.

The key secondary endpoints are rate of complete response (CRR) and duration of overall response (DoR), according to mRECIST in laBCC patients and RECIST 1.1 in mBCC patients, as determined by central review.

This study met its primary endpoint, which was defined as achieving at least 30% ORR, in either of the two arms per independent central review. In addition, the lower bound of the 95% confidence interval (CI) of ORR exceeds 20% which is clinically relevant in both arms. The endpoint was met both by using the primary efficacy analysis set (pEAS), or the Full Analysis Set (FAS), as described in the introduction of this briefing book. Main results are summarized in the clinical background section of the March 6, 2014 briefing book (section 3.4.5), and provided in more detail in [Appendix 3 of the briefing materials].

In summary, sonidegib was associated with a clinically relevant, durable ORR in the target patient population, with a median follow-up of 13.9 months. The results of ORR, CRR, DoR based on the primary efficacy analysis set (pEAS) and the full analysis set (FAS) are provided below.

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Table 2-1 ORR, CRR, and DoR summary table per central review using mRECIST for laBCC
(b) (4)

	(b) (4)	laBCC		(b) (4)
		LDE225 200 mg	**LDE225 800 mg**	
Population = pEAS		**N=42**	**N=93**	
ORR n (%)		18 (42.9)	35 (37.6)	
95% CI(%)[a]		(27.7, 59.0)	(27.8, 48.3)	
CRR n (%)		2 (4.8)	0 (0.0)	
DoR*				
No. of progressio events/deaths		3	1	
No. censored		15	34	
Median (95% CI) (mo)		NE	NE	
% event-free probabilit (95% CI)		82 (44, 95)	92 (57, 99)	
9 months		NE	92 (57, 99)	
12 months				
Population = FAS		**N=66**	**N=128**	
ORR n (%)		31 (47.0)	45 (35.2)	
95% CI(%)		(34.6, 59.7)	(26.9, 44.1)	
CRR n (%)		2 (3.0)	0 (0.0)	
DoR*				
No. of progressio events/deaths		4	3	
No. censored		27	42	
Median (95% CI) (mo)		NE	NE	
% event-free probabilit (95% CI)		82 (54, 94)	83 (54, 94)	
9 months		66 (26, 88)	83 (54, 94)	
12 months				

NE = not estimable
* DoR is defined as the time from the first observed response (CR or PR) to the first documented disease progression or death and it is summarized for patients with confirmed responses only.

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Notably, the criteria to obtain CR were very stringent and included a thorough examination of histology data with confirmed CRs requiring multiple punch biopsy samples per lesion at multiple time points Low CR rates were attributed to the stringent response criteria that were applied and the extent/magnitude of lesions at baseline.

However, most importantly, responses were durable, particularly for patients with laBCC. In fact, neither the median duration of response (DoR) nor the median PFS was estimable for laBCC patients in the sonidegib 200 mg group. Estimated DoR rates at 9 months were 82.4% (95% CI: 53.9, 94.1) and [redacted] (b) (4) for patients in sonidegib 200 mg group with laBCC [redacted] (b) (4), per central review based on the FAS. Estimated 12-month PFS rates were 83.5% (95%CI: 64.6, 92.9) [redacted] (b) (4) for patients with laBCC [redacted] (b) (4) in sonidegib 200 mg per central review, based on FAS. Furthermore, the pharmacological effect of sonidegib was demonstrated as shown by a substantial and durable GLi reduction (corresponds to hedgehog pathway inhibition) at both 200 and 800 mg dose daily in the vast majority of patients regardless of disease status ([Appendix 3]). In addition to these analyses carried out by using mRECIST for laBCC patients [redacted] (b) (4) the Reporting and Analysis Plan (RAP) also made provision for a pre-planned sensitivity analysis to replicate the methodology ([Appendix 4]) used for the vismodegib Erivance study (Sekulic et al 2012). This sensitivity analysis allows a more accurate interpretation of the clinical data in the context of an already approved agent. Results are discussed in section 2.9.

Furthermore, in view of the clinical benefit in patients with locally advanced [redacted] (b) (4) disease, the safety profile is considered to be acceptable, with toxicities being manageable. The safety and tolerability profile of sonidegib 200 mg is more favorable than the 800 mg dose. Muscle toxicity and the teratogenic potential represent the most important clinical issues, both of which are considered to be well-known class effects of Hedgehog pathway inhibitors. Each of these events can be managed effectively.

At the recommended dose of 200 mg, the most commonly occurring adverse events (AEs) reported with an incidence of ≥ 10% and regardless of study drug relationship, were muscle spasms (49.4%), dysgeusia (38.0%), alopecia (43.0%), nausea (32.9%), blood creatine phosphokinase (CK) increased (29.1%), weight decreased (26.6%), fatigue (29.1%), decreased appetite (19.0%), myalgia (19.0%), diarrhea (24.1%), headache (15.2%), and arthralgia (12.7%). Grading (severity) of these events was modest; reports were typically grade 1 or grade 2. The most common grade 3/4 AEs in the 200 mg dose group, with an incidence of ≥ 2%, were blood CK increased (6.3%), lipase increased (5.1%), muscle spasms (2.5%), hypertension (2.5%), and asthenia (2.5%). These events can be effectively managed with concomitant medications, non-drug therapies, dietary intervention, and dose interruptions. AEs led to discontinuation of study treatment in 21.5% of patients that were treated with 200 mg, and in 36.0% of patients treated with 800 mg.

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In the 200 mg group (N=79), there were no deaths on treatment. In the 800 mg group (N=150), 4 patients died either on treatment or within 30 days after last date of study treatment. All 4 of the deaths in the 800 mg group were considered to be unrelated to study drug. Overall, the nature of adverse events was similar between the treatment arms. However, both the frequency and the severity of events were lower in the 200 mg group.

The overall evaluation of safety will be based on data from approximately 300 patients; 85 of whom were exposed to sonidegib at the recommended 200-mg daily dose. This population allows for an informed assessment of the safety profile of sonidegib and a judgment of the overall benefit-risk in the target patient population. This population is also considered appropriate for the detection and characterization of common AEs and to provide guidance on toxicity management.

Novartis' Conclusions
Data from Study A2201 demonstrate that sonidegib at both 200 mg and 800 mg is an effective treatment for patients with advanced BCC with the 200-mg daily dose having a better safety profile than 800 mg. Therefore, sonidegib treatment at 200 mg once daily is considered to have a positive benefit-risk profile for patients with laBCC who are not amenable to further surgery or radiation (b) (4) The data that will be provided in the application and the full characterization of these data in the label support the use of sonidegib in the target indication.

In conclusion, Novartis considers that the outcome of this randomized, double-blind, Phase 2 study does support the submission of an NDA for the treatment of patients with laBCC who are not amenable to curative surgery or radiation therapy (b) (4) and believes it provides a highly effective and generally safe treatment option in this patient population.

1. **Does the Agency agree that the data from the registration Study CLDE225A2201 are adequate to substantiate the efficacy and safety of sonidegib, and that the robust results of this study support filing these data for the proposed indication "*Treatment of adult patients with locally advanced basal cell carcinoma (BCC) who are not amenable to curative surgery or radiation therapy* (b) (4) at a recommended dose of 200 mg?**

   FDA Written Response to Question 1 sent April 14, 2014: No, the findings from Study A2201 do not support the filing of an NDA. FDA re-iterates the advice given to Novartis at the End of Phase 1 (EOP1) meeting held on June 9, 2011, during which FDA stated that an efficacy estimation based on ORR will need to be supported by adequate magnitude **and duration** [emphasis added] with an acceptable risk/benefit ratio. Since a majority of the data on duration of response is not available, an NDA submission based on the data proposed would not be acceptable. The data provided on the proportion of patients without disease progression or death at 9 months and at 12 months is not interpretable in this trial because, although there is a dose-comparison, there is no

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information on the natural history in the absence of sonedigib in order to determine whether sonedigib treatment improves progression-free survival rates at 9 and 12 months. Furthermore, this data cannot substitute for duration of response in responding patients.

Finally, FDA has concerns regarding the small number of patients available for safety evaluation at the proposed dose (approximately 85 patients) therefore FDA will also consider safety information obtained at the 800 mg dose for this patient population as well as all available safety information in the development program.

Discussion During April 15, 2014 Meeting: Novartis presented several slides addressing FDA's concern regarding lack of clarity on durability of responses. Novartis stated during the meeting that the pre-specified endpoint of overall response rate measured at 24 weeks post-treatment in all patients was greater than or equal to 30% and the 95% lower Confidence Level (CL) was greater than or equal to 20% demonstrating efficacy for both doses in the slide presented for the Full Analysis Population of the LaBCC subset. Novartis stated that among the responders, the minimum duration of response is 1.9 months and this response is ongoing. FDA expressed concerns regarding a clear understanding regarding the duration of responses and requested that Novartis provide individual patient listing for the duration of response. Novartis agreed to provide the data in the NDA submission.

Novartis Position to Question 2: Plan for submission of clinical pharmacology studies and data

The draft clinical pharmacology package was initially presented to the FDA as part of an EOP1 meeting in June 2011, and later as part of a request for written feedback in April 2013. Feedback on this request was received from FDA in July 2013 generally agreeing with the proposed clinical pharmacology studies to be submitted but provided additional recommendations which we have specifically described below and detailed in Section 3.4.3 of the March 6, 2014 briefing document for the FDA's agreement. Novartis plans to include the completed study reports from four clinical pharmacology studies (A1102, A2108, A2110, and A2114) in the NDA. This includes a phase 1 PK, relative bioavailability/food effect studies (A1102 and A2114), a drug-drug interaction study with a CYP3A4 inducer/inhibitor (A2108), and an ADME study (A2110). Further, the clinical pharmacology package will include several pooled analyses, namely a PK-QTc analysis, a PK-efficacy analysis, a PK-CK analysis, a population PK analysis, and an ethnic sensitivity analysis for PK. Two studies will be ongoing at the time of submission: a drug-drug interaction study with warfarin and bupropion (Study A2112) and a hepatic impairment study (Study A2113).

In the absence of a study report for the dedicated hepatic impairment study, Novartis will submit all relevant and available information on the potential for intrinsic and extrinsic factors to influence the exposure of sonidegib. This includes a population PK analysis characterizing the covariate effects of ALT, total bilirubin, and albumin on the apparent clearance of sonidegib using the full covariate model approach. The impact of hepatic dysfunction on the PK of

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sonidegib will be evaluated by summarizing the mean and 95% prediction intervals of the steady-state exposure metrics (AUC0-24h,ss, Cmax,ss, and Cmin,ss) by the four liver function groups as per the National Cancer Institute organ dysfunction working group (NCI-ODWG) criteria (NCI-ODWG 2011). In addition, simulation from the full covariate model will be used to characterize the 90% confidence interval of the geometric mean ratio of AUC0-24h,ss for each of the hepatic dysfunction groups relative to the normal hepatic function. In the absence of a study report for the drug-drug interaction study with warfarin and bupropion (A2112) at the time of NDA submission, appropriate labeling will be proposed regarding DDI with substrates of CYP2C9 or CYP2B6. This labeling would inform that sonidegib is a competitive inhibitor of CYP2B6 and CYP2C9 in vitro, requiring for caution if substrates of these enzymes would be concomitantly used, especially those with a narrow therapeutic range. As stated above, in the written feedback provided on 08-Jul-2013, FDA generally agreed with the list of proposed clinical pharmacology studies to be submitted, but had additional recommendations for support of an NDA submission. (b) (4)

Gastric pH-elevating agents are not prohibited in any studies with sonidegib, and nor is special caution required. Novartis intends to include concomitant use of proton pump inhibitors or H2 receptor antagonists as a covariate in the population PK analysis that will be included in the NDA. An efficacy subgroup analysis by concomitant use of gastric pH elevating agents (proton pump inhibitors or H2 receptor antagonists) will be also conducted as part of the Study A2201 report. This analysis will provide information about the concomitant use of these drugs and whether they lead to an impact on exposure and efficacy. Refer to the background section of this briefing book for a detailed description of all clinical pharmacology studies (Section 3.4.3).

In summary, Novartis considers that the presented plan and timing for provision of results of clinical pharmacology studies adequately supports the overall determination of benefit/risk of sonidegib safety and efficacy in the indication.

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2. **Does the Agency agree with the proposed plan for the inclusion of clinical pharmacology data as described above?**

FDA Written Response to Question 2 sent April 14, 2014: The proposed submission plan for clinical pharmacology studies, as stated in the Novartis position statement for Question 2, is acceptable. FDA notes that the hepatic impairment study and a drug-drug interaction (DDI) study with warfarin, and bupropion will be ongoing (b) (4) is planned to be conducted at the time of the original NDA submission. The original NDA submission should contain justification for not including these studies and a description of the proposed post marketing requirements, including proposed timelines for completion of the studies and submission of the final study reports, for the hepatic impairment study and DDI studies with warfarin, bupropion (b) (4)

Please see the additional clinical pharmacology comments below.

Discussion During April 15, 2014 Meeting: Novartis agreed with FDA response. No discussion occurred.

Novartis Position to Question 3: Risk Minimization Measures

In addition to appropriate labelling, including a medication guide, Novartis plans for two main risk minimization measures for the use of sonidegib in the treatment of BCC. One measure will address the teratogenic potential of sonidegib, and a second measure will address the potential for muscle toxicity.

Teratogenicity

(b) (4)

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Muscle toxicity

Muscle toxicity is a well-known class effect of Hedgehog pathway inhibitors (Sekulic et al 2012). All cases of high grade CK elevation, reported cases of myopathy and rhabdomyolysis from all sonidegib studies were reviewed by a panel of independent experts to better characterize this toxicity and define an appropriate management plan.

Novartis proposes to include information on muscle-related toxicity in the Warnings and Precautions section in the Product Information. (b) (4)

(b) (4)

3. **Novartis believes that the risks associated with treatment with sonidegib can be managed adequately with appropriate labelling, proposed risk management measures and routine pharmacovigilance activities. Does the Agency agree?**

FDA Written Response to Question 3 sent April 14, 2014: No, FDA does not agree. Adequacy of risk mitigation strategies can only be determined upon review of the application.

Regarding the risk of teratogenicity, FDA strongly recommends that Novartis submit a proposed risk management plan for teratogenicity and other serious risks. FDA refers recommends that Novartis include additional activities in a Risk Management Plan such as the pregnancy registry and evaluation of drug interactions with oral contraceptives outlined in the January 30, 2012 approval letter for NDA 203388 found at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/

Discussion During April 15, 2014 Meeting: Novartis acknowledged FDA's response and agreed to submit a proposed risk management plan for teratogenicity and other serious risks. No additional discussion occurred during the meeting.

Novartis Position to Question 4: 120-day safety and efficacy update

The NDA, which is planned for submission by the end of April 2014, will include data of the pivotal Study A2201 based on a data cut-off date of 28-Jun-2013. The 120-day safety report will incorporate updated safety information from Study A2201 only. In addition, Novartis proposes to provide an efficacy update based on relevant efficacy endpoints from Study A2201.

This study had ongoing patients at the time of the data cut-off for the database lock for the primary clinical study report. The respective update of the narrative text of the SCS will be

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provided in the eCTD Section 2.7.4. Post-text tables and listings will be provided in Module 5. In addition, the safety update will include an updated listing from Novartis' ARGUS safety database for deaths, and SAEs from those patients in any ongoing sonidegib studies with a cutoff date approximately 3 months after the submission.

Novartis proposes to submit an efficacy update (to include revised labeling) at the same time as the mandated 120-day safety update, based on a data cut-off date of 31-Dec-2013. At the time of the data cut-off date for the original NDA (28-Jun-2013), 37.0% of patients were still on treatment in Study A2201 (49.4% of patients treated with 200 mg and 30.5% of patients treated with 800 mg, respectively).

While it is not expected that the results for the primary endpoint would significantly change as a result of such a follow-up analysis, such an update would provide a more current estimate of the duration of response. In Novartis' view, a sustained duration of response underscores the benefit from sonidegib treatment of advanced basal cell carcinoma.
Therefore, in order to further determine the benefit/risk for this medicinal product, it is deemed reasonable to provide after 120 days a limited number of relevant updated efficacy endpoints analyses as proposed in Table 2-2, in addition to the safety update. This is considered particularly valuable since 49.4% of patients that are treated with the proposed recommended dose of 200 mg were still on treatment at the time of the data cut-off.

Table 1 Proposed efficacy analysis to be provided along with the 120 day safety update

	Endpoint	RECIST criteria	Source of data	Analysis set
Primary Analyses	ORR DoR PFS	mRECIST (laBCC), (b) (4)	Central	FAS/pEAS
Supportive Analyses	ORR DoR PFS	mRECIST (laBCC), (b) (4)	Local (investigator)	FAS/pEAS
Supportive Analyses	OS	Not applicable	Not applicable	FAS

Therefore, it is proposed that addenda to Modules 2.7.3 Summary of Clinical Efficacy (SCE) and 2.7.4 Summary of Clinical Safety (SCS) be provided.

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4. **Does the Agency agree to the proposed content of the 120-day safety update and inclusion of updated efficacy data as described above?**

FDA Written Response to Question 4 sent April 14, 2014: No. FDA reminds Novartis that under the PDUFA V program, major components are expected to be submitted with the original application and are not subject to agreement for late submission. If during the review of the NDA, however FDA determines that the updated efficacy results identifying new responses or updating the duration of responses identified in the original NDA submission are crucial to a complete benefit: risk assessment for the application, FDA may accept the additional data for review as proposed.

In addition, FDA does not agree with the proposed contents of the 120-day safety update. The safety update should include a summary of updated information from all ongoing studies, including narrative summaries of treatment related deaths and serious adverse events, through a specified data cut-off date.

Finally, please provide justification for the proposed data cut-off date for the 120-day safety update of **December 31, 2013**. A safety data cut-off for serious adverse events of more than 6 months is not appropriate. Provide an alternative data cut-off date for serious adverse events (including expected events of special interest, such as rhabdomyolysis) in the 120-day safety update.

Discussion During April 15, 2014 Meeting: Novartis presented a proposal for the 120-day safety update on slide 4 (attached) and agreed to provide text summarizing the updated safety information as part of the 120-day safety update to be submitted to the NDA. In addition, Novartis will include updated efficacy data for ORR and response duration through the December 31, 2013, cut-off date. FDA stated this proposal is acceptable.

Novartis Position to Question 5: QT Analysis Plan

(b) (4)

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(b) (4)

[redacted]

5. **Does the Agency agree that based on the pre-clinical studies that were conducted, and on the central tendency and PK-QTc analysis results, the additional planned analyses as described in the QT analysis plan are adequate to assess the potential for QT/QTc interval prolongation** [redacted] (b) (4) **?**

FDA Written Response to Question 5 sent April 14, 2014: No, FDA does not agree. FDA only considers Novartis' justification adequate in indicating that large QTc prolongation (i.e., >20 ms) caused by sonidegib at the therapeutic dose is not likely. However, pre-clinical information, cardiovascular safety in clinical trials, the central tendency analysis from the PK/ECG sub-study of A2201, and PK-QTcF analyses are not sufficient to rule out small increases in the QTc interval (<10 ms) because of lacks of controls and assay sensitivity.

Pre-clinical information indicates sonidegib inhibits hERG currents significantly at concentrations within clinical Cmax exposure achieved after multiple doses. Novartis' PK-QTcF analyses in patients also indicate a significant positive relationship. Therefore,

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a thorough QT (TQT) study should be conducted. As shown in Table 3-11, a single dose of 800 mg administered with a high-fat meal can fully cover the steady state therapeutic exposures. The relationship between plasma concentrations (of the parent drug and/or metabolite(s)) and ΔQTc/ ΔΔQTc from the TQT study, as well as your previous PK-QTcF analyses, should be used to estimate the QT prolongation risk at an expected high clinical exposure scenario if supratherapeutic exposures are not achievable with a single dose administered with a high-fat meal in the TQT study.

Discussion During April 15, 2014, Meeting: Novartis slides 5 and 6 (attached) provided Novartis' response to FDA's comments above. Novartis concluded that the HeRG assay is negative at clinically relevant exposures and FDA agreed. However, representatives of FDA's QT IRT reiterated that pre-clinical information, cardiovascular safety in clinical trials, the central tendency analysis from the PK/ECG sub-study of A2201, and PK-QTcF analyses are not sufficient to rule out small increases in the QTc interval (<10 ms) because of lacks of controls and assay sensitivity and (b) (4) FDA agreed that a request for a waiver of the thorough QT Study could be provided in the NDA and that the specific labeling would be agreed upon during labeling negotiations.

Novartis Position to Question 6: Provision of Photographic and MRI documentation

(b) (4)

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(b) (4)

6. **Does the agency agree** (b) (4) **from CLDE225A2201 with locally advanced and metastatic BCC?**

FDA Written Response to Question 6 sent April 14, 2014: No; (b) (4) photographic documentation of IRC determined responses (only for responding patients) should be included in the application. Submit these data/images in PDF format that can be archived along with the remainder of the application. The files should be submitted under the specific study's Study Tagging File (STF) and tagged as 'image". The leaf titles should be clear and indicative of the content.

In addition, FDA recommends bundling of multiple images into one or more pdf file (not more than 200 MB) and provide clear and proper bookmarks, table of contents and functional hyperlinks.

Discussion During April 15, 2014 Meeting: Novartis agreed with FDA response to Question 6. No discussion occurred during the meeting.

Novartis Position to Question 7: Electronic Datasets (CDISC & SAS transport format)
As described within the briefing book submitted in April 2013, Novartis plans to provide the following datasets for the review of efficacy and safety of sonidegib in CDISC-compliant format (SDTM, ADaM, define.xml and annotated CRF):

- Datasets for the pivotal study CLDE225A2201 for which data was collected using a CDISC-compliant data model.
- Datasets for the SCS pool (comprising studies CLDE225A2201 and CLDE225X2101) and the summary of clinical pharmacology (SCP) patient pool (comprising studies

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CLDE225A2201, CLDE225X2101, CLDE225X1101, and CLDE225B2209) will be provided in a CDISC-compliant format (Pooled ADaM and define.xml only).

As described within the briefing book submitted in April 2013 (with feedback received in July 2013), all clinical pharmacology studies that are using single doses in healthy volunteers studies will have their CSRs based on non-CDISC compliant datasets.

The datasets from these clinical pharmacology studies as well as the pooled datasets from healthy volunteer studies that support PK-QT analysis, will not be provided in a CDISC-compliant format. As described earlier in April 2013, these will be provided in a format that is compliant to Novartis' internal legacy standards which is a non-CDISC compliant format. Case Report Tabulations (CRT) will be provided and will consist of:

- Raw and derived datasets (Subject demographic, dose exposure, adverse events, ECG, laboratory, vital signs, concomitant medications, PK concentrations and PK parameters) in SAS v5 XPORT transport format.
- Data definition tables for raw and derived datasets (define.pdf), which provides the source derivation for each variable in the datasets. The hypertext links will also be provided from the define.pdf to the SAS transport files and the annotated case report forms.
- Annotated Case Report Forms in pdf format.

In addition, datasets for population pharmacokinetic analyses will not be in a CDISC-compliant format but will be NONMEM input datasets and will be provided as SAS transport files. Analysis programs and outputs of key modeling steps will be provided.

The raw datasets will include all the final complete data in the clinical database based on the database lock, as no cut-off date for the four healthy volunteer studies included in the NDA was employed. The derived datasets are based on the raw datasets.

Although the CSRs for studies LDE225X2101, LDE225X1101 and LDE225B2209 will be included in the NDA, Novartis will not submit the source or derived datasets in the form of CRTs for these studies as they do not support the indication that is being sought.

In addition, Novartis plans to provide the analysis programs for the analysis of the primary and key secondary efficacy endpoints for the pivotal Phase II Study A2201.

7. **In the earlier briefing book submitted to the FDA in April 2013, Novartis described the proposal for the submission of electronic datasets, which was acceptable to the Agency as per the feedback received in July 2013. Novartis wishes to confirm that this proposal remains acceptable, particularly with regard to the clinical pharmacology sections and the population pharmacokinetic reports where FDA**

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indicated in the July 2013 written feedback that additional recommendations would be provided at the time of a pre-NDA meeting.

FDA Written Response to Question 7 sent April 14, 2014: In addition to the analysis programs for the analysis of the primary and key secondary efficacy endpoints for the pivotal study, please provide the following information:

- Adequate data/documentation to verify the randomized treatment assignments.
- Raw and derived datasets with adequate document(s) in PDF file (define.pdf). For example, the efficacy data tabulation should be organized such that the IRC derived composite assessment is clearly traceable to assessment of individual component modalities of assessments.
- Executive SAS program with sufficient comments within the code to verify the derivation of the analysis dataset from the raw dataset, and the analyses associated with the results presented in the proposed package insert. If the SAS programs use any SAS macro, please provide all necessary macro programs.
- Provide adequate documentation for all SAS programs

The proposed submission plan for clinical pharmacology studies is acceptable. Please refer to the response for Question 2 and to the additional clinical pharmacology comments below.

Discussion During April 15, 2014 Meeting: Novartis will provide all of the information FDA requested; however, Novartis requested a clarification on bullet 3. Novartis will provide SAS programs for all primary and key secondary endpoints. For ORR and duration of response primary data that were evaluated using RECIST, Novartis will provide the raw dataset both in CDISC and non CDISC-compliant format.

Novartis requested that the documentation for SAS programs (reviewer guide and/or SAS code) for any data that is included in the USPI be submitted within 30 days of the NDA submission as a late component. FDA agreed with Novartis' proposal.

Novartis Position to Question 8: Proposed eCTD table of contents

The content of the proposed NDA was discussed to a large degree in earlier briefing books that were submitted and reviewed by the agency. Briefly, Modules 1 and 2 of the NDA will contain the standard documentation in line with the eCTD structure. Module 3 will contain documentation in support of the 200 mg sonidegib capsule formulation, with 12 months stability data being available. Module 4 contains the standard reports in support of non-clinical pharmacology, non-clinical pharmacokinetics, and toxicology.

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The clinical studies (Module 5) in support of this NDA were discussed and presented in the Briefing Book submitted in April 2013, and were generally considered acceptable by the Agency in support of clinical efficacy and safety. Earlier comments that were received on the clinical pharmacology package are discussed in detail in Question 2 of this briefing book.
In summary, Novartis considers the content of the submission as outlined in the proposed eCTD TOC ([Appendix 7]) to be sufficiently complete to permit a substantive review of the NDA in support of the proposed indication.

8. **Does the Agency agree with the content of the NDA as outlined in the proposed electronic Common Technical Document (eCTD) table of contents (TOC) constitutes a complete application?**

FDA Written Response to Question 8 sent April 14, 2014: As outline in the TOC, the application would not be considered complete. Please confirm that Novartis will provide the following information and identify the location in the TOC.

- The meeting minutes, data, and reports to data and safety monitoring board (DSMB). The DSMB reports and minutes should be embedded within the CSR (probably somewhere in the appendix).
- The summary of clinical safety should include a discussion of safety information from ongoing clinical studies.
- Place meeting minutes in m1.6.3 (Correspondence regarding meetings) as a single pdf file (instead of separate pdf files for each document) with proper bookmarks of all correspondence, table of contents and hyperlinks.
- Please use clear and concise leaf titles so it indicates the content of the document to help reviewers quickly and easily differentiate from the actual study report body and there should be hyperlink from the individual CSRs, to the DSMB materials in 5.3.5.4.

Discussion During April 15, 2014 Meeting: Novartis agreed with FDA response to Question 8. No discussion occurred during the meeting.

Novartis Position to Question 9: Request for priority review

(b) (4)

[redacted]

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9. **Novartis intends to request priority review** (b) (4) **Does the Agency agree with the following justification as a basis for priority review?**

FDA Written Response to Question 9 sent April 14, 2014: Please see FDA's response to Question 1 regarding the lack of data on response durability necessary to support the filing of this application.

Novartis may submit a request for priority review in the New Drug Application (NDA) application that contains justification as to how sonidegib meets these criteria. A determination on whether FDA will grant priority review will be made after the submission of the NDA.

Discussion During April 15, 2014 Meeting: Novartis agreed with FDA response to Question 9. No discussion occurred during the meeting.

ADDITIONAL FDA COMMENTS SENT ON APRIL 14, 2014:

Additional Clinical Pharmacology Comments Sent on April 14, 2014:

Please address the following clinical pharmacology related questions in the NDA submission:

10. What is the basis for selecting the dose(s) and dosing regimen used in the registration trial(s)?

11. What are the exposure-response relationships (dose-response, exposure-response) for efficacy?

12. What are the exposure-response relationships (dose-response, exposure-response) for safety?

13. How is the QT prolongation potential of sonidegib assessed? What are the conclusion and proposed labeling description?

14. What are the characteristics of absorption, distribution, metabolism and excretion of sonidegib?

15. What are the effects of food on the bioavailability of sonidegib? and dosing recommendation with regard to meals or meal types?

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16. What influence do the intrinsic factors (as listed below but not limited to) have on sonidegib 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

17. What influence do the extrinsic factors (as listed below but not limited to) have on sonidegib 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

    Discussion During April 15, 2014 Meeting: Novartis agreed with FDA's additional clinical pharmacology comments 10-17 above. No discussion occurred during the meeting.

In addition, please apply the following advice in preparing clinical pharmacology sections of the NDA submission:

18. Submit bioanalytical method(s) and validation reports for clinical pharmacology and biopharmaceutics studies.

19. 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.

20. 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.

21. Present the PK parameter data as geometric mean with coefficient of variation (and mean ± standard deviation) and median with range as appropriate in the study reports.

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Discussion During April 15, 2014 Meeting: Novartis agreed with FDA's additional clinical pharmacology comments 18-21 above. No discussion occurred during the meeting.

22. Provide a table listing of patients with renal or hepatic impairment who have received sonidegib, 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.

Discussion During April 15, 2014 Meeting: Novartis stated that the clinical pharmacology datasets and the report of the popPK analysis will be included in the original NDA submission; however, the table listing requested in item 22 (above) will be provided within 30 days of the NDA submission as a late component. FDA acknowledged and agreed to Novartis' proposal.

23. Submit the following datasets to support the population PK analysis:
    - SAS transport files (*.xpt) for all datasets used for model development and validation
    - 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
    - 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)
    - Model development decision tree and/or table which gives an overview of modeling steps

    For the population analysis reports, submit
    - Standard model diagnostic plots
    - Individual plots for a representative number of subjects including observed concentrations, the individual prediction line and the population prediction line
    - Model parameter names and units in tables. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1).
    - 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

24. Explore exposure-response (measures of effectiveness, biomarkers and toxicity) relationships for sonidegib and its major active metabolite(s) if any in the targeted patient

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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.

Discussion During April 15, 2014 Meeting: Novartis stated that the clinical pharmacology datasets and the report of the ER analysis will be included in the original NDA submission. FDA acknowledged and agreed to Novartis proposal.

25. Submit the following items for QTc study/assessment
    - Copy of the QT/QTc study protocol
    - Copy of the Investigator's Brochure
    - Annotated CRF
    - Define file which describes the contents of the electronic data sets
    - Electronic data sets as SAS transport files (in CDISC SDTM format – if possible) and all the SAS codes for the analyses
    - ECG waveforms to the ECG warehouse (www.ecgwarehouse.com)
    - Completed Highlights of Clinical Pharmacology Table

    Discussion During April 15, 2014 Meeting: Novartis agreed with FDA Additional Comments 23 and 25. No discussion occurred during the meeting.

Additional Comments from Chemistry, Manufacturing, and Controls (CMC):

26. FDA notes that the last CMC meeting with Novartis was held on June 5, 2012, and that no specific CMC information was provided in the March 6, 2014, meeting briefing materials. In order to allow FDA to reach agreement with Novartis on the contents of a complete application and to attempt to avoid unresolved or inadequately addressed issues regarding the CMC information to be provided in the NDA submission, FDA strongly recommends that a CMC only pre-NDA meeting be scheduled prior to the submission of the original NDA.

    Discussion During April 15, 2014 Meeting: Novartis stated that since the standard Module 3 will be submitted, Novartis did not intend to request a pre-NDA, CMC meeting. FDA strongly recommended that a CMC meeting be held to resolve any outstanding issues and to reach PDUFA V agreements for a complete application. Novartis agreed to request a CMC meeting and provide the briefing package with the meeting request.

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Additional Comments from Office of Scientific Investigations (OSI):

27. FDA refers to Novartis' March 9, 2014, meeting briefing materials, and notes that while the proposed eCTD TOC shows that Module 1 will contain a BIMO reviewers guide, there is no clarity on whether Novartis is committing to providing Part I and II and possibly Part III of current OSI requests for application for the pivotal study. The proposed TOC does not show the level of detail for Module 5 to confirm OSI submission intent on the part of Novartis. FDA requests Novartis commitment to provide Parts I, II and III. Please refer to section 6.0 of these meeting minutes.

    Discussion During Meeting: Novartis agreed to provide Parts 1 and 2 in amendments 1 and 2 in the original NDA submission.

3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. FDA acknowledged Novartis' agreement to submit a CMC pre-NDA meeting request in advance of the submission of the NDA. FDA stated that Novartis should reference the minutes of that meeting for any additional agreements that will be reached on CMC issues.

  Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. FDA and Novartis agreed that the following minor application components may be submitted within 30 calendar days after the submission of the original application.

  - With regard to documentation for SAS programs, Novartis agreed to provide documentation (reviewer guide and/or SAS code) for any data included in the proposed USPI within 30 days of the NDA submission as a late component as described and discussed in Comment #7 of these meeting minutes.

  - The table listing described and discussed in FDA's Additional Comment #22 of these meeting minutes will be provided by Novartis within 30 days of the NDA submission as a late component. This table will include: a listing of patients with renal or hepatic impairment who have received sonidegib, organized by trial number and will 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

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- Prominently identify each submission containing your late component(s) with the following wording in bold capital letters at the top of the first page of the submission:

  NDA 205266: LATE COMPONENT - BIOMETRICS

  NDA 205266: LATE COMPONENT - CLINICAL PHARMACOLOGY

- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application. Novartis confirmed that this information will be included in the original NDA.

- A preliminary discussion on the need for a REMS was held; based on the information provided in the meeting package, FDA agreed with Novartis's proposal not to include a REMS in the initial NDA submission. FDA advised that during the review of the NDA, FDA may identify safety information that would require Novartis to prepare a REMS, to ensure that the benefits of the drug outweigh the risks. FDA strongly recommended that Novartis submit a proposed risk management plan to monitor for teratogenicity and other serious risks such as myopathy and rhabdomyolysis. FDA also recommended that Novartis include additional activities in a Risk Management Plan such as the pregnancy registry and evaluation of drug interactions with oral contraceptives outlined in the January 30, 2012, approval letter for NDA 203388 found at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/

4.0 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.

On February 6, 2014, FDA confirmed agreement to Novartis' January 8, 2014, Agreed iPSP, in which Novartis stated that Novartis' plan is to request a waiver from all requirements from PREA in a marketing application for all pediatric age groups for the indication of basal cell carcinoma (BCC).

For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

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5.0 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 responsible for the commercial process, 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.

In addition to commercial manufacturing facilities, please include all manufacturing facilities where batches were made to support the application (if they differ from facilities intended for commercial manufacturing). Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				

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2.				

6.0 OFFICE OF SCIENTIFIC INVESTIGATIONS

OSI requests that the items in Attachment 1 be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., Phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe the location or provide a link to the requested information. Site-specific individual data listings for the pivotal study may be submitted prior to the submission of the NDA, but no later than the final component, of the NDA, for all clinical study sites that enrolled subjects in the pivotal study. Provision of complete information as requested in Parts I and II will facilitate, and more importantly accelerate, development of clinical investigator and sponsor/monitor/CRO inspection assignments and the preparation of the inspection-supporting background packages. In order for the application to be considered complete at submission, it should contain elements that fully address Part I (General Study Related Information and Comprehensive Clinical Investigator Information) and Part II (Subject Level Data Listings by Site) of the OSI Pre-NDA/NDA Request (See Attachment 1).

Attachment 2 provides instructions for where all OSI requested items should be placed within an eCTD submission

7.0 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 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.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

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8.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no additional items that required further discussion.

9.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Novartis to submit CMC pre NDA meeting request	Novartis	Submitted April 16, 2014
Novartis to submit meeting briefing materials for the CMC meeting no later than April 28, 2014	Novartis	April 28, 2014

10.0 ATTACHMENTS AND HANDOUTS

- Office of Scientific Investigations Attachment 1
- Office of Scientific Investigations Attachment 2- Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format
- Novartis Slides provided as handouts during April 15, 2014 meeting which were formally submitted to this IND on April 30, 2014

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Office of Scientific Investigations Attachment 1

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g. Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g. as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).

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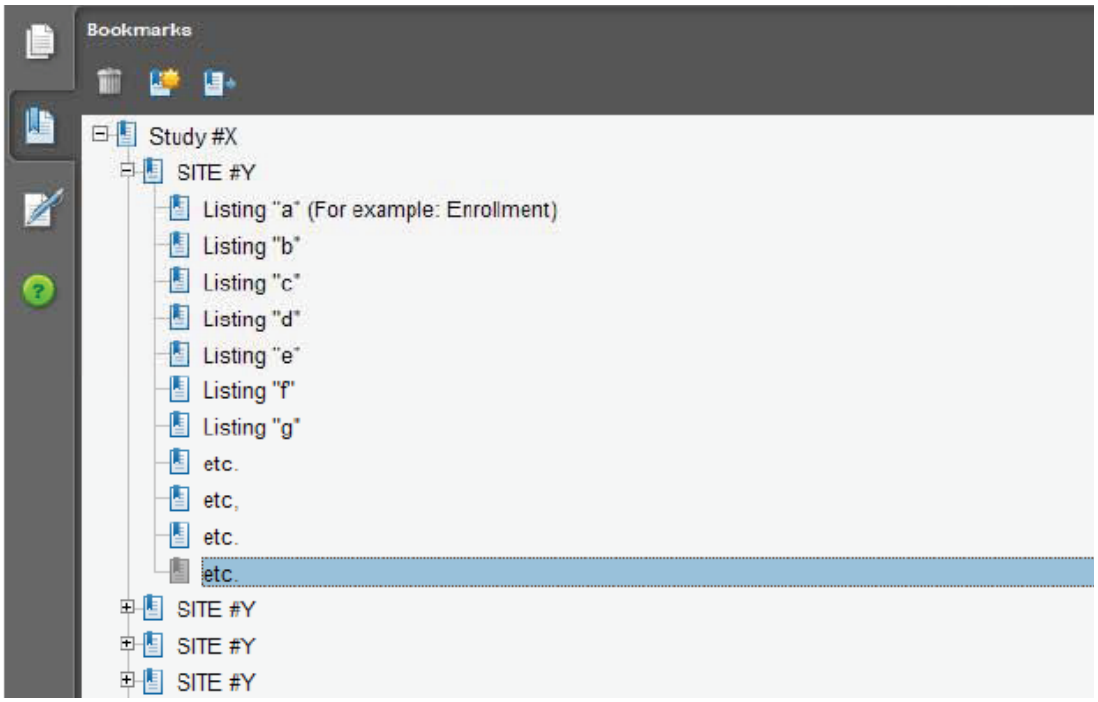
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
    a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
    b. Subject listing for treatment assignment (randomization)
    c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
    d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
    e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
    f. By subject listing, of AEs, SAEs, deaths and dates
    g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
    h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
    i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
    j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:

Reference ID: 3506369



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft "Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Reference ID: 3506369

Office of Scientific Investigations Attachment 2
Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

OSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

Reference ID: 3506369

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1 (http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

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/s/

ANUJA PATEL
05/14/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 102961

ADVICE/INFORMATION REQUEST

Novartis Pharmaceutical Corporation
Attention: John Robinson, Ph.D.
Director, Drug Regulatory Affairs Oncology
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Robinson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for "sonidegib (LDE225)."

We also refer to your amendment dated January 8, 2014, containing an Agreed Initial Pediatric Study Plan (iPSP) submitted in response to our letter of December 9, 2013.

We confirm our agreement to your January 8, 2014, Agreed iPSP, in which you state that your plan is to request a waiver from all requirements from PREA in a marketing application for all pediatric age groups for the indication of basal cell carcinoma (BCC).

As sponsor of this IND, you are responsible for compliance with the FDCA (21 U.S.C. §§ 301 et. seq.) as well as the implementing regulations [Title 21 of the Code of Federal Regulations (CFR)]. A searchable version of these regulations is available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm. Your responsibilities include:

- Reporting any unexpected fatal or life-threatening suspected adverse reactions to this Division no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)].

  Because your IND is in eCTD format, submit 7-day reports electronically in eCTD format via the FDA Electronic Submissions Gateway (ESG). To obtain an ESG account, see information at the end of this letter.

- Reporting any (1) serious, unexpected suspected adverse reactions, (2) findings from other clinical, animal, or in-vitro studies that suggest significant human risk, and (3) a clinically important increase in the rate of a serious suspected adverse reaction to this Division and to all investigators no later than 15 calendar days after determining that the information qualifies for reporting [21 CFR 312.32(c)(1)]. If your IND is in eCTD

format, submit 15-day reports to FDA electronically in eCTD format. If your IND is not in eCTD format, you may submit 15-day reports in paper format; and

- Submitting annual progress reports within 60 days of the anniversary of the date that the IND went into effect (the date clinical studies were permitted to begin) [21 CFR 312.33].

Secure email between CDER and sponsors 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 (except for 7-day safety reports for INDs not in eCTD format).

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. If your IND is in eCTD format, you should obtain an ESG account. For additional information, see http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/.

If you have any questions, contact Anuja Patel, Regulatory Health Project Manager, at (301) 796-9022.

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

Enclosures:
Agreed Initial Pediatric Study Plan (iPSP) submitted January 8, 2014

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/s/

PATRICIA KEEGAN
02/06/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 102961

ADVICE/INFORMATION REQUEST

Novartis Pharmaceutical Corporation
Attention: John Robinson, Ph.D.
Director, Drug Regulatory Affairs Oncology
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Robinson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for "sonidegib (LDE225)."

We refer to your amendment dated October 2, 2013 containing a proposed initial Pediatric Study Plan (iPSP).

Your initial PSP states your intent to request a disease specific waiver from the requirements of PREA for all pediatric age groups for the indication of basal cell carcinoma (BCC) based on the following criteria:

- the indication of BCC has extremely limited applicability to pediatric patients; and,
- the disease occurs primarily in the adult population and is listed in Attachment A of "*FDA's Guidance for Industry How to Comply with the Pediatric Research Equity Act*" of studies that are impossible or highly impractical in pediatric patients. The link to the guidance is found at: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm079756.pdf

We have the following comments and requests:

1. We have completed our review of the proposed initial Pediatric Study Plan. We do not find that a meeting is necessary and do not have proposed modifications to that plan. We acknowledge that your iPSP plan, which states that you do not intend to conduct studies in pediatric subjects and will submit a request for waiver from all requirements from PREA in a marketing application for sonidegib (LDE225).

2. Please submit a letter within 90 days of receipt of this communication, stating your agreement or disagreement with our understanding of the initial Pediatric Study Plan. If you agree, the cover letter should be titled "Agreed Initial Pediatric Study Plan" and

should document your agreement with the initial pediatric study plan as re-stated by the FDA and include a copy of the agreed upon initial Pediatric Study Plan.

As sponsor of this IND, you are responsible for compliance with the FDCA (21 U.S.C. §§ 301 et. seq.) as well as the implementing regulations [Title 21 of the Code of Federal Regulations (CFR)]. A searchable version of these regulations is available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm. Your responsibilities include:

- Reporting any unexpected fatal or life-threatening suspected adverse reactions to this Division no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]. If your IND is in eCTD format, submit 7-day reports electronically in eCTD format. If your IND is not in eCTD format, you may submit 7-day reports by telephone or fax;

- Reporting any (1) serious, unexpected suspected adverse reactions, (2) findings from other clinical, animal, or in-vitro studies that suggest significant human risk, and (3) a clinically important increase in the rate of a serious suspected adverse reaction to this Division and to all investigators no later than 15 calendar days after determining that the information qualifies for reporting [21 CFR 312.32(c)(1)]. If your IND is in eCTD format, submit 15-day reports to FDA electronically in eCTD format. If your IND is not in eCTD format, you may submit 15-day reports in paper format; and

- Submitting annual progress reports within 60 days of the anniversary of the date that the IND went into effect (the date clinical studies were permitted to begin) [21 CFR 312.33].

If you have any questions, contact Anuja Patel, Regulatory Health Project Manager, at (301) 796-9022.

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

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/s/

PATRICIA KEEGAN
12/09/2013

INTERNAL MEMORANDUM OF MEETING MINUTES

MEETING DATE: August 8, 2013
TIME: 11:30 AM to 12:30 PM
LOCATION: Teleconference, WO 22, Room 2376
APPLICATION: IND 102961
DRUG NAME: sonidegib (LDE225)
TYPE OF MEETING: Informal Teleconference (non-PDUFA meeting)

FDA ATTENDEES:
Suzanne Demko - DOP2 Clinical Team Leader
Kaushik Shastri - DOP2 Clinical Team Leader
Anuja Patel - DOP2 RPM

NOVARTIS ATTENDEES:
Neil Gallagher – Global Program Head, LDE225
Dereck Amakye – Global Clinical Program Head, LDE225
Ying Wang – Global Clinical Leader, LDE225
Manisha Mone – Sr. Clinical Trial Head, LDE225
Kalyanee Appanna – Executive Director, Biostatistics
Tingting Yi – Associate Director, Biostatistics
Stephan Haemmerli – Global Program Team Director, LDE225
Sandra Chica – Global Head Imaging, Oncology Clinical Development
David Lebwohl – Global Head, Oncology Clinical Development
Matthias Jauslin – Global Program Regulatory Director, LDE225
Gabriela Gruia – Global Head, Drug Regulatory Affairs
Shanthi Ganeshan – North America Head, Drug Regulatory Affairs

MEETING PURPOSE: A teleconference took place on August 8, 2013, between FDA and Novartis during which IND 102961 was discussed. Novartis provided a slide deck to facilitate discussion which included as an attachment to this memo. Specifically discussed were a June 12, 2013, submission to the IND containing the fifth amendment to Protocol CLDE225A2201 and FDA comments on July 8, 2013 and August 2, 2013.

Our discussion points, Novartis responses, and the meeting summary are included in the Discussion section below.

BACKGROUND: On April 3, 2013, Novartis submitted an amendment requesting written feedback from FDA as we had we had denied their type C meeting request to discuss the development plan for LDE225 for potential NDA submission. On July 8, 2013, FDA issued a written response to the April 3, 2013, submission and informed Novartis that there is insufficient information provided in the April 3, 2013 submission to determine whether Study CLDE225A2201 has demonstrated substantial evidence of a treatment effect on a surrogate endpoint or of an effect that is a measure of direct clinical benefit, sufficient to support filing of the proposed NDA. In addition, in the July 8, 2013 written response, FDA informed Novartis

that there is inadequate information to determine whether there is sufficient data for either the 200 mg or the 800 mg daily doses of sonidegib to determine whether the safety database is adequate to characterize serious risks and describe the adverse reaction profile in sufficient detail in product labeling.

On June 12, 2013, Novartis submitted a fifth amendment of Protocol CLDE225A2201. FDA issued a written response on August 2, 2013 in response to Novartis June 12,2013 submission and informed Novartis that the proposed revisions to the response criteria, specifically the revisions regarding (b) (4) are not acceptable and may alter the acceptability of these data to support labeling claims.

Summary Discussion:
A teleconference took place on August 8, 2013, between FDA and Novartis during which IND 102961 was discussed. Novartis provided a slide deck to facilitate discussion, it is included as an attachment to this memo. Specifically discussed were a June 12, 2013, submission to the IND containing the fifth amendment to Protocol CLDE225A2201 and FDA comments on July 8, 2013, and August 2, 2013.

During the teleconference, FDA informed Novartis that the provision in amendment 5 of the protocol (b) (4) is not acceptable. FDA strongly recommended that Novartis amend Protocol CLDE225A2201 to make it clear that response assessments will be harmonized to include evaluation of the same target lesions by each modality included in the composite assessment plan, and that all versions (current and future) of Protocol CLDE225A2201 ensure that, for patients with locally advanced basal cell carcinoma, a composite overall response assessment for each target lesion incorporates photographic, MRI and histological evaluation as described in Appendix 2 of the protocol. In addition, FDA informed Novartis that the algorithm for determining responses, contained in Appendix 2 of the protocol, is incomplete. As written, the algorithm does not provide for assessment situations in which MRIs of target lesions are not available (either because the lesion(s) are not amenable to being captured or are missing), partial response, or stable disease is observed and photographed and biopsy of the lesion is negative. In such a case, Novartis agreed that the composite assessment would lead to a determination that the patient had either a partial response or stable disease, not a complete response, as suggested by the current algorithm.

FDA informed Novartis that in order to provide data that would be reviewable should a regulatory filing be submitted to FDA, the above issues with disease assessments will need to be rectified. FDA agreed to review Novartis proposed changes to be included in amendment 6 in advance of the amendment being submitted to the IND.

The following agreements were captured during the teleconference:

- Novartis will clarify that for laBCC patients assessed with all modalities (photo, MRI and histology) the same lesion has been evaluated, i.e. surface component (by photo and biopsy), sub-dermal component (by MRI and biopsy, where practicable).
- Novartis will update Appendix 2, table 3-1 to capture all possible assessment scenarios

- Rather than withdrawing Amendment 5, Novartis agreed to submit Amendment 6 to provide clarity and propose a plan for integrated evaluation of lesions using the three modalities
- FDA agreed to review the draft of Amendment 6 prior to implementation

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/s/

ANUJA PATEL
08/15/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 102961

Novartis Pharmaceuticals Corporation
Attention: John Robinson, Ph.D.
Sr. Associate Director, DRA Oncology
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080

ADVICE/INFORMATION REQUEST

Dear Dr. Robinson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for "sonidegib (LDE225)."

We also refer to guidance provided on this development program during the End-of-Phase 1 meeting held on June 9, 2011, to the clinical protocol for Study CLDE225A2201 submitted on July 5, 2011, and to FDA's correspondence regarding this protocol dated December 22, 2011. In addition, we refer to your February 13, 2013, correspondence requesting a type C meeting to discuss the planned analyses from the LDE225 development program in preparation for a planned NDA submission. This meeting was denied because your meeting request was premature and this was communicated to you via meeting denied letter dated March 6, 2013. Lastly, we refer to your submission dated April 3, 2013 containing a briefing package requesting a written feedback from FDA in lieu of the Type C meeting that was denied. The purpose of your briefing package was to obtain written comment from the FDA on the planned analyses from the sonidegib development program in preparation for a possible NDA submission for the following indication:

> "Sonidegib is indicated for the treatment of patients with locally advanced (b) (4) basal cell carcinoma (BCC) who are not amenable to curative surgery or radiation therapy."

BACKGROUND

According to the April 3, 2013 briefing package, the key efficacy data supporting the proposed NDA would be derived from Study CLDE225A2201. Novartis also intends to submit the results of all completed studies of oral sonidegib.

In the April 3, 2013 briefing package, Novartis describes Study CLDE225A2201 as an ongoing randomized (2:1), non-comparative, parallel cohort, multicenter phase 2trial evaluating the anti-tumor activity of two doses of sonidegib in 233 patients with patients with locally advanced basal cell carcinoma (laBCC) or metastatic basal cell carcinoma (mBCC). Novartis further states in the April 3, 2013 briefing package that enrollment is complete for Study CLDE225A2201. Randomization was stratified by stage of disease (laBCC or mBCC), disease histology for laBCC patients (aggressive or non-aggressive), and geographic region of enrollment (Australia, Europe, or North America). Eligible patients were randomly assigned to the following two treatment arms:

- Arm 1: sonidegib 800 mg orally in capsule form, once daily
- Arm 2: sonidegib 200 mg orally in capsule form, once daily

Treatment was to be continued until documented disease progression as confirmed by central review, discontinuation due to intolerable toxicity, withdrawal of consent to study treatment, death, at the discretion of the investigator, or early termination of the study.

The primary endpoint is objective response rate (ORR), defined as the proportion of patients with a partial response (PR) or complete response (CR), as determined by central review. The central committee will assess ORR according to the protocol-specified modified RECIST (mRECIST) criteria for patients with laBCC and according to RECIST version 1.1 for patients with mBCC. The primary analysis will be performed on the primary efficacy analysis set (pEAS), a subset of the all patient, including laBCC patients with tumors that have been adequately assessed by photographs or MRI or both, and including all mBCC patients. The primary analysis will be performed when all patients have been treated for 24 weeks or discontinued treatment. No formal comparisons between two treatment groups are planned. The final analysis of efficacy and safety will be performed at 78 weeks following enrollment of the last patient. For ORR and CRR, their maximum likelihood estimates for each treatment arm and their 95% exact binomial confidence intervals (Clopper and Pearson 1934) will be provided.

The key secondary endpoints include duration of overall response (DoR) and complete response rate (CRR). The DoR and CRR are determined by central review, according to mRECIST for laBCC patients and RECIST 1.1 for mBCC patients. Other secondary objectives of the study include progression-free survival (PFS), time to tumor response (TTR) and overall survival (OS).

GENERAL COMMENTS:
Regarding your development program intended to support a proposed NDA:

There is insufficient information provided in the April 3, 2013 submission to determine whether Study CLDE225A2201 has demonstrated substantial evidence of a treatment effect on a surrogate endpoint or of an effect that is a measure of direct clinical benefit, sufficient to support filing of the proposed NDA. In addition, there is inadequate information to determine whether there is sufficient data for either the 200 mg or the 800 mg daily doses of sonidegib to determine whether the safety database is adequate to characterize serious risks and describe the adverse reaction profile in sufficient detail in product labeling.

In addition, we have the following responses to the questions included in your briefing package. **These responses do not constitute FDA's agreements on the final contents of a complete application for an NDA submitted under the PDUFA V program.**

FDA RESPONSES TO SPONSOR QUESTIONS:

1. ***Does the Agency agree with the clinical studies to be included in the eCTD to support the submission of the NDA for the proposed indication?***

FDA Response: With regard to the clinical studies as proposed in Table 2.1 of the Novartis briefing document, FDA generally agrees with the proposal to submit studies LDE225X2101, LDE225B2209, and LDE225A2201 to support clinical safety and efficacy.

Because Study LDE225X1101 is ongoing, inclusion of this preliminary and possibly incomplete or unaudited data is not recommended in the proposed NDA.

FDA generally agrees with the list of proposed clinical pharmacology studies to be submitted, but has the following additional recommendations for support of an NDA submission:

a. Include the final study report from the ongoing food effect study (LDE225A2114) in your NDA.

b. Conduct a drug-drug interaction study with a gastric pH elevating drug (proton pump inhibitor, histamine receptor antagonist, or antacid) (b) (4) .

c. Conduct a drug-drug interaction study with a known BCRP substrate (e.g., rosuvastatin) given *in vitro* data suggesting that sonidegib is a BCRP inhibitor. Coadministration of sonidegib and rosuvastatin (BCRP substrate) may potentially result in a clinically important drug-drug interaction and increased risk for rhabdomyolysis or other muscle related adverse events.

d. Evaluate the *in vitro* ability of sonidegib to act as an inhibitor of OATP to determine the need for a drug-drug interaction study. If sonidegib is found to be an OATP inhibitor, coadministration of sonidegib and statins (OATP substrate) may potentially result in a clinically important drug-drug interaction and increased risk for rhabdomyolysis or other muscle related adverse events.

e. Evaluate the *in vitro* ability of sonidegib to act as a potential inducer of CYP1A2 and CYP2B6 or a potential substrate of BCRP.

With regard to comments b through e above, please identify the status of these requested studies at the time of your pre-NDA meeting. Please also see FDA Response to Question 6.

2. ***Does the Agency agree that the analysis methods for the primary and secondary endpoints for the pivotal Phase II study as described in the statistical analysis plan for Study A2201 are adequate to support the filing of sonidegib in the proposed indication?***

FDA Response: FDA recommends that the primary analysis of objective response rate (ORR) and key secondary analyses of progression-free survival (PFS) and overall survival (OS) be performed in the intent to treat population (all randomized patients who received study treatment), while the analysis of ORR in the "Primary Efficacy Analysis Set (pEAS)," which is a subset of all patients who are assigned study treatment and comprises all mBCC patients and all laBCC patients who are adequately assessed according to mRECIST should be considered a supportive analysis. Please identify the number of laBCC patients for whom sufficient data were obtained using the criteria of "adequately assessed by photographs, MRI, or both." If there are substantial differences between the two analyses, the most appropriate analysis for establishing efficacy and to support labeling claims will be determined during the review of the NDA.

FDA acknowledges that treatment effects in the two dose cohorts will not be formally compared. As noted by FDA during the June 9, 2011, end-of-Phase 1 meeting, (b) (4) FDA cautioned that the possibility of response rate being similar in both arms which might pose regulatory issues.

3. ***Does the Agency agree to the proposed pooling strategies and plan for the Summary of Clinical Efficacy (SCE) and Summary of Clinical Safety (SCS) as described below?***

FDA Response: No, FDA does not agree to the proposed pooling strategies and plan for the Summary of Clinical Efficacy (SCE) and Summary of Clinical Safety (SCS). Safety and efficacy data should be provided by subgroups based on dose administered.

In addition, Novartis must provide case report forms for all patients who died or dropped out during the study or within 30 days of the last dose and must provide a narrative summary for all serious adverse events for the ongoing studies of sonidegib, with a data cut-off date of July 31, 2013.

4. ***Does the Agency agree to the proposed approach to satisfy the requirements for an Integrated Summary of Efficacy (ISE) and an Integrated Summary of Safety (ISS)?***

FDA Response: Yes, FDA agrees that Novartis' proposed approach is consistent with the guidance on "Integrated Summaries of Effectiveness and Safety: Location within the Common Technical Document"

5. ***Does the Agency agree to the Novartis proposal for the submission of electronic datasets as described below?***

FDA Response: The proposed plan for submission of electronic datasets appears acceptable. Additional recommendations for the clinical pharmacology sections of the NDA submission and population pharmacokinetic analysis reports will be provided at the time of a Type B Pre-NDA meeting.

6. ***Does the Agency agree with the proposed analysis plan to assess the potential for QT/QTc interval prolongation?***

FDA Response: No, FDA does not agree. (b) (4) In the Investigator's Brochure, the steady-state C_{max} is reported to be 3µM (1455 ng/mL) based on simulations. These concentrations were exceeded in a pilot relative bioavailability study (LDE225A2114) when the 800 mg capsule was administered with a high-fat meal (C_{max} = 1730 ng/mL). Therefore, it appears to be possible to achieve therapeutic and supratherapeutic exposures in a thorough QT study when a single dose is administered with a high fat meal in healthy volunteers.

7. ***Does the Agency agree with Novartis proposal for providing CRFs and Patient Narratives to fulfill the NDA review requirements?***

FDA Response: Yes, FDA agrees that Novartis' proposal for providing CRFs and Patient Narratives fulfills the NDA requirements under 21 CFR 314.50.

8. ***Does the Agency agree to Novartis request for a full waiver of the requirement to submit pediatric assessments for sonidegib in BCC as well as inclusion of the Type C meeting minutes in the NDA as documentation of FDA's agreement to grant the full waiver?***

FDA Response: Novartis should submit a request for a waiver of pediatric studies that is disease-specific with the NDA. The waiver request should contain the proposed indication for which the waiver is sought, what pediatric age groups are included, a rationale and justification for requesting the waiver, and a certification statement indicating that sonidegib (LDE225) qualifies for a disease-specific waiver as outlined in the draft FDA Guidance: "How to Comply with the Pediatric Research Equity Act" (September 2005). A determination regarding a request for waiver will be made during review of the NDA.

In addition, 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. Since you do not intend to request an EOP2 meeting for this development program, 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. 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.

If you have any questions, contact Anuja Patel, Regulatory Project Manager, at (301) 796-9022.

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

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/s/

PATRICIA KEEGAN
07/08/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 102961

MEETING DENIED

Novartis Pharmaceuticals, Corporation
Attention: John Robinson, PhD
Senior Associate Director, Oncology Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Robinson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for LDE225.

We also refer to your February 13, 2013, correspondence requesting a type C meeting to discuss the planned analyses from the LDE225 development program in preparation for a planned NDA submission.

We are denying the meeting because based on the information contained in your meeting request and your March 6, 2013 electronic mail correspondence, your request is premature. Specifically, your request is more appropriately classified as a Type B End-of-Phase 2/Pre-NDA meeting. Please resubmit your meeting request as a Type B meeting when the high-level data to support your pivotal trial is available.

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

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
03/06/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 102961

MEETING MINUTES

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080

Attention: Chandrika Kumar, PhD
Associate Director, Drug Regulatory Affairs

Dear Dr. Kumar:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for LDE225.

We also refer to the meeting between representatives of your firm and the FDA on June 9, 2011. The purpose of the meeting was to discuss specific aspects of the development plan of LDE225 in patients with locally advanced [redacted] (b) (4) basal cell carcinoma that is not amendable to radiation therapy or curative surgery (End-of-Phase 1).

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 me at (301) 796-4256.

Sincerely,

{See appended electronic signature page}

Christy Cottrell
Regulatory Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End-of-Phase 1

Meeting Date and Time: June 9, 2011 at 11:00 am
Meeting Location: WO22, Room 1419

Application Number: IND 102961
Product Name: LDE225
Indication: **Basal cell carcinoma**
Sponsor/Applicant Name: Novartis Pharmaceuticals Corporation

Meeting Chair: Patricia Cortazar, MD
Meeting Recorder: Christy Cottrell

FDA ATTENDEES

Anthony Murgo, MD, MS, FACP, Associate Director OODP IO, Acting Deputy Director DDOP
Patricia Cortazar, MD, Lead Medical Officer
Genny Schechter, MD, Medical Officer
Shenghui Tang, PhD, Team Leader, DB 5
Qiang (Casey) Xu, PhD, Mathematical Statistician, DB 5
Christy Cottrell, Regulatory Project Manager

SPONSOR ATTENDEES

Margaret Dugan MD, Vice President, Global Program Head, LDE225, Oncology Clinical Development
Dereck Amakye MD, Global Clinical Program Head, LDE225, Oncology Clinical Development
Jyotirmoy Dey PhD, Senior Associate Director, Biostatistics
Eunju Hurh PhD, Senior Fellow, Clinical Pharmacokinetics
Soraya Madani PhD, US Regulatory Policy and FDA Liason
Shanthi Ganeshan PhD, Executive Director, Oncology Drug Regulatory Affairs
Matthias Jauslin PhD, Global Program Regulatory Director, LDE225, Oncology Drug Regulatory Affairs
Chandrika Kumar PhD, Associate Director, Oncology Drug Regulatory Affairs
(b) (4)

BACKGROUND

Study LDE225A2201 is a multi-center, adaptive, randomized double-blind Phase II study to investigate the safety and efficacy of LDE225 in patients with locally advanced (b) (4) basal cell carcinoma who are not eligible for curative surgery or radiotherapy. One hundred twenty (120) patients will be randomized 2:1 to receive either 800 mg or 200 mg of LDE225 on a continuous once daily dosing schedule. Stratification factors will include locally advanced and

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metastatic BCC and aggressive and non-aggressive histological subtypes. The primary endpoint is objective response rate (ORR) determined by local investigator assessments. Secondary endpoints include time to tumor response and duration of overall response. An interim analysis to assess safety and efficacy will be performed when the first 48 randomized patients either have been treated for 16 week so have discontinued treatment or have completed withdrawn from the study. Data will be reviewed by an independent data monitoring committee. Futility in terms of efficacy will be based on the observed overall response rate on each treatment arm per pre-specified criteria.

DISCUSSION

1. Novartis believes study A2201 is adequately designed to assess benefit/risk of oral LDE225 in the treatment of locally advanced [redacted] (b) (4) BCC and support submission of a NDA for this indication. Does the Agency agree with the overall design in general and the following design elements in particular:

   a) Choice of treatment arms?

   FDA RESPONSE: No. We strongly encourage you to select the appropriate dose before you embark in a registration study. [redacted] (b) (4) **Please discuss your rationale for assuming that a dose response effect will be observed.**

   Novartis Response: Novartis would like to discuss further the rationale for the potential to observe a dose response effect at the face to face meeting-Please see attached slides.

   MEETING DISCUSSION: See appendix for slides shown during the meeting. The Division cautioned again about the possibility of response rate being similar in both arms which might pose regulatory issues. The Division further commented that the sample size in both arms is small. The Division would prefer at least 100 patients in the 800 mg arm to provide additional data on drug safety and activity.

   b) Rationale for dose selection?

   FDA RESPONSE: See response to Question #1a.

   Novartis Response: Novartis would like to discuss further the rationale for dose selection at the face to face meeting-Please see attached slides.

   MEETING DISCUSSION: See above.

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c) Adequacy of the eligibility criteria to define the target population on which safety and efficacy will be established?

FDA RESPONSE: No.

- **According to the protocol submitted in the meeting package both treated (except patients treated with Hh pathway inhibitors) and untreated patients with locally advanced for metastatic BCC could be enrolled on this study. As these populations may respond differently either restrict enrollment to untreated patients or stratify randomization based on history of prior therapy for locally advanced / metastatic BCC.**

  Novartis Response:

  - *Typically patients with local disease would have been treated with surgery and/or radiation or other local therapies; therefore it is not feasible to restrict the study to only untreated patients.*
  - *Novartis recognizes stage of disease (locally advanced BCC, metastatic BCC) and histological subtype (aggressive and non-aggressive histology) to be important prognostic factors. The study protocol therefore incorporates stratification by these factors and ensures that they are balanced across treatment arms. Additional stratification factors were not considered feasible in view of the sample-size of the study.*
  - *Novartis proposes to include in the Report and Analysis Plan document a provision for summarizing the overall response rate in locally advanced BCC patients with or without prior radiation therapy. In view of the sample size of the study, these subgroup analyses should be interpreted with caution.*

  MEETING DISCUSSION: Clarification: The Division stated that there is a need to have a complete undestanding of the patient population to be treated in the proposed study. Therefore, the Division asked the sponsor to clarify in the protocol if patients have progressed on an existing therapy, no therapy is indicated or are no longer responding to recognized therapies for their current stage of disease (e.g., if metastatic, patient has not been treated for that metastatic disease). If you choose to enroll previously treated patients and are not stratified by these factors, you will at least need to collect the information for later analysis.

- **You will need to better define the locally advanced BCC population. The eligibility criteria should clearly state that the study is limited to locally advanced BCC patients for whom surgery or radiation therapy or other local therapy is not an option, such as patients with large periorbital tumors, etc. In addition, for patients with locally advanced BCC, you will need to collect**

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information as to the reason why these patients are not amenable to surgery management, local therapies, or radiation.

Novartis Response:

Section 4.1 (inclusion criteria) of the protocol states, "Patients with a histologically confirmed diagnosis of locally advanced BCC that is not amenable to radiation therapy or curative surgery." We will amend the protocol to also include patients for whom other local therapies are not curative as suggested by the Agency. While it is not possible to provide an exhaustive list of specific criteria for defining non- curative lesions, we will collect information as to the reason why these patients are not amenable to surgery management, local therapies, or radiation in the CRF. Reasons for eligibility may include, but not limited to:

- *Patients with BCCs in anatomically challenging locations, for example, the eye, inner canthus, nose and ears, for which surgery and/or radiation therapy may result in severe disfigurement or dysfunction.*
- *Patients with significant local extension outside of such anatomic areas that have penetrated so widely and/or deeply as to preclude complete resection or where attempt to completely resect will result in severe disfigurement or dysfunction.*
- *Patients who are considered to be poor surgical risk due to multiple comorbidities.*
- *Patients where radiation therapy is not appropriate due to: prior cumulative radiation treatment, judgment of radiation oncologist that such tumor is unlikely to respond to therapy, or for whom radiation treatment is contraindicated for other reasons, for example, Basal Cell Nevoid Syndrome patients*

MEETING DISCUSSION: The Division clarified that the eligibility criteria needs to be clear so that patients who may be eligible for continued local therapy are excluded. The sponsor will be collecting this information. The Division suggested collecting information including prior treatments and duration of treatment, statements that the patient is not a candidate for surgical intervention and/or that the location is not amendable to radiation therapy. The sponsor should also include descriptive analyses about the population enrolled in the statistical analysis plan.

- **Revise the eligibility criteria to specifically state that patients who have radiation therapy to a lesion must have progression confirmed by biopsy after radiation therapy.**

Novartis Response:

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As stated in Section 3 of the protocol (Investigational plan, tumor biopsies), all patients with locally advanced BCC (including previously radiation-treated) will have biopsies and MRI scans performed prior to starting study therapy.

A biopsy may be used to document the presence of tumor (including that which might be due to recurrence following initial clearance or tumor remaining that never responded to initial treatment). However, since it cannot measure extent of disease, it is not a measure of disease progression by itself. Imaging studies and clinical assessment together with biopsy information will help determine progression and extent of disease.

MEETING DISCUSSION: None

- **Patients who enroll on study should have central histopathologic review of most recent biopsy of the lesion by a dermatopathologist to assure that the lesions are basal cell carcinoma without other malignant components.**

  Novartis Response: *Agree*

  Section 3 (Investigational plan, tumor biopsies) of the protocol has a provision for the collection of tumor biopsies prior to initiation of therapy for central biomarker and histological analyses. Inclusion criterion 2 (page 36) also states that eligible patients will have histologically confirmed diagnosis of BCC.

  Archival or fresh tumor biopsies from metastatic BCC patients will be collected where possible and centrally analyzed.

  MEETING DISCUSSION: The sponsor is stratifying by histopathology (metatypical and major squamous components) to balance more aggressive tumors. The Division commented that if a large percentage of patients have primarily squamous cell or other histologies and are found to be ineligible, this could be problematic. The Division advised that the sponsor define patients very well and capture histopathology to ensure that basal cell carcinoma is the primary and not squamous. The Division wants to review the pathology reports of the central review and recommends central review of all eligible patients.

- **Since metastatic BCC metastasizes not only to lung but also to bone, discuss the omission of bone scans at study entry for patients with metastatic disease.**

  Novartis Response:

  In metastatic BCC patients, the incidence of metastasis to bone is less common. Novartis will amend the protocol to perform bone scans if clinically indicate, e.g., in patients with bone symptoms and also if other imaging techniques such as CT/MRI of chest and abdomen suggest presence of bone lesions.

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MEETING DISCUSSION: None

- **For enrollment on this study patients should have adequate organ function including a platelet count ≥ 100,000/ul, unless you can provide justification for a lower cutoff.**

  Novartis Response: Agree

- **Should the sponsor allow enrollment of patients previously treated for advanced local or metastatic BCC, prior therapy should be discontinued at least 4 weeks prior to initiation of LDE225 and all toxicity from prior therapy should be ≤ Grade 1 at time of initiation of therapy.**

  Novartis Response: Agree

d) Adequacy of the primary and secondary end points to assess the efficacy and safety of LDE225 in the target population?

FDA RESPONSE: Yes, the primary endpoint of ORR is acceptable provided that the responses are of clinically meaningful magnitude and duration and the safety profile is acceptable. The secondary endpoints are acceptable. We recommend the first secondary endpoint be duration of response rather than time to response.

Novartis Response: Agree

- **With regard to the primary endpoint of ORR, an independent review board should confirm the investigator determination of response.**

  Novartis Response: Agree

- **A window of two weeks for each assessment period is too lengthy when assessments are required every 8 weeks. The time period should be reduced to one week to avoid problems with determining the exact time to response, duration of response, and progression.**

  Novartis Response: Agree

- **Discuss your rationale for an assessment at four weeks for locally advanced BCC patients (and optionally for metastatic BBC patients). In addition, discuss your rationale for doing the first assessment for all patients at 9 weeks rather than 8 weeks. An irregular study calendar may result in missing data due to investigator confusion and create difficulties in interpreting the duration of response data.**

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Novartis Response:

In our experience tumor response has been observed as early as 7 weeks after initiating therapy. Given that available treatments for early-stage BCC, such as surgery, provide immediate results, it is considered important to assess the time to response to LDE225 therapy. Performing MRI scans in patients with locally advanced disease at week 5 will potentially allow a better assessment of the onset of tumor response following LDE225 therapy.

For clarification, tumor assessment during week 9 implies that patients would have completed 8 weeks of therapy. It is expected that scans will be performed early in the stipulated weeks e.g. on day 1 of week 9. Following the week 9 scan, further scans occur regularly at 8-week intervals. Novartis will proactively follow-up with investigators to adhere to the schedule of assessments.

MEETING DISCUSSION: None

- **Please confirm whether all locally advanced patients will have both MRI and photographs with ruler measurements at each assessment. Provide information as to how accurately depth of invasion, protruberance above the skin surface, and diameter can be measured in locally advanced BCC with only visual observation.**

Novartis Response: Agree

Novartis acknowledges that clinical photography alone cannot accurately assess the depth of the lesions. All patients with locally advanced BCC will have MRI scans at each tumor assessment.

MEETING DISCUSSION: None

- **Provide definitions for response and progression in locally advanced BCC carcinoma addressing issues of ulceration and measurement of scar / fibrosis formation as RECIST does not totally address response / progression in locally advanced skin lesions.**

Novartis Response:

Novartis acknowledges the difficulty in handling response assessments for ulcerated lesions and residual scars according to RECIST. Sections 3 (tumor biopsies) and 6.2.1 (efficacy) of the protocol state that biopsies will be performed following confirmation of complete response to determine histological clearance.

In addition, where there is uncertainty about the nature of the residual lesion (eg. scar/fibrous tissue), biopsies will be performed to determine the extent of tumor response.

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Tumor progression will be determined as per RECIST.

MEETING DISCUSSION: The sponsor needs to work on the protocol definition for response categories and progression for locally advanced in terms of ulceration and protuberance (these are not covered well in RECIST)- criteria for skin pictures and imaging. How will you define response, partial response, stable disease etc in this population? Propose modified RECIST criteria for those components not covered by RECIST. The Division would like to review this definition before you proceed.

- **Discuss the response categorization for patients with locally advanced disease who, on observation of response, have surgical resection of residual tumor. Discuss the statistical management of this type of patient with regard to response categorization and duration of response assessment.**

  Novartis Response:

  The primary endpoint, overall response rate, will be based only on tumor assessments prior to curative surgery or any other anti-neoplastic therapy.

  Should a patient undergo surgery after experiencing a partial response (PR), time-to-event endpoints dependent on response assessment (such as duration of response and PFS) will be censored on the date of final tumor assessment prior to surgery. If substantial numbers of patients undergo curative surgery, additional statistical methodology may be considered as supportive analysis for these endpoints. These contingencies will be described in the Report and Analysis Plan document for the study.

  MEETING DISCUSSION: None

- **Confirm that all patients considered to have a complete response (CR) will be biopsied with central review of pathology to confirm absence of tumor otherwise response assessment will be considered as PR.**

  Novartis Response:

  Complete response will be determined by RECIST. Following confirmation of CR, biopsies will be taken from the site of the original lesion to confirm histological clearance. The proportion of complete responders with histological clearance will also be reported.

  MEETING DISCUSSION: Include modified RECIST for locally advanced patients.

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e) Adequacy of the proposed sample size and randomization plan?

FDA RESPONSE: We recommend that you conduct a single arm study at a dose level known to be active in a sample size ≥ 120 patients so that the lower limit of the 95% confidence interval exceeds 20%, assuming the true ORR is 30%. Please also see response to Question #1a.

Novartis Response: Novartis would like to discuss the proposed sample size and randomization plan with the Agency at the face to face meeting.

MEETING DISCUSSION: See 1a.

f) Appropriateness of adaptation of the trial design based on the planned interim analysis?

FDA RESPONSE: See response to Question #1a and #1e. An interim analysis for futility conducted by a DMC would be acceptable.

Novartis Response: Agree

2. The safety data base at the time of NDA submission for the oral LDE225 program will consist of more than 350 patients, including at least 125 patients with BCC. Novartis considers that the expected safety data base is adequate to support the submission of an NDA in the proposed indication, which constitutes an unmet medical need in a rare subset of BCC patients. Does the Agency agree?

FDA RESPONSE: While the size of the safety database appears to be adequate, final determination of the adequacy of the safety database will be a review issue.

Novartis Response: Agree

MEETING DISCUSSION: None

3. Novartis considers that the safety monitoring plan proposed in the protocol section 7 will adequately safeguard patient safety during the course of the trial. Does the Agency agree?

FDA RESPONSE: Yes

MEETING DISCUSSION: None

4. Novartis considers that the range of clinical pharmacology studies planned as outlined below is sufficient to support registration and the proposed indication. Does the Agency agree?

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FDA RESPONSE: Your plan appears acceptable except for the following:

- **We recommend that you conduct *in vitro* studies with your drug to assess whether it is an inducer of any CYP isozymes. Please refer to the Guidance for Industry "Drug Interactions Studies — Study Design, Data Analysis, and Implications for Dosing and Labeling" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072101.pdf for more information.**

  Novartis Response: *Agree*

- **Submit your plan to assess the potential for QT/QTc interval prolongation for QT/IRT review.**

  Novartis Response: *Agree*

  MEETING DISCUSSION: None

5. Provided that the trial CLDE225A2201 meets the primary endpoint and demonstrates a favorable benefit/risk profile, Novartis considers that this trial could support full approval for the indication "treatment of patients with locally advanced (b) (4) basal cell carcinoma that is not amenable to curative surgery or radiotherapy". Does the Agency agree?

   FDA RESPONSE: The approval and the type of approval will be determined at the time of review.

   In a single-arm trial, all statistical analyses are considered as descriptive. Efficacy estimation based on ORR will need to be supported by adequate magnitude and duration with an acceptable risk/benefit ratio. Please also note that analyses for time to event endpoints (PFS and OS) are not interpretable in a single-arm study.

   Novartis Response: *Novartis acknowledges the Agency's comments*

   MEETING DISCUSSION: None

6. Novartis acknowledges FDA's views discussed recently at the Feb 8th 2011 ODAC for the appropriateness of a single arm trial for approval.

   Given that locally advanced (b) (4) constitutes a rare population, has high unmet medical need with no approved treatment options, Novartis is seeking the Agency's opinion on the acceptability of a single arm study which demonstrates substantial clinical benefit in this patient population for sub part H approval in order to make the drug available to patients in the earliest time frame possible.

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FDA RESPONSE: See responses to Question #1e and Question #5 above. Unmet medical need will be determined at the time of review of your NDA submission.

Novartis Response: Novartis acknowledges the Agency's comments

MEETING DISCUSSION: None

ADDITIONAL COMMENTS

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for 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 studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of 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 the following link:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

ISSUES REQUIRING FURTHER DISCUSSION
None

ACTION ITEMS
None

ATTACHMENTS AND HANDOUTS
Slides shown during the meeting are included.

_____	Concurrence:	_____
Christy Cottrell		Patricia Cortazar, MD
Regulatory Project Manager		Clinical Team Leader

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Reference ID: 2973331

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/s/

CHRISTY L COTTRELL
07/13/2011

PATRICIA CORTAZAR
07/13/2011

LATE-CYCLE COMMUNICATION DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205266

LATE-CYCLE MEETING MINUTES

Novartis Pharmaceuticals Corporation
Attention: Jessica Wang, Pharm.D.
Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Wang:

Please refer to your New Drug Application (NDA) dated September 26, 2014, received September 26, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Odomzo (sonidegib), 200 mg capsules.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on June 9, 2015.

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 Anuja Patel, Senior Regulatory Project Manager at (301) 796-9022.

Sincerely,

{See appended electronic signature page}

Suzanne G. Demko, P.A-C.
Cross Discipline Team Leader (CDTL)
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: Tuesday, June 9, 2015 11:00 A.M. to 12: 30 P.M., EST
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1415
Silver Spring, Maryland 20903

Application Number: 205266
Product Name: sonidegib (LDE 225), capsule, 200 mg, oral
Applicant Name: Novartis Pharmaceutical Corporation

Meeting Chair: Suzanne Demko
Meeting Recorder: Anuja Patel

FDA ATTENDEES
Richard Pazdur, Director, Office of Hematology and Oncology Products (OHOP)
Joseph Gootenberg, Deputy Director, Division of Oncology Products (DOP 2), OHOP
Jeffrey Summers, Deputy Director for Safety, DOP 2
Suzanne Demko, Clinical and Cross Discipline Team Leader, DOP 2
Denise Casey, Clinical Reviewer, DOP 2
Monica Hughes, Chief, Project Management Staff
Anuja Patel, Senior Regulatory Project Manager
Karen Hennessy, Safety RPM, DOP 2
Whitney Helms, Nonclinical Team Leader, Division of Hematology, Oncology, Toxicology (DHOT)
Alex Putman, Nonclinical Reviewer, DHOT
Kun He, Statistics (TL)
Huanyu (Jade) Chen, Statistics Reviewer
Hong Zhao, Clinical Pharmacology (TL)
Stacy Shord, Clinical Pharmacology Reviewer
Liang Zhou, ONDQA Application Team Lead (ATL), Office of Product Quality (OPQ)
William Adams, Drug Product (DP) Product Quality Reviewer, ONDQA
Lauren Iacono-Connor, OSI Reviewer, OSI Inspections
Nick Senior, OPDP Reviewer
Otto Townshend, DMEPA Safety Reviewer
Naomi Redd, DRISK Reviewer (TL)
Tamara Johnson, Maternal Health Acting Team Leader, Division of Pediatric and Maternal Health
Latonia Ford, Office of Safety Evaluation (OSE), Safety RPM
Morgan Walker, Patient Labeling Reviewer
Tracy Salaam, Team Lead for our Oncology Team for Division of Pharmacovigilance (DPV)
Shaily Arora, DPV Reviewer

EASTERN RESEARCH GROUP ATTENDEES
Christopher Sesi, Independent Assessor

APPLICANT ATTENDEES
Neil Gallagher, Global Program Head, Oncology
Dalila Sellami, Global Clinical Program Head, Oncology
Patrick Burnett, Global Program Medical Director, Immunology and Dermatology
Stephane Levy, Medical Unit Head, Immunology and Dermatology
Lily Zhao, Director, Oncology Biostatistics
Jocelyn Zhou, Fellow, Oncology Clinical Pharmacology
Michael Levine, Brand Safety Leader, Integrated Medical Safety, Oncology
Jessica Wang, Senior Associate Director, Oncology Drug Regulatory Affairs
Shanthi Ganeshan, NA Region Head, Oncology Drug Regulatory Affairs
Paula Rinaldi, US Head, Drug Regulatory Affairs, General Medicines
Michael Buska, Senior Global Program Regulatory Director, Drug Regulatory Affairs

APPLICANT ATTENDEES ON THE PHONE
Dominic Brees, Executive Director, Preclinical Safety
Nancy Turner, Director, Preclinical Safety
Henry Castro, Senior Global Clinical Leader, Oncology Clinical Development
Tingting Yi, Associate Director, Biostatistics, Oncology
Joyce Ann Sinno, Director, Senior Regulatory Expert, Global Regulatory CMC Oncology
Matthias Jauslin, Global Program Regulatory Director, Drug Regulatory Affairs
Lisa Krueger, Drug Regulatory Affairs

BACKGROUND

NDA 205266 was submitted on September 26, 2014 for Odomzo (sonidegib), 200 mg capsules.

Proposed indication(s): for the treatment of patients with locally advanced basal cell carcinoma (BCC) who are not amenable to curative surgery or radiation therapy (b) (4)

PDUFA goal date: September 26, 2015

FDA issued a Background Package in preparation for this meeting on May 28, 2015.

Reference ID: 3789638

DISCUSSION

Introductory Comments

Welcome, Introductions, Ground rules, Objectives of the meeting

***Discussion*: FDA informed Novartis that the purpose of the late cycle meeting was to exchange information and to inform Novartis of the status of the review. FDA provided ground rules for the discussion as provided in the Late Cycle Meeting Background Package that issued May 28, 2015. Novartis acknowledged the ground rules and no additional discussion occurred.**

Discussion of Upcoming Advisory Committee Meeting

***Discussion*: FDA stated that an Advisory Committee meeting is not planned; however. SGEs with an expertise in basal cell carcinoma were consulted with regard to aspects of the sonidegib application.**

REMS or Other Risk Management Actions

***Discussion*: FDA stated that no issues related to risk management have been identified to date and no REMS is planned.**

Discussion of Minor Review Issues

a. Clinical: FDA proposes (b) (4) the indication to the treatment of patients with locally advanced basal cell carcinoma (BCC) who are not amenable to curative surgery or radiation therapy.

***Discussion*: FDA informed Novartis that there were no outstanding issues or information requests.** (b) (4)

Reference ID: 3789638

b. Office of Scientific Investigations

Discussion: ***FDA stated that four site inspections were conducted; of which 2 were clinical sites. One of the clinical sites had compliance issues identified, in particular a large number of protocol deviations relative to other clinical sites, and some missed laboratory assessments and electrocardiograms (ECGs). A detailed review of these inspectional observations determined that the protocol deviations did not affect the study outcome or subject safety. The other inspected clinical site had no major issues.***

FDA also informed Novartis that 2 contract research organizations (CROs), [redacted] (b) (4) ***and*** [redacted] (b) (4) ***were inspected for their roles in the determination of efficacy outcomes. There were no major issues identified for these inspections.***

Finally, FDA stated that the site-specific subject data listings that Novartis provided in the application were extremely helpful in preparing and conducting the clinical inspections.

Novartis acknowledged FDA's response and no further discussion occurred.

c. Chemistry, Manufacturing, and Control: No minor review issues identified at this time.

Discussion: ***FDA stated that there were no issues at this time regarding the product quality review and the manufacturing facility inspections. FDA also stated that there are no planned CMC-related post-marketing requirements or commitments. Novartis acknowledged and no discussion occurred.***

Discussion of Postmarketing Requirements/Postmarketing Commitments

d. Pharmacology/Toxicology Post-Marketing Requirement:

- PMRs to evaluate the carcinogenicity of sonidegib in rats and mice.

Discussion: ***FDA reiterated that because of the life expectancy of the intended patient population, PMRs for carcinogenicity studies of sonidegib are warranted.***
[redacted] (b) (4)

Reference ID: 3789638

(b) (4)
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FDA acknowledged (b) (4) ***but stated that there may be strategies, such as changing the dosing frequency to maintain a reasonably level exposure, that would make these studies feasible.*** (b) (4)

FDA did not object to Novartis submitting additional data with the proposed study protocols for further consideration (b) (4)***, but emphasized that Novartis also provide tentative milestone dates for the requested PMRs. FDA additionally stated that Novartis should consider providing dates that allow flexibility in the scheduling of these studies to avoid missing milestones.***

e. Clinical Pharmacology Post-Marketing Requirements:

- A PMR clinical study to evaluate the effect of moderate and severe hepatic impairment on the pharmacokinetics of sonidegib and determine an appropriate dose for patients with hepatic impairment.

Discussion: Novartis agreed with the postmarketing requirement and no further discussion occurred.

- A PMR clinical study to evaluate the effect of acid-reducing agents on the pharmacokinetics of sonidegib and how to dose sonidegib for patients concurrently taking acid-reducing agents

Discussion: FDA found the minor revision of the wording for the PMR in Novartis' June 8, 2015, submission acceptable.

f. Chemistry, Manufacturing and Control (CMC) Post-Marketing Commitment:

- There are no PMRs or PMCs identified at this time

Discussion: Novartis acknowledged and no discussion occurred.

Reference ID: 3789638

g. Pregnancy Pharmacovigilance Program

Conduct a Pregnancy Pharmacovigilance Study to evaluate pregnancy outcomes and infant outcomes following exposure to sonidegib. This study will include a mechanism to collect, classify, and analyze data on direct exposures (women exposed to sonidegib as treatment) and indirect exposures (women exposed to sonidegib through the seminal fluid of a male partner). The Pregnancy Pharmacovigilance Study will be initiated and functioning at the time of product launch. There will be interim annual reporting of the data collected from the study. The study, at a minimum, will include the following key elements (see the Guidance for Industry Establishing Pregnancy Exposure Registries for a detailed description of these elements):

- Data collection of prospective and retrospective data points, adequate to produce informative, reliable data outcomes.

- Data analysis utilizing descriptive statistics for summarizing data that will fully capture outcomes of concern. Data collected prospectively analyzed separate from data collected retrospectively.

- Description of procedures including the patient recruitment, along with healthcare provider awareness of potential safety risk and existence of this study, and the monitoring of pregnancy and infant outcomes.

Each annual interim and final report should constitute a stand-alone report of cumulative pregnancy and infant outcomes data.

Schedule Milestones:
Final Protocol Submission: June 2015
Study/Trial Completion: Applicant to provide date
Final Report Submission: Applicant to provide date

***Discussion*: FDA acknowledged receipt, on June 2, 2015, of the draft protocol for the pregnancy study, which appeared to be adequate. There are no additional comments at this time and comments on the draft protocol will be provided to Novartis by end of June in time for them to submit their final protocol. Novartis acknowledged FDA's response.**

Reference ID: 3789638

Discussion of Major Labeling Issues

FDA issued preliminary comments on the Package Insert and the Medication Guide via electronic mail (e-mail) on May 14, 2015 and June 2, 2015 respectively. Novartis submitted their response formally to the NDA on June 8, 2015. On June 5, 2015, Novartis sent an email communication requesting additional discussion during the Late Cycle Meeting on the following labeling topics:

1) Section 5.2 Warnings and Precautions:
   a. Class labeling for musculoskeletal adverse reactions including serum CK elevation
2) Section 14 Clinical Studies:
   a. Description of highly stringent mRECIST criteria
   b. Inclusion of the CR rate based on negative histology
   c. Inclusion of estimated median duration of response based on a sensitivity analysis using conservative assumptions
3) Section 2.2 Dose Modifications

***Discussion*: FDA acknowledged Novartis' request for additional discussion regarding the labeling topics above; however, FDA stated that Novartis' June 8, 2015, submission containing the revised labeling is currently under FDA review. A separate teleconference will be scheduled with Novartis to discuss labeling after the team has completed a detailed review of Novartis edits to the Package Insert and the Medication Guide.**

Discussion of Review Plans

***Discussion*: FDA referred Novartis to Discussion under Item 6 above. FDA also stated that a Press Release and ACSO Burst are planned. FDA informed Novartis that an early action is planned; however, the action date was not disclosed.**

Discussion of Other Items

***Discussion*: Novartis requested that FDA label musculoskeletal toxicity as a class effect. FDA stated that the discussion regarding class effect is under internal review, and that appropriate class labeling language will be included in the sonidegib label if warranted.**

Wrap-up

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.

Reference ID: 3789638

Action Items

Novartis will submit proposed milestone dates for pharmacology/toxicology post-marketing requirements.

FDA will provide Novartis with comments on the proposed pregnancy pharmacovigilance study

Reference ID: 3789638

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/s/

SUZANNE G DEMKO
07/09/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205266

LATE CYCLE MEETING
BACKGROUND PACKAGE

Novartis Pharmaceuticals Corporation
Attention: Jessica Wang, Pharm.D.
Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Wang:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Odomzo (sonidegib), 200 mg capsules.

We also refer to the Face to Face Late-Cycle Meeting (LCM) scheduled for Tuesday, June 9, 2015. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Anuja Patel, Senior Regulatory Project Manager, at (301) 796-9022.

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: Tuesday, June 9, 2015 from 11:00 A.M. to 12:30 PM, EST
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1415
Silver Spring, Maryland 20903

Application Number: NDA 205266
Product Name: sonidegib
Proposed Indication: for the treatment of patients with locally advanced basal cell carcinoma (BCC) who are not amenable to curative surgery or radiation therapy (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 or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

Discipline Review Letters

No Discipline Review letters have been issued to date and none are expected at this time.

Substantive Review Issues

There are no substantive review issues at this time.

Reference ID: 3767171

ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned; however. SGEs with an expertise in basal cell carcinoma were consulted with regard to aspects of the sonidegib application.

REMS OR OTHER RISK MANAGEMENT ACTIONS

No issues related to risk management have been identified to date.

LATE CYCLE MEETING (LCM) AGENDA

1. **Introductory Comments** – 5 minutes

   Welcome, Introductions, Ground rules, Objectives of the meeting

2. **Discussion of Minor Review Issues –** 10 minutes

   a. Clinical: FDA proposes (b) (4) the indication to the treatment of patients with locally advanced basal cell carcinoma (BCC) who are not amenable to curative surgery or radiation therapy.

   b. Chemistry, Manufacturing, and Control: No minor review issues identified at this time.

3. **Review of Post-Marketing Requirements (PMRs) and Post-Marketing Commitments (PMCs)–** 10 minutes

   a. Pharmacology/Toxicology Post-Marketing Requirement:

      - PMRs to evaluate the carcinogenicity of sonidegib in rats and mice.

   b. Clinical Pharmacology Post-Marketing Requirements:

      - A PMR clinical study to evaluate the effect of moderate and severe hepatic impairment on the pharmacokinetics of sonidegib and determine an appropriate dose for patients with hepatic impairment.

      - A PMR clinical study to evaluate the effect of acid-reducing agents on the pharmacokinetics of sonidegib and how to dose sonidegib for patients concurrently taking acid-reducing agents

   c. Chemistry, Manufacturing and Control (CMC) Post-Marketing Commitment:

      - There are no PMRs or PMCs identified at this time

Reference ID: 3767171

d. Pregnancy Pharmacovigilance Program

Conduct a Pregnancy Pharmacovigilance Study to evaluate pregnancy outcomes and infant outcomes following exposure to sonidegib. This study will include a mechanism to collect, classify, and analyze data on direct exposures (women exposed to sonidegib as treatment) and indirect exposures (women exposed to sonidegib through the seminal fluid of a male partner). The Pregnancy Pharmacovigilance Study will be initiated and functioning at the time of product launch. There will be interim annual reporting of the data collected from the study. The study, at a minimum, will include the following key elements (see the Guidance for Industry Establishing Pregnancy Exposure Registries for a detailed description of these elements):

- Data collection of prospective and retrospective data points, adequate to produce informative, reliable data outcomes.

- Data analysis utilizing descriptive statistics for summarizing data that will fully capture outcomes of concern. Data collected prospectively analyzed separate from data collected retrospectively.

- Description of procedures including the patient recruitment, along with healthcare provider awareness of potential safety risk and existence of this study, and the monitoring of pregnancy and infant outcomes.

Each annual interim and final report should constitute a stand-alone report of cumulative pregnancy and infant outcomes data.

Schedule Milestones:
Final Protocol Submission: June 2015
Study/Trial Completion: Applicant to provide date
Final Report Submission: Applicant to provide date

4. Major labeling issues – 30 minutes

5. Review Plans – 5 minutes

- Labeling Discussions Ongoing
- Press Release and ASCO Burst Planned

6. Wrap-up and Action Items – 5 minutes

Reference ID: 3767171

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/s/

JOSEPH E GOOTENBERG on behalf of PATRICIA KEEGAN
05/28/2015