

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205266Orig1s000**

**OTHER REVIEW(S)**



The carcinogenicity study requested will identify the tumorigenic potential of sonidegib in rats and assess the relevant risk to humans.

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

***If not a PMR, skip to 4.***

– **Which regulation?**

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

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

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

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

Analysis of spontaneous postmarketing adverse events?

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

Analysis using pharmacovigilance system?

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

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

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

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

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

A long-term rodent carcinogenicity study in the rat.

Required

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

Continuation of Question 4

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

Agreed upon:

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

- Other
- 

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

- Does the study/clinical trial meet criteria for PMRs or PMCs?
  - Are the objectives clear from the description of the PMR/PMC?
  - Has the applicant adequately justified the choice of schedule milestone dates?
  - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

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

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

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**PMR/PMC Development Coordinator:**

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

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/s/  
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ALEXANDER H PUTMAN  
07/09/2015

WHITNEY S HELMS  
07/09/2015

JEFFERY L SUMMERS  
07/09/2015



The carcinogenicity study requested will identify the tumorigenic potential of sonidegib in mice and assess the relevant risk to humans.

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

***If not a PMR, skip to 4.***

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
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Analysis of spontaneous postmarketing adverse events?

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

Analysis using pharmacovigilance system?

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

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

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

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

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

A 6-month rodent carcinogenicity study in the transgenic mouse.

Required

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

Continuation of Question 4

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

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- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
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- Quality study without a safety endpoint (e.g., manufacturing, stability)
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***If so, does the clinical trial meet the following criteria?***

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
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/s/  
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ALEXANDER H PUTMAN  
07/09/2015

WHITNEY S HELMS  
07/09/2015

JEFFERY L SUMMERS  
07/09/2015

## PMR/PMC Development Template

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

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NDA/BLA # 205266  
Product Name: Sonidegib

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PMR/PMC Description: 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.

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	June 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

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

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

Sonidegib is a teratogen which interrupts hedgehog pathway signaling and interferes with normal embryo-fetal development. The registration trial did not contain any cases of sonidegib exposure in pregnant women. Locally advanced BCC is a very rare disease. The low prevalence of this disease in women of childbearing potential and standard pregnancy precautions make fetal exposure a rare event not likely to be captured in a standard premarketing safety database.

Additionally, pregnancies are expected to be uncommon in the population receiving sonidegib due to average patient age and product labeling that recommends the need for highly effective contraception. The Applicant estimates approximately 1500 women of childbearing potential and approximately 2200 men with a female partner of childbearing potential could be treated with sonidegib in the US through the year 2029.

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

In animal studies, sonidegib was shown to be embryotoxic and fetotoxic as evidenced by abortion or complete resorption of fetuses, and teratogenic, resulting in severe malformations. Fetotoxicity was seen down to low maternal doses where maternal exposure was below the limit of detection. The goal of the pregnancy pharmacovigilance program is to assess the outcomes of developing embryos and pregnancy after exposure to sonidegib.

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

***If not a PMR, skip to 4.***

– **Which regulation?**

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

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

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

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

Analysis of spontaneous postmarketing adverse events?

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

Analysis using pharmacovigilance system?

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

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

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

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

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

A pharmacovigilance study should be conducted in accordance with "FDA Guidance for Industry: E2E Pharmacovigilance Planning."

A pregnancy pharmacovigilance study is not a formal pregnancy registry, however, should at a minimum include many key elements outlined in the Guidance for Industry Establishing Pregnancy Exposure Registries. The program should include a plan for collection of prospective and retrospective data, analysis of collected data, patient contact and follow up efforts, plan to communicate program existence and plan to evaluate the effectiveness of the program. The program may not have a comparison group, as would be found in a formal registry. Collected data points should be adequate to produce reliable data outcomes.

Required

Observational pharmacoepidemiologic study

Registry studies

Primary safety study or clinical trial

Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety

Thorough Q-T clinical trial

Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)

Pharmacokinetic studies or clinical trials

Drug interaction or bioavailability studies or clinical trials

Dosing trials

Continuation of Question 4

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

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

Immunogenicity as a marker of safety

Other (provide explanation)

---

Agreed upon:

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

Other

---

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

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

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

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

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

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**PMR/PMC Development Coordinator:**

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

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/s/  
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DENISE A CASEY  
06/19/2015

SUZANNE G DEMKO  
06/19/2015

JEFFERY L SUMMERS  
06/24/2015

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## MEMORANDUM

### REVIEW OF REVISED LABEL AND LABELING

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

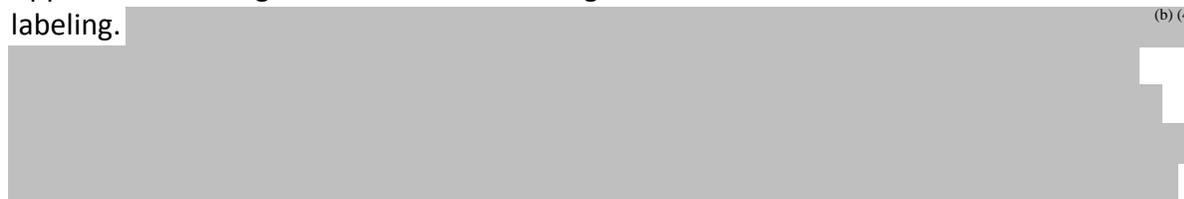
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**Date of This Memorandum:** June 15, 2015  
**Requesting Office or Division:** Division of Oncology Products 2 (DOP2)  
**Application Type and Number:** NDA 205266  
**Product Name and Strength:** Odomzo (sonidegib) Capsules, 200 mg  
**Submission Date:** June 12, 2015  
**Applicant/Sponsor Name:** Novartis  
**OSE RCM #:** 2014-2009-2  
**DMEPA Primary Reviewer:** Otto L. Townsend, PharmD  
**DMEPA Team Leader:** Chi-Ming (Alice) Tu, PharmD

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#### 1 PURPOSE OF MEMO

DOP2 requested that we review the revised container labels and carton labeling (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions were submitted to provide revised container labels and carton labeling to reflect the Agency's recommended changes to the storage statement, "Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]." We note that the Applicant has changed the color of the strength statement on the container labels and carton labeling. (b) (4)



#### 2 CONCLUSIONS

The revised container labels and carton labeling is acceptable from a medication error perspective.

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

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/s/  
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OTTO L TOWNSEND  
06/15/2015

CHI-MING TU  
06/15/2015

## PMR/PMC Development Template

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

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NDA/BLA #                      205-266, Sonidegib (Odomzo)  
Product Name: \_\_\_\_\_

PMR/PMC Description: Hepatic Impairment Pharmacokinetic Trial

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>Submitted</u>
	Study/Trial Completion:	<u>09/30/2015</u>
	Final Report Submission:	<u>07/31/2016</u>
	Other: _____	_____

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

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

The mass balance study suggests that hepatic elimination is the major route of elimination. Patients with hepatic impairment may have higher sonidegib exposures than patients with normal hepatic function, which may lead to more treatment limiting severe musculoskeletal toxicity.

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

The goal of the clinical pharmacokinetic trial is to determine appropriate sonidegib dose in patients with moderate or severe hepatic impairment.

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

***If not a PMR, skip to 4.***

- **Which regulation?**

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

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

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

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

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

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

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."

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
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- Other
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## PMR/PMC Development Template

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NDA/BLA # 205-266, Sonidegib (Odomzo)  
Product Name: \_\_\_\_\_

PMR/PMC Description: Drug Interaction Trial

PMR/PMC Schedule Milestones: Final Protocol Submission: ongoing  
Study/Trial Completion: completed  
Final Report Submission: 01/31/2016  
Other: \_\_\_\_\_

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

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

(b) (4) Therefore, gastric acid-reducing agents (ARA) may affect the bioavailability of sonidegib when an ARA is given concurrently with sonidegib. It is not known how to dose ARA with sonidegib.

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

The goal of the clinical pharmacokinetic trial is to determine how to dose an ARA with sonidegib.

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

***If not a PMR, skip to 4.***

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
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- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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

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

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
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Agreed upon:

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/s/  
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STACY S SHORD  
06/10/2015

HONG ZHAO  
06/10/2015  
I concur.

JEFFERY L SUMMERS  
06/11/2015



**DEPARTMENT OF HEALTH & HUMAN SERVICES** Public Health Service

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

**Division of Pediatric and Maternal Health Review**

**Date:** June 1, 2015      **Consult Received:** February 2, 2015

**From:** Carol H. Kasten, MD, Medical Officer  
Division of Pediatric and Maternal Health,  
Office of Drug Evaluation IV (ODE IV)

**Through:** Tamara Johnson, MD, MS, Acting Team Leader  
Division of Pediatric and Maternal Health, ODE IV

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

**To:** Division of Oncology 2

**Drug:** ODOMZO (Sonidegib) 200 mg (b) (4) NDA 205-266  
IND 102-961

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

**Subject:** Labeling Review

**Sponsor:** Novartis Pharmaceuticals Corporation

**Consult Request:** Labeling review for this new molecular entity NDA application  
from Novartis for sonidegib (proposed proprietary name:  
ODOMZO), 200 mg capsules.

## Materials Reviewed:

- Novartis Core Safety Risk Management, Integrated Medical Safety Sonidegib, LDE225 Plan, November 3, 2014.
- Novartis Response to Potential Safety/Risk Management Postmarketing Requirement (PMR): Pregnancy Pharmacovigilance Study, Nault B, Levine M, Burnett P, Safi J. Release date: April 16, 2015.

## INTRODUCTION

Novartis Pharmaceuticals submitted this application for the new molecular entity (NME) Odomzo (Sonidegib), a hedgehog inhibitor, on October 7, 2014, with the proposed indication, “for the treatment of locally advanced basal cell carcinoma (BCC) in patients whose tumors are not amenable to curative surgery or radiation therapy [REDACTED] (b) (4)

[REDACTED] The Division of Oncology Products 2 (DOP2) consulted the Division of Pediatric and Maternal Health - Maternal Health Team (DPMH) to review and provide labeling recommendations in all sections appropriate for a drug of teratogenic potential.

## BACKGROUND

### Basal Cell Carcinoma (BCC)

BCC is a non-melanoma skin cancer (NSMC) and is the most common malignancy in fair skinned people. BCC comprises approximately 80% of all NSMC.<sup>1</sup> The major inducer of BCC is sunlight exposure and consequently the most common locations of BCC tumors are on the face, head and neck. BCC is a slow growing tumor; however, it has several features which confer a high morbidity. BCC tumors may invade and destroy local tissues including the areas around the eyes, ears and nose. This usually occurs due to neglect of the tumor over a period of years. Once removed, BCC may also recur *in situ* and form multiple tumors although they rarely metastasize.<sup>2</sup>

The prevalence of BCC is difficult to estimate because it is the one malignancy that is not required to be reported to cancer registries.<sup>3,4,5</sup> However, the data do demonstrate that the prevalence of BCC varies greatly by geography. In the U.S., the incidence of BCC is between about 212 and 407 per 100,000 individuals. In Europe, the incidence is between 45 to 130 per 100,000. The highest incidence of BCC is in Australia where it is estimated to occur in about 2 per 100 Australians.<sup>6</sup>

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<sup>1</sup> See Basset-Seguin *et al.*

<sup>2</sup> See Basset-Seguin *et al.*

<sup>3</sup> Urba WJ, Curti BD. Cancer of the Skin. In: Kasper D, Fauci A, Hauser S, Longo D, Jameson J, Loscalzo J. eds. Harrison's Principles of Internal Medicine, 19e. New York, NY: McGraw-Hill; 2015. <http://accessmedicine.mhmedical.com/content.aspx?bookid=1130&Sectionid=79729820>. Accessed May 19, 2015.

<sup>4</sup> American Cancer Society, <http://www.cancer.org/cancer/skincancer-basalandsquamouscell/detailedguide/skin-cancer-accessed> May 20, 2015, last revised April 3, 2015.

<sup>5</sup> Lomas A, Leonardi-Bee J, Bath-Hextall F. A systematic review of worldwide incidence of nonmelanoma skin cancer British Association of Dermatologists 2012 166, pp1069–1080.

<sup>6</sup> See Basset-Seguin *et al.*

### Sonidegib

Sonidegib is the second in the class of signal transduction inhibitors (STI) which block the hedgehog pathway.<sup>7</sup> The drug binds to Smoothed, a transmembrane protein, thereby inhibiting Smoothed signaling. The hedgehog pathway regulates normal cell growth, differentiation and hair growth, as well as being a critical enzyme in mammalian morphogenesis.<sup>8</sup> Dysregulation of the hedgehog pathway has been found to be one of the pathogenic mechanisms for the induction of basal cell carcinoma.

Sonidegib is administered as a 200 mg (b) (4) taken orally once daily. The drug has a low bioavailability with less than 10% of the drug being absorbed from the gut. Once absorbed Sonidegib is slowly metabolized with a half-life of 28 days.<sup>9</sup>

### Regulatory Information

On October 17, 2014, following this NDA's submission, the Division declined the applicant's request for a priority review based on the absence of data supporting a conclusion that sonidegib provides a significant improvement in safety or effectiveness compared to vismodegib, the first drug approved in the hedgehog STI class (b) (4)

Sonidegib is expected to be a highly teratogenic drug based on its mechanism of action as a signaling transduction inhibitor (STI) of the Hedgehog pathway which is fundamental to embryonic neural development. Management of this risk was fully evaluated with vismodegib in a Regulatory Briefing held on December 9, 2011.<sup>10,11</sup> The recommendation from the Briefing was that a Risk Evaluation and Mitigation Strategy (REMS) was not required and a post-marketing requirement (PMR) pregnancy pharmacovigilance study was appropriate to assess the risk of adverse pregnancy outcomes with vismodegib use in the advanced BCC population.<sup>12</sup>

### Literature and Database Review

Sonidegib is a new molecular entity and there are no publications regarding its use in pregnancy or lactation; nor are there any reviews of the drug in the teratology databases (ReproTox, TERIS, Shepard's Catalog) or in LactMed.

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<sup>7</sup> Basset-Seguin N, Sharpe H, de Sauvage F, Efficacy of Hedgehog Pathway Inhibitors in Basal Cell Carcinoma. *Mol Cancer Ther* 2015; 14:633-641. doi: 10.1158/1535-7163.MCT-14-0703

<sup>8</sup> Clinical pharmacology online©, [www.clinicalpharmacology-ip.com](http://www.clinicalpharmacology-ip.com) Elsevier. Gold Standard. Revision date: November 6, 2014. Accessed: March 31, 2014.

<sup>9</sup> Sonidegib labeling (12.3) January 23, 2015 version from applicant.

<sup>10</sup> Regulatory Briefing Minutes, Meeting Chair: Sandy Kweder, MD, Meeting Recorder: Mona Patel, PharmD, RPM DOP2, OHOP, CDER.

<sup>11</sup> Risk Evaluation and Mitigation Strategy (REMS) Options Review meeting, held January 9, 2012, Reviewer: Amarilys Vega, MD, MPH, Office of Medication Error Prevention and Risk Management, OSE, CDER, Reference ID: 3072058.

<sup>12</sup> See the REMS Options Review and Regulatory Briefing Minutes.

In their Core Safety Risk Management Plan with a data lock of December 31, 2013,<sup>13</sup> the applicant reported that the female partner of a male patient being treated with sonidegib may have become pregnant. The study site tried three or more times to contact the patient's partner without success. No pregnancy outcome information was available from this presumed prenatal exposure via a male patient.

## **DISCUSSION**

### Pregnancy and Lactation Labeling Rule

On December 4, 2014, the Food and Drug Administration (FDA) announced the publication of the "Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling,"<sup>14</sup> also known as the Pregnancy and Lactation Labeling Rule (PLLR). The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation, and creates a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) will be removed from all prescription drug and biological product labeling and a new format will be required for all products that are subject to the 2006 Physicians Labeling Rule<sup>15</sup> format to include information about the risks and benefits of using these products during pregnancy and lactation.

DPMH provided labeling recommendations for the sonidegib labeling to ensure compliance with the PLLR requirements.

### Rationale for Duration of Female Contraception Use

The long half-life of sonidegib ( $t_{1/2} = 28$  days) is of concern because the potential exposure period to a fetus and the potential length of time that a female of reproductive potential should consider use of contraception. Based on the applicant's animal reproduction studies, the estimated human plasma sonidegib concentration below which drug-induced teratogenesis was considered unlikely was exceedingly low at (3 pg/ml). Additionally, using the 3 pg/ml threshold, the applicant's PK modeling estimated that a treated patient would need to wait 20 months after their final sonidegib dose before their plasma sonidegib concentration fell below the 3 pg/ml. Based on the above calculations, DPMH recommends that female contraception should be used for the same duration, 20 months.

### Rationale for Duration of Condom Use

Using the same 3 pg/ml sonidegib concentration threshold and assuming: (a) the concentration of sonidegib in semen is equal to that in plasma; (b) 100% absorption from the vagina of the sonidegib in the semen; (3) a daily maternal exposure of 6 mL of semen; the applicant calculated that treated male partners of females of reproductive potential should use condoms for (b) (4) months after their final sonidegib dose for 95% of exposed females to have a plasma concentration below the safety threshold. DOP2

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<sup>13</sup>Integrated Medical Safety Sonidegib, LDE225 Core Safety Risk Management Plan, November 3, 2014.

<sup>14</sup> *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).

<sup>15</sup>*Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).

extended the recommended duration of condom use to eight months from (b) (4) because the applicant had not demonstrated with nonclinical studies that the 3 pg/mL threshold was without teratogenic risk. The applicant had used pharmacokinetic modeling only on which to base their recommendation.

*Reviewer comment:*

*At the present time, there are no data on which to base an assessment of the benefit/risk to a fetus using calculated levels of a teratogenic drug in semen. However, DPMH is actively reviewing this hypothetical risk across products which may lead to improved understanding of the risk of teratogenicity associated with potential exposures related to detectable drug concentrations in semen. Therefore, in the meantime, DPMH agrees with the DOP2 conservative approach that males of reproductive potential should use condoms for eight months after their final dose of sonidegib and wait eight months before donating semen.*

Lactation Labeling

There are no data available about the presence of sonidegib in breast milk. If sonidegib is present in breast milk, the drug itself has low bioavailability and it is unlikely that a nursing infant would be exposed to a quantifiable systemic exposure to sonidegib. Nevertheless, there is a risk of serious adverse events from any systemic exposure to sonidegib. The Hedgehog pathway is still active in neurodevelopment postnatally and a theoretical risk exists if an infant is exposed to sonidegib. Therefore, breastfeeding is not recommended in a woman being treated with sonidegib for a duration of 20 months.

Post-Marketing Requirement: Pregnancy Pharmacovigilance Study

At the sonidegib Mid-Cycle Communication Meeting on March 5, 2015, the Division informed the applicant of the Agency's intent to request a PMR for a pregnancy pharmacovigilance study and shared the proposed PMR language with the applicant. The sonidegib PMR was based on that used for vismodegib. On April 17, 2015, in response to the Agency's proposed PMR, the applicant submitted an amendment describing their proposed Pregnancy Monitoring Program.<sup>16</sup>

DPMH has reviewed the applicant's Pregnancy Monitoring Program and found it addressed all the key elements described in the proposed PMR with only a few exceptions. These exceptions are listed below.

- (b) (4).  
The applicant should plan to assess infant outcomes at birth, at one year of age, and at a time point in between.
- The applicant has not specified the duration for which the pregnancy pharmacovigilance program will run.
- The applicant should describe the anticipated enrollment for the program, including the number of anticipated enrollees annually and the anticipated total sample size by the end of the study. Adequate justification to support these estimates should be provided.

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<sup>16</sup> FDA Guidance Establishing Pregnancy Exposure Registries, 2002

The applicant has agreed to address DPMH's comments with submission of a draft protocol. DPMH will provide additional comments on the Pregnancy Monitoring Program upon the applicant's submission of their full protocol.

## CONCLUSIONS

- DPMH agrees with the DOP2 approach and recommends the following based on sonidegib's long half-life and toxicity at very low concentrations:
  - female patients should use contraception during treatment with and for 20 months following their final sonidegib dose.
  - female patients should not breastfeed during treatment with and for 20 months after their final sonidegib dose.
  - male patients should use condoms, irrespective of vasectomy status, for during treatment with and six months following their final sonidegib dose.
  - male patients should not donate semen during treatment with and for six months following their final sonidegib dose.
- The applicant's proposal for a pregnancy pharmacovigilance program is acceptable to DPMH, except for the specific issues regarding infant outcomes, anticipated enrollment, and projected duration. The applicant has agreed to address these specific issues with submission of a draft protocol.

## RECOMMENDATIONS

DPMH attended meetings with DOP2 in March, April and May 2015.

The following are the DPMH recommendations for the proposed sonidegib labeling to comply with PLLR format.

Language was provided in the following sections of the ODOMZO labeling:

## HIGHLIGHTS OF PRESCRIBING INFORMATION

**ODOMZO<sup>®</sup> (sonidegib) capsules, for oral use**

### WARNING: EMBRYO-FETAL TOXICITY

- **Can cause embryo-fetal death or severe birth defects. (5.1, 8.1)**
- **Verify pregnancy status of females of reproductive potential. (8.3)**
- **Advise use of effective contraception during and after therapy. (5.1, 8.1, 8.3)**
- **Advise of the potential risk of exposure through semen. (8.3)**
- (b) (4)

### -----WARNINGS AND PRECAUTIONS-----

- (b) (4)

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

- Lactation:  (b) (4) (8.2)

**FULL PRESCRIBING INFORMATION: CONTENTS\***  
**WARNING: EMBRYO-FETAL TOXICITY**

**5 WARNINGS AND PRECAUTIONS**

5.1 Embryo-fetal Toxicity

(b) (4)

**8 USE IN SPECIFIC POPULATIONS**

8.1 Pregnancy

8.2 Lactation

8.3 Females and Males of Reproductive Potential

**17 PATIENT COUNSELING INFORMATION**

**FULL PRESCRIBING INFORMATION**

**WARNING: EMBRYO-FETAL TOXICITY**

(b) (4)

**ODOMZO can cause embryo-fetal death or severe birth defects** (b) (4) **pregnant woman. Verify the pregnancy status of females of reproductive potential prior to initiating** (b) (4) **therapy. Advise females of reproductive potential to use effective contraception during** (b) (4) **. Advise males of the potential risk of ODOMZO exposure through semen and to use condoms with a pregnant partner or a female partner of reproductive potential.** (b) (4)

**5 WARNINGS AND PRECAUTIONS**

**5.1 Embryo-fetal Toxicity**

(b) (4), ODOMZO can cause fetal (b) (4) severe birth defects when administered to a pregnant woman. In (b) (4), sonidegib was fetotoxic and teratogenic, embryotoxic at exposures below the (b) (4) recommended human dose of 200 mg. Advise pregnant women of the potential risk to a fetus [See Use in Specific Populations (8.1)] (b) (4).

Verify pregnancy status of females of reproductive potential prior to initiating ODOMZO treatment (b) (4) advise use of effective contraception during treatment with ODOMZO, (b) (4). Advise male patients to use condoms, even after a vasectomy, to avoid potential drug exposure in pregnan (b) (4) and female partners of reproductive potential during treatment with, and for 8 months after the final dose of ODOMZO [see Use in Specific Populations (8.3)].

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### *Risk Summary*

Based on its mechanism of action, ODOMZO (b) (4) cause fetal harm when administered to a pregnant woman [see *Clinical Pharmacology (12.1)*]. There are no available data on ODOMZO use in pregnant women (b) (4). In animal reproduction studies, administration of sonidegib (b) (4) during organogenesis at doses below the (b) (4) recommended human dose (b) (4) of 200 mg (b) (4) teratogenic effects, (b) (4)

(b) (4)  
(b) (4)  
(b) (4)  
(b) (4). Advise pregnant women of the potential risk to a fetus. Report Pregnancies to the Novartis (b) (4) (b) (4) at 1-888-669-6682.

## Data

### Animal Data

(b) (4)  
(b) (4) abortion (b) (4) complete resorption of fetuses (b) (4)  
(b) (4) severe malformations at  $\geq 5$  mg/kg/day. Teratogenic effects included vertebral, distal limb and digit malformations, severe craniofacial malformations and other severe midline defects. (b) (4)  
(b) (4) maternal exposure was below the limit of detection.

### **8.2 Lactation**

No data are available regarding the presence of sonidegib in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. Because of the potential for serious adverse reactions in breastfed infants from sonidegib, advise a nursing woman (b) (4) during treatment with ODOMZO and for 20 months after the final dose.

### **8.3 Females and Males of Reproductive Potential**

#### *Pregnancy Testing*

Verify the pregnancy status of females of reproductive potential prior to initiating ODOMZO therapy.

#### *Contraception*

##### Females

Advise females of reproductive potential to use effective contraception (b) (4)  
(b) (4)  
(b) (4)

##### Males

It is not known if sonidegib is present in semen. Advise male patients to use condoms, even after a vasectomy, to avoid potential drug exposure to pregnant partners and female partners of reproductive potential during treatment with, and for at least 8 months after the (b) (4) dose (b) (4). (b) (4)

(b) (4) Advise males not to donate semen during treatment with and for at least 8 months after the (b) (4) dose (b) (4).

#### *Infertility*

(b) (4).  
Based on findings from animal studies, female fertility may be compromised with ODOMZO [see *Nonclinical Toxicology (13.1)*].

## **17 PATIENT COUNSELING INFORMATION**

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

### Embryo-Fetal Toxicity

- Advise (b) (4) of the potential risk to a fetus (b) (4)
- Advise females of reproductive potential to use effective contraception during treatment with, and for at least 20 months after the (b) (4) dose (b) (4)
- Advise males, even those with prior vasectomy, to use condoms, to avoid potential drug exposure in both pregnant partners and female partner of reproductive potential during treatment with, and for at least 8 months after the (b) (4) dose of ODOMZO [see *Warnings and Precautions (5.1) and Use in Specific Populations (8.1, 8.3)*].
- Advise female patients and female partners of male patients to contact their healthcare provider with a known or suspected pregnancy. (b) (4)

### Lactation

- Advise (b) (4) during treatment with ODOMZO (b) (4) [see *Use in Specific Populations (8.2)*].

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/s/  
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CAROL H KASTEN  
06/01/2015

TAMARA N JOHNSON  
06/01/2015

LYNNE P YAO  
06/11/2015

**MEMORANDUM**  
DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion

**\*\*PRE-DECISIONAL AGENCY MEMO\*\***

**Date:** May 28, 2015

**To:** Anuja Patel  
Regulatory Project Manager  
Division of Oncology Products 2  
Office of Hematology and Oncology Products

**From:** Nick Senior, PharmD, JD  
Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

**Subject:** OPDP Comments on NDA 205266  
ODOMZO<sup>®</sup> capsules, for oral use

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OPDP has reviewed the proposed product labeling (PI) for ODOMZO<sup>®</sup> capsules, for oral use (Odomzo), including carton and container labeling, as requested in the consult dated November 10, 2014. Our comments, using the proposed substantially complete, marked-up version of the PI emailed to OPDP by Anuja Patel on May 14, 2015, are provided below. We have no comments at this time with regards to the carton and container labeling.

Please note that comments on the proposed Odomzo Med Guide will be provided under a separate cover as a collaborate review between OPDP and the Division of Medical Policy Programs.

If you have any questions, please feel free to contact me (contact information: 240-402-4256; Nicholas.Senior@fda.hhs.gov)

Thank you! OPDP appreciates the opportunity to provide comments on these materials.

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NICHOLAS J SENIOR  
05/28/2015

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

**PATIENT LABELING REVIEW**

Date: May 28, 2015

To: Patricia Keegan, MD  
Director  
**Division of Oncology Products 2 (DOP2)**

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

Sharon R. Mills, BSN, RN, CCRP  
Senior Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**

From: Morgan Walker, PharmD, MBA  
Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**

Nicholas Senior, PharmD, JD  
Regulatory Review Officer  
**Office of Prescription Drug Promotion (OPDP)**

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): ODOMZO (sonidegib)

Dosage Form and Route: capsules, for oral use

Application Type/Number: NDA 205266

Applicant: Novartis Pharmaceuticals Corporation

## 1 INTRODUCTION

On September 26, 2014, Novartis Pharmaceuticals Corporation submitted for the Agency's review an original New Drug Application (NDA) 205266 for ODOMZO (sonidegib) capsules. The proposed indication for ODOMZO (sonidegib) capsules is for the treatment of adult patients with locally advanced basal cell carcinoma (BCC) who are not candidates for surgery or radiation therapy.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology Products 2 (DOP2) on November 21, 2014 and November 10, 2015 respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for ODOMZO (sonidegib) capsules.

## 2 MATERIAL REVIEWED

- Draft ODOMZO (sonidegib) MG received on September 26, 2014, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 14, 2015.
- Draft ODOMZO (sonidegib) Prescribing Information (PI) received on September 26, 2014, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 14, 2015.

## 3 REVIEW METHODS

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

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

In our collaborative review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20

- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

#### **4 CONCLUSIONS**

The MG is acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

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

Please let us know if you have any questions.

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/s/  
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MORGAN A WALKER  
05/28/2015

NICHOLAS J SENIOR  
05/28/2015

SHARON R MILLS  
05/28/2015

BARBARA A FULLER  
05/28/2015

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## MEMORANDUM

### REVIEW OF REVISED LABEL AND LABELING

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

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**Date of This Memorandum:** May 13, 2015  
**Requesting Office or Division:** Division of Oncology Products 2 (DOP2)  
**Application Type and Number:** NDA 205266  
**Product Name and Strength:** Odomzo (sonidegib) Capsules, 200 mg  
**Submission Date:** May 6, 2015  
**Applicant/Sponsor Name:** Novartis  
**OSE RCM #:** 2014-2009-1  
**DMEPA Primary Reviewer:** Otto L. Townsend, PharmD  
**DMEPA Team Leader:** Chi-Ming (Alice) Tu, PharmD

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#### 1 PURPOSE OF MEMO

DOP2 requested that we review the revised container labels and carton labeling (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.<sup>1</sup> (b) (4)

[REDACTED]

#### 2 CONCLUSIONS

The revised container labels and carton labeling is acceptable from a medication error perspective.

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<sup>1</sup> Townsend O. Label and Labeling Review for Odomzo (sonidegib) (NDA 205266). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 NOV 21. 8 p. OSE RCM No.: 2014-2009.

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OTTO L TOWNSEND  
05/13/2015

CHI-MING TU  
05/13/2015

MEMORANDUM

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

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**CLINICAL INSPECTION SUMMARY**

**DATE:** April 28, 2015

**TO:** Anuja Patel, Regulatory Project Manager  
Denise Casey, M.D., Medical Reviewer  
Division of Oncology Products 2

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

**THROUGH:** Susan Thompson, M.D.  
Team Leader  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

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

**SUBJECT:** Evaluation of Clinical Inspections

**NDA:** 205266

**APPLICANT:** Novartis Pharmaceutical Corporation

**DRUG:** Odomzo (sonidegib)

**NME:** Yes

**THERAPEUTIC CLASSIFICATION:** Standard

**INDICATION:** For the treatment of locally advanced basal cell carcinoma (BCC) who are not amenable to curative surgery or radiation therapy [REDACTED] (b) (4)

CONSULTATION REQUEST DATE: November 24, 2014  
INSPECTION SUMMARY GOAL DATE: May 29, 2015  
DIVISION ACTION GOAL DATE: July 24, 2015  
PDUFA DATE: September 28, 2015

## I. BACKGROUND:

Novartis Pharmaceutical Corporation [Novartis] seeks approval to market sonidegib for adult patients with locally advanced basal cell carcinoma (laBCC) who are not amenable to curative surgery or radiation therapy (b)(4). Molecular and genetic studies have shown that almost all BCCs contain genetic alterations in the hedgehog (Hh) signaling pathway, resulting in aberrant pathway activation and uncontrolled proliferation and survival of basal carcinoma cells. Most commonly, these alterations cause loss of function of patched homologue 1, which normally acts to inhibit the signaling activity of smoothened homologue (SMO), a transmembrane protein. Sonidegib is a small molecule inhibitor of the Hh signaling pathway, which acts by binding to and corrupting SMO function.

The application is supported primarily by data from a single pivotal study, Study CLDE225A2201, entitled, "A Pivotal 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 (BOLT)", sponsored by Novartis. The study population consists of subjects  $\geq 18$  years old with a histologically confirmed diagnosis of advanced BCC (metastatic or locally advanced basal cell carcinoma). Eligible patients were randomly assigned (1:2) to treatment with either sonidegib 200 mg orally once-daily or sonidegib 800 mg orally once-daily.

The primary efficacy endpoint is objective response rate (ORR) per central review. Radiographic, photographic, and histological data were each independently reviewed by a separate central Contract Research Organization (CRO), and an Independent Review Committee (IRC) was subsequently formed to enable an integrated composite response to be provided. The IRC, blinded to treatment assignment, consisted of two dermato-oncologists and one radiologist, in order to integrate centrally-reviewed radiographic imaging, photographic, and histological data and to determine the composite overall time point response for patients with locally advanced basal cell carcinoma (laBCC) according to modified Response Evaluation Criteria In Solid Tumors (mRECIST).

(b)(4) a CRO, functioned under Charter as the Independent Review Facility for assessment of radiographic images for this study and photo analysis for mBCC patients only. (b)(4) also was responsible for direct support of the IRC, and IRC data collection and transfer. (b)(4) a CRO, functioned under Charter as the Independent Review Facility for photographic images for this study.

Two hundred and ten patients were planned to be enrolled. A total of 230 patients were randomized: 79 to treatment with sonidegib 200 mg and 151 to treatment with sonidegib 800 mg. This study enrolled subjects at 58 study centers in 12 countries: Australia (2 centers),

Belgium (2 centers), Canada (2 centers), France (5 centers), Germany (10 centers), Greece (1 center), Hungary (2 centers), Italy (1 center), Spain (3 centers), Switzerland (3 centers), United Kingdom (7 centers), and United States (21 centers).

This study was conducted under IND 102961.

Two clinical sites were chosen for inspection: Site 1513 (Dr. Geoffrey Gibney, Tampa, FL), and Site 1503 (Karl Lewis, Aurora, CO), based on enrollment of large numbers of study subjects and significant primary efficacy results pertinent to decision making. Site 1513 had a large number of protocol deviations relative to other study sites, including not performing key procedures and laboratory assessments on schedule. Two study Contract Research Organizations (CROs) were also inspected. Briefly, (b)(4) was inspected for their conduct of medical image analysis of MRI and CT scans as well as photograph analysis for mBCC. (b)(4) was inspected for their conduct of medical image analysis of photographs. The record audits were in accordance with the clinical investigator compliance program (CP 7348.811) and in accordance with the Sponsor/Monitor/CRO data validation compliance program (CP 7348.810).

**II. RESULTS (by Site):**

Name of CI or Sponsor/CRO, Location	Protocol #, Site #, and # of Subjects	Inspection Date	Final Classification
<b>CI#1: Geoffrey Gibney</b> 1513 University of South Florida H. Lee Moffett 12902 Magnolia Drive FOB-2 MCB 10302 Tampa, FL 33612	Protocol: CLDE225A2201  Site Number: 1513  Number of Subjects: 16	January 5, 2015 to February 11, 2015	Pending  Interim classification: VAI
<b>CI#2: Dr. Karl Lewis</b> University of Colorado 1665 Aurora Ct. Rm. 3236 Aurora, CO 80045	Protocol: CLDE225A2201  Site Number: 1503  Number of Subjects: 14	February 9-20, 2015	NAI
<b>CRO#1:</b> (b)(4) (b)(4)	(b)(4)	(b)(4)	NAI
<b>CRO#2:</b> (b)(4) (b)(4)		(b)(4)	NAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

**1. CI#1: Dr. Geoffrey Gibney (Site 1513)**

- a. What was inspected:** The site screened 16 subjects, and 16 subjects were enrolled. The study records of 16 enrolled subjects were audited. The record audit included comparison of source documentation to CRFs and data listings submitted to NDA 205266, with particular attention paid to inclusion/exclusion criteria compliance, adverse events, treatment regimens, and reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent documents, test article accountability, and monitoring reports.
- b. General observations/commentary:** Generally, the investigator's execution of the protocol was found to be adequate. The inspection revealed no significant deficiencies. Records and procedures were clear, and generally well organized. The primary efficacy endpoints were verified. The source records audited at this site also supported the independent central review-reported efficacy outcome measure submitted to NDA 205255. There was no evidence of underreporting of adverse events. Review of source documentation for eligibility, randomization, treatment regimens, study drug administration cycles, and drug accountability found no discrepancies. The site didn't always report SAEs in a timely fashion, resulting in 2 SAEs that occurred prior to the data cut off, but were not included in the datalistsings submitted to the NDA because they were reported to the sponsor after the data cutoff date of June 28, 2013. Some protocol-specified assessments were not always performed. A Form FDA 483 was issued citing one inspectional observation.

**Observation 1.** An investigation was not conducted in accordance with the signed statement of investigator and investigational plan.

Specifically,

- A. A screening dipstick urinalysis was not performed for six of the sixteen subjects (Subjects 1513001, 1513002, 1513003, 1513004, 1513005, and 1513007).

*OSI Reviewer Notes: Dr Gibney provided a written response, dated March 2, 2015, to the Form FDA 483. He agreed with the observation. Dr. Gibney stated that the April 19, 2011 version of the protocol, in Section 6.2.2.5.3, Urinalysis, defines urinalysis as*

*"Specific gravity, pH, semi-quantitative "dipstick" evaluation of protein, glucose, bilirubin, ketones, blood cells and leukocytes... If there is an abnormal result revealed by dipstick, the remaining specimen should be sent to the central laboratory for full analysis, including microscopic exam, if applicable. A microscopic examination will include WBC, RBC, bacteria, and casts."*

*According to Dr. Gibney, the nursing policy at [Moffitt] states that all tests are sent to the laboratory for processing, unless otherwise described in the Waived Testing standard (W-04). For the Clinical Research Unit, where research patients are seen, the only test that is able to be performed "bedside", such as a dipstick urinalysis would be, is blood glucose. For this reason, the dipstick method of testing was not used to complete screening urinalyses for Subjects 1513001, 1513002, 1513003, 1513004, and 1513005. Instead, urine samples were sent to the central laboratory and urinalyses with microscopic evaluation were performed for each of these subjects. These urine studies included those required by protocol for screening purposes. This procedural change was previously noted by the sponsor; a deviation was submitted to the IRB on September 23<sup>rd</sup>, 2011 and was acknowledged by the IRB on October 3<sup>rd</sup>, 2011. Moving forward from October 3<sup>rd</sup>, 2011, all subjects had basic urinalysis and urine microscopy performed on site by the Moffitt laboratory.*

*However, in error, Subject 1513007 did not have a screening urinalysis completed during the screening visit on December 12<sup>th</sup>, 2011. Dr. Gibney indicated that corrective actions have already been implemented. Basically, study staff were re-educated regarding the importance of adhering to protocol requirements. During Site Initiation Visits for new protocols requiring urine studies, sponsors will be made aware that urine dipsticks are not used for immediate results at Moffitt and confirmation on how to proceed in order to be in compliance with the protocol will be discussed ahead of time.*

*The inspectional observation was limited to Subject 1513007, and should not importantly impact study outcomes for safety and efficacy.*

- B. Protocol required photographs were not completed for three of the sixteen subjects.
1. Subject 1513008 did not have photographs taken at their Week 33 visit.
  2. Subject 1513009 did not have photographs taken at their Week 33 visit.
  3. Subject 1513011 did not have an annotated photograph taken at their Week 5 visit.

*OSI Reviewer Notes: Dr Gibney provided a written response, dated March 2, 2015, to the Form FDA 483 inspectional observations. He agreed with the observation. Dr. Gibney explained that in error, Subject 1513008 did not have photographs taken at the week 33 visit, on September 30, 2012. This was entered into the (b) (4) data system as missed. Subject 1513009 did have photos taken at his week 33 visit; however, they were not annotated. Photographs were reported in the (b) (4) data system as missed, as it was not possible to reshoot the photos with annotation due to the visit window having closed. Finally, Subject 1513011 did have photos taken at the week 5 visit on June 18<sup>th</sup>,*

2012; however, they were not annotated. Photos were reported in the (b) (4) data system as missed as it was not possible to reshoot the photos with annotation since the visit window having closed.

Dr. Gibney indicated that corrective actions have already been implemented. Deviation reports have been completed on the missed procedures and will be submitted to the IRB. The current study staff has been re-educated on the appropriate procedures for taking photographs and submitting in the (b) (4) system.

OSI reviewer Lauren Iacono-Connors shared this inspectional observation with DOP2 Clinical Reviewer Denise Casey on April 20, 2015. Dr. Casey informed that any “missed” entries, as described above, were taken care of by the prespecified statistical analysis plan with regard to missing data and would not affect the primary outcome. Therefore, OSI and DOP2 are in agreement that this inspectional observation should not importantly impact study outcome.

C. Protocol required creatinine phosphokinase (CK) laboratory assessments were not completed for four of the sixteen subjects.

1. Subject 1513005 did not have a CK assessment performed at Visits 2 and 6.
2. Subject 1513013 did not have a CK assessment performed at Visits 4 and 8.
3. Subject 1513014 did not have a CK assessment performed at Visits 4 and 8.
4. Subject 1513016 did not have a CK assessment performed at Visits 2 and 6

OSI Reviewer Notes: Dr Gibney provided a written response, dated March 2, 2015, to the Form FDA 483 inspectional observations. He agreed with the observation and has taken corrective actions to remedy the study records as well as mitigate the violations moving forward. Deviation reports have been created on the study procedures missed and will be submitted to the IRB. The current study staff has been re-educated on the importance of adhering to all study required procedures.

OSI reviewer Lauren Iacono-Connors shared this inspectional observation with DOP2 Clinical Reviewer Denise Casey on April 20, 2015. Dr. Casey indicated that this observation was not uncommon among clinical centers due to the frequency of testing for this value throughout the study. CK was tested weekly for the first nine weeks, then every 2 weeks through week thirteen and then every 4 weeks thereafter. Therefore, OSI and DOP2 are in agreement that these limited missed CK tests described in the inspectional observation should not importantly impact study outcome or subject safety.

- c. **Assessment of data integrity:** The data for Dr. Gibney’s site, associated with Study CLDE225A2201 submitted to the Agency in support of NDA 205266, appear reliable based on available information.

**Note:** The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

**2. CI#2: Dr. Karl Lewis (Site 1503)**

- a. What was inspected:** The site screened 16 subjects, and 14 subjects were enrolled. The study records of all subjects were audited. The record audit included comparison of source documentation to CRFs and data listings submitted to NDA 205266, with particular attention paid to inclusion/exclusion criteria compliance, adverse events, treatment regimens, and reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent documents, test article accountability, and monitoring reports.
  
- b. General observations/commentary:** Generally, the investigator’s execution of the protocol was found to be adequate. Records and procedures were clear, and generally well organized. The primary efficacy endpoints were verifiable. There was no evidence of underreporting AEs. Review of source documentation for eligibility, treatment regimens, study drug administration cycles and drug accountability found no discrepancies. The inspection found a few minor issues but nothing that would impact study safety and efficacy outcomes or subject safety. The minor issues were recognized by site staff and corrected. Thus, the site had already implemented corrective actions to address the minor observations, prior to the initiation of the current inspection. A Form FDA 483 was not issued.
  
- c. Assessment of data integrity:** The data for Dr. Lewis’ site, associated with Study CLDE225A2201 submitted to the Agency in support of NDA 205266, appear reliable based on available information.

**3. CRO#1:** [Redacted] (b) (4)

**a. What was inspected:** [Redacted] (b) (4)

[Redacted] (b) (4)

**b. General observations/commentary:** (b) (4)

[Redacted text block]

**c. Assessment of data integrity:** . The data from this CRO submitted to the Agency in support of NDA 205266 appear reliable.

**4. CRO#2:** (b) (4)

[Redacted text block]

**a. What was inspected:** (b) (4)

[Redacted text block]

**b. General observations/commentary:** (b) (4)

[Redacted text block]

**c. Assessment of data integrity:** The data from this CRO submitted to the Agency in support of NDA 205266 appear reliable.

### III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Based on the review of inspectional findings for clinical investigators Dr. Gibney (Site 1513), Dr. Lewis (Site 1503), the CRO (b)(4) and the CRO (b)(4) the Study CLDE225A2201 data appear reliable.

The preliminary classification for clinical investigator Dr. Lewis (Site 1503), the CRO (b)(4) and the CRO (b)(4) is No Action Indicated (NAI). The preliminary classification for clinical investigator Dr. Gibney (Site 1513) is Voluntary Action Indicated (VAI).

With respect to the inspectional findings at Dr. Gibney's site (Site 1513), the site didn't always report SAEs in a timely fashion, resulting in 2 SAEs that occurred prior to the data cut off, but were not included in the datalistings submitted to the NDA because they were reported to the sponsor after the data cutoff date of June 28, 2013. Some protocol-specified assessments were not always performed. Briefly, the site did not always perform screening dipstick urinalysis, protocol required photographs, and CK periodic testing on study subjects. CK was tested weekly for the first nine weeks, then every 2 weeks through week thirteen and then every 4 weeks thereafter. Therefore, OSI and DOP2 agreed that these inspectional observations should not importantly impact study outcome or subject safety.

Based upon available information the overall data for Study CLDE225A2201 in support of this application may be considered reliable based on available information.

**Note:** Certain observations noted above are based on the preliminary communications provided by the FDA field investigators. An inspection summary addendum will be generated if conclusions change significantly upon receipt and complete review of the EIRs.

{ See appended electronic signature page }

Lauren Iacono-Connors, Ph.D.  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
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/s/  
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LAUREN C IACONO-CONNORS  
04/28/2015

SUSAN D THOMPSON  
04/29/2015

KASSA AYALEW  
04/29/2015



**DEPARTMENT OF HEALTH & HUMAN SERVICES** Public Health Service

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Food and Drug Administration  
Office of New Drugs, ODE-IV  
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**MEMORANDUM TO FILE**

**From:** Ethan D. Hausman, MD, Medical Officer  
Division of Pediatric and Maternal Health (DPMH)

**Through:** Hari Cheryl Sachs, MD, Medical Team Leader  
DPMH  
Lynne P. Yao, MD, Acting Division Director  
DPMH

**NDA Number:** 202,266

**Sponsor:** Novartis Pharmaceuticals

**Drug:** Sonidegib (Odomzo)

**Dosage form, Route of Administration, Regimen:** 200 mg capsules, once daily oral administration

**Pediatric dosing regimen:** Not recommended in pediatric patients

**Indication:** Treatment of adult patients with locally advanced basal cell carcinoma (BCC) who are not amenable to curative surgery or radiation therapy

**Date of internal labeling meetings:** March 12, 18, 23, and 25, 2015

**Division Consult Request:** The Division of Oncology Products 2 (DOP-2) requested DPMH participation in labeling for this hedgehog pathway inhibitor intended for treatment of adults with BCC, to conform with Physician Labeling Rule (PLR) format.

## Background

Sonidegib is a hedgehog pathway inhibitor being developed for treatment of adults with locally advanced basal cell carcinoma (BCC), not amenable to curative surgery or radiation therapy.

The NDA was submitted on September 26, 2014, and the expected regulatory action date is July 25, 2015. Per communication with the DOP-2 medical officer on March 13, 2015, Sonidegib will not be developed for treatment of BCC in children. (b) (4)

This labeling consult is based on the label version in the SharePoint document site as of March 12, 2015. The consult is limited to Boxed Warning describing known teratogenic, embryotoxic, and fetotoxic effects common to all hedgehog pathway inhibitors, and Sections 1 (Indications and Usage), 8.4 (Pediatric Use), and the Highlights section. DPMH recommendations for Sections 8.1 (Pregnancy) and 8.3 (Nursing Mothers) will be addressed in the separate DPMH-Maternal Health labeling consult.

For each section, the proposed language is presented first, followed by recommended changes, if any, in *bold italics*.

## Boxed Warning

### Proposed

The Boxed Warning describing embryotoxicity, fetotoxicity, and teratogenicity of hedgehog pathway inhibitors is shown below.

*Reviewer comment: The draft Boxed Warning is consistent with the Boxed Warning for Erivedge (NDA 203,388, vismodegib, approved January 30, 2012), another hedgehog pathway inhibitor, and appears appropriate. There are no specific pediatric safety issues currently known except those which overlap with the toxicities described in the Boxed Warning, no additional pediatric comments are recommended for the Highlights section of labeling; however, additional descriptions of hedgehog toxicities related to pregnancy may be found in the separate Maternal Health Labeling consult (pending).*

## 1 Indications and Usage

### Proposed

ODOMZO (sonidegib) is indicated for the treatment of adult patients with locally advanced basal cell carcinoma (BCC) who are not amenable to curative surgery or radiation therapy.

*Reviewer comment: The indication appears appropriate and clearly indicates that the drug is not intended for pediatric use. Per discussions with DOP-2, there are no pediatric specific safety issues other than the toxicities described in the Boxed Warning.*

## 5 Warnings and Precautions

### Proposed

5.1

(b) (4)

(b) (4)

*Reviewer comment: This description is similar to the description in vismodegib labeling (NDA 203,388) and appears generally appropriate. Additional comments may be found in the separate Maternal Health labeling review (pending) and final negotiated labeling (pending).*

## 8.4 Pediatric Use

### Proposed

The safety and effectiveness of ODOMZO has not been established in pediatric patients

(b) (4)  
[Redacted text block]

*Reviewer comment: DPMH proposed the following modifications for clarity.*

The safety and effectiveness of ODOMZO has not been established in pediatric patients.

### *Juvenile Animal Data*

[Redacted text block] (b) (4)

### Summary and Recommendations

The DPMH Pediatric reviewer participated in the internal labeling meetings held on March 12, 18, 23, and 25, 2015. The above comments were provided to DOP-2 on March 13, 2015. The reader is directed to the Maternal Health labeling review (pending) and final negotiated labeling (pending) which may include additional revisions not discussed in this review.

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/s/  
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ETHAN D HAUSMAN  
04/15/2015

HARI C SACHS  
04/15/2015  
I agree with these recommendation

LYNNE P YAO  
04/16/2015

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

<b>IND or NDA</b>	205266
<b>Brand Name</b>	ODOMZO®
<b>Generic Name</b>	Sonidegib (LDE225)
<b>Sponsor</b>	Novartis Pharmaceutical Corporation
<b>Indication</b>	Locally advanced basal cell carcinoma (laBCC) <sup>(b)</sup> <sup>(4)</sup>
<b>Dosage Form</b>	Oral (capsules)
<b>Drug Class</b>	Hh and Smo antagonist
<b>Therapeutic Dosing Regimen</b>	200 mg q.d.
<b>Duration of Therapeutic Use</b>	Chronic
<b>Maximum Tolerated Dose</b>	800 mg q.d.
<b>Submission Number and Date</b>	000 / 9/26/2014
<b>Review Division</b>	DOP2

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

## 1 SUMMARY

### 1.1 OVERALL SUMMARY OF FINDINGS

No large mean change (i.e., > 20 ms) in the QTc interval was detected when LDE225 was administered at 200 mg and 800 mg orally once-daily at week 17. The sponsor did not submit placebo and positive control (moxifloxacin) arms.

This was Phase-II, randomized, parallel, international, multicenter, 230 subjects received LDE225 200 mg and LDE225 800 mg. Overall summary of findings is presented in Table 1.

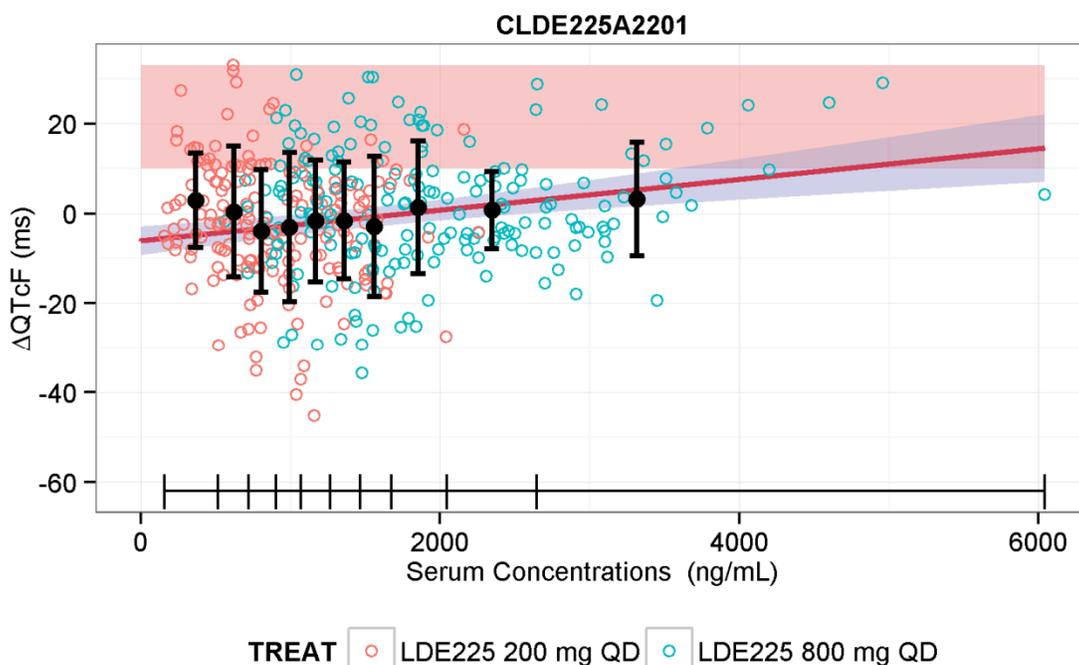
**Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for LDE225 (200 mg and 800 mg)**

<b>Treatment</b>	<b>Time (hour)</b>	<b>ΔQTcF (ms)</b>	<b>90% CI (ms)</b>
LDE225 200 mg QD	2	-0.6	(-5.2, 4.1)
LDE225 800 mg QD	2	3.3	(-0.6, 7.2)

Although the suprathreshold dose (800 mg) produces mean  $C_{max}$  values 2-fold the mean  $C_{max}$  for the therapeutic dose (200 mg), these concentrations did not cover that at the predicted worst case scenario (food interaction a high fat meal is expected to increase LDE225 exposure 7- to 8-fold compared to administration at fasting conditions). However, this may not be a significant clinical concern because LDE225 is proposed to be taken on an empty stomach, at least 1 hour before, or 2 hours after a meal.

A pooled analysis of studies CLDE225A2201, CLDE225X2101, and CLDE225X1101 shows no significant concentration effect relationship. However, an analysis with data study CLDE225A2201 only, which has relatively high quality ECG/PK data (i.e., with valid baseline ECG information, triplicate ECG records, and matched PK/ECG monitoring), shows a statistically significant positive relationship (Figure 1).

**Figure 1:  $\Delta$ QTcF vs. Drug concentration (Study CLDE225A2201)**



## 1.2 QT INTERDISCIPLINARY REVIEW TEAM'S COMMENTS

The results from the current submission may be able to rule out large mean QT prolongation (i.e., >20 ms) for LDE225 at the therapeutic dose.

However, a significant positive relationship between LDE225 concentration and QTc may exist and clear QTc changes were observed in patients with high LDE225 concentration (e.g. >3500 ng/mL, see Figure 1).

Because a thorough QT (TQT) study, which is able to rule out small QT prolongation (i.e., 10 ms), is feasible for LDE225 in healthy subjects, given the limitation of this

submission we consider a TQT study is needed (please also see QT-IRT's previous review dated 7/11/2013 and 3/17/2014).

## 2 PROPOSED LABEL

### 2.1 THE SPONSOR'S LABEL:

#### 12.2 PHARMACODYNAMICS

*Cardiac Electrophysiology*

(b) (4)

### 2.2 QT-IRT RECOMMENDATIONS

*Our recommendations are suggestions only. We defer final labeling decisions to the review division.*

#### 12.2 PHARMACODYNAMICS

*Cardiac Electrophysiology*

(b) (4)

## 3 BACKGROUND

### 3.1 PRODUCT INFORMATION

LDE225 is an orally bioavailable Smoothed (Smo)- and Hedgehog (Hh)- antagonist.

(b) (4)

### 3.2 MARKET APPROVAL STATUS

LDE225 (sonidegib) is not approved for marketing in any country

### 3.3 PRECLINICAL INFORMATION

From the IB (March 2012)

A GLP study entitled "Electrophysiological safety measurements of hERG currents in stably transfected HEK293 cells" [Study 0770726] was conducted. The hERG channel activity was significantly decreased at the highest analytically measured test concentration of 0.5µM (0.3 µg/ml) by 20.7%. However, the nominal concentration

prepared was 7.8 µg/ml

(b) (4)

Therefore, attribution of an effect of LDE225 on the hERG channel, or the concentration where this occurs, must be interpreted cautiously.

In 2 non-GLP studies entitled “Electrophysiological study of LDE225 in isolated heart” [Study 0718501] and [Study 0718539], LDE225 was evaluated in the isolated rabbit heart according to the Langendorf technique. At LDE225 concentrations above 2 µM, (b) (4) At the (b) (4) concentration of 2 µM, there was no risk for QT interval prolongation and related arrhythmia. A slowing of intraventricular conduction velocity and shortened ventricular repolarization occurred at 2 µM during a 30 min perfusion.

Single dose cardiovascular data in dogs at 30, 100 and 300 mg/kg were obtained in the non-GLP study “An oral (capsule) pilot toxicity study in male dogs with non-invasive telemetry” [Study 0670734]. There was no effect on clinical pathology, food consumption or body weight. Following the 300 mg/kg dose there was apparent compound in the feces followed by feces with apparent blood, mucoid feces and diarrhea. There was no effect on ECG parameters, as measured by jacket telemetry up to 8 hours post-dose. Exposure was very variable and increased over-proportionally with increasing dose. The highest AUC(0-96h) was 107,000 ng\*hr/mL for male 1001 with a Cmax of 5490 ng/mL. Tmax ranged between 1 and 4 hrs.

Single dose cardiovascular data in dogs at 150, 300, 600 and 1000 mg/kg were obtained in the non-GLP study “Oral (gavage) single dose rising-dose study in dogs including non-invasive telemetry” [Study 0770514]. There were no treatment-related effects on clinical signs, food consumption or body weight. There was no effect on ECG parameters as measured by jacket telemetry up to 6 hours post-dose. Exposure increased in a roughly dose proportional manner. The AUC(0-96h) was 558,000 and 286,000 ng\*h/mL and Cmax was 8560 and 5050 ng/mL for M and F at 1000 mg/kg.

Cardiovascular safety pharmacology was evaluated in the GLP study “Single-dose oral telemetry study in dogs” [Study 0770734]. Dogs received single oral doses of 0, 100, 300 and 1000 mg/kg in a crossover design. LDE225 was well tolerated with no treatment-related clinical signs or relevant changes in body weight or food consumption. No clearly overt treatment-related effects were observed up to 1000 mg/kg for mean (n=4) heart rate, core body temperature, systolic and diastolic arterial blood pressure, and ECG interval durations. ECG morphology and rhythm showed no treatment-related changes up to 1000 mg/kg.

*Reviewer’s comments: LDE225 decrease hERG currents activity significantly by 21% at the highest analytically measured test concentration of 0.5µM (0.3 µg/mL) which is below clinical Cmax exposure achieved after multiple doses (~0.9 ug/mL and ~2 ug/mL at the 200 mg and 800 mg QD respectively). However, no IC50 was obtained* (b) (4)

### 3.4 PREVIOUS CLINICAL EXPERIENCE

From the IB (March 2012)

**CLDE225X2101.** I First-In-Human (FIH), multi-center, open label dose escalation trial with the aim to evaluate the maximum tolerated dose (MTD) of LDE225, with additional assessments of its pharmacokinetics (PK), pharmacodynamics (PD) (b) (4) in advanced solid tumors. Eligible patients are adults, aged  $\geq 18$  years, with malignant tumors (including locally advanced and metastatic basal cell carcinoma and recurrent or refractory medulloblastoma) that have progressed despite the use of standard therapies or for which no therapies exist. LDE225 is administered orally in a continuous 28-day dosing schedule.

In CLDE225X2101, the starting dose of LDE225 was 100 mg and as of the data cut-off of October, 2011, data were available on 103 patients with cancer who have been treated with LDE225 at dose levels of 100, 200, 400, 800, 1000, 1500, and 3000 mg once daily (QD) and 250, 400 and 750 mg twice daily (BID).

Across all the doses, the commonly (>10%) reported CTCAE grade 1 or 2 adverse events in this study that are suspected to be treatment-related include: nausea, vomiting, dysgeusia, decreased appetite, myalgia, muscle spasms, blood CK increased, alopecia, asthenia and fatigue (Table 5-1). No treatment-related clinically significant changes in the other safety laboratory data (hematology, and urinalysis), vital signs or ECGs have been observed for any of the patients treated in the study.

Table 5-1 Adverse Events Suspected to be Related with LDE225, Occurring in greater or equal to 5% of Patients in Study CLDE225X2101 as of October 2011

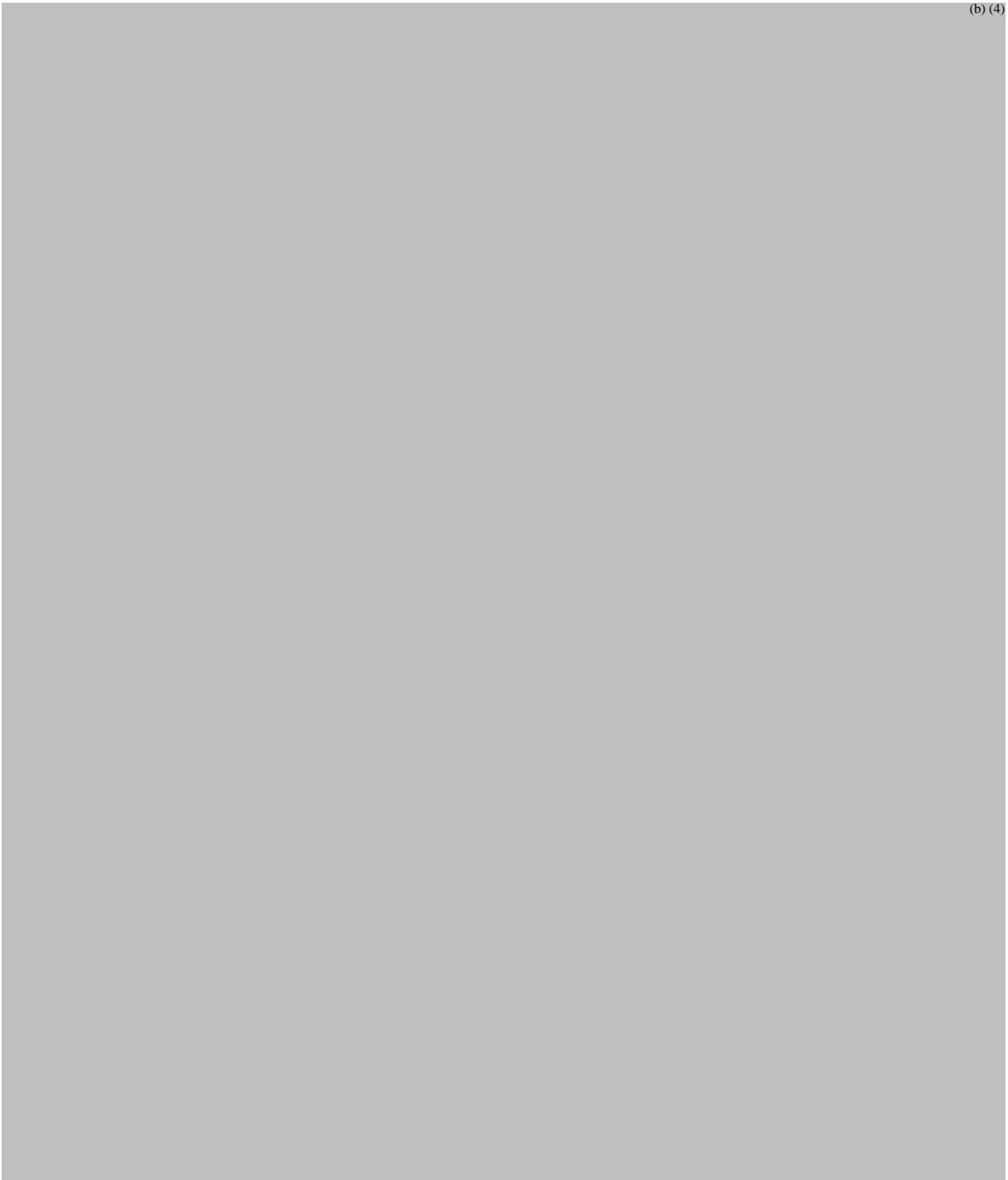
	800 mg QD* (n=26)		All doses** (n=103)	
	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Nausea	3 (11.5)		26 (25.2)	
Dysgeusia	5 (19.2)		29 (28.2)	
Weight decrease	4 (15.4)		10 (9.7)	
Decreased appetite	4 (15.4)		18 (17.5)	
Vomiting	2 (7.7)		13 (12.6)	
Diarrhea	2 (7.7)		7 (6.8)	
Constipation	1 (3.8)		6 (5.8)	
Muscle spasms	9 (34.6)		31 (30.1)	
Myalgia	5 (19.2)		18 (17.5)	
Blood CK increased	6 (23.1)	2 (7.7)	30 (29.1)	19 (18.4)
AST increased	1 (3.8)		8 (7.8)	3 (2.9)
ALT increased	1 (3.8)		7 (6.8)	3 (2.9)
Fatigue	1 (3.8)		15 (14.6)	
Asthenia	5 (19.2)	1 (3.8)	11 (10.7)	2 (1.9)
Alopecia	3 (11.5)		11 (10.7)	
Lethargy	3 (11.5)		7 (6.8)	

(b) (4)  
\*\*All doses, including BID and QD schedule

*Reviewer's comments: Safety data from 103 patients from studies CLDE225X2101, CLDE225X1101, and CLDE225X2104 and one Phase II clinical trial, CLDE225A2201, were provided so far. No seizures, ventricular arrhythmias or clinically relevant ECG changes were reported. One report of sudden death in the 800-mg q.d. arm was reported in study CLDE225X2101.*

### **3.5 CLINICAL PHARMACOLOGY**

Key features of LDE225's clinical pharmacology is summarized below (from the proposed package insert).



## **4 SPONSOR'S SUBMISSION**

### **4.1 OVERVIEW**

The QT-IRT reviewed the protocol of Study CLDE225A2201 prior to conducting this study under IND 102961. However, QT-IRT did not agree with the sponsor's QT

analysis plan (see QT-IRT's previous review dated 7/11/2013 and 3/17/2014). In the current submission, the sponsor conducted a central tendency analysis using data from Study A2201 in which a PK/ECG subgroup of patients was implemented for time-matched PK and triplicate ECG collection at steady state (Week 17 predose, 1 hr, 2 hr, 4 hr, and 6 hr postdose), including electronic datasets and waveforms to the ECG warehouse.

The sponsor also conducted a pooled PK-QTcF analysis of 4 patient studies (A2201, B2209, X2101, and X1101) and separately of 4 healthy volunteer studies (A1102, A2114, A2108 control, and A2110).

## **4.2 TQT STUDY**

### **4.2.1 Title**

- 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 (BOLT)
- QT/QTc analysis of sonidegib in healthy volunteers and patients with advanced solid tumors

### **4.2.2 Protocol Numbers**

CLDE225A2201

### **4.2.3 Study Dates**

Study initiation date: 20-Jul-2011 (first patient first visit)

Data cut-off date: 28-Jun-2013

### **4.2.4 Objectives**

The primary objective was to evaluate the efficacy of sonidegib as measured by ORR assessed by central review according to:

- mRECIST in patients with laBCC
- RECIST 1.1 in patients with mBCC

Secondary objectives:

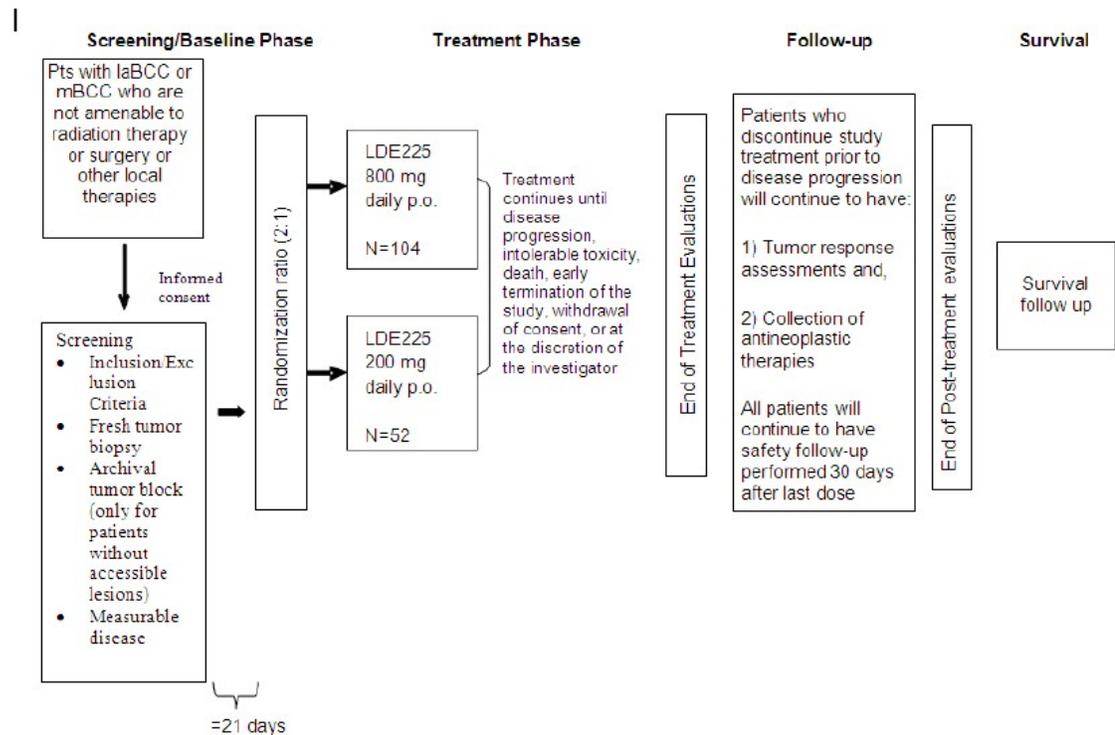
- To determine the DoR as assessed by central review according to mRECIST in patients with laBCC and to RECIST 1.1 in patients with mBCC
- To determine the rate of complete response (CR) as assessed by central review according to mRECIST in patients with laBCC and to RECIST 1.1 in patients with mBCC

### **4.2.5 Study Description**

#### **4.2.5.1 Design**

This was a multi-center, adaptive, randomized, double-blind, Phase II study designed to evaluate the safety and antitumor activity of two doses of sonidegib in 230 patients with laBCC or mBCC. Eligible patients were randomly assigned in a 1:2 ratio to treatment with sonidegib 200 mg or sonidegib 800 mg on a continuous

once-daily dosing schedule. Figure below shown a schematic representation of the study design.



#### 4.2.5.2 Controls

No placebo and positive (moxifloxacin) controls included in the study.

#### 4.2.5.3 Blinding

Patients, investigator staff, persons performing any assessments, all Novartis personnel, and individuals at central laboratories (including central imaging) were to remain blinded to the identity of the treatment from the time of randomization until database lock for the primary analysis using the following methods:

- Randomization data were kept strictly confidential until the time of treatment unblinding and were not accessible by anyone in the study with the following exceptions: the bioanalyst, the independent biostatistician, and the independent programmer who performed the interim analyses
- The identity of the treatments was concealed by the use of study treatments that were identical in packaging, labeling, schedule of administration, appearance, and odor

#### 4.2.6 Treatment Regimen

##### 4.2.6.1 Treatment Arms

The study include two treatment arms:

- LDE225 800 mg q.d.
- LDE225 200 mg q.d.

#### **4.2.6.2 Sponsor's Justification for Doses**

The applicant is using the highest tolerable dose (800 mg) as the suprathreshold dose in Study CLDE225A2201.

*Reviewer's Comment: The Agency agreed to this dose at the time of the review of the protocol. However, influence of extrinsic and intrinsic factors was unknown at the time. Of special note is the relatively large increase in exposure when taken with food. Please see comments below.*

#### **4.2.6.3 Instructions with Regard to Meals**

Capsules were to be administered orally once-daily (including days which involved PK blood sampling) approximately 2 hours after a light breakfast (e.g. consisting of juice, toast, and jam). If breakfast was completed at 08:00 am, then study drug administration occurred at 10:00 am. Food intake was to be avoided for at least 1 hour after study drug administration.

*Reviewer's Comment: C<sub>max</sub> and AUC<sub>inf</sub> were increased 7- to 8-fold, respectively, when a single 800-mg dose of sonidegib capsule was administered with a high-fat meal compared to a fasted state. This was unknown at the time of study design and FDA review of the QT protocol. The label proposes that sonidegib should be taken on an empty stomach.*

#### **4.2.6.4 ECG and PK Assessments**

PK and ECG were collected at 0, 1, 2, 4, and 6 hours post dose following 17 weeks of administrations in Study CLDE225A2201.

*Reviewer's Comment: Based on expected time to reach C<sub>max</sub> and time to reach pharmacokinetic steady state, the sampling schedule seems reasonable.*

#### **4.2.6.5 Baseline**

Baseline is defined as the average of all ECG measurements taken prior to the first dose of any study drug on Week 17.

#### **4.2.7 ECG Collection**

A standard 12-lead ECG will be performed at screening and during the study (pre-dose). The ECGs will be collected and reviewed by a central laboratory. Triplicate 12-lead ECGs will be extracted at predetermined timepoints. A copy of the ECG tracing should be printed and kept in the source documents at the study site. Only clinically significant abnormalities should be reported in the Adverse Event CRF.

#### **4.2.8 Sponsor's Results**

##### **4.2.8.1 Study Subjects**

Two-hundred and ten patients were planned to be enrolled and a total of 230 patients were randomized: 79 to treatment with sonidegib 200 mg and 151 to treatment with

sonidegib 800 mg.

## 4.2.8.2 Statistical Analyses

### 4.2.8.2.1 Primary Analysis

The primary endpoint was mean change from baseline of QTcF. Sponsor was collected data of Study A2201 at steady state (Week 17 predose, 1 h, 2 h, 4 h, and 6 h postdose). A total of 62 patients (27 in 200-mg qd arm and 35 in 800-mg qd arm) had baseline triplicate ECGs and at least one Week 17 matched PK/triplicate ECG data available. Sponsor's descriptive statistics included N, mean, standard deviation, minimum, and maximum presented in Table 2 and Figure 2. The highest means  $\Delta$ QTcF at steady state of LDE225 200 mg qd and 800 mg qd were -3.9 ms and 2.7 ms, respectively.

**Table 2: Sponsor's Change from Baseline QTcF by Treatment and Timepoint (PK/ECG set from A2201)**

Treatment: LDE225 200 mg qd													
Week 17 hour	n	Baseline				Post baseline				Change from baseline			
		Mean	SD	Median	Min-Max	Mean	SD	Median	Min-Max	Mean	SD	Median	Min-Max
Pre-dose	25	423.2	19.04	424.4	390.7-458.7	419.3	21.88	418.0	389.7-471.0	-3.9	13.13	-2.1	-37.3-17.8
1 hr	21	427.3	25.04	424.4	390.7-493.5	422.6	25.38	418.5	383.3-487.7	-4.7	12.50	-5.8	-37.0-23.8
2 hr	22	426.7	23.76	425.7	390.7-493.5	422.5	25.42	419.0	380.0-490.7	-4.3	15.83	-9.1	-41.7-25.3
4 hr	23	428.1	24.15	427.0	390.7-493.5	423.7	27.71	428.7	368.0-502.7	-4.3	14.69	-2.4	-33.7-15.8
6 hr	20	428.2	24.94	425.7	390.7-493.5	423.0	24.71	418.4	377.7-488.3	-5.2	13.59	-4.5	-30.7-17.3
Time averaged	27	426.6	23.03	427.0	390.7-493.5	422.7	24.37	422.7	380.2-492.4	-3.9	11.90	-5.4	-36.1-18.2

Treatment: LDE225 800 mg qd													
Week 17 hour	n	Baseline				Post baseline				Change from baseline			
		Mean	SD	Median	Min-Max	Mean	SD	Median	Min-Max	Mean	SD	Median	Min-Max
Pre-dose	33	412.8	15.25	411.8	386.0-452.6	411.8	17.31	413.3	385.7-449.7	-1.0	10.93	-0.7	-23.0-15.0
1 hr	33	413.7	15.78	411.8	386.0-452.6	412.7	17.70	413.7	381.7-450.0	-1.0	13.39	-1.2	-28.1-24.8
2 hr	31	412.9	15.40	411.8	386.0-452.6	415.6	14.05	415.3	377.3-439.3	2.7	13.08	3.9	-18.0-29.7
4 hr	32	414.5	15.33	411.9	386.0-452.6	416.5	12.99	412.2	387.7-439.0	2.0	12.97	3.5	-35.6-30.5
6 hr	33	413.7	15.78	411.8	386.0-452.6	414.2	13.97	415.3	383.7-440.0	0.5	13.03	0.3	-29.3-22.5
Time averaged	35	413.5	15.67	411.8	386.0-452.6	413.6	14.55	412.2	387.1-443.3	0.2	11.80	2.2	-30.1-23.1

Baseline is defined as the average of all ECG measurements taken prior to the first dose of study drug as confirmed by date and time.

Time averaged is the average by patient across all available Week 17 timepoints.

n is number of patients who had baseline and post baseline at a given time point.

Change from baseline: post baseline - baseline.

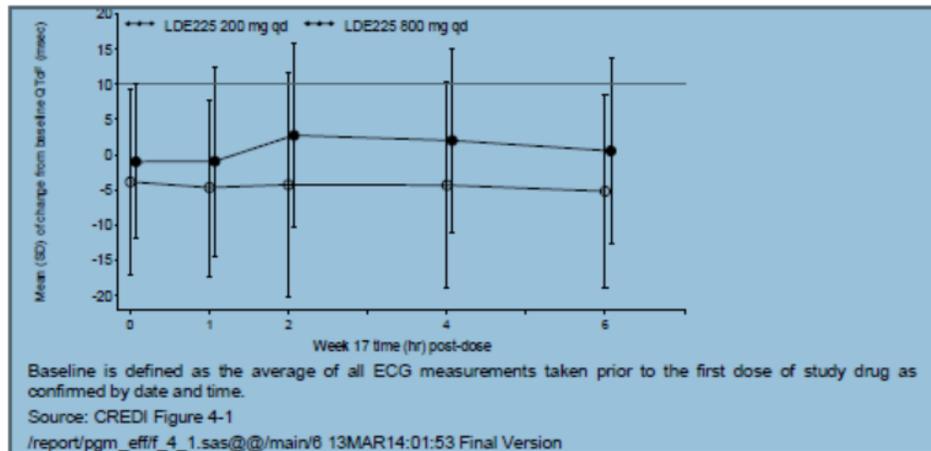
If >1 ECG is taken for a given patient and time point, the average of those ECG is used.

Unscheduled visits are not included.

Source: CREDI Table 4-1

/report/pgm\_effit\_4\_1.sas@@/main/7 13MAR14:01:53 Final Version

**Figure 2: Sponsor's Mean (SD) Change from Baseline QTcF by Treatment and Timepoint**



Reviewer's Comments: We will provide our independent analysis results in Section 5.2.

#### 4.2.8.2.2 Assay Sensitivity

No assay sensitivity established in this study because no positive control arm was included.

#### 4.2.8.2.3 Categorical Analysis

Categorical analysis was used to summarize in the categories of QTc  $\leq$ 450 ms, between 450 ms and 480 ms, between 480 ms and 500 ms, and  $>$ 500 ms, and changes from baseline QTc  $\leq$ 30 ms, between 30 and 60 ms, and  $>$ 60 ms. Two subjects' absolute QTcF was  $>$ 500 ms and no subjects'  $\Delta$ QTcF was  $>$ 60 ms.

	LDE225 200 mg qd N= 79 Total n %	LDE225 800 mg qd N=150 Total n %	All patients N=229 Total n %
<b>QTcF (msec)</b>			
New > 450	72 10 13.9	140 11 7.9	212 21 9.9
New > 480	78 0 0.0	146 3 2.1	224 3 1.3
New > 500	79 1 1.3	146 1 0.7	225 2 0.9
Increase from baseline > 30	79 6 7.6	146 21 14.4	225 27 12.0
Increase from baseline > 60	79 0 0.0	146 0 0.0	225 0 0.0
<b>QTcB (msec)</b>			
New > 450	69 14 20.3	130 27 20.8	199 41 20.6
New > 480	77 3 3.9	143 6 4.2	220 9 4.1
New > 500	77 0 0.0	146 2 1.4	223 2 0.9
Increase from baseline > 30	79 13 16.5	146 24 16.4	225 37 16.4
Increase from baseline > 60	79 0 0.0	146 2 1.4	225 2 0.9
<b>QT (msec)</b>			
New > 450	74 6 8.1	138 15 10.9	212 21 9.9
New > 480	79 4 5.1	145 9 6.2	224 13 5.8
New > 500	79 0 0.0	146 3 2.1	225 3 1.3
Increase from baseline > 30	79 36 45.6	146 67 45.9	225 103 45.8
Increase from baseline > 60	79 0 0.0	146 13 8.9	225 13 5.8

#### 4.2.8.3 Safety Analysis

The safety and tolerability profile of sonidegib 200 mg was more favorable than for sonidegib 800 mg, with lower overall incidences in each AE category reported. Adverse

events were primarily grade-1 or grade-2 events. Most AEs were manageable and reversible with dose adjustments.

Four deaths (2.7%) while on treatment (considered as deaths which occurred up to 30 days after the discontinuation of study treatment) occurred in the sonidegib 800-mg group of note, no deaths were reported in the sonidegib 200-mg group.

Serious AEs, AEs leading to study drug discontinuation, and AEs leading to dose reduction and/or temporary interruption of therapy were all reported less frequently in the sonidegib 200-mg treatment group than in the 800-mg group (SAEs: 13.9% vs 30.0%; discontinuations: 21.5% vs 36.0%; dose reduction/temporary interruption: 31.6% vs 60.0%)

**Table 12-4 Overview of adverse event categories (Safety set)**

	Sonidegib 200 mg N=79 n (%)	Sonidegib 800 mg N=150 n (%)
Adverse events (AEs)	75 (94.9)	150 (100)
Grade 3-4 AEs	24 (30.4)	84 (56.0)
Grade 3-4 AEs with suspected causality	18 (22.8)	63 (42.0)
AEs with suspected causality	68 (86.1)	142 (94.7)
On-treatment deaths <sup>a</sup>	0	4 (2.7)

#### 4.2.8.4 Clinical Pharmacology

##### 4.2.8.4.1 Pharmacokinetic Analysis

The sponsor did not perform a formal pharmacokinetic analysis. Concentration time profiles are visualized in Figure 4 and Figure 5 by the reviewer.

##### 4.2.8.4.2 Exposure-Response Analysis

Applicant performed a exposure response analysis based on linear mixed effect modeling.

*Reviewer's Analysis: A plot of  $\Delta QTc$  vs. drug concentrations is presented in Figure 6.*

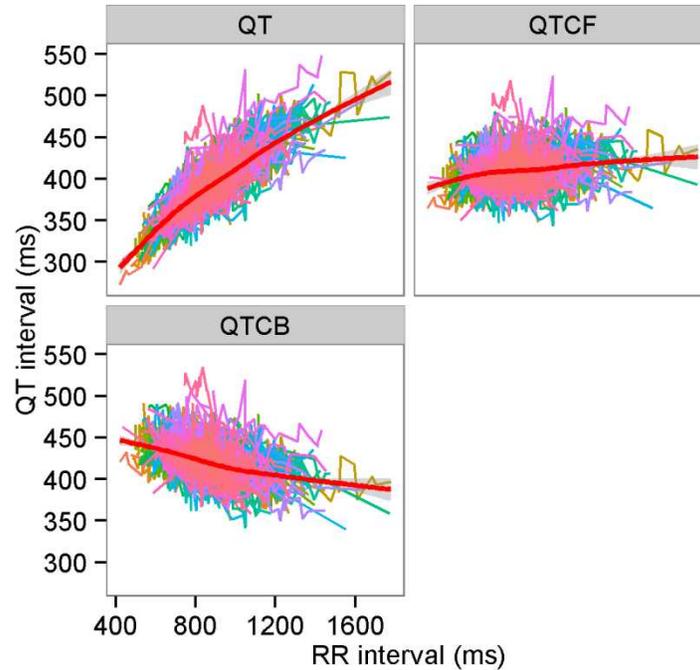
## 5 REVIEWERS' ASSESSMENT

### 5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

This review did not evaluate of the QT/RR correction method because the sponsor provided QTcB and QTcF correction intervals. This reviewer chooses to present QTcF for the primary statistical analysis.

The relationship between different correction methods and RR is presented in Figure 3.

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



## 5.2 STATISTICAL ASSESSMENTS

### 5.2.1 QTc Analysis

#### 5.2.1.1 The Primary Analysis for the Study Drug

The primary endpoint is change from the baseline of QTcF. The descriptive statistics are listed in Table 3. The largest upper bounds of the 2-sided 90% CI for the mean differences of LDE225 200 mg qd and 800 mg qd are 4.1 ms and 7.2 ms, respectively.

**Table 3: Analysis Results of  $\Delta$ QTcF for LDE225 at doses of 200 mg and 800 mg (Week 17)**

Treatment	Time	N	Mean	Std Dev	90% CI for Mean
LDE225 200 mg QD	0	39	-2.3	12.2	(-5.6, 1.0)
	1	34	-3.2	12.2	(-6.7, 0.4)
	2	35	-0.6	16.3	(-5.2, 4.1)
	4	36	-1.8	14.7	(-5.9, 2.4)
	6	31	-3.5	12.7	(-7.4, 0.3)
LDE225 800 mg QD	0	40	-0.1	12.4	(-3.4, 3.2)
	1	38	0.0	13.9	(-3.8, 3.8)
	2	36	3.3	13.8	(-0.6, 7.2)
	4	37	2.1	13.4	(-1.7, 5.8)
	6	38	1.0	13.9	(-2.8, 4.8)

### 5.2.1.1 Assay Sensitivity Analysis

No assay sensitivity analysis established because no positive control arm included in the study.

### 5.2.1.2 Categorical Analysis

Table 4 lists the number of subjects as well as the number of observations whose QTcF values are  $\leq 450$  ms, between 450 ms and 480 m, and  $>500$  ms. One subject's QTcF is above 500 ms.

**Table 4: Categorical Analysis for QTcF**

Table of TREAT by QTcF				
TREAT	QTcF			Total
	Value $\leq$ 450 ms	450 ms<Value $\leq$ 480 ms	Value $>$ 500	
LDE225 200 mg QD	39	5	1	45
	86.67	11.11	2.22	
LDE225 800 mg QD	44	0	0	44
	100.00	0.00	0.00	
<b>Total</b>	83	5	1	89

Table 5 lists the categorical analysis results for  $\Delta$ QTcF. No subject's change from baseline is above 60 ms.

**Table 5: Categorical Analysis for  $\Delta$ QTcF**

Table of TREAT by QTcF_CFB			
TREAT	QTcF_CFB		
	Value $\leq$ 30 ms	30 ms<Value $\leq$ 60 ms	Total
LDE225 200 mg QD	44 97.78	1 2.22	45
LDE225 800 mg QD	42 95.45	2 4.55	44
Total	86	3	89

### 5.2.2 HR Analysis

The primary endpoint is change from the baseline of HR. The descriptive statistics are listed in Table 6. The largest upper bounds of the 2-sided 90% CI for the mean differences of LDE225 200 mg qd and 800 mg qd are 6.4 bpm and -0.2 bpm, respectively. Table 7 presents the categorical analysis of HR. No subject who experienced HR interval greater than 100 bpm is in LDE225 treatment group.

**Table 6: Analysis Results of  $\Delta$ HR of for LDE225 at doses of 200 mg and 800 mg (Week 17)**

Treatment	Time (Hour)	N	Mean	Std Dev	90% CI for Mean
LDE225 200 mg QD	0	39	-2.4	10.0	(-5.1, 0.3)
	1	34	-3.0	9.0	(-5.6, -0.4)
	2	35	-2.2	8.1	(-4.5, 0.1)
	4	36	3.7	9.6	(1.0, 6.4)
	6	31	2.0	10.5	(-1.2, 5.2)
LDE225 800 mg QD	0	40	-5.2	8.1	(-7.4, -3.0)
	1	38	-7.4	10.8	(-10.3, -4.4)
	2	36	-6.1	9.5	(-8.8, -3.4)
	4	37	-3.7	12.6	(-7.2, -0.2)
	6	38	-4.0	12.3	(-7.4, -0.7)

**Table 7: Categorical Analysis for HR**

Table of TREAT by HR		
TREAT	HR	
	HR <= 100 ms	Total
LDE225 200 mg QD	45 100.00	45
LDE225 800 mg QD	44 100.00	44
<b>Total</b>	<b>89</b>	<b>89</b>

### 5.2.3 PR Analysis

The primary endpoint is change from the baseline of PR. The descriptive statistics are listed in Table 8. The largest upper bounds of the 2-sided 90% CI for the mean differences of LDE225 200 mg qd and 800 mg qd are 9.2 ms and 10.1 ms, respectively. Table 9 presents the categorical analysis of PR. Nine subjects who experienced PR interval greater than 200 ms are in both LDE225 200-mg and 800-mg groups.

**Table 8: Analysis Results of  $\Delta$ PR for LDE225 at doses of 200 mg and 800 mg (Week 17)**

Treatment	Time (hour)	N	Mean	Std Dev	90% CI for Mean
LDE225 200 mg QD	0	39	0.1	12.7	(-3.3, 3.5)
	1	33	5.5	12.0	(2.0, 9.0)
	2	34	5.0	14.4	(0.8, 9.2)
	4	35	3.8	15.2	(-0.5, 8.2)
	6	30	1.3	13.9	(-3.0, 5.6)
LDE225 800 mg QD	0	39	1.6	19.9	(-3.8, 7.0)
	1	38	3.5	24.1	(-3.0, 10.1)
	2	36	0.6	26.6	(-6.9, 8.1)
	4	37	2.1	21.5	(-3.9, 8.0)
	6	38	2.5	26.4	(-4.7, 9.8)

**Table 9: Categorical Analysis for PR**

Table of TREAT by PR			
TREAT	PR		
	PR $\leq$ 200 ms	PR >200 ms	Total
LDE225 200 mg QD	41 93.18	3 6.82	44
LDE225 800 mg QD	37 86.05	6 13.95	43
<b>Total</b>	78	9	87
Frequency Missing = 2			

#### 5.2.4 QRS Analysis

The primary endpoint is change from the baseline of QRS. The descriptive statistics are listed in Table 10. The largest upper bounds of the 2-sided 90% CI for the mean differences of LDE225 200 mg qd and 800 mg qd are 3.9 ms and 3.7 ms, respectively. Table 11 presents the categorical analysis of QRS. Twelve subjects who experienced QRS interval greater than 110 ms are in LDE225 200-mg and 800-mg groups.

**Table 10: Analysis Results of  $\Delta$ QRS for LDE225 at doses of 200 mg and 800 mg (Week 17)**

Treatment	Time (hour)	N	Mean	Std Dev	90% CI for Mean
LDE225 200 mg QD	0	39	1.3	4.6	(0.0, 2.5)
	1	34	0.2	5.5	(-1.5, 1.8)
	2	35	0.6	5.7	(-1.0, 2.3)
	4	36	1.3	5.7	(-0.3, 2.9)
	6	31	2.2	5.7	(0.4, 3.9)
LDE225 800 mg QD	0	40	1.6	7.6	(-0.4, 3.7)
	1	38	1.7	6.4	(-0.0, 3.5)
	2	36	1.2	8.3	(-1.1, 3.6)
	4	37	1.1	7.5	(-1.0, 3.1)
	6	38	1.1	8.2	(-1.1, 3.4)

**Table 11: Categorical Analysis for QRS**

Table of TREAT by QRS			
TREAT	QRS		
	QRS $\leq$ 110 ms	QRS $>$ 110 ms	Total
LDE225 200 mg QD	39 86.67	6 13.33	45
LDE225 800 mg QD	38 86.36	6 13.64	44
Total	77	12	89

### 5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The mean drug concentration-time profile for study CLDE225A2201 is depicted in Figure 4. The samples are collected at week 17 when the patients are considered to be on pharmacokinetic steady state. Data from Figure 4 are tabulated in Table 12.

**Table 12. Sonidegib exposure following 17 weeks of 200 mg or 800 mg QD administration**

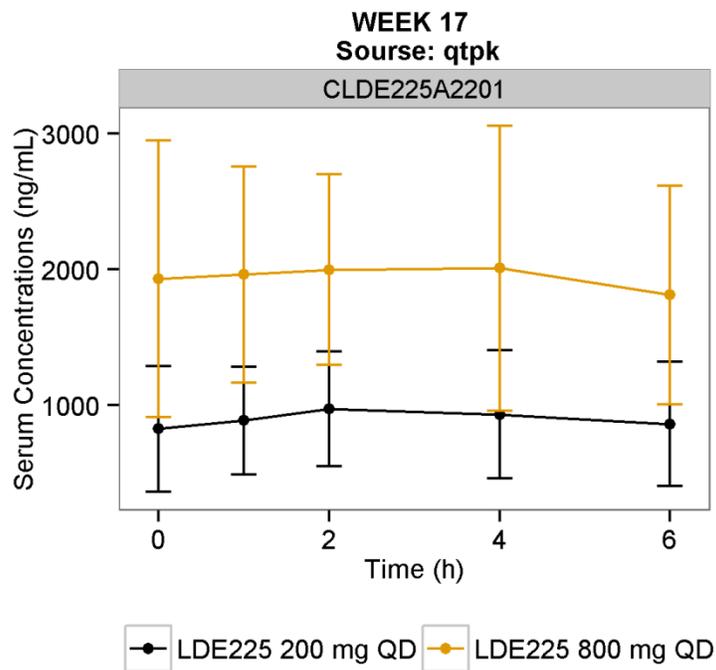
STUDYID	VISIT	TREAT	TIME	Mean	SD	n
CLDE225A2201	WEEK 17	LDE225 200 mg QD	0	825.0000	463.5805	44
CLDE225A2201	WEEK 17	LDE225 200 mg QD	1	886.3824	398.1383	37
CLDE225A2201	WEEK 17	LDE225 200 mg QD	2	971.9429	421.5942	35
CLDE225A2201	WEEK 17	LDE225 200 mg QD	4	932.4722	473.1964	36
CLDE225A2201	WEEK 17	LDE225 200 mg QD	6	861.3226	457.7119	34
CLDE225A2201	WEEK 17	LDE225 800 mg QD	0	1931.5500	1019.3847	45
CLDE225A2201	WEEK 17	LDE225 800 mg QD	1	1962.1053	796.2404	38
CLDE225A2201	WEEK 17	LDE225 800 mg QD	2	1998.6667	701.2456	37
CLDE225A2201	WEEK 17	LDE225 800 mg QD	4	2008.1622	1048.4453	38
CLDE225A2201	WEEK 17	LDE225 800 mg QD	6	1812.2632	806.1063	38

Source: *qtpk*.

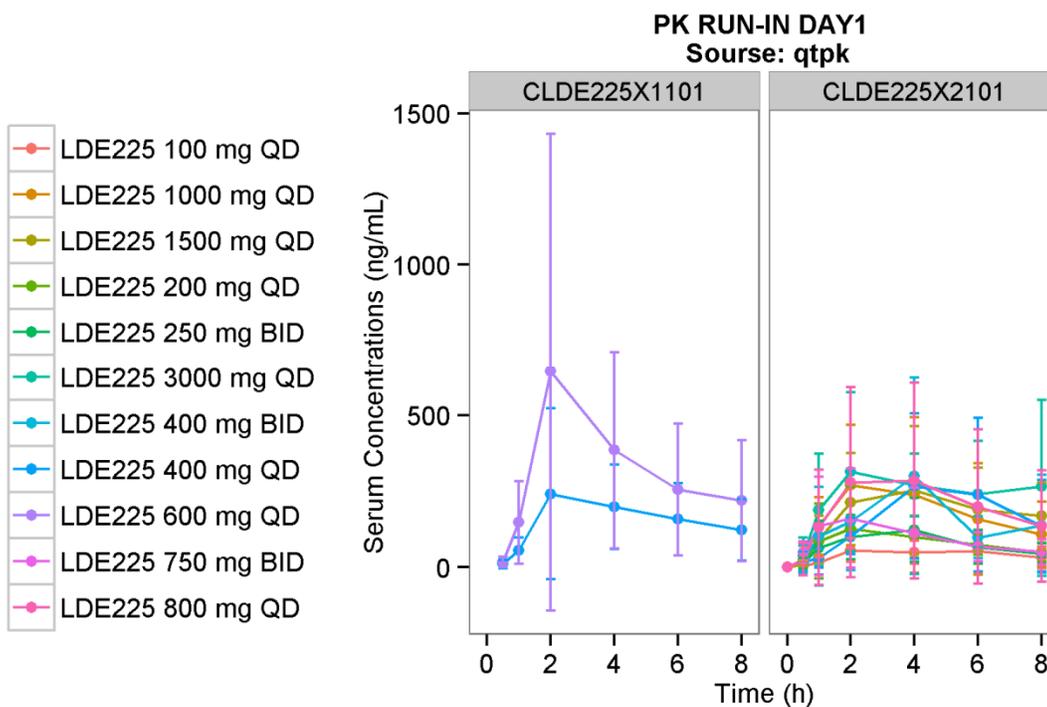
Note: Central tendency and variability of exposure is expressed in units of ng/mL

The mean drug concentration-time profile for studies CLDE225X2101 and CLDE225X1101 is depicted in and Figure 5. The samples presented in that figure were collected at day one during the PK runin period. Additional trough samples are available collected at cycles 1 to 15. These are not graphically displayed but were included in the exposure response analysis.

**Figure 4: Mean  $\pm$ SD Sonidegib concentration-time profiles for 800 mg (yellow line) and 200 mg Sonidegib (black line)**



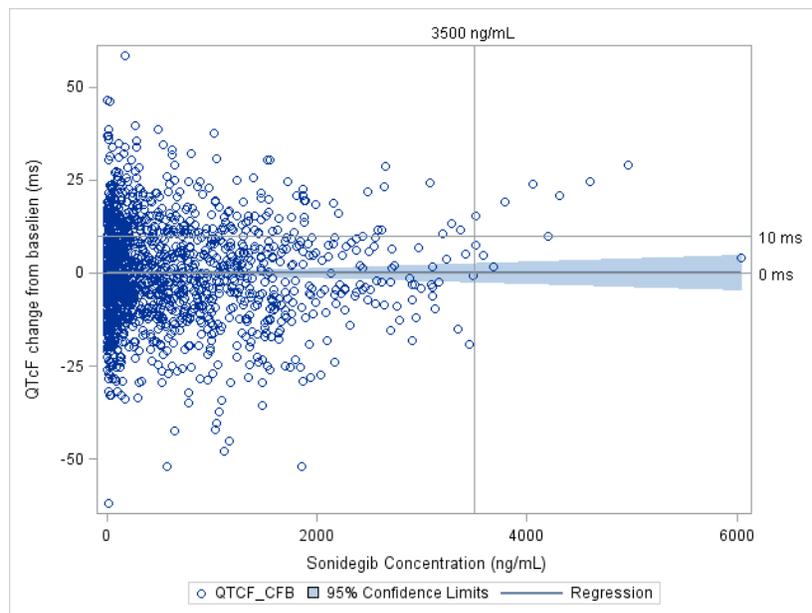
**Figure 5. Mean  $\pm$ SD Sonidegib concentration-time profiles**



The relationship between  $\Delta$ QTcF and Sonidegib concentrations is visualized in Figure 6a with no evident exposure-response relationship. Data (with clear time, baseline and matched PK/ECG record) from studies CLDE225A2201, CLDE225X2101, and CLDE225X1101 were used in the analysis (Figure 6).

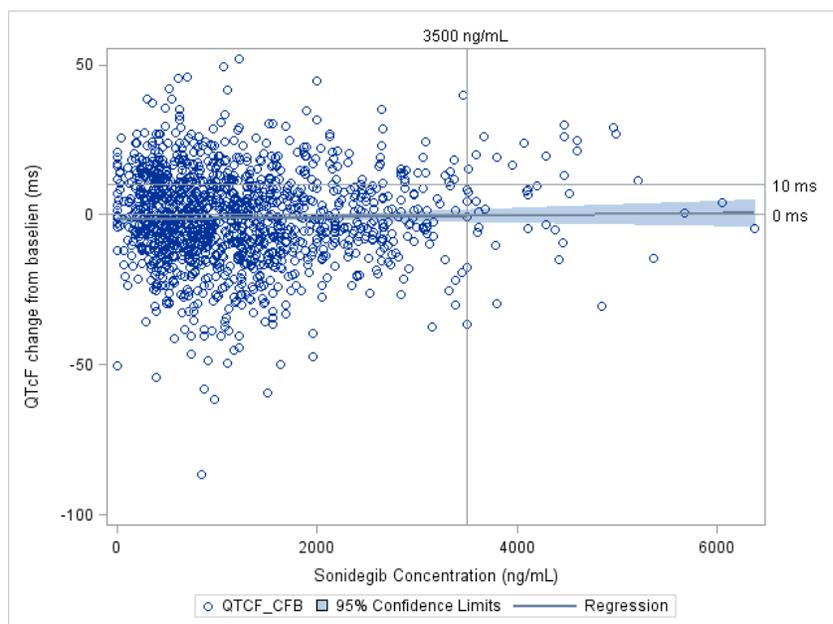
However, an analysis with data study CLDE225A2201 only, which has relatively high quality ECG/PK data (i.e., with valid baseline ECG information, triplicate ECG records, and matched PK/ECG monitoring), shows a statistically significant positive relationship (Figure 1) and clear QTc changes were observed in patients with high LDE225 concentration (e.g. >3500 ng/mL, see Figure 1 and Figure 6). However, the positive concentration-QTc relationship and robust QTc changes in patients with high LDE225 concentration were not observed if all data from study CLDE225A2201 (which includes ECG data with a single measurement and without clear sampling time record) were used (Figure 7). Given the limitation of the data, a TQT study is needed.

**Figure 6:  $\Delta$  QTcF vs. Drug concentration (Studies CLDE225A2201, CLDE225X2101, and CLDE225X1101 )**



*Data with clear time, baseline and matched PK/ECG records were used*

**Figure 7:  $\Delta$  QTcF vs. Drug concentration (Studies CLDE225A2201)**



*All data from study CLDE225A2201 (which includes ECG data with a single measurement and without clear sampling time record) were used*

## **5.4 ASSESSMENTS**

### **5.4.1 Safety assessments**

There are several cases of syncope, but there are no other events that might represent arrhythmias.

### **5.4.2 ECG assessments**

Overall ECG acquisition and interpretation in this study appears acceptable.

### **5.4.3 PR and QRS Interval**

Nine subjects had post-baseline PR > 200 ms and twelve subjects had QRS > 110 ms. PR and QRS increases were not clinically relevant.

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

MOH JEE NG  
03/09/2015

QIANYU DANG  
03/09/2015

DINKO REKIC  
03/09/2015

JIANG LIU  
03/09/2015

MICHAEL Y LI  
03/09/2015

NORMAN L STOCKBRIDGE  
03/09/2015

## RPM FILING REVIEW

(Including Memo of Filing Meeting)

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

Application Information		
NDA # 205266 BLA#	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: <input type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Animal Rule Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Pediatric
Proprietary Name: Odomzo Established/Proper Name: sonidegib Dosage Form: capsules Strengths: 200 mg		
Applicant: Novartis Pharmaceuticals Corporation Agent for Applicant (if applicable): N/A		
Date of Application: September 26, 2014 Date of Receipt: September 26, 2014 Date clock started after UN: N/A		
PDUFA Goal Date: September 26, 2015		Action Goal Date (if different): July 26, 2015
Filing Date: November 25, 2014		Date of Filing Meeting: November 12, 2014
Chemical Classification (original NDAs only) : <input checked="" type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input type="checkbox"/> Type 4- New Combination <input type="checkbox"/> Type 5- New Formulation or New Manufacturer <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): treatment of adult patients with locally advanced basal cell carcinoma (BCC) who are not amenable to curative surgery or radiation therapy <span style="float: right;">(b) (4)</span>		
Type of Original NDA: AND (if applicable)	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i> <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a>		

Type of BLA	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)
<b>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</b>	
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
<i>The application will be a priority review if:</i>	<input type="checkbox"/> Pediatric WR <input type="checkbox"/> QIDP <input type="checkbox"/> Tropical Disease Priority Review Voucher <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher
<ul style="list-style-type: none"><li><i>A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)</i></li><li><i>The product is a Qualified Infectious Disease Product (QIDP)</i></li><li><i>A Tropical Disease Priority Review Voucher was submitted</i></li><li><i>A Pediatric Rare Disease Priority Review Voucher was submitted</i></li></ul>	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B) <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
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Collaborative Review Division (if OTC product):

List referenced IND Number(s): IND 102961 (primary), (b) (4)

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system?  <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the established/proper and applicant names correct in tracking system?  <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		Requested Doc Room correct product name to "sonidegib (LDE 225)"

<i>system.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</a> <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>		
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>	Payment for this application ( <i>check daily email from <a href="mailto:UserFeeAR@fda.hhs.gov">UserFeeAR@fda.hhs.gov</a>:</i> ) <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf</a>	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> <input type="checkbox"/> Yes <input type="checkbox"/> No			
<b>505(b)(2) (NDAs/NDA Efficacy Supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application a 505(b)(2) NDA? ( <i>Check the 356h form, cover letter, and annotated labeling</i> ). If yes, answer the bulleted	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

questions below:				
<ul style="list-style-type: none"> <li>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</li> </ul>	<input type="checkbox"/>	<input type="checkbox"/>		
<ul style="list-style-type: none"> <li>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</li> </ul>	<input type="checkbox"/>	<input type="checkbox"/>		
<ul style="list-style-type: none"> <li>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</li> </ul> <p><i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>		
<ul style="list-style-type: none"> <li>Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</li> </ul> <p><b>Check the Electronic Orange Book at:</b>  <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a></p>	<input type="checkbox"/>	<input type="checkbox"/>		
<b>If yes, please list below:</b>				
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration	
<p><i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>				
<b>Exclusivity</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Does another product (same active moiety) have orphan exclusivity for the same indication? <b>Check the Orphan Drug Designations and Approvals list at:</b> <a href="http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</a>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<b>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</b>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>				
<b>NDA/NDA efficacy supplements only:</b> Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	*Applicant requested marketing exclusivity but did not specify number of years in the NDA submission.
<b>If yes, # years requested:</b> *5 years as this is a new molecular entity				
<i>Note: An applicant can receive exclusivity without requesting it;</i>				

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

<b>Format and Content</b>				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)  <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<b>If mixed (paper/electronic) submission,</b> which parts of the application are submitted in electronic format?				
<b>Overall Format/Content</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>If electronic submission,</b> does it follow the eCTD guidance? <sup>1</sup> <b>If not, explain</b> (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Index:</b> Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Certain statistical datasets were not readily located, therefore a sponsor

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)  <b>If no, explain.</b>				meeting was held after the Application Orientation Meeting on 11.18.14 and Novartis agreed to provide a table for STATS reviewer to cross-reference to location of datasets. The Applicant formally submitted this table on 11.24.14.
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?  <b>If yes, BLA #</b>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>Forms and Certifications</b>				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, <b>paper</b> forms and certifications with hand-written signatures must be included. <b>Forms</b> include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); <b>Certifications</b> include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?  <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?  <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>  <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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

<p><b><u>PREA</u></b></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting<sup>2</sup></i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		<p>Pediatric Page was sent to PERC via email on 11.19.14 for review and will be uploaded in DARRTS once PeRC has approved. Pediatric Record ID is 2544</p>
<p><b>If the application triggers PREA</b>, is there an agreed Initial Pediatric Study Plan (iPSP)?</p> <p><i>If no, may be an RTF issue - contact DPMH for advice.</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<p><b>If required by the agreed iPSP</b>, are the pediatric studies outlined in the agreed iPSP completed and included in the application?</p> <p><i>If no, may be an RTF issue - contact DPMH for advice.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<p>Novartis intends to request a full waiver of the requirement to provide data from pediatric studies <sup>(b)</sup><sub>(4)</sub></p>  <p>therefore, sonidegib qualifies for a disease-specific waiver; FDA confirmed our agreement to Novartis' January 8, 2014, Agreed iPSP, on February 6, 2014.</p>
<p><b><u>BPCA:</u></b></p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p>Is a proposed proprietary name submitted?</p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<p>Confirmed that supporting document category states</p>

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

3

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

<i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>				"Proprietary Name/Request for Review"
<b>REMS</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a REMS submitted?  <i>If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<b>Prescription Labeling</b>	<input type="checkbox"/> <b>Not applicable</b>			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format?  <i>If no, request applicant to submit SPL before the filing date.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the PI submitted in PLR format? <sup>4</sup>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Consult uploaded 11.10.14
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Consult uploaded 11.18.14
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Consult uploaded 11.19.14
<b>OTC Labeling</b>	<input checked="" type="checkbox"/> <b>Not Applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample			

4

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

Version: 10/20/2014

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	<input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?  <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)?  <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If representative labeling is submitted, are all represented SKUs defined?  <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
All labeling/packaging sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)  <i>If yes, specify consult(s) and date(s) sent:</i> QT IRT consult uploaded 11.12.14 and additional clinical pharmacology details regarding the consult sent to D. Kozeli via email on 11.18.14  Patient Labeling Consult (OMP) for Medication Guide uploaded 11.20.14  OSI Consult: to be submitted, under clinical review as of 11.20.14	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s) <b>Date(s):</b> -EOP 1 Type B Meeting held June 9, 2011 (Meeting Minutes Issued July 13, 2011). The purpose was to discuss specific aspects of the development plan of LDE 225 in patients with locally advanced <sup>(b) (4)</sup> basal cell carcinoma that is not amenable to radiation therapy or curative surgery.  -Type C Meeting Request submitted February 13, 2013 (Meeting Denied letter issued March 6, 2013). The purpose was 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 written comment from the FDA on the planned analyses from the sonidegib development program in preparation for a possible NDA submission  <i>If yes, distribute minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Minutes were distributed during planning meeting that was held on 10.21.14

<p>Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)?  <b>Date(s):</b> Clinical Type B pre-NDA Meeting held April 15, 2014  CMC Type B pre-NDA Meeting held June 18, 2014</p> <p><i>If yes, distribute minutes before filing meeting</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		<p>Minutes were distributed during the planning meeting held on 10.21.14. In addition to the pre-NDA meetings, CMC General Advice letters were issued 7.21.14 and 8.1.14 and clinical Advice letters were issued 9.8.14 and 9.13.14</p>
<p>Any Special Protocol Assessments (SPAs)?  <b>Date(s):</b></p> <p><i>If yes, distribute letter and/or relevant minutes before filing meeting</i></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** November 12, 2014

**BACKGROUND:**

Sonidegib is a Hedgehog (Hh) pathway inhibitor, has been investigated in basal cell carcinoma (BCC) under IND 102961. 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. The purpose of this 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. 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.

For this NDA, the proposed indication is for the treatment of patients with locally advanced basal cell carcinoma (laBCC) (b) (4)

**REVIEW TEAM:**

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Anuja Patel	Y
	CPMS/TL:	Monica Hughes	Y
Cross-Discipline Team Leader (CDTL)	Suzanne Demko		Y
Division Director/Deputy	Patricia Keegan		Y
Office Director/Deputy	Richard Pazdur		N
Clinical	Reviewer:	Denise Casey	Y
	TL:	Suzanne Demko	Y
Social Scientist Review ( <i>for OTC products</i> )	Reviewer:	N/A	
	TL:	N/A	

OTC Labeling Review ( <i>for OTC products</i> )	Reviewer:	N/A	
	TL:	N/A	
Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:	N/A	
	TL:	N/A	
Clinical Pharmacology	Reviewer:	Stacey Shord	Y
	TL:	Hong Zhao	Y
Biostatistics	Reviewer:	Huanyu Chen	Y
	TL:	Kun He	Y

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Alex Putman	Y
	TL:	Whitney Helms	Y
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:	N/A	
Immunogenicity (assay/assay validation) ( <i>for protein/peptide products only</i> )	Reviewer:	N/A	
	TL:	N/A	
Product Quality (CMC)	Reviewer:	Mike Adams	Y
	TL:	Liang Zhou	Y
Biopharmaceutics	Reviewer:	Okpo Eradiri	N
	TL:	Angelica Dorantes	N
Quality Microbiology	Reviewer:	Steve Langille	N
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:	Robert Wittorf	Y
	TL:		
OSE/DMEPA (proprietary name,	Reviewer:	Otto Townhend	Y

carton/container labels))	TL:	Alice Chi-Ming Tu	N
	Reviewer:	Amarilys Vega	Y
OSE/DRISK (REMS)	TL:	Naomi Redd	Y
	Reviewer:		
OC/OSI/DSC/PMSB (REMS)	TL:		
	Reviewer:		

Bioresearch Monitoring (OSI)	Reviewer:	Lauren Iacono-Connor	Y
	TL:	Susan Thompson	Y
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:		
Other reviewers/disciplines	Reviewer:	OPDP- Nick Senior	Y
	TL:		
Other attendees	Teicher Agosto, ONDQA, Regulatory Business Process Manager (RBPM) Catherine Tran-Zwanetz, ONDQA, RBPM (TL) Frances Fahnbulleh, OSE, Safety RPM QT Review Team Sriram Subramaniam, DCRPV/OCP Dow- Chung Chi, OHOP/DOP 2		

**FILING MEETING DISCUSSION:**

<p><b>GENERAL</b></p> <ul style="list-style-type: none"> <li>• 505(b)(2) filing issues: <ul style="list-style-type: none"> <li>○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</li> <li>○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature?</li> </ul> </li> </ul> <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
--	---

<ul style="list-style-type: none"> <li>Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Electronic Submission comments</li> </ul> <p><b>List comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> No comments
<p><b>CLINICAL</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><b><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></b></p> <ul style="list-style-type: none"> <li><i>this drug/biologic is not the first in its class</i></li> <li><i>the clinical study design was acceptable</i></li> <li><i>the application did not raise significant safety or efficacy issues</i></li> <li><i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason: drug/biologic is not first in its class
<ul style="list-style-type: none"> <li>If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CONTROLLED SUBSTANCE STAFF</b></p> <ul style="list-style-type: none"> <li>Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p><b>BIostatISTICS</b></p> <p><b>Comments:</b> Formal submission received 11.24.14 deemed acceptable by reviewer.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b> No issues with carcinogenicity studies</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>IMMUNOGENICITY</b> (protein/peptide products only)</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>PRODUCT QUALITY (CMC)</b></p> <p><b>Comments:</b> Biopharmaceutics and Drug Substance comments for Day 74 letter</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p><b>New Molecular Entity (NDAs only)</b></p> <ul style="list-style-type: none"> <li>Is the product an NME?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Environmental Assessment</u></b></p> <ul style="list-style-type: none"> <li>Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p><b>If no,</b> was a complete EA submitted?</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES

<p><b>If EA submitted, consulted to EA officer (OPS)?</b></p> <p><b>Comments:</b> Submitted by T. Agosto via Panorama</p>	<input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Quality Microbiology</u></b></p> <ul style="list-style-type: none"> <li>Was the Microbiology Team consulted for validation of sterilization?</li> </ul> <p><b>Comments:</b> Yes, a consult was submitted by T. Agosto. Micro reviewer has comments for Day 74 letter.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>Establishment(s) ready for inspection?</li> <li>Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ?</li> </ul> <p><b>Comments:</b> Submitted by RBPM T. Agosto via Panorama; during the filing meeting, R. Wittorf stated ORA is proposing to waive inspections for (b) (4) and perform inspections for Drug Product only.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b><u>CMC Labeling Review</u></b></p> <p><b>Comments:</b> Per L. Zhou email 11.20.14, CMC has no comments on the PI at this time since this NDA is under the OPQ model.</p>	<input type="checkbox"/> Review issues for 74-day letter

<p><b>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</b></p> <ul style="list-style-type: none"> <li>• Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application?</li> <li>• If so, were the late submission components all submitted within 30 days?</li> </ul>	<p><input type="checkbox"/> N/A</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> <li>• What late submission components, if any, arrived after 30 days?</li> </ul>	<p>N/A</p>
<ul style="list-style-type: none"> <li>• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?</li> </ul>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?</li> </ul>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?</li> </ul>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<b>REGULATORY PROJECT MANAGEMENT</b>	
<p><b>Signatory Authority:</b> Richard Pazdur, Office Director, Office of Hematology and Oncology Products</p> <p><b>Date of Mid-Cycle Meeting</b> (for NME NDAs/BLAs in “the Program” PDUFA V): February 19, 2015</p> <p><b>21<sup>st</sup> Century Review Milestones (see attached)</b> (listing review milestones in this document is optional):</p> <p><b>Comments:</b> Planned Action Date: July 24, 2015</p>	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<input type="checkbox"/>	<p>The application is unsuitable for filing. Explain why:</p>

<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter.</p> <p><u>Review Classification:</u></p> <p><input checked="" type="checkbox"/> Standard Review</p> <p><input type="checkbox"/> Priority Review</p>
<b>ACTIONS ITEMS</b>	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, orphan drug).
<input type="checkbox"/>	If RTF, notify everyone who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	351(k) BLA/supplement: If filed, send filing notification letter on day 60
<input type="checkbox"/>	<p>If priority review:</p> <ul style="list-style-type: none"> <li>• notify sponsor in writing by day 60 (see CST for choices)</li> <li>• notify OMPQ (so facility inspections can be scheduled earlier)</li> </ul>
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input checked="" type="checkbox"/>	Update the PDUFA V DARRTS page (for applications in the Program)
<input type="checkbox"/>	Other

Annual review of template by OND ADRAAs completed: September 2014

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ANUJA PATEL  
11/25/2014

NORMA S GRIFFIN  
11/25/2014

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

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

**Application:** NDA 205266

**Application Type:** New NDA

**Name of Drug/Dosage Form:** Odomzo (sonidegib) and 200 mg capsules

**Applicant:** Novartis Pharmaceuticals Corporation

**Receipt Date:** September 26, 2014

**Goal Date:**

**PDUFA (12 month- standard review):** September 26, 2015

**Division Planned Action Goal Date:** July 24, 2015

## 1. Regulatory History and Applicant's Main Proposals

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. The purpose of this 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 this NDA, the proposed indication is 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.

## 2. Review of the Prescribing Information

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

## 3. Conclusions/Recommendations

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

In addition, labeling issues were identified by the clinical review team.

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and

## Selected Requirements of Prescribing Information

resubmit the PI in Word format by December 29, 2014. The resubmitted PI will be used for further labeling review.

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### Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

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### Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

#### HIGHLIGHTS GENERAL FORMAT

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

**Comment:**

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

**Comment:**

- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

**Comment:**

- NO** 4. 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.

**Comment:** *Heading for DRUG INTERACTIONS do not appear centered. Please check centering throughout the Highlights section*

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

**Comment:**

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

**Comment:** *Periods are inconsistently placed (either before or after reference). Applicant will be instructed to use one convention throughout the labeling to be consistent.*

## Selected Requirements of Prescribing Information

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

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

\* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

*Comment:*

### HIGHLIGHTS DETAILS

#### Highlights Heading

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

*Comment:*

#### Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**"

The name of drug product should appear in UPPER CASE letters.

*Comment:*

#### Product Title in Highlights

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

*Comment:*

#### Initial U.S. Approval in Highlights

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

*Comment:*

#### Boxed Warning (BW) in Highlights

- YES** 12. All text in the BW must be **bolded**.

## Selected Requirements of Prescribing Information

### Comment:

- YES** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

### Comment:

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

### Comment:

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

### Comment:

### Recent Major Changes (RMC) in Highlights

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

Comment: *This is a new molecular entity (NME) NDA Application*

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

### Comment:

- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

### Comment:

### Indications and Usage in Highlights

- YES** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

### Comment:

### Dosage Forms and Strengths in Highlights

- N/A** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment: *Only one dosage form (capsules) for this drug.*

## Selected Requirements of Prescribing Information

### Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

### Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

### Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

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

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

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

Comment:

### Revision Date in Highlights

- YES** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment:

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## Contents: Table of Contents (TOC)

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

- YES** 25. The TOC should be in a two-column format.

Comment:

- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.

Comment:

- YES** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

## Selected Requirements of Prescribing Information

- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.  
Comment:
- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].  
Comment:
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.  
Comment:
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the full prescribing information are not listed.”  
Comment:

## Full Prescribing Information (FPI)

### FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

<b>BOXED WARNING</b>
<b>1 INDICATIONS AND USAGE</b>
<b>2 DOSAGE AND ADMINISTRATION</b>
<b>3 DOSAGE FORMS AND STRENGTHS</b>
<b>4 CONTRAINDICATIONS</b>
<b>5 WARNINGS AND PRECAUTIONS</b>
<b>6 ADVERSE REACTIONS</b>
<b>7 DRUG INTERACTIONS</b>
<b>8 USE IN SPECIFIC POPULATIONS</b>
<b>8.1 Pregnancy</b>
<b>8.2 Labor and Delivery</b>
<b>8.3 Nursing Mothers</b>
<b>8.4 Pediatric Use</b>
<b>8.5 Geriatric Use</b>
<b>9 DRUG ABUSE AND DEPENDENCE</b>
<b>9.1 Controlled Substance</b>
<b>9.2 Abuse</b>
<b>9.3 Dependence</b>
<b>10 OVERDOSAGE</b>
<b>11 DESCRIPTION</b>
<b>12 CLINICAL PHARMACOLOGY</b>
<b>12.1 Mechanism of Action</b>

## Selected Requirements of Prescribing Information

12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
<b>13 NONCLINICAL TOXICOLOGY</b>
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
<b>14 CLINICAL STUDIES</b>
<b>15 REFERENCES</b>
<b>16 HOW SUPPLIED/STORAGE AND HANDLING</b>
<b>17 PATIENT COUNSELING INFORMATION</b>

**Comment:**

- YES** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

**Comment:**

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

**Comment:**

### FULL PRESCRIBING INFORMATION DETAILS

#### FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

**Comment:**

#### BOXED WARNING Section in the FPI

- YES** 36. In the BW, all text should be **bolded**.

**Comment:**

- YES** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

**Comment:**

#### CONTRAINDICATIONS Section in the FPI

- YES** 38. If no Contraindications are known, this section must state “None.”

**Comment:**

## Selected Requirements of Prescribing Information

### ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

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

**Comment:**

- N/A** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

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

**Comment:**

### PATIENT COUNSELING INFORMATION Section in the FPI

- YES** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

**Comment:**

- YES** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

**Comment:**

# Selected Requirements of Prescribing Information

## Appendix A: Format of the Highlights and Table of Contents

### HIGHLIGHTS OF PRESCRIBING INFORMATION

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

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]  
Initial U.S. Approval: [year]

#### WARNING: [SUBJECT OF WARNING]

*See full prescribing information for complete boxed warning.*

- [text]
- [text]

#### RECENT MAJOR CHANGES

[section (X.X)] [m/year]  
[section (X.X)] [m/year]

#### INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

#### DOSAGE AND ADMINISTRATION

- [text]
- [text]

#### DOSAGE FORMS AND STRENGTHS

[text]

#### CONTRAINDICATIONS

- [text]
- [text]

#### WARNINGS AND PRECAUTIONS

- [text]
- [text]

#### ADVERSE REACTIONS

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

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

#### DRUG INTERACTIONS

- [text]
- [text]

#### USE IN SPECIFIC POPULATIONS

- [text]
- [text]

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

Revised: [m/year]

### FULL PRESCRIBING INFORMATION: CONTENTS\*

WARNING: [SUBJECT OF WARNING]

#### 1 INDICATIONS AND USAGE

#### 2 DOSAGE AND ADMINISTRATION

2.1 [text]

2.2 [text]

#### 3 DOSAGE FORMS AND STRENGTHS

#### 4 CONTRAINDICATIONS

#### 5 WARNINGS AND PRECAUTIONS

5.1 [text]

5.2 [text]

#### 6 ADVERSE REACTIONS

6.1 [text]

6.2 [text]

#### 7 DRUG INTERACTIONS

7.1 [text]

7.2 [text]

#### 8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

#### 9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

#### 10 OVERDOSAGE

#### 11 DESCRIPTION

#### 12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

#### 13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

#### 14 CLINICAL STUDIES

14.1 [text]

14.2 [text]

#### 15 REFERENCES

#### 16 HOW SUPPLIED/STORAGE AND HANDLING

#### 17 PATIENT COUNSELING INFORMATION

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

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11/24/2014

NORMA S GRIFFIN  
11/25/2014

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**LABEL AND LABELING REVIEW**

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

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

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**Date of This Review:** November 21, 2014  
**Requesting Office or Division:** Division of Oncology Products 2 (DOP2)  
**Application Type and Number:** NDA 205266  
**Product Name and Strength:** Odomzo (sonidegib) Capsules, 200 mg  
**Product Type:** Single Ingredient Product  
**Rx or OTC:** Rx  
**Applicant/Sponsor Name:** Novartis  
**Submission Date:** September 26, 2014  
**OSE RCM #:** 2014-2009  
**DMEPA Primary Reviewer:** Otto L. Townsend, PharmD  
**DMEPA Team Leader:** Chi-Ming (Alice) Tu, PharmD

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## 1 REASON FOR REVIEW

As a part of the New Drug Application, this review evaluates the proposed prescribing information, container labels, and carton labeling for Odomzo (sonidegib) capsules, 200 mg, for areas of vulnerability that could lead to medication errors.

## 2 MATERIALS REVIEWED

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

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

N/A=not applicable for this review

## 3 CONCLUSION & RECOMMENDATIONS

The proposed container label and carton labeling can be improved to promote the safe use of the product. The proposed Prescribing Information is acceptable from a medication error perspective.

### 3.1 RECOMMENDATIONS FOR THE DIVISION

1. We note the statement (b) (4) in the Dosage and Administration Section of the Prescribing Information. Since the recommended dose of 200 mg is clearly communicated, we suggest deleting this statement in the Dosage and Administration Section but defer to the Review Team.

### 3.2 RECOMMENDATIONS FOR THE NOVARTIS

#### A. 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.<sup>1</sup>

#### B. Container Labels (30- (b) (4)-count Bottles)

1. See comment A1.
2. 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).

#### C. Unit-Dose Carton Labeling

1. See comment A1.
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.

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<sup>1</sup> Guidance for Industry: Safety considerations for container labels and carton labeling design to minimize medication errors (Draft Guidance). April 2013.

**APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED**

**APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION**

Table 2 presents relevant product information for Odomzo that Novartis submitted on September 26, 2014.

<b>Table 2. Relevant Product Information for Odomzo</b>	
<b>Initial Approval Date</b>	N/A
<b>Active Ingredient</b>	Sonidegib
<b>Indication</b>	<p>Treatment of:</p> <ul style="list-style-type: none"> <li>Adult patients with locally advanced basal cell carcinoma (BCC) who are not amenable to curative surgery or radiation therapy.</li> </ul> <p>(b) (4)</p>
<b>Route of Administration</b>	Oral
<b>Dosage Form</b>	Capsule
<b>Strength</b>	200 mg
<b>Dose and Frequency</b>	200 mg orally once daily
<b>How Supplied</b>	<p>Bottle of 30 capsules (b) (4)</p> <p>Unit dose (blister pack of 30 capsules)</p>
<b>Storage</b>	<p>(b) (4) 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). (b) (4)</p>
<b>Container Closure</b>	<p>30 Count – 90 cc square HPDE Bottle (b) (4)</p> <p>(b) (4)</p> <p>Unit Dose – (b) (4) film blister formed component with aluminum foil blister backing.</p>

## **APPENDIX G. LABELS AND LABELING**

### **G.1 List of Labels and Labeling Reviewed**

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>2</sup> along with postmarket medication error data, we reviewed the following Odomzo labels and labeling submitted by Novartis on September 26, 2014.

- Container label
- Carton labeling
- Unit-Dose Blister labels
- Unit-Dose Carton Labeling
- Medication Guide
- Prescribing Information

### **G.2 Label and Labeling Images**



(b) (4)

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

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<sup>2</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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11/21/2014

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11/21/2014