DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205266

NDA APPROVAL

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

Dear Dr. Wang:

Please refer to your New Drug Application (NDA) dated September 26, 2014, received September 26, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Odomzo (sonidegib), 200 mg capsules.

We acknowledge receipt of your amendments dated October 8, 2014; October 23, 2014; November 14, 2014; November 17, 2014; November 19, 2014; November 20, 2014 (2); November 24, 2014; December 2, 2014; December 3, 2014; January 6, 2015; January 9, 2015; January 15, 2015; January 20, 2015 (2); January 21, 2015; January 23, 2015; January 30, 2015; February 6, 2015 (2); February 18, 2015; February 25, 2015 (2); March 10, 2015; March 13, 2015; March 16, 2015; March 17, 2015; March 20, 2015; March 24, 2015 (2); March 30, 2015 (2); March 31, 2015; April 7, 2015 (2), April 8, 2015; April 14, 2015; April 15, 2015; April 16, 2015; April 17, 2015 (3); April 22, 2015; April 23, 2015; April 24, 2015; April 29, 2015; April 30, 2015(2); May 6, 2015; May 20, 2015; June 2, 2015; June 5, 2015; June 8, 2015; June 12, 2015; June 17, 2015; June 22, 2015; June 23, 2015; June 24, 2015; July 2, 2015; July 13, 2015; July 20, 2015; July 21, 2015; July 22, 2015; and July 23, 2015.

This new drug application provides for the use of Odomzo (sonidegib) 200 mg capsules for treatment of adult patients with locally advanced basal cell carcinoma (BCC) that has recurred following surgery or radiation therapy or those who are not candidates for surgery or radiation therapy.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling text for the package insert and Medication Guide. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the enclosed carton and immediate container labels and the carton and immediate container labels submitted on June 12, 2015, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 205266**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

DATING PERIOD

The dating period for Odomzo shall be 24 months from the date of manufacture for the 30-count blister package and 18 months for the 30-count bottle of 200 MG tablets when stored at 25°C; excursions permitted to 15°C and 30°C (59°F to 86°F).

ADVISORY COMMITTEE

Your application for sonidegib was not referred to an FDA advisory committee because

- this drug/biologic is not the first in its class;
- the safety profile is similar to that of other drugs approved for this indication and is acceptable for this indication;

- the application did not raise significant public health questions on the role of Odomzo for this indication and there were no controversial issues that would benefit from advisory committee discussion; and

- the clinical trial design is similar to previously approved products in the class.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because the necessary studies are impossible or highly impracticable.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of carcinogenicity or assess a signal of a serious risk of teratogenicity.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

2931-1 A 6-month carcinogenicity study in the transgenic mouse. Submit the carcinogenicity protocol for a Special Protocol Assessment (SPA) prior to initiating the study.

The timetable you submitted on June 22, 2015, states that you will conduct this study according to the following schedule:

SPA Submission:	June 2017
Final Protocol Submission:	June 2018
Study Completion:	December 2021
Final Report Submission:	December 2022

2931-2 A long-term rodent carcinogenicity study in the rat. Submit the carcinogenicity protocol for a Special Protocol Assessment (SPA) prior to initiating the study.

The timetable you submitted on June 22, 2015, states that you will conduct this study according to the following schedule:

SPA Submission:	June 2017
Final Protocol Submission:	June 2018
Study Completion:	December 2021
Final Report Submission:	December 2022

2931-3 A Pregnancy Pharmacovigilance Study to evaluate pregnancy outcomes and infant outcomes following exposure to Odomzo (sonidegib). This study will include a mechanism to collect, classify, and analyze data on direct exposures (women exposed to Odomzo (sonidegib) as treatment) and indirect exposures (women exposed to Odomzo (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.

The timetable you submitted on June 8, 2015, states that you will conduct this study according to the following schedule:

Annual Interim Report for nine years:	September 2016
	September 2017
	September 2018
	September 2019
	September 2020
	September 2021
	September 2022
	September 2023
	September 2024
Study Completion:	July 2025
Final Report Submission:	July 2026

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify an unexpected serious risk of severe musculoskeletal toxicity in patients with impaired hepatic function and an unexpected serious risk of toxicity from potential drug-drug interactions.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

2931-4 Complete the ongoing pharmacokinetic trial to determine an appropriate dose of Odomzo (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."

The timetable you submitted on June 5, 2015, states that you will conduct this trial according to the following schedule:

Trial Completion:	September 2015
Final Report Submission:	July 2016

2931-5 Submit the Final Report for the clinical pharmacokinetic (drug interaction) trial to determine how to dose a gastric acid-reducing agent with Odomzo (sonidegib).

The timetable you submitted on June 5, 2015, states that you will conduct this trial according to the following schedule:

Final Report Submission:	January 2016

Submit the protocols to your IND 102961 with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii), requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

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

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf.

Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf.

For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

METHODS VALIDATION

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application within two weeks of receipt of this communication.

PDUFA V APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ('the Program'). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a PDUFA V applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

If you have any questions, call Anuja Patel, Senior Regulatory Project Manager, at (301) 796-9022.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure(s):
Content of Labeling
Carton and Container Labeling

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

/s/

RICHARD PAZDUR
07/24/2015