DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205755

ACCELERATED APPROVAL

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

Dear Dr. Gutman:

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

We also refer to your presubmissions dated November 27, 2013, and December 12, 2013, and your NDA amendments dated January 8, January 24, January 29 (2), February 3, February 5, February 6, February 10 (2), February 12, February 14 (2), February 18 (2), February 19 (3), February 20 (2), February 21, February 24, February 25, February 26, March 3 (2), March 10, March 12, March 13, March 14, March 18, March 19 (3), March 21, March 26, March 28, April 7, April 8 (2), April 10 (2), April 16, April 24, and April 28, 2014.

This new drug application provides for the use of Zykadia (ceritinib) capsules, for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.

This indication is approved under accelerated approval based on tumor response rate and duration of response. An improvement in survival or disease-related symptoms has not been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved under the provisions of the accelerated approval regulations (21 CFR 314.500), effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text. Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

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 text for the patient package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" 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 container labels that are identical to the immediate container labels submitted on March 14, 2014, 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 titled "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 205755." Approval of this submission by FDA is not required before the labeling is used.

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

ADVISORY COMMITTEE

Your application for ceritinib was not referred to an FDA advisory committee because the safety profile is acceptable for the treatment of patients with (ALK)-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib, the application did not raise significant public health questions on the role of the ceritinib for this indication, and outside expertise was not necessary since there were no controversial issues that would benefit from an advisory committee discussion.

ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled studies/clinical trials to verify and describe clinical benefit. You are required to conduct such studies/clinical trials with due diligence. If postmarketing studies/clinical trials fail to verify clinical benefit or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 314.530, withdraw this approval.

We remind you of your postmarketing requirement specified in your submission dated April 10, 2014. This requirement, along with required completion dates, is listed below.

2146-1 Conduct and submit the results of at least one multicenter, randomized clinical trial establishing the superiority of ceritinib over standard therapy in adult patients with ALK-rearranged (ALK-positive) metastatic NSCLC who have been previously treated with crizotinib or in adult patients with previously untreated ALK-positive metastatic NSCLC.

The timetable you submitted on April 10, 2014, states that you will conduct this trial according to the following schedule:

Trial Completion:	April 30, 2019
Final Report Submission:	October 31, 2019

Submit final reports to this NDA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated **"Subpart H Postmarketing Requirement(s)."**

REQUIRED PEDIATRIC ASSESSMENTS

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

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

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 assess signals of:

- a serious risk of toxicity from drug over-exposure when taking Zykadia (ceritinib) capsules with food;
- serious risk of toxicity from drug over-exposure due to impaired hepatic function on the pharmacokinetics of Zykadia (ceritinib) capsules;
- serious risk of toxicity from altered drug exposure due to drug-drug interactions of Zykadia (ceritinib) capsules with substrates of CYP3A4 and CYP2C9; and

- potential toxicity from altered GI absorption of Zykadia (ceritinib) capsules with concomitant gastric acid reducing agents.

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.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess these serious risks.

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

2146-2 Conduct a clinical trial to evaluate the systemic exposure and safety of 450 mg Zykadia (ceritinib) taken with a meal and 600 mg Zykadia (ceritinib) taken with a light meal as compared with that of 750 mg Zykadia (ceritinib) taken in the fasted state in metastatic ALK-positive NSCLC patients.

The timetable you submitted on April 10, 2014, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	October 31, 2014
Interim Analysis Report Submission:	August 31, 2016
Final Report Submission:	September 30, 2017

2146-3 Complete a pharmacokinetic trial to determine the appropriate dose of Zykadia (ceritinib) in patients with hepatic impairment in accordance with the FDA Guidance for Industry entitled "Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling."

The timetable you submitted on April 10, 2014, states that you will conduct this trial according to the following schedule:

Final Report Submission:	June 30, 2016

2146-4 Conduct a clinical trial to evaluate the effect of repeat doses of Zykadia (ceritinib) on the single dose pharmacokinetics of midazolam (a sensitive CYP3A4 substrate) in accordance with the FDA Guidance for Industry entitled "Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations."

The timetable you submitted on April 10, 2014, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	October 31, 2014
Final Report Submission:	March 31, 2017

2146-5 Conduct a clinical trial to evaluate the effect of repeat doses of Zykadia (ceritinib) on the single dose pharmacokinetics of warfarin (a sensitive CYP2C9 substrate) in accordance with the FDA Guidance for Industry entitled "Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations."

The timetable you submitted on April 10, 2014, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	October 31, 2014
Final Report Submission:	March 31, 2017

2146-6 Conduct a clinical trial to evaluate if proton pump inhibitors, H_2-receptor antagonists, and antacids alter the bioavailability of Zykadia (ceritinib) and to determine how to dose Zykadia (ceritinib) with regard to concomitant gastric acid reducing agents.

The timetable you submitted on April 10, 2014, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	February 28, 2015
Final Report Submission:	March 31, 2016

Submit the protocols to your IND 109272, 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.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

2146-7 Submit a revised testing monograph (TM) that will include a (b) (4) method and specification for LDK378 drug product (capsule content) as post-approval commitment.

The timetable you submitted on April 10, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission: April 30, 2014

2146-8 Submit 9 months stability data for the 3 registration stability batches (batches 1010000660, 1010000958 and 1010001326) and up to 24 months for one batch from supportive stability (batch AEUS/2012-0023).

The timetable you submitted on April 10, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission: May 16, 2014

Submit chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

Under 21 CFR 314.550, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 314.550, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three

copies each of the promotional materials, annotated references, and approved package insert (PI)/Medication Guide/patient PI (as applicable).

Send each submission directly to:

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

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 the 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, contact the Regulatory Project Manager for this application within two weeks of receipt of this letter.

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 Ms. Karen Boyd, Senior Regulatory Project Manager, at (301) 796-7032.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURES:
Content of Labeling
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
04/29/2014