

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***

**205755Orig1s000**

**SUMMARY REVIEW**

## Division Director Summary Review

<b>Date</b>	April 18, 2014
<b>From</b>	Patricia Keegan
<b>Subject</b>	Division Director Summary Review
<b>NDA #</b>	205755
<b>Applicant Name</b>	Novartis Pharmaceuticals Corporation
<b>Date of Submission</b>	December 24, 2013
<b>PDUFA Goal Date</b>	August 24, 2014
<b>Proprietary Name / Established (USAN) Name</b>	Zykadia/ ceritinib
<b>Dosage Forms / Strength</b>	capsules for oral administration / 150 mg
<b>Proposed Indication(s)</b>	[BRAND] is indicated for the treatment of patients with (b) (4) metastatic non-small cell lung cancer (NSCLC) who have (b) (4) the effectiveness of [BRAND] is based on response rate and duration of response. Studies are ongoing and further data will be required to determine long-term outcome.
<b>Recommended Action:</b>	<i>Approval</i>

<b>Material Reviewed/Consulted</b>	<b>Names of discipline reviewers</b>
OND Action Package, including:	
Regulatory Project Manager Review	Karen Boyd
Joint Clinical/Statistical Review	Sean Khozin & Lijun Zhang
Quality Review (ONDQA)	Jean Tang, Donghao Lu, Ramesh Sood
Biopharmaceutics Review	Okponanabofi Eradiri
Quality Microbiology Review	Jessica Cole
Non-clinical Pharmacology/Toxicology Review	Margaret Brower, Emily Fox, Whitney Helms
Clinical Pharmacology Review	Ruby Leong, Pengfei Song, Yuzhuo Pan
OPDP	Quynh-Van Tran, Sharon R Mills
OSI	Lauren Iacono-Connors
CDTL Review	Gideon Blumenthal
OSE/DMEPA	Otto Townsend
OSE/DRISK	Naomi Redd
Maternal Health Team	Miriam Dinatale
QT IRT Consult	Fang Li

OND=Office of New Drugs  
 ONDQA=Office of New Drug Quality Assurance  
 OPDP=Office of Prescription Drug Promotion  
 OSE= Office of Surveillance and Epidemiology  
 DMEPA=Division of Medication Error Prevention and Analysis  
 OSI=Office of Scientific Investigations  
 OC=Office of Compliance  
 DRISK=Division of Risk Management  
 CDTL=Cross-Discipline Team Leader

# Division Director Summary Review

## 1. Introduction

Ceritinib is an inhibitor of the ALK receptor tyrosine kinase. Genetic rearrangements (translocations) in the ALK gene, most commonly EML4 translocation, result in expression of a fusion protein with ligand-independent, constitutive activation. In vitro studies demonstrate that ceritinib inhibits autophosphorylation of ALK, ALK-mediated phosphorylation of downstream signaling proteins; ceritinib also inhibits proliferation of ALK-dependent cancer cell lines in vitro and in tumor xenograft models.

The safety and efficacy of ceritinib is primarily based on data from Study CLDK378X2101, an open-label, multi-stage, dose-escalation and multiple parallel cohort, activity-estimating trial investigating the safety, pharmacokinetics, and anti-tumor activity of ceritinib in patients with tumors confirmed to have genetic abnormalities in ALK or who had previously received an ALK inhibitor (Arms A and B of the dose-cohort expansion).

The efficacy and safety of ceritinib was established in an open-label, single-arm study enrolling 163 patients with metastatic ALK-positive NSCLC whose cancer had progressed while receiving or were intolerant to crizotinib. All patients received ceritinib 750 mg once daily. The objective response rate (ORR) in this population, as determined by a Blinded Independent Central Review Committee (BIRC) was 44% (95% CI: 36, 52) and the median duration of responses was 7.1 months (95% CI: 5.6, NE). These results are similar to those reported by clinical investigator assessment. In addition, these results are supported by anti-tumor activity observed in patients who had never received crizotinib.

The major concern identified in this application was the appropriateness of the dose used in the major efficacy trial, which is poorly tolerated and may be higher than required to achieve the observed anti-tumor effect. At the proposed recommended dose of 750 mg orally, taken without food, 98% of patients experienced gastrointestinal (GI) adverse reactions consisting of diarrhea (86%), nausea (80%), vomiting (60%), and abdominal pain (54%). Additional common adverse reactions (incidence  $\geq 25\%$ ) were fatigue, decreased appetite, and constipation. The most common laboratory abnormalities reported in patients receiving ceritinib were increased alanine transaminase (ALT) (80%), increased aspartate transaminase (AST) (75%), increased creatinine (58%), increased glucose (51%), increased lipase (29%), and increased bilirubin (16%). The most common NCI CTCAE Grade 3 or 4 adverse reactions (per-patient incidence  $\geq 5\%$ ) were diarrhea and fatigue; the most common or clinically significant NCI CTCAE Grade 3-4 laboratory abnormalities ( $\geq 5\%$ ) were elevated transaminases (alanine transaminase (ALT) and/or aspartate transaminase (AST)), new or worsening hyperglycemia, and increased serum lipase levels. Serious and including fatal adverse reactions of ceritinib identified in clinical trials were hepatotoxicity, interstitial lung disease, prolongation of the corrected QT interval, and hyperglycemia. Based on nonclinical findings, the observations of clinically significant elevations in serum lipase, pancreatitis was identified as a potential serious adverse reaction of ceritinib. Identification of this adverse

reaction may have been confounded by attribution of symptoms to general GI toxicity, given the near universal occurrence of GI symptoms. Since no clinical cases of pancreatitis were identified, the animal findings are described in Section 13 of the labeling.

During the review, concerns were raised by both the clinical and clinical pharmacology reviewers regarding the appropriateness of the proposed recommended dose. Approximately 60% of patients treated with the recommended Phase 2 dose (750 mg daily) required at least one dose reduction; the most common reason for dose reduction was GI toxicity. Furthermore, the population pharmacokinetic analysis of the exposure-response (ORR) relationship did not clearly identify that exposure correlated with the objective response rate; this finding however is based almost entirely on patients who received ceritinib as a dose of 750 mg daily.

While product labeling appears adequate to allow safe use, off-label treatment recommendations (to take ceritinib with food in patients with GI toxicity) may increase the risks of toxicity. Therefore, FDA has required post-marketing trials to further assess the safety, tolerability, and pharmacokinetics of ceritinib at various doses taken with and without food.

## **2. Background**

### *Indicated Population*

Lung cancer is the leading cause of cancer-related mortality in the United States, with an estimated 228,190 new cases predicted and 159,480 deaths from lung cancer estimated to occur in 2013.<sup>1</sup> The 5-year survival rate for patients with lung cancer between 1995 and 2001 was 15.7%. An estimated that 3-6% of patients with non-small cell lung cancer have a gene rearrangement between anaplastic lymphoma kinase (ALK) and echinoderm microtubule-associated protein like 4 (EML-4) genes resulting in a novel tyrosine kinase protein that is a driver mutation for lung cancer; this gene rearrangement was first identified in 2007.

The only drug approved specifically for patients with NSCLC bearing an ALK gene rearrangement is Xalkori (crizotinib). Since the proposed indication is for treatment of patients who are no longer responding to or are intolerant to crizotinib, crizotinib cannot be considered an available therapy for the proposed indication supported by this NDA.

The date and basis for approval for three FDA-approved drugs for the second- or third-line treatment of non-small cell lung cancer in patients without specific genetic mutations are summarized below; it is noted that none of these available therapies have response rates of more than 10%. Based on their mechanism of action, treatment with agents directed at other mutations (e.g., erlotinib and afatinib) would not be considered available therapy for patients with ALK-positive NSCLC. These potential available therapies are:

- On December 23, 1999, docetaxel (Taxotere; Aventis) received approval for the treatment of locally advanced or metastatic non-small cell lung cancer after failure of prior platinum-based chemotherapy. Approval was based on a randomized trial comparing docetaxel to

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<sup>1</sup> <http://www.cancer.gov/cancertopics/types/lung>. Last accessed October 26, 2013

best supportive care, which demonstrated nominally significant improvements in overall survival (9.5 months vs. 4.6 months), one-year survival rates (40% vs 16%), and time-to-progression (12.3 weeks vs. 7.0 weeks).

- On August 19, 2004, pemetrexed (Alimta) was approved for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after prior chemotherapy. The effectiveness of pemetrexed in second-line NSCLC was based on the surrogate endpoint, response rate. Approval was based on a multi-center, randomized, open label, trial comparing pemetrexed with docetaxel as second-line treatment for NSCLC. The study failed demonstrate superior survival [HR 0.99 (95% CI: 0.82, 1.20); p=0.93] or superior progression-free survival [HR 0.97 (95% CI: 0.82, 1.16); p=0.75, Wald], time to progressive disease [HR 0.97 (95% CI: 0.80, 1.17); p=0.72, Wald], or objective response rate [9.1% vs. 8.8%, p=0.89, Fisher]. The application was referred to the Oncologic Drugs Advisory Committee on July 27, 2004; the ODAC advised FDA that pemetrexed was an active agent, based on the 9.1% response rate to single agent pemetrexed and similar progression-free survival and time-to-progression in pemetrexed and docetaxel arms, with a more favorable toxicity profile for single agent pemetrexed (significantly less neutropenia, febrile neutropenia, neutropenic infections and need for granulocyte/macrophage colony stimulating factors as compared to the docetaxel arm).
- On November 18, 2004, erlotinib (Tarceva, OSI Pharmaceuticals) received initial approval for treatment of locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen. Approval was based on the BR.21 trial, a randomized (2:1), double-blind, placebo-controlled trial comparing erlotinib plus best supportive care (BSC) to placebo plus BSC. The trial demonstrated a significant improvement in overall survival [HR 0.73, p<0.001; median OS of 6.7 months vs. 4.7 months] supported by significantly longer progression-free survival [HR 0.59, p<0.001; median PFS 9.9 vs. 7.9 weeks] and higher overall response rate (8.9% vs. 0.9%, p<0.001).

#### *Pre-submission regulatory history*

The ceritinib clinical development program for ceritinib as a single agent was conducted under IND 109272, submitted October 8, 2010; the IND-enabling clinical study was CLDK378X2101.

November 20, 2012: End of Phase 1/Pre-Phase 3 with Novartis. The purpose of the meeting was to seek advice on the ongoing trial (CLKD378X2101) to support a request for accelerated approval under 21 CFR 314.510 (Subpart H), on the proposed confirmatory trial (CLDK378A2303), and to discuss the clinical pharmacology program for LDK378. Key discussions and agreements reached were regarding Study CLDK378X2101:

- FDA agreed that ALK-rearranged NSCLC patients who have received prior chemotherapy and prior crizotinib represent a population with an unmet medical need and that demonstration of durable objective tumor shrinkage (ORR) may be used to support market authorization under 21 CFR 314 Subpart H regulations if both the magnitude of the response rate and duration of responses appear likely to predict clinical benefit and the risk-benefit analysis appears favorable at the time of review.
- An NDA submission would be based on demonstration of an ORR of more than 52% observed in at least 80 patients (corresponding to an exact binomial 95% CI with a

lower bound greater than 40%). Novartis confirmed that the efficacy population would include at least 80 patients who met all of the following criteria: (1) previously treated with crizotinib, (2) received LDK378 at a dose of at least 750 mg/day, and (3) followed for at least 12 weeks unless discontinued for treatment earlier.

- For regulatory purposes, the determination of overall response rate and response duration would be based upon independent review.
- The NDA will contain all available additional data from the clinical trial up to the data cut-off point.
- In the absence of any unexpected safety signals, the size of the proposed safety database appears to be adequate for a preliminary assessment of the benefit/risk profile of LDK378.
- FDA did not agree that the methodology for the determination of ALK status for inclusion in Study CLDK378X2101 would be acceptable for the proposed trial intended to verify clinical benefit.
- The indicated population in a proposed NDA can only be defined by the eligibility criteria used to enroll patients in the trial. Novartis stated their intent to retrospectively document ALK-positivity in tumor samples obtained prior to crizotinib treatment. In order to support the statement that re-testing to confirm continued ALK-positivity is not necessary, FDA requested that Novartis submit the literature (referenced).
- The effect of hepatic impairment on the LDK378 systemic exposure will determine the need for dose adjustment in this patient population and appropriate dose and regimen recommendations will be included in the product labeling; the hepatic impairment study can be conducted in non-cancer subjects with hepatic impairment; and the proposed PMR study protocol and timelines of completion and final study report submission should be included in the NDA submission.
- FDA strongly recommended that the proposed drug interaction studies with ketoconazole and rifampin and the proposed study in patients with hepatic impairment be completed at the time of the NDA submission.
- FDA found the proposed ECG monitoring plan in clinical trials is acceptable. FDA requested submitting the QT evaluation plan for QT-IRT review before the NDA submission.

March 6, 2013: Breakthrough Therapy Designation was granted for LDK378 for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) that is ALK-positive as detected by an FDA-approved test and which has progressed during treatment with crizotinib or where patients are intolerant to crizotinib.

April 9, 2013: FDA advised Novartis via e-mail communication of a memo that the drug interaction studies be performed with multiple doses of LDK378, in light of the non-linear pharmacokinetics of LDK378 upon multiple dosing.

On May 13, 2013, preliminary comments were issued to Novartis in response to Novartis' March 18, 2013 meeting request to obtain FDA guidance on drug substance starting materials and drug substance and drug product stability data for the NDA submission for the treatment of patients with (b) (4) metastatic non-small cell lung cancer

(NSCLC) who have (b) (4) with crizotinib. After receipt of FDA's comments, Novartis elected to cancel the meeting.

On May 15, 2013, an End-of-Phase 2 meeting was held to discuss the clinical development program of LDK378 in previously untreated patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive. The protocols discussed during the meeting was Protocol CLDK378A2301, an open-label, randomized, active-controlled, multi-center, active-controlled, phase III trial in 348 previously untreated adult patients with ALK-positive, stage IIIB or IV, non-squamous NSCLC (b) (4)

May 20, 2013: FDA provided written response to a Type C meeting request regarding the general content and format of an NDA to be supported primarily by the results of Study CLDK378X2101. Advice provided by FDA included

- Advice on the Summary of Clinical Effectiveness, to include additional analyses and to provide data separately for patients progressing on or within 2 weeks of prior crizotinib separately from patients who discontinue crizotinib for other reasons; to identify the prior ALK inhibitor administered, to clarify nature of disease progression on prior therapy (clinical vs. radiologic).
- FDA stated that the primary analysis must be conducted in all patients who received at least part of any dose of LDK378, that the BIRC-assessment would be the primary analysis for regulatory purposes, that any patient without a BIRC assessment should be identified as a non-responder, and that the results of PFS and OS from this study would not be interpretable, given the "single-arm" design of the trial.
- Agreement on the proposed content of the 90-day safety update, to include updated efficacy results.
- Extensive comments on the contents of the Clinical Pharmacology section of the NDA

July 11, 2013: The treatment protocol, CLDK378A2402, entitled: "An Open-label, Multi-center, Expanded Treatment Protocol (ETP) of Oral LDK378 in Adult Patients with Non-small cell lung cancer (NSCLC) Characterized by ALK(+) Rearrangements in Patients Previously Treated with an ALK Inhibitor" was allowed to proceed.

August 14, 2013: FDA provided clarification, as requested on June 10, July 18, and July 29, 2013, regarding FDA's written responses issued on May 20, 2013. These clarifications were

- The primary analysis should best be based on full analysis set (FAS), consisting of all patients who receive at least one full or partial dose of LDK378, as defined in the briefing document. Results from the efficacy analysis set (EAS) should be submitted as supportive evidence. FDA will take into account Novartis' concerns regarding the lack of sufficient follow-up and limited data on the duration of response with the FAS at the time of NDA review. FDA recommends further discussions on this topic during the pre-NDA meeting when more data is available.

- Novartis stated that the protocol was amended to require BIRC review in response to FDA's advice during the November 20, 2012, however Novartis anticipates that images will not be obtainable for all patients. In light of this, FDA agreed that the BIRC-assessment would be supportive, with investigator-assessed responses as primary.
- Novartis confirmed that the duration of response will be defined as the time from first documented response (PR or CR) to the date of first documented disease progression or death due to any cause.
- Novartis' proposal to provide SAE and death listings for ongoing phase 2 and 3 studies (listed in table 2-1 of Novartis' July 29, 2013 communication), is acceptable. Based on Novartis' explanation, FDA agreed that providing listings of adverse events leading to discontinuation or dose modification is not required for these ongoing studies.

September 27, 2013: ceritinib (identified as [5-Chloro-N2-[2-isopropoxy-5-methyl-4-(4-piperidinyl) phenyl]-N4-[2(isopropyl sulfonyl) phenyl]-2,4-pyrimidinediamine]) was designated as an orphan drug for the indication of treatment of non-small cell lung cancer that is anaplastic lymphoma kinase (ALK)- positive.

November 20, 2013: Pre-NDA meeting to discuss the content of the NDA and format of the 120-day safety update. The proposed NDA would provide assessment of efficacy outcomes for patients receiving LDK378 750 mg daily in (1) Arms A1 and A2 combined, (2) Arm B, and (3) Arm C, as well as in pooled populations of all patients with NSCLC and all patients with prior ALK inhibitor therapy (Arms A1, A2, and B). The proposed data cut-off date of August 2, 2013 for the analyses of ORR, DoR, and PFS was based on inclusion of patients who had completed 18 weeks of follow-up from their first dose of LDK378. Key advice provided and agreements reached were

- Agreement on the content of the NDA, provided labeling was provided in SPL format in the last component or within 30 days of receipt of the last component of the NDA.
- Agreement that these data (based on the summary information in the background package) would allow an assessment of benefit-risk
- Agreement on the proposed timelines for the rolling NDA submissions
- As previously stated, FDA considers the BIRC-assessed analyses to be the primary analyses for efficacy, conducted in all patients receiving at least one dose of LDK378, with analyses in the "evaluable analysis set" to be supportive. FDA acknowledged Novartis' concerns that the primary analysis is affected by accrual rates and stated that submission of the efficacy update may mitigate these concerns. Novartis stated that the efficacy update will include investigator-determined and IRC-determined response. FDA agreed to review all of the available data including investigator- and IRC-determined ORR in the FAS and EAS in order to arrive at a decision regarding approval; FDA stated that the exact data that will be included in the label will be a review decision. Novartis agreed to provide the analysis of concordance between the IRC- and investigator-determined responses. FDA agreed with submission of a risk management plan only in the NDA; a final decision on the need for a REMS would be made during the NDA review.



- The safety/efficacy update should be submitted within 60 days of the final component of the NDA, using a data cut-off date of October 31, 2013. Narratives for new SAEs, including deaths and an amended SCS would also be provided.

#### *History of NDA 205755*

The NDA was submitted as a rolling application in three parts, received on November 27, 2013, December 12, 2013, and completed with the final submission on December 24, 2013

February 5, 2014: The NDA was amended to include adverse event data (8 serious and 112 non-serious adverse events) with onset on or prior to the NDA cut-off date of August 2, 2013 inadvertently not included in the original NDA.

February 10, 2014: The NDA was amended to included updated safety datasets using a data cut-off date of October 31, 2013 and including the data identified in the February 5, 2014 submission; this also constitutes a portion of the “120-day” safety update.

February 12, 2014: The NDA was amended with updated efficacy data and datasets using the October 31, 2013 data cut-off date as the last component of the “120-day” safety update.

### **3. CMC/Biopharmaceutics**

I concur with the conclusions reached by the quality, quality microbiology, and biopharmaceutics reviewers regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections for drug product and drug substance were acceptable; it is my opinion that possible deficiencies at the manufacturing site for the starting materials should not preclude approval, given acceptance testing of these materials at the drug substance manufacturing site and that FDA does not routinely require inspections of such facilities. Stability testing supports an expiry of 18 month at 25°C for the drug product. There are no outstanding issues.

The drug substance, ceritinib, is a white/almost white or light yellow powder (b) (4). The drug substance quality is assured through quality control of all starting materials and (b) (4) in-process controls, and the appropriate drug substance specifications. The drug substance synthesis is (b) (4).

The drug product quality is assured through appropriate product specification testing and appropriately described and validated analytical procedures. Methods validation testing is pending. The proposed dissolution method and acceptance criteria are acceptable; the proposed microbiological testing procedures are acceptable. The request for categorical exclusion from environmental assessment was granted.

The product will be marketed as 150 mg capsules in blue and white-colored hard gelatin capsules. The capsules will be packaged in bottles of 70 capsules each; there is no external carton.

Agreed-upon post-marketing commitments requested by CMC are:

- To submit a revised testing monograph (TM) that will include a (b) (4) method and specification for LDK378 drug product (capsule content).
- To submit the 9-month stability data for registration stability batches and 24-month stability data from on supportive stability.

## **4. Nonclinical Pharmacology/Toxicology**

I concur with the conclusions reached by the pharmacology/toxicology reviewers that there are no outstanding pharmacology/toxicology issues that preclude approval.

The application contained the results of non-clinical pharmacology, single- and multiple dose toxicology studies, embryofetal toxicology, and safety pharmacology studies for cardiovascular and neurologic effects. Reproductive toxicology and carcinogenicity studies were not conducted by Novartis and were required for approval given the proposed indication, in patients with metastatic lung cancer.

In both humans and animals, ceritinib has low to moderate bioavailability, is highly protein bound ( $\geq 97\%$ ), has a prolonged terminal half-life, and is metabolized in the liver with fecal excretion. The pharmacologic class was supported by nonclinical pharmacology studies. Biochemical screening and in vitro cellular assays indicated that ceritinib inhibits ALK, two members of the insulin receptor superfamily, InsR and IGF-1R, and ROS-1 at exposures (e.g., 10 nM) of the free drug that are achievable in the humans with 750 mg oral daily dosing. In 13-week toxicology studies in rats and non-human primates, the major target organs for toxicological findings were the pancreas, bilio-pancreatic ducts, bile ducts, gastrointestinal tract, and liver. The lung was identified as a major target organ in rats. With the exception of pancreatic toxicity, all findings observed in general toxicology studies were also observed in clinical trials.

Ceritinib demonstrated the potential for QTc prolongation in an in vitro hERG assay at exposures of  $\geq 0.3$  microM and in a cardiac safety pharmacology study in non-human primates receiving a single dose of ceritinib of 100 mg/kg. Ceritinib crossed the blood-barrier in rats, however no significant behavioral or physiological changes were observed in a CNS safety pharmacology study following a single dose of ceritinib.

Ceritinib was not mutagenic in the bacterial reverse mutation assay and no adverse effects were observed for male or female reproductive organs in the general toxicology studies. In embryofetal development studies conducted in rats and rabbits, dose-related increases skeletal toxicity were observed in both species. At higher doses, maternal toxicity, spontaneous abortions, and embryoletality were observed in rabbits.

The nonclinical reviewers' assessment of the nonclinical studies supported FDA's modifications to proposed product labeling for Use in Specific Populations (8.1, 8.7), Clinical Pharmacology (12.1), and Nonclinical Pharmacology/Toxicology (13).

## **5. Clinical Pharmacology**

I concur with the conclusions reached by the clinical pharmacology reviewers that there are no outstanding clinical pharmacology issues that preclude approval. I also concur that there are several outstanding concerns regarding safe dosing of ceritinib in patients with hepatic impairment, taking food to alleviate gastrointestinal toxicity, or taking pH lowering agents, as well as unaddressed issues regarding the effects of ceritinib on CYP3A4 and CYP2C9 substrates that can be addressed through post-marketing requirements, given the agreed-upon statements in product labeling regarding limitations of knowledge in these areas.

As noted in their review, the NDA contained information on ADME ((absorption, distribution, metabolism, excretion) of ceritinib, single and repeat-dose pharmacokinetics of ceritinib in patients with cancer, and a population pharmacokinetic (PK) analysis in patients with ALK-positive cancers (almost exclusively ALK-positive, metastatic NSCLC). In addition, the NDA contained the results of a food-effects study, an evaluation of the effects of ceritinib in on QT interval based on analyses of ECGs obtained in clinical studies, two drug-drug interaction studies in healthy subjects, and in vitro studies to assess the drug interaction potential of ceritinib with cytochrome P450 (CYP) and transporters.

The single dose PK of ceritinib was evaluated in samples obtained from healthy subjects enrolled in one of four clinical pharmacology studies or in patients with ALK-positive tumors enrolled in the major efficacy trial (Study X2101) or in a small study (n=19) conducted in Japanese patients. The multiple-dose PK of ceritinib was evaluated in patients in Study X2101, and in Japanese patients; approximately 85% of the data were obtained in patients who received ceritinib at a dose of 750 daily. Following oral administration,  $C_{max}$  was reached at 4-6 hours with a terminal half-life of 41 hours. Ceritinib exhibits nonlinear time-dependent PK, with greater than dose proportional exposure after repeat doses over recommended doses (and under recommended dose modifications). At the recommended initial dose, steady state is achieved within 15 days, with a six-fold accumulation. Based on ADME studies, hepatic metabolism is the major route of elimination (92% of the radiolabeled dose was recovered in feces); given these findings, a post-marketing requirement (PMR) trial has been imposed to assess the effects of hepatic impairment on ceritinib exposure. ADME studies demonstrated that 1.3% of the administered radiolabeled dose was recovered in the urine, therefore studies in patients with renal impairment were not required.

The aqueous solubility of ceritinib is pH-dependent; ceritinib is completely soluble at pH=1 and 55,000-fold less soluble at pH=6.8. Since gastric acid reducing agents may decrease the solubility of ceritinib and thus reduce its bioavailability, a post-marketing requirement PMR has been imposed to investigate the effects of pH lowering agents on ceritinib pharmacokinetics. Ceritinib is primarily metabolized by CYP3A and is a reversible and time-

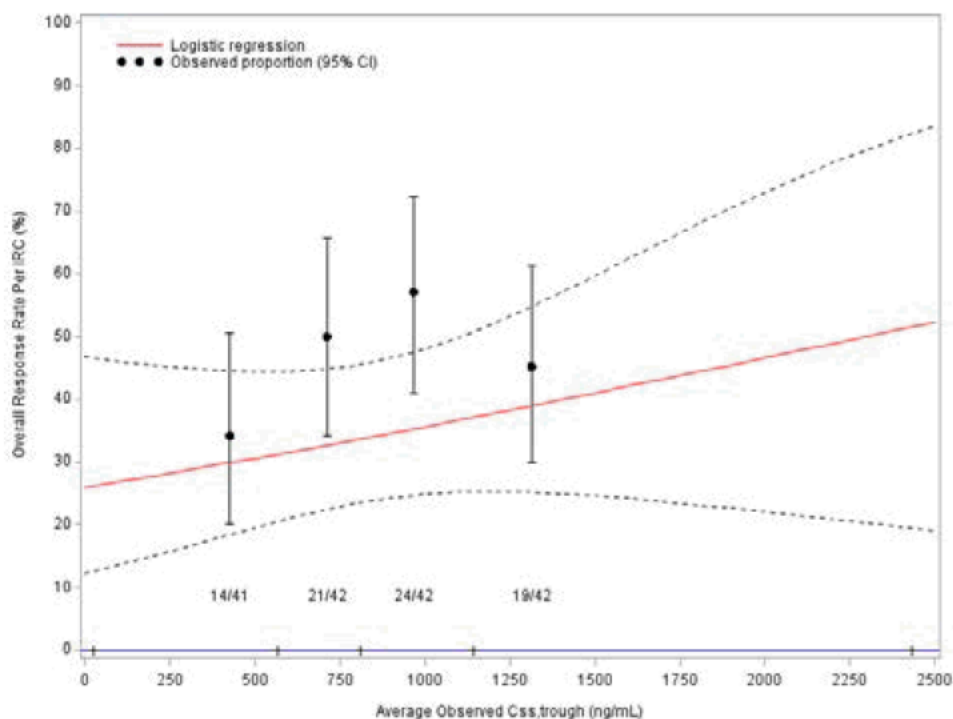
dependent inhibitor of CYP3A and an inhibitor of CYP2C9 in vitro; PMRs have been imposed to further evaluate drug interactions between ceritinib and CYP3A and CYP2C9 substrates.

The pharmacokinetics of ceritinib were assessed in 304 patients with ALK-positive cancers (predominantly NSCLC) in Study CLKD378X2101, a first-in-human, multicenter, open-label, sequential dose-escalation and activity estimating trial conducted in adult patients with ALK-positive cancers. There were 59 patients enrolled in the dose-escalation phase and 245 enrolled in one of 4 disease-specific cohorts (Arms A-D) in the activity estimating stage of the trial.

Population pharmacokinetic (PopPK) analyses using pharmacokinetic data obtained in 167 patients with ALK-positive NSCLC who had received prior treatment with crizotinib and who received ceritinib at doses ranging from 50 mg to 750 mg daily. The PopPK analysis indicated that age, gender, race (White vs. Asian), mild or moderate renal impairment, and mild hepatic impairment did not have clinically important influences on the PK of ceritinib.

There were no evident exposure-response (E-R) relationships for effectiveness (ORR), as displayed in the graph abstracted from the clinical pharmacology review below. Limitations of this analysis noted by in the clinical pharmacology review were

- (1) The distribution of the available exposure data (primarily driven by the data from patients who received 750 mg daily dose), which may not adequately characterize the full exposure-efficacy curve for ORR; and
- (2) The small sample size may limit the robustness for the predicted exposure-efficacy relationship.



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The clinical pharmacology review noted that higher ceritinib exposure may correlate with a higher incidence and earlier onset of serious adverse events, early time to first dose modification (reduction or interruption), and higher incidence of transaminitis (ALT/AST) and hyperglycemia. There was no clear relationship between systemic exposure and the incidence of GI toxicity. The clinical pharmacology review postulated that the risk of GI toxicity may be related to drug concentrations locally (in the GI tract) rather than systemic exposure.

A formal bioavailability study was not conducted; however the clinical pharmacologists predicted that the bioavailability of ceritinib is low. The food effect study demonstrated clinically important increases in ceritinib exposure with a high-fat, high-calorie meal (AUC increased by 73% and  $C_{max}$  by 41%) and with a low-fat meal (AUC increased by 58% and  $C_{max}$  by 43%) compared with ceritinib taken under fasting conditions.

Ceritinib prolonged the QTc interval in a concentration dependent manner based on analyses of population concentration-QTc analyses using time-matched ECG and PK data from the major efficacy trial. Following repeat daily doses of 750 mg ceritinib, large changes (i.e., >20 ms) in the QTc interval were detected at steady-state (Cycle 2 Day 1 and beyond).

Based on their review, the clinical pharmacology reviewers identified the need for the following post-marketing requirements to assess the risks of ceritinib dosing in the following specific settings:

- To conduct an additional trial evaluating the safety, including changes in the pharmacokinetic profile, of food effects on one or more doses on ceritinib at or below the recommended dose of 750 mg daily.
- To complete and submit the results of a pharmacokinetic trial to determine the appropriate dose of ceritinib in patients with hepatic impairment.
- To conduct a drug interaction trial evaluating the effects of ceritinib on the pharmacokinetics of midazolam (CYP3A4 substrate).
- To conduct a drug interaction trial evaluating the effects of ceritinib on the pharmacokinetics of diclofenac (CYP2C9 substrate).
- Conduct a clinical trial assessing the effects of pH elevating agents on the pharmacokinetics of ceritinib.

## **6. Clinical Microbiology**

Not applicable.

## **7. Clinical/Statistical-Efficacy**

Agreements regarding the clinical development program are summarized in Section 2 of this review. The development program was adequate to characterize anti-tumor activity in support

of approval under the accelerated approval provisions, however the adequacy of the program to identify serious risks occurring at a low incidence (<0.5%) and to establish the appropriateness of the recommended dose were limited. The former concern will be addressed in clinical trials required to verify clinical benefit, which will provide a larger and comparative safety experience. The latter concern is discussed in greater detail, immediately below and will be addressed in product labeling and in post-marketing requirements evaluating various doses of ceritinib administered with or without food.

The proposed recommended dose of 750 mg orally, once daily, taken on an empty stomach (defined as no food eaten at least two hours before **and** for at least two hours after ceritinib dosing) is based on the 304 patients enrolled in Study CLKD378X2101, a first-in-human, multicenter, open-label, sequential dose-escalation and activity estimating trial conducted in adult patients with ALK-positive cancers. There were 59 patients enrolled in the dose-escalation portion of the trial at the following dose levels

- 2 patients at 50 mg daily
- 2 patients at 100 mg daily
- 3 patients at 200 mg daily
- 3 patients at 300 mg daily
- 14 patients at 400 mg daily
- 10 patients at 500 mg daily
- 10 patients at 600 mg daily
- 5 patients at 700 mg daily
- 10 patients at 750 mg daily

The design of the trial is discussed in more detail later in this section of the Summary Review, however it is notable that the proposed recommended dose (and recommended Phase 2 dose) of ceritinib of 750 mg once daily was based on the first stage of the trial, which employed a Bayesian logistic regression model, in which the recommended dose is the one with the highest posterior probability of the DLT rate falling in the target interval (16%, -33%) among the doses fulfilling EWOC, i.e. it is unlikely (<25% posterior probability) that the DLT rate at the dose falls in the excessive toxicity interval. Using these criteria, the probability of overdose (>25% probability that the DLT rate  $\geq$ 33%) at Cycle 1 was 3.3% at the 750 mg dose level. Novartis, in consultation with investigators, determined that further dose-escalation was considered to be medically inappropriate based on the observed incidence of persistent grade 1-2 GI toxicity (nausea, vomiting and diarrhea), and the incidence of grade 3-4 liver tests (ALT and AST) in subsequent treatment cycles.

Both the clinical and clinical pharmacology reviewers were concerned that the optimal dose of ceritinib has not been identified. It was noted that approximately 60% of patients initiating treatment at 750 mg required at least one dose reduction; the primary reason for dose reduction was gastrointestinal (GI) toxicity (nausea, vomiting, abdominal pain, and/or diarrhea) which occurred in 98% of patients and resulted in dose modifications in 42% of patients. It appeared that the majority of dose reductions occurred early in the treatment (after approximately one month), indicating that the 750 mg dose was not tolerable in many patients. More concerning are public statements made by at least one investigator in the trial, recommending that patients with GI toxicity take ceritinib with food at the same or a reduced dose of 600 mg daily. The

safety of this advice is **not** supported by the results of food effects studies, which predict that such actions would result in a clinically important (and potentially unacceptably toxic) increase in ceritinib exposure levels.

*Protocol CLKD378X2101 (X2101)*

Title: “A phase I, multicenter, open-label, dose-escalation study of LDK378, administered orally in adult patients with tumors characterized by genetic abnormalities in anaplastic lymphoma kinase (ALK)”

Objectives were determination of the maximum-tolerated dose, characterization of the PK of ceritinib, assessment of the toxicity profile, and assessment of anti-tumor activity (objective response rate).

Key eligibility criteria were age  $\geq 18$  years, measurable disease, ECOG PS  $\leq 2$ , adequate organ function, and evidence of an ALK translocation in  $\geq 15\%$  of tumor cells, as measured by FISH, in patients with NSCLC or evidence of an ALK translocation by FISH or overexpression of ALK protein in tumor cells for patients with other primary tumors (i.e. not NSCLC). [note: Since an FDA-approved or qualified assay was not required to determine eligibility, Novartis retrospectively confirmed ALK mutation status with an FDA-approved test (Vysis) in approximately 90% of patients in the efficacy population). Patients with impairment of the GI tract, GI symptoms  $>$  NCI CTCAE Grade 1, history of pancreatitis, history of acute or chronic liver disease, clinical significant cardiovascular disease or uncontrolled hypertension, and symptomatic CNS metastases were excluded.

Trial design: The dose-escalation stage of the trial evaluated doses of 50, 100, an adaptive Bayesian logistic regression model (BLRM) with 2 parameters, guided by the escalation with overdose control (EWOC) principle to determine the maximum tolerated dose. While awaiting sufficient follow-up data to determine whether to enroll in the next dose level, additional patients could be enrolled in cohort, which did not contribute to determination of the MTD. The dose-expansion phase evaluated anti-tumor activity in 10-100 patients per disease-specific cohort (as listed below) at the recommended Phase 2 dose established in the dose escalation phase of the trial.

- *Arm A1*: Patients with ALK-translocated NSCLC who had disease progression during treatment or within 2 weeks of the last dose of an ALK inhibitor and planned initiation of LDK378 within 60 days of the last dose of the prior ALK inhibitor,
- *Arm A2*: Patients with ALK-translocated NSCLC who were previously treated with an ALK inhibitor and do not meet the criteria for Arm 1A, above.
- *Arm B*: Patients with NSCLC previously treated with an ALK inhibitor that was not refractory to prior ALK inhibitor, but who had experienced disease progression since last ALK inhibitor therapy (which need not have been the last prior therapy)
- *Arm C*: Patients with NSCLC not previously treated with an ALK inhibitor

- *Arm D:* Patients with a malignancy with genetic abnormalities in ALK, other than NSCLC

Patients were permitted to receive LDK378 until unacceptable toxicity that precludes any further treatment, disease progression, or treatment discontinuation at the discretion of the investigator or by patient request.

Tumor assessments are to be conducted every other cycle (i.e., every 6 weeks plus 14 day window). Response assessment by investigator is per RECIST (Response Evaluation Criteria in Solid Tumors) v1.0 based on local interpretation of radiology.

In the final version of the protocol, the proposed sample size of 350 patients was based on the assumption that 40 patients would be enrolled in the dose-escalation phase including at least 6 patients treated at the maximum tolerated dose. The proposed sample size for the dose-expansion cohorts were 25 to 100 patients each in Arms A (A1 plus A2) B, and C, and a maximum of 10 patients in Arm D for a maximum enrollment in the dose-expansion stage of 310 patients. There was clear justification for these sample sizes. Data from patients who received the recommended Phase 2 dose in the dose-escalation stage were to be pooled with data from patients in the expansion phase for the evaluation of ORR, with a statement that an ORR of >25% would be considered to be clinically relevant.

The analysis plan was limited to descriptive statistics, with calculation of the objective response rate and respective 95% confidence intervals around the observed response rate in each treatment subgroup (Arms A1, A2, B, or C). Descriptive statistics would also be applied to the assessment of duration of response, progression-free survival, and overall survival, including assessment of time-to-event endpoints at 3, 6, 12, 18, and 24 months.

The protocol was amended 6 times after initiation of the study (first patient enrolled). Significant amendments for regulatory purposes included:

- Added criteria for determination of ALK-positive status, requiring detection of ALK rearrangement by FISH in  $\geq 15\%$  of tumor cells in patients with NSCLC (Amendment 1)
- Creating two subgroups from original Study Arm A (now A1 and A2) and increase in sample size for Arms A1, A2, and B to 25 patients each (amendment 2)
- Increase in sample size for the expansion cohorts to a total of 100 patients each in Arms A1, A2, and B (amendment 3)
- Clarification that the data cut-off for the safety evaluable population would occur after all patients had completed at least 6 cycles of therapy
- addition of the assessment of tumor status by a Blinded Independent Review Committee (b) (4) in Amendment 4

### *Results*

The trial was conducted at 20 centers across 11 countries. The first patient initiated treatment on March 21, 2011 and the last patient was enrolled and initiated treatment on July 31, 2013: the data cut-off date in the original NDA submission was August 2, 2013, the safety update contained data through a cut-off date of October 31, 2013.



A total of 304 patients enrolled in Study X2101 and all patients receive at least one dose of ceritinib (i.e., were in the “full analysis dataset”). Of these, 59 patients were treated in the dose-escalation phase of the trial. There were 255 patients treated with a ceritinib dose of 750mg (246 patients with NSCLC and 9 with other primary cancers); this includes 10 patients who received ceritinib in the 750 mg dose cohort in the dose-escalation stage of the trial. The primary efficacy population was comprised of 163 patients with NSLCL who were accrued in Arms A1 (n=115) or A2 (n=48); all 163 patients had received prior crizotinib and only 14 patients enrolled in Arm A2 had experienced disease progression during or within 2 weeks of the last dose of crizotinib. Supportive efficacy data were provided from investigator-reported responses in 83 patients enrolled in Arm C (crizotinib-naïve).

In the efficacy population (N=163), the demographics and baseline characteristics were 54% female, median age of 52 years with 86.5% less than 65 years, 66% White and 29% Asian, 53% accrued in the US, 22% in Europe and 25% in Asia/Pacific regional sites, 67% were never smokers and only 3% were current smokers and the ECOG PS was 0 in 23% and 1 in 64%. The vast majority (91.4%) had progressed on crizotinib, 93% had adenocarcinoma as the histologic subtype, however approximately one-fifth (21.5%) did not meet the eligibility criteria for ALK-positivity in that <15% of tumor cells with ALK mutations as detected by FISH. Of the 163 patients, 39% had more than 4 sites of metastatic disease at baseline and 60% had CNS metastases.

The results of the BIRC- and investigator-assessed overall response rate and response duration, as determined in the intent-to-treat population defined as all patients enrolled in the trial who received any part of a dose of ceritinib, are presented in the table below. Since only 2 of the 163 patients refused to give consent for BIRC review, as originally requested by FDA in November 2012, the primary efficacy analysis for overall response rate and response duration should be based on the BIRC-assessment and the investigator-assessment is considered secondary.

<b>Efficacy Parameter</b>	<b>BIRC Assessment (N=163)</b>	<b>Investigator Assessment (N=163)</b>
Overall Response Rate (95% CI)	44% <sup>1</sup> (36, 52)	55% (47, 62)
CR	2.5%	1.2%
PR	41%	53%
Median duration of response (mos) (95% CI)	7.1 (5.6, NE)	7.4 (5.4, 10.1)
<sup>1</sup> Overall Response Rate and Duration of Response determined by RECIST v1.0 BIRC, blinded independent review committee; CR, complete response; NE, not estimable; PR, partial response.		

Exploratory analyses of the overall response rates in relevant subgroups were conducted; all subgroups (region, age, race, number of metastatic sites, and number of prior regimens)

demonstrated significant anti-tumor activity with response rates ranging from 34% to 68% in subgroups containing more than 15 patients).

Based on concerns regarding tolerability of the 750 mg dose, the clinical & statistical reviewers performed a subgroup analysis by dose, using investigator-assessed responses. These data, abstracted from the joint clinical/statistical review, are presented in the table below and support further exploration of the optimal dose.

**Table 14. ORR and DOR in X2101 based on investigator and BIRC assessments in patients treated with 750mg versus lower doses [review analysis]**

	<b>Ceritinib 750mg (n=246)</b>	<b>Ceritinib &lt;750mg (n=44)</b>
<b>Investigator assessment</b>		
ORR, n (%)	144 (58.5%)	22 (50.0%)
(95% CI)	(52.1%, 64.8%)	(34.6%, 65.4%)
Median DoR (mos)	9.7	8.2
(95% CI)	(7.0, 11.4)	(5.9, 18.1)
<b>BIRC assessment</b>		
ORR, n (%)	121 (49.2%)	17 (38.6%)
(95% CI)	(42.8%, 55.6%)	(24.4%, 54.5%)
Median DoR (mos)	NE	8.3
(95% CI)	(7.1, NE)	(7.0, 18.6)

DoR = duration of response; NE = not estimable

Although Novartis provided summary data for (b) (4) these data cannot be interpreted in the context of a single arm study and are not included in product labeling or in this Summary Review.

While Novartis noted that (b) (4) in the indicated population, the information was anecdotal (b) (4) and thus was considered premature for inclusion in product labeling.

## 8. Safety

### *Size of the database*

The size of the safety database was adequate to observe adverse reactions occurring at an incidence of between 0.5 and 1%. Safety evaluation of LDK278 was based on 255 ALK-positive patients in X2101 (246 patients with NSCLC and 9 patients with other cancers who received ceritinib at a dose of 750 mg daily) and was augmented by data and summaries from studies in Japanese patients with cancer and healthy volunteer studies. The characteristics of the 246 patients with NSCLC enrolled in X2101 is 54% female, median age of 53 years with 84% less than 65 years of age; 63% White, 33% Asian, 1.6% Black, and 1.6% "other;" 26%

had an ECOG PS of 0; 50% had evidence of CNS metastases; and 6.5% with no prior treatment and 26% with only one prior treatment for NSCLC.

Across the safety database of 255 patients enrolled in Study X2101, the median duration of exposure to ceritinib was 6 months. Dose reductions due to adverse events occurred in 59% of patients. The most frequent adverse events that led to dose reductions or interruptions were gastrointestinal toxicity (42%) [nausea (20%), diarrhea (16%), and vomiting (16%)] and severe liver test abnormalities [elevated ALT (29%) and elevated AST (16%)]. Ten percent of patients permanently discontinued ceritinib for adverse reactions; the most common reasons for termination of ceritinib were pneumonia/pneumonitis and decreased appetite.

The most common adverse reactions of ceritinib were diarrhea (86%), nausea (80%), vomiting (60%), fatigue (52%), decreased appetite (34%) constipation (29%), esophageal disorder (dyspepsia, gastroesophageal reflux disease, dysphagia) (16%), and rash (rash, maculopapular rash, acneiform dermatitis) (16%). The most common laboratory abnormalities reported in patients receiving ceritinib were increased alanine transaminase (ALT) (80%), increased aspartate transaminase (AST) (75%), increased creatinine (58%), increased glucose (51%), increased lipase (29%), and increased bilirubin (16%).

*Major safety concerns related to labeling*

There were no absolute contraindications identified for this product which would outweigh its potential benefits in the indicated population.

Severe serious adverse drug reactions identified by Novartis and listed under Warnings and Precautions in the proposed product labeling. These were:

- Gastrointestinal toxicity: (b) (4) severe or persistent. Diarrhea, nausea, vomiting, or abdominal pain occurred in 96% of 255 patients (b) (4) 14% were severe. Dose modifications (b) (4) for diarrhea, nausea, vomiting, or abdominal pain in 38% of patients.
- Drug-induced hepatotoxicity: (b) (4) in ALT of greater than 5 times the upper limit of normal occurred in 27% of 255 patients (b) (4) one patient (0.4%) required permanent discontinuation due to elevated transaminases and jaundice.
- Severe, life-threatening, or fatal ILD/pneumonitis: Pneumonitis occurred in 4% of 255 patients; ILD of Grade 3 or 4 (b) (4) in 3% of patients, and was fatal in 1 patient (0.4%). One percent of patients discontinued ceritinib due to ILD/pneumonitis.
- QTc interval prolongation (increase over baseline of greater than 60 msec) occurred in 3% of 255 patients. One of 304 patients (less than 1%) was found to have a QTc greater than 500 msec and 3% of patients had an increase from baseline QTc greater than 60 msec. (b) (4)
- Hypertension of Grade 3-4 (b) (4) occurred in 13% of 255 patients. The risks of hypertension (b) (4) in patients with (b) (4) diabetes (6-fold higher) or on steroids (2-fold higher) (b) (4)

- Sinus bradycardia, defined as less than 50 beats per minute, (b) (4) in 1% of 255 patients and was reported as an adverse drug reaction in 3% of 255 patients.

In addition, the following serious adverse drug reaction was identified based on non-clinical studies and included in product labeling. The rationale for inclusion of these adverse reactions in Warnings is discussed under Section 4 of this Summary Review

- Embryofetal toxicity

#### *REMS*

Novartis provided a Risk Management Plan consisting of product labeling and routine pharmacovigilance for the risks of hepatotoxicity, QT prolongation, interstitial lung disease, bradycardia, and hyperglycemia. I concur with the conclusions of the DRISK and clinical review team members that a REMS is not required to ensure safe use as other drugs with these same risks have been safely prescribed by oncologists and used by patients with cancer. Specifically, many of these risks are also present with crizotinib, a drug which all patients falling within the indicated population have already received.

#### *PMRs and PMCs*

There was one post-marketing requirement to address safety concerns identified by both the clinical and clinical pharmacology reviewers

To conduct an additional trial evaluating the safety, including changes in the pharmacokinetic profile, of food effects on one or more doses on ceritinib at or below the recommended dose of 750 mg daily.

A post-marketing study is required to verify efficacy under the provisions of 21 CFR 314.510. In addition, multiple PMRs are required to characterize safe dosing, as described under section 5 of this review. Finally, post-marketing commitments have been agreed-upon to provide additional characterization of the product manufacturing, as discussed in section 3 of this review.

## **9. Advisory Committee Meeting**

This NDA for a new molecular entity was not referred to the Oncologic Drugs Advisory Committee for review for the following reasons: 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. Two Special Government Employees, a physician and a patient representative, were identified to provide advice on the risk:benefit assessment and product labeling. Both agreed that the risk:benefit assessment was positive for the indicated population but expressed concerns regarding the high incidence of GI toxicity, frequently resulting in dose reduction.

## 10. Pediatrics

Ceritinib received orphan drug designation for the treatment of patients with NSCLC that is ALK-positive on September 27, 2013. Therefore, this NDA was exempt from the requirements of the Pediatric Research Equity Act (PREA). Novartis does not intend to conduct assessments of the safety and effectiveness of ceritinib in pediatric patients.

## 11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

As noted in the review by the Office of Scientific Integrity, three clinical sites were chosen for inspection based on a larger proportion of patients enrolled at these sites (relative to other clinical sites) for the major efficacy trial. In addition, the site of the blinded independent radiological review committee was also inspected. Based on the interim classifications, the data from these sites were deemed reliable.

An assessment of the financial disclosure information to not identify any concerns that would influence the study results, particularly given that the primary assessment of efficacy was based on an independent review of radiologic studies and clinical data.

## 12. Labeling

- Proprietary name: The proposed proprietary name, (b) (4) was submitted to IND 109272 on October 31, 2013 and to the first component of the rolling NDA on November 27, 2013. Novartis was informed on January 27, 2014, that the proposed name, (b) (4) was determined to be unacceptable due to phonetic similarities to the proprietary name, (b) (4). Novartis submitted the proposed name, (b) (4) on February 6, 2014. FDA informed Novartis on March 17, 2014, that (b) (4) was also determined to be unacceptable in a prescription simulation study (confusion with (b) (4)). On March 19, 2014, Novartis submitted the proposed name of Zykadia (intended pronunciation: zye kaye' dee ah); this name was determined to be acceptable from both a promotional and safety perspective by DMEPA, OPDP, and clinical reviewers. Novartis was informed that the name, Zykadia, was acceptable on March 25, 2014.
- Physician labeling: all major issues were resolved; FDA modifications to the proposed labeling are summarized below.
  - Indications and Usage: The proposed indication statement was narrowed to reflect the population for whom an unmet need exists (i.e., those progressing on or intolerant to crizotinib); to reflect the population studied by limited the indication to patients with ALK-positive metastatic NSCLC only (b) (4); and to specify (b) (4) with crizotinib, which is the only FDA-approved ALK-inhibitor. Added the following language to clarify that ceritinib received accelerated approval "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.” (1) .
- Dosage and Administration: Edited for brevity and essential information; moved information on dosing in patients with hepatic impairment to section 2.1, for emphasis and to ensure it is not overlooked; included information on frequency that patients required dose reductions for emphasis and modified table for dose modification for clarity, brevity, and consistency with clinical trial recommendations; added information on dose modifications for intolerable GI symptoms, hyperglycemia, and asymptomatic bradycardia as these were commonly observed adverse reactions that resulted in dose modifications in the clinical trial; included specific subsection for dosing recommendations for patients taking strong CYP3A4 inhibitors. Dosage Forms and Strengths: editorial changes only
  - Contraindications: no modifications
  - Warnings and Precautions: added subsection on Severe or Persistent GI Toxicity as this was both common and frequently required dose modifications in the clinical trial; added a subsection on Hyperglycemia as a common adverse reaction whose risks can be mitigated through monitoring particularly in at risk populations; expanded the sections on hepatotoxicity, ILD, QT prolongation and bradycardia to provide specific information on risks as observed in clinical trials as recommended by FDA Guidance for Industry on this section of product labeling and modified description of dosing modifications for consistency with the trial conduct and clarity. Strengthened wording in the subsection on Embryofetal Toxicity and included additional information on nonclinical findings, in accordance with current FDA policy on this subsection of labeling.
  - Adverse Reactions: added information on the demographics and baseline characteristics of the safety population; included more detailed information on serious adverse reactions and those resulting in dose modification or drug discontinuation in accordance with FDA Guidance for Industry on this labeling section. Removed exculpatory statements. Created a separate table for description of laboratory abnormalities using laboratory results rather than AE reports; included a listing of clinically significant adverse events is not already described in other sections of the label
  - Drug Interactions: modified to create to subsections (effects on other drugs on ceritinib and effects of ceritinib on other drugs) for clarity and consistency with current FDA practices for this section of the label; Included dosing recommendations for ceritinib or for advance of certain drugs based on metabolic pathways; moved food effects information to Section 12
  - Use in Specific Populations: Revised Section 8.1 and added Section 8.7 based on current FDA policy regarding this section of labeling. Edited subsection on geriatric use for consistent with regulations (21 CFR 201.57); edited subsection on Hepatic Impairment to provide more specific advice on dosing; deleted (b) (4) for reasons discussed in Section 5 of this summary review.
  - (b) (4) Deleted this section as no information is available
  - Description: editorial changes only

- Clinical Pharmacology: in section 12.1, removed (b) (4); removed (u) (4); expanded information on ceritinib targets (IGF-1R, InsR, and ROS-1) to clarify that ceritinib is not (b) (4) but in fact may have (b) (4). Section 12.2 revised to include additional subsections (e.g., cardiac electrophysiology) which is discussed first based on the risks of QT prolongation and bradycardia with ceritinib; information on mechanism of action removed (now in Section 12.1), edited ADME section for brevity and essential information; added subsections on pharmacokinetics in special populations that support dosing recommendations; added PK data in subsection on drug interactions that support dosing recommendations; added subsection on potential effects of pH lowering agents on solubility/bioavailability. Nonclinical Pharmacology/Toxicology: Added nonclinical information on effects on fertility observed in general toxicology studies; removed information on (b) (4) as non-essential information; limited information in Section 13.2 to essential information (b) (4) and included information on effects in pancreas and biliary tract in toxicology studies to identify this as a potential risk of ceritinib.
  - Clinical Studies: Edited for brevity and to describe the study population to the indicated population; included assessment of response by the BIRC; removed information (b) (4) as this cannot be interpreted in a single arm study; removed (b) (4) consistent with current FDA approaches and because this is not essential to the determination of anti-tumor activity; deleted information on the (b) (4) as this information is anecdotal. Although initially proposed by the clinical reviewer, FDA agreed with Novartis that subgroup analyses were not required for inclusion in product labeling to ensure safe use.
  - How Supplied: Added product name (Zykadia) to this section
  - Patient Counseling: edited for command language and brevity; all adverse reactions described in Section 5, information for Nursing Mothers and use of contraception added.
- Carton and immediate container labels: Zykadia will be supplied in bottles with an immediate container label but no carton; the package insert will be physically attached to the bottles. All FDA-requested revisions to the immediate container were incorporated into the final container labeling.
  - Patient labeling/Medication guide: Novartis proposed patient labeling for this product, which is self-administered as capsule, orally, on a daily basis. The patient labeling was revised for consistency with the agreed-upon physician labeling and consistency with FDA Guidances and policy for patient labeling.

FDA reviewers agreed with Novartis that a medication guide was not required to ensure safe use of ceritinib for the proposed indication.

### 13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: I recommend that this NDA be approved.
- Risk Benefit Assessment  
Recurrent ALK-positive NSCLC is a serious disease with unmet medical needs. The identification of the ALK gene rearrangement is recent, thus data on the natural history in this subgroup of NSCLC is being developed, however the 5-year survival rate for patients with lung cancer between 1995 and 2001 was 15.7%. Given the evidence of durable objective responses by independent review in approximately half of the patients treated with ceritinib, when available therapy offers a response rate of less than 10%, and that the risks identified in clinical studies or non-clinical evaluation are similar to approved drugs for treatment of cancer including lung cancer, I find the risk:benefit assessment to be positive and support a recommendation for approval with the agreed-upon labeling.

In an open-label, single-arm study enrolling 163 patients with metastatic ALK-positive NSCLC whose cancer had progressed while receiving or were intolerant to crizotinib, the objective response rate (ORR) in this population, as determined by a Blinded Independent Central Review Committee (BIRC) was 44% (95% CI: 36, 52) and the median duration of responses was 7.1 months (95% CI: 5.6, NE).

At the proposed recommended dose of 750 mg orally, taken without food, adverse drug reactions were common with 98% of patients experiencing gastrointestinal (GI) adverse reactions consisting of diarrhea (86%), nausea (80%), vomiting (60%), and abdominal pain (54%). Additional common adverse reactions (incidence  $\geq 25\%$ ) were fatigue, decreased appetite, and constipation. The most common NCI CTCAE Grade 3 or 4 adverse reactions (per-patient incidence  $\geq 5\%$ ) were diarrhea and fatigue; the most common or clinically significant NCI CTCAE Grade 3-4 laboratory abnormalities ( $\geq 5\%$ ) were elevated transaminases (alanine transaminase (ALT) and/or aspartate transaminase (AST)), new or worsening hyperglycemia, and increased serum lipase levels. Serious and including fatal adverse reactions of ceritinib identified in clinical trials were hepatotoxicity, interstitial lung disease, prolongation of the corrected QT interval, and hyperglycemia. Both the serious and common adverse reactions of ceritinib can be mitigated through dose modifications and appropriate patient monitoring.

Although there are drugs approved for second-line treatment of NSCLC, none of these drugs provide such a high magnitude or durable responses. Thus this population has no satisfactory alternative therapy and the observed findings in Study X2101 support Novartis' request for accelerated approval.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies  
I concur with the conclusions of the clinical and DRISK reviewers that a REMS is not required to ensure safe use of ceritinib in the indicated population for the reasons summarized in Section 8 of this review.



- Recommendation for other Postmarketing Requirements and Commitments  
Under the provisions of 21 CFR 314.510, post-marketing trials are required to verify clinical benefit. Novartis has identified two trials (identified below); both trials are adequately designed and may be sufficient to fulfill this requirement. Therefore the post-marketing requirement under 21 CFR 314.501 was written broadly to cover submission of either (or both) trials
  - Protocol A2303, titled “A phase III multicenter, randomized study of oral ceritinib versus standard chemotherapy in adult patients with ALK-rearranged (ALK-positive) locally advanced or metastatic NSCLC who have been treated previously with one chemotherapy regimen (platinum doublet) and crizotinib”
  - Protocol A2301, titled “A phase III multicenter, randomized study of oral ceritinib versus standard chemotherapy in previously untreated adult patients with ALK rearranged (ALK-positive), stage IIIB or IV, nonsquamous non-small cell lung cancer”

To 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.

Post-marketing requirements under 505(o) are listed below. The rationale for these PMRs are described in Section 5 of this Summary Review

- 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.
- 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.”
- 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.”
- 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.”
- Conduct a clinical trial to evaluate if proton pump inhibitors, H<sub>2</sub>-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.

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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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PATRICIA KEEGAN  
04/19/2014