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APPLICATION NUMBER:

205755Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	April 11, 2014
From	Gideon M. Blumenthal, M.D. Clinical Team Leader, Thoracic and Head and Neck Oncology Division of Oncology Products- 2 (DOP-2) Office of Hematology Oncology Products (OHOP)
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 205755
Applicant	Novartis Pharmaceuticals Corporation
Date of Submission	Part 1: November 27, 2013 Part 2: December 12, 2013 Part 3: December 24, 2013
PDUFA Goal Date	August 24, 2014
Proprietary Name / Established (USAN) names	Zykadia (Ceritinib, LDK378)
Dosage forms / Strength	Capsules, 150 mg
Proposed Indication(s)	For the treatment of patients with (b) (4) or metastatic non-small cell lung cancer (NSCLC) who have (b) (4) with an anaplastic lymphoma kinase (ALK) inhibitor
Recommended:	Approval

Discipline and Consultants	Primary/ Secondary Reviewer
Clinical Review	Sean Khozin, M.D./ Gideon Blumenthal, M.D.
Statistical Review	Lijun Zhang, Ph.D./ Shenghui Tang, Ph.D.
Regulatory Project Manager	Karen Boyd/ Karen Jones
Pharmacology Toxicology Review	Margaret Brower, Ph.D. & Emily Fox, Ph.D./ Whitney Helms, Ph.D.
ONDQA-CMC and Biopharmaceutical Reviews	CMC: Donghao (Robert) Lu, Ph.D. & Jean Tang, Ph.D./ Liang Zhou, Ph.D. Biopharm: Okpo Eradiri, Ph.D./ Angelica Dorantes, Ph.D. Microbiology: Jessica Cole, Ph.D./ Bryan Riley, Ph.D. ONDQA: Jewell Martin
Clinical Pharmacology Review	Clin Pharm: Ruby Leong, Ph.D./ Hong Zhao, Ph.D. Pharmacometrics: Pengfei Song, Ph.D./ Qi Liu, Ph.D. PBPK Modeling: Yuzhuo Pan, Ph.D./ Ping Zhao, Ph.D.
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Facility Inspection Review (OC/OMPQ/DGMPA)	Robert Wittorf, PharmD, Mahesh Ramanadham, PharmD

1. Introduction

On December 24, 2013, Novartis Pharmaceuticals Corp (Applicant) submitted part 3 of New Drug Application (NDA) 205755 to complete a rolling submission. The Applicant proposed the following indication: for the treatment of patients with ^{(b) (4)} metastatic non- small cell lung cancer (NSCLC) who have ^{(b) (4)} with an anaplastic lymphoma kinase (ALK) inhibitor.

Ceritinib is a new molecular entity (NME) oral ATP-competitive tyrosine kinase inhibitor of ALK. The goal of the ceritinib discovery and development program was to pursue a potent and selective ALK inhibitor to overcome intrinsic and acquired mechanisms of resistance to the first generation ALK inhibitor crizotinib (Xalkori, Pfizer).

The primary basis for the NDA is the results from CLDK378X2101 (heretofore referred to as X2101), an open-label, single arm expansion cohort of a phase 1 dose escalation trial of ceritinib. The primary efficacy population is comprised of 163 patients with ALK positive metastatic NSCLC who progressed on or were intolerant to crizotinib and received ceritinib 750 mg once daily in the fasted state. Randomized trials of ceritinib in ALK-positive NSCLC are in progress.

2. Background

Lung cancer is the leading cause of cancer death in the U.S., with more people dying of lung cancer than of colon, breast, and prostate cancers combined. Estimated new lung cancer cases for 2014 are 224,210 contributing to 159,260 deaths. Non-small cell lung cancer (NSCLC) accounts for approximately 85% of lung cancer cases, with an expected 5-year survival of 1-5% for advanced disease. In unselected patients, cytotoxic platinum doublet based chemotherapy has historically been the backbone of first-line treatment for patients with metastatic disease, with median survival of approximately 10 to 12 months. In the second-line treatment setting of unselected patients with advanced NSCLC, docetaxel, pemetrexed (non-squamous), and erlotinib are FDA-approved. However, response rates are low, less than 10%.

With improved genomic screening techniques, NSCLC “driver oncogenes” have been identified within the past decade. In 2007, rearrangements in ALK were identified as oncogenic drivers in non-clinical models and were found in a subset of archived patient lung cancer specimens. ALK is a receptor tyrosine kinase involved in oncogenesis of several cancers due to translocation of the kinase domain with multiple fusion partners resulting in ligand-independent constitutive activation. Within NSCLC, ALK rearrangements (herein referred to as ALK-positive) are detected in about 5% of patients overall, but are more common in younger patients, never-smokers, and patients with adenocarcinoma histology.

In August 2011, FDA approved crizotinib under the Subpart H accelerated approval regulations for patients with ALK-positive metastatic NSCLC (mNSCLC). The approval was based on the results of two single arm studies enrolling a total of 255 ALK-positive mNSCLC patients with overall response rates (ORR) of 50 and 61%, corresponding to a median duration of response (DOR) of 9.7 and 11 months, respectively. Crizotinib received regular approval in November 2013 based on a randomized trial (n=347) that demonstrated superior progression-free survival (PFS) for crizotinib-treated patients compared to chemotherapy (pemetrexed or docetaxel) in patients with ALK-positive mNSCLC with disease progression after platinum-based doublet chemotherapy (PFS HR 0.49, median 7.7 versus 3.0 months, $p < 0.001$). ORR was 65% for crizotinib (median DOR 7.4 months) versus 20% (median DOR 5.6 months) for chemotherapy. In an interim Overall Survival (OS) analysis, no difference was observed (HR 1.02, median OS 20.3 versus 22.8 months, $p = 0.54$), however 64% of patients chemotherapy-treated patients received crizotinib after progression.

Unfortunately, nearly all patients with ALK-positive mNSCLC ultimately develop progressive disease on crizotinib, frequently in the Central Nervous System (CNS) with new brain metastasis. Approximately one third of patients with ALK-positive NSCLC progress due to acquired mutations within the ALK tyrosine kinase domain or amplification of the ALK fusion gene. In the remaining cases, the ALK tyrosine kinase domain and gene are unchanged, and resistance occurs through alternate pathways. Once patients progress on crizotinib, options are limited to chemotherapy or supportive care. Therefore, new therapies are needed for patients with ALK-positive NSCLC who progress on crizotinib.

3. CMC/Device

- Device (in vitro diagnostic)
During IND and pre-NDA discussions with the Applicant, FDA determined that a parallel PMA/ companion diagnostic submission to CDRH was not required to ensure the safe and effective use of ceritinib. Most of the patients enrolled in study X2101 were previously enrolled on crizotinib trials and were tested with the to-be-marketed ALK FISH assay. Furthermore, based on retrospective reviews of patient tumor pathology reports, the Applicant verified that 99% of patients enrolled on X2101 study were ALK positive.
- General product quality considerations
Drug Substance: The drug substance is Ceritinib. The chemical name is 5-Chloro-N4-[2-[(1-methylethyl)sulfonyl]phenyl]-N2-[5-methyl-2-(1-methylethoxy)-4-(4-piperidinyl)phenyl]-2,4-pyrimidinediamine. It has a molecular formula of C₂₈H₃₆ClN₅O₃S and its molecular weight is 558.14.

Data from the studies of elemental analysis, UV, IR, NMR and MS demonstrated that the structure was adequately defined. The synthesis route (b) (4) are adequate for the manufacturing of the ceritinib drug substance. Science and risk based

approaches were applied during CMC evaluation to make the regulatory decisions on manufacturing control strategies.

The impurities detected during the synthesis and development of the drug substance was evaluated. Analytical methods were developed for the control of the impurities listed in the submission. Comprehensive information for all the impurities at the starting material level, at the intermediate level and at the final synthesis level were adequately presented. Science and risk based approaches were applied during CMC evaluation to make the regulatory decisions on impurity control strategies.

Ceritinib was studied for its stability under the ICH stability test conditions. The drug substance was physically and chemically stable based on evaluation of the testing data. The drug substance has a retesting period of (b) (4) months. Science and risk based approaches were applied during CMC evaluation to make the regulatory decisions on stability data acceptance.

Drug Product: The drug product is an immediate release hard gelatin capsule for oral administration. The drug product contains 150 mg LDK378 (ceritinib) formulated using excipients meeting pharmacopoeia quality standards. The manufacturing process of ceritinib 150 mg hard gelatin capsule consists of (b) (4). The final (b) (4) is (b) (4) in the blue and white hard gelatin capsules. The Applicant provided two stability studies for 150 mg ceritinib hard gelatin capsules. One supportive study contains two batches that were manufactured during the development and used in the clinical studies, which provided stability data up to 24 months for one batch and 12 months for another batch. The registration stability contains three batches representative of the final manufacturing process and support the intended to be marketed product. The registration stability study covers stability data up to 6 months. The Applicant anticipated that the updated stability data up to 9 months for the 3 registration stability batch and up to 24 months for one batch from supportive stability (batch AEUS/2012-0023) being available by mid May 2014. However, the registration and supportive stability studies have been performed using the (b) (4) (cap and body) colored ceritinib 150 mg hard gelatin capsule, which was the color of the capsule shell during early and late development and differs from the commercial product (blue and white hard gelatin capsules). Novartis will perform additional bridging stability studies on 3 additional blue-white color capsule batches manufactured at the commercial site using the commercial manufacturing process. Based on the current available stability data using science and risk management approaches, 18 months shelf life for ceritinib 150 mg hard gelatin capsule stored at 25 degree C (77 degree F) in tight containers is granted.

Biopharmaceuticals: ONDQA-Biopharmaceutics has reviewed the information provided in NDA 205755 for Certitinib 150 mg capsules and find the biopharmaceutics data/information acceptable. In a teleconference on March 24, 2014, the Applicant accepted FDA's recommended acceptance criterion of $Q = (b) (4)$ at 15 minutes. Therefore, from the biopharmaceutics perspective, approval is recommended.

Product Quality Microbiology: The application for Ceritinib/LDK 378 is acceptable from a Product Quality Microbiology perspective and this submission is recommended for approval. The lack of routine microbiological testing for the drug product has been adequately justified. The Applicant has provided data from 12 batches that demonstrate adequate microbial at release and/or six months. Microbial testing will be conducted for the three registration and first three commercial batches through expiry. The (b) (4) (b) (4) will prevent any microbial proliferation during storage. These studies are adequate to support the continued microbial control of this product and are consistent with Agency expectations.

- Facilities review/inspection: On March 27, 2014 the Office of Compliance issued an overall recommendation of acceptable for the inspections of the manufacturing and testing facilities for the drug substance and drug product.
- Additional Items: The Office of Compliance (OC) had cGMP concerns with (b) (4) (b) (4) which manufactures the (b) (4) (b) (4) for the ceritinib API. These concerns were discussed with senior management in DOP-2, OHOP and the CDER Center Director on April 9, 2014. A final decision on the impact of these concerns on the timing of NDA action is pending at this time.

Overall CMC recommendation: The drug product, Zykadia (Ceritinib) Capsule 150 mg is recommended for approval from a CMC perspective.

Tertiary Review (Ramesh K Sood, Ph.D., Acting Director, DPA I/ONDQA (April 8, 2014): The application is recommended for “Approval” from CMC perspective.

4. Nonclinical Pharmacology/Toxicology

- General nonclinical pharmacology/toxicology considerations (including pharmacologic properties of the product, both therapeutic and otherwise):

In clinical trials at the 750 mg daily dose level, C_{max} was approximately 1010 ng/mL (~1.8 μ M). Given that ceritinib is highly protein bound ($\geq 97\%$), a C_{max} of 1.8 μ M would result in a free drug concentration of approximately 50 nM in plasma at the recommended dose. Against a panel of 36 recombinant human kinases, ceritinib exhibited strong inhibition of ALK ($IC_{50}=0.15$ nM); this inhibition is approximately 50-fold higher than inhibition of other members of the insulin receptor superfamily (InsR; $IC_{50}= 27$ nM and IGF-1R; $IC_{50}= 8$ nM) included in the panel and 700-fold more selective than for the other 33 kinases tested. Therefore, ceritinib is expected to inhibit ALK, InsR and IGF-1R at clinically achievable concentrations. In cellular assays, ceritinib exhibited anti-proliferative activity against Ba/F3 cells transduced with constitutively active NPM-ALK ($IC_{50}= 35$ nM), EML4-ALK ($IC_{50}= 27$ nM), TEL-ALK ($IC_{50}= 56$ nM), TEL-IGF-1R ($IC_{50}= 220$ nM), TEL-InsR ($IC_{50}= 400$ nM) and TEL-ROS1 ($IC_{50}= 180$ nM).

Incubation with ceritinib resulted in concentration-dependent phosphorylation of ALK in vitro and a downstream mediator STAT 3 in vitro and in vivo. Treatment with ceritinib inhibited the in vitro proliferation of human NSCLC H2228 (IC₅₀= 11nM) and ALCL Karpas 299 (IC₅₀= 45 nM) cell lines expressing ALK translocations, and human neuroblastoma cells with ALK amplification (IC₅₀= 24 nM). Daily dosing with ceritinib resulted in dose-dependent inhibition of H2228 and Karpas299 xenograft growth in SCID mice and nude rats and induced tumor regression at exposures achievable in patients at the recommended dose. Pharmacodynamic studies suggested that a $\geq 70\%$ reduction in ALK signaling may be required to achieve tumor regression. Ceritinib exhibited inhibitory activity in in vitro and in vivo models of NSCLC with demonstrated resistance to crizotinib, at clinically achievable concentrations.

The major target organs identified in general toxicology studies conducted in rats and monkeys included the pancreas, biliopancreatic ducts, bile duct, gastrointestinal tract and liver. The lungs were also identified as a target organ in rats with phospholipidosis observed following 4 weeks of dosing at 1.5-fold clinical exposure, and lung macrophage aggregates following 13 weeks of dosing at similar exposures to that observed clinically. In animals, high levels of ceritinib were present in the pancreas in distribution studies, and pancreatic atrophy was observed in monkeys and in rats at doses resulting in exposures 0.15 and 1.5-fold the ceritinib exposure at the recommended dose. Effects on the biliopancreatic and bile ducts were observed in animals at exposures lower than the clinical exposure of ceritinib. Hyperglycemia may be related to pancreatic effects of the drug or to inhibition of IGF-1R and InsR.

In a CNS safety pharmacology study, no significant behavioral or physiological changes were observed following a dose of ceritinib. The drug does cross the blood brain barrier. In rats, exposure of ceritinib in the brain was approximately 15% that of the plasma exposure by AUC.

Ceritinib demonstrated potential for causing QTc prolongation in the in vitro hERG assay as well as in vivo in a single dose cardiac safety pharmacology study conducted in monkeys.

- **Carcinogenicity**
Ceritinib was not mutagenic in vitro in the bacterial reverse mutation (Ames) assay but was aneugenic (induced numerical aberrations) in both the in vitro cytogenetic assay using human lymphocytes and in micronuclei in the in vitro micronucleus test using TK6 cells. Ceritinib was not clastogenic in the in vivo mouse micronucleus assay. Seven process impurities were assayed by (b) (4) screening and predicted to be genotoxic, but were controlled to acceptable levels for a drug intended for the treatment of patients with cancer.
- **Reproductive toxicology**
Administration of ceritinib to pregnant rats during the period of organogenesis resulted in dose-related skeletal anomalies at doses resulting in maternal exposures less than 50% the human exposure by AUC at the recommended dose. Findings included delayed

ossification and skeletal variations. Ceritinib did not induce embryoletality or fetotoxicity at doses tested in rats. In pregnant rabbits administered ceritinib daily during organogenesis, dose-related skeletal and visceral anomalies, including incomplete ossification, absent or malpositioned gallbladder and retroesophageal subclavian cardiac artery were observed at exposures of approximately 13% of the recommended human exposure by AUC. Higher doses resulted in significant maternal toxicity and abortion in rabbits. In addition, ALK inhibition has been reported to be associated with fetal toxicities including effects on neural development. Therefore, the Pharmacology/ Toxicology team recommended pregnancy category D. Given the 41 hour half-life of ceritinib at the recommended clinical dose, females are advised to use effective contraception during treatment and for up to 2 weeks following cessation of treatment.

Overall Recommendation from Pharmacology/ Toxicology (3/25/2014): Recommended for approval. The non-clinical studies submitted to this NDA provide sufficient information to support the use of ceritinib for the treatment of patients with advanced or metastatic NSCLC who have progressed following prior treatment with crizotinib.

Tertiary Review by John Leighton, PhD, DABT, Acting Director Division of Hematology Oncology Toxicology (4/9/2014): I have examined pharmacology/toxicology supporting and labeling reviews for Zykadia conducted by Drs. Brower and Fox, and secondary memorandum and labeling provided by Dr. Helms. I concur with Dr. Helms' conclusion that Zykadia may be approved and that no additional nonclinical studies are needed for the proposed indication.

5. Clinical Pharmacology

- General clinical pharmacology/biopharmaceutics considerations, including absorption, metabolism, half-life, food effects, bioavailability, etc.

The Applicant proposed an oral dosing regimen of 750 mg once daily on an empty stomach 2 hours before and 2 hours after food. Pharmacokinetic (PK) data to support the clinical pharmacology program were submitted from the pivotal single-arm study in metastatic ALK-positive cancer (X2101, N=304, 59 in dose escalation and 245 in expansion), and 5 additional trials [Japanese patients with ALK+ cancer (N=19), Drug drug interaction (DDI) study with ketoconazole in healthy subjects (N=19), DDI study with rifampin in healthy subjects (N=19), food effect in healthy subjects (n=28), and ADME study in healthy subjects (N=6)].

Ceritinib exhibits nonlinear time-dependent PK, with exposures that are dose proportional after a single dose [estimated AUC_{0-24h} slope 0.99 (90% CI: 0.7, 1.3)], but greater than dose proportional after repeat doses [estimated C_{trough} slope 1.47 (90% CI: 1.1, 1.8)] in the dose range of 50 to 750 mg. Following ceritinib 750 mg daily, steady state is achieved by approximately 15 days with 6-fold accumulation after three weeks. Apparent clearance (CL/F) at steady-state (33L/h) is lower than after a single dose (89 L/h), likely due to auto-inhibition of CYP3A. The terminal half-life ($t_{1/2}$) at the 750 mg

dose is 41 hours. The median ceritinib T_{max} ranged from 4 to 6 hours. The mean accumulation ratio for AUC_{0-24h} is 4.7 (day 8/day 1 of cycle 1) and 6.2 (day 1 of cycle 2/cycle 1). Inter-patient variability in steady state AUC and C_{max} at the dose of 750 mg is 74% and 76%, respectively.

Administration of a single 500 mg dose of ceritinib with a high-fat, high-calorie meal in healthy subjects resulted in a 73% increase in AUC and 41% increase in C_{max} as compared with fasted conditions while a low-fat meal increased AUC by 58% and C_{max} by 43% as compared to fasted conditions. Given that apparent passive permeability of ceritinib is low and ceritinib is a substrate for P-glycoprotein (P-gp), ceritinib absorption is likely limited.

Ceritinib is 97% bound to human plasma proteins independent of concentration. The mean blood to plasma ratio in human blood in vitro is 1.35.

The ADME in 6 healthy subjects who received a single dose of 750 mg [^{14}C] ceritinib with blood samples collected up to 336 hours and urine and feces collected up to 384 hours post-dose, suggests hepatic as the major route of elimination. The mean recovery of the administered dose was 92% (68% as unchanged parent compound) in the feces and 1.3% in the urine. The major circulating component in plasma was unchanged ceritinib, constituting 82% of plasma radioactivity.

- Drug-drug interactions and Pathway of elimination

Hepatic oxidative metabolism of ceritinib is primarily mediated by CYP3A (>90%) as demonstrated in a human liver microsome in vivo study. See extrinsic factors for further discussion of drug-drug interactions.

- Intrinsic and extrinsic factors

Intrinsic factors: No formal studies have been conducted to assess the effect of age, race, weight, height, or organ dysfunction of exposure and response to ceritinib. The Applicant's population PK (popPK) analysis, verified by FDA, did not identify clinically important effects of body weight, age gender, mild and moderate renal impairment, and mild hepatic impairment as covariates on clearance or volume of distribution of ceritinib. No data was submitted to evaluate the pharmacokinetics of ceritinib in pediatric patients.

Hepatic impairment: Based on a population pharmacokinetic analysis of 48 patients with mild hepatic impairment (total bilirubin \leq ULN and AST $>$ ULN or total bilirubin $>$ 1.0 to 1.5 times ULN and any AST) and 254 patients with normal hepatic function (total bilirubin \leq ULN and AST \leq ULN), ceritinib exposures were similar in patients with mild hepatic impairment and normal hepatic function. The pharmacokinetics of ceritinib has not been studied in patients with moderate to severe hepatic impairment.

Renal impairment: Based on a population pharmacokinetic analysis of 97 patients with mild renal impairment (CL_{cr} 60 to <90 mL/min), 22 patients with moderate renal impairment (CL_{cr} 30 to <60 mL/min) and 183 patients with normal renal function (\geq 90 mL/min), ceritinib exposures were similar in patients with mild and moderate renal impairment and normal renal function. Patients with severe renal impairment (CL_{cr} <30 mL/min) were not included in the clinical trial.

Extrinsic factors: the effect of extrinsic factors including concomitant medications was evaluated in vitro and by popPK analysis.

Strong CYP3A4 inhibitors on Ceritinib: In vitro studies show that ceritinib is a substrate of CYP3A. Co-administration of a single 450 mg ZYKADIA dose with ketoconazole (a strong CYP3A inhibitor) 200 mg twice daily for 14 days increased ceritinib AUC (90% CI) by 2.9-fold (2.5, 3.3) and C_{max} (90% CI) by 22% (7%, 39%) in 19 healthy subjects. The steady-state AUC of ceritinib at reduced doses after co-administration with ketoconazole 200 mg bid for 14 days was predicted by simulations to be similar to steady-state AUC of ceritinib alone.

Strong CYP3A4 inducers on Ceritinib: Co-administration of a single 750 mg ZYKADIA dose with rifampin (a strong CYP3A inducer) 600 mg daily for 14 days decreased ceritinib AUC (90% CI) by 70% (61%, 77%) and C_{max} (90% CI) by 44% (24%, 59%) in 19 healthy subjects.

Effect of Transporters on Ceritinib Disposition: Ceritinib is a substrate of efflux transporter P-gp, but is not a substrate of Breast Cancer Resistance Protein (BCRP), Multidrug Resistance Protein (MRP2), Organic Cation Transporter (OCT1), Organic Anion Transporter (OAT2), or Organic Anion Transporting Polypeptide (OATP1B1) in vitro.

Effect of Gastric Acid Reducing Agents on Ceritinib: Gastric acid reducing agents (e.g., proton pump inhibitors, H₂-receptor antagonists, antacids) may alter the solubility of ceritinib and reduce its bioavailability as ceritinib demonstrates pH-dependent solubility and becomes poorly soluble as pH increases in vitro.

- Exposure-Response

The Pharmacometrics review concluded that based on currently available data, the proposed dose of 750 mg daily is acceptable. The results of E-R analyses for efficacy did not show a clear relationship between systemic exposure and ORR or PFS. Higher systemic exposure is associated with more frequent and earlier overall Grade 3-4 AEs, and higher incidence of individual AEs including Grade 3-4 AST/ALT elevations and Grade 2 or worse hyperglycemia. Higher systemic exposure is also associated with earlier and more frequent dose reductions or dose interruptions. Given that permanent

discontinuations due to AEs occurred in only 10% of patients, the proposed dose of 750 mg with management of AEs via dose reductions or interruptions appears acceptable.

- QT assessment

In Study X2101, time-matched ECG and PK samples were collected at pre-dose, 4, 8, and 24 hours post-dose on days 1 and 8 (escalation phase only) of cycle 1, pre-dose on day 1 of cycles 2-6, and end of treatment. The relationship between Δ QTcF and ceritinib concentrations was determined by pooling data from Cycle 2 Day 1 and beyond in patients who received doses from 50 mg to 750 mg. The QT-IRT review concluded that ceritinib prolonged the QTc interval in a concentration-dependent manner based on population concentration-QTc analyses using a linear mixed effects model. Following repeat daily doses of 750 mg ceritinib, large changes (i.e., >20 ms) in the QT interval were detected at steady-state (Cycle 2 Day 1 and beyond). The largest mean change from baseline was 19.3 ms with the upper bound of the 2-sided 90% confidence interval of 22.2 ms, observed at cycle 6 Day 1.

- Unresolved Dosing Issue with Regard to gastrointestinal (GI) tolerability

The proposed dosing regimen for ceritinib with regard to food is 750 mg daily on an empty stomach at least 2 hours before or 2 hours after food. At the recommended dose under fasted conditions, the majority of patients experienced GI adverse reactions including diarrhea (86%), nausea (80%), vomiting (60%), and abdominal pain (54%). The absolute bioavailability of ceritinib has not been studied but is expected to be low. The food effect study showed that a high-fat, high calorie meal increased ceritinib AUC by 73% and Cmax by 41%; a low-fat meal increased AUC by 58% and Cmax by 43% as compared to fasted conditions. Administration of ceritinib at 750 mg with food may improve GI tolerability and compliance, but could lead to exposure-related toxicities such as AST/ALT elevations, hyperglycemia, and QTc prolongation. The Applicant proposed to conduct a clinical trial to evaluate (b)(4) the PK of ceritinib in healthy subjects based on the hypothesis that the magnitude of increase in ceritinib exposure would be smaller with a (b)(4) light (b)(4) or (b)(4) full meals while alleviating GI adverse events. FDA recommends determination of an exposure-matched dose of ceritinib taken with food to improve GI tolerability and compliance in patients without compromising efficacy. A postmarketing trial should be conducted to evaluate the GI tolerability, efficacy, and PK of 450 mg ceritinib taken with a meal as compared with that of 750 mg ceritinib taken in the fasted state in metastatic ALK-positive NSCLC patients.

Overall Recommendation from Clinical Pharmacology (3/25/2014): The NDA 205755 is acceptable from a clinical pharmacology perspective provided that the Applicant and the FDA come to an agreement regarding the labeling language and the identified clinical pharmacology trials to be conducted as postmarketing requirements.

6. Clinical/Statistical- Efficacy

I agree with the conclusions of the statistical reviewer (Dr. Lijun Zhang) and clinical reviewer (Dr. Sean Khozin) regarding the efficacy of ceritinib for patients with ALK-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib.

The following summarizes the key milestones in the regulatory history. The Applicant submitted the IND for ceritinib on October 8, 2010. Study X2101 was initiated on January 24, 2011. An End of Phase 1/ Pre Phase 3 meeting occurred on November 20, 2012. On March 6, 2013, breakthrough designation was granted based on a 77% unconfirmed and 47% confirmed ORR in 57 patients treated with ceritinib at 400 mg daily or higher who were previously treated with crizotinib. On November 22, 2013, the multi-disciplinary pre-NDA meeting occurred. Table 1 summarizes the clinical studies submitted to the NDA.

Table 1: Clinical studies submitted to NDA 205755 (October 31, 2013 data cut-off)

Title	Design	Tumor	Status	Prior treatment	Number of patients	NDA location
X2101	Ph1	ALK+ tumors	Ongoing, enrollment complete	Any	304 (59 dose escalation, 245 expansion)	CSR; SCE; SCS
X1101	Ph1 (Japan)	ALK+ tumors	Ongoing	Any	19	CSR; SCE; SCS
A2201	Ph2	ALK+ NSCLC	Ongoing	Chemo, crizotinib	140	SAE and death; SCS
A2203	Ph2	ALK+ NSCLC	Ongoing	None	82	SAE and death; SCS
X2303	Ph3 RCT ceritinib vs. chemo	ALK+ NSCLC	Ongoing	chemo doublet, crizotinib	14	SAE and death; SCS
X2102	Ph1b ceritinib + AUY 922	ALK+ NSCLC	Ongoing	Any	6	SAE and death; SCS
X2301	Ph3 RCT ceritinib vs. doublet chemo	ALK+ NSCLC	Ongoing	None	8	SAE and death
A2402	Expanded Access	ALK+ NSCLC	Ongoing	Crizotinib	4	SAE and death
X2103	Ph1 pediatrics	ALK+ tumors	Ongoing	Standard therapy	5	SAE and death

Ph=phase; RCT= randomized controlled trial; CSR= clinical study report; SCE = summary clinical efficacy; SCS= summary clinical safety

Efficacy Summary:

The efficacy of ceritinib was evaluated in 163 patients with ALK+ metastatic NSCLC who progressed on or were intolerant to crizotinib treated with ceritinib at a dose of 750 mg once daily. The 163 patients comprised the Full Analysis Set (FAS), defined as all patients who received at least one full or partial dose of ceritinib 750 mg once daily. The median age was 52 years (range 24 – 80), 54% of patients were female, 66% were Caucasian, 29% were Asian, 97% were never or former smokers, 87% had ECOG Performance Status 0 or 1, 84% had two or more prior therapies, and 93% had adenocarcinoma histology. Sites of extra-thoracic metastasis included 60% brain, 42% bone, and 42% liver. ALK positivity was verified retrospectively by review of local test results for 99% of patients.

Ceritinib was administered orally at 750 mg once daily until disease progression or unacceptable toxicity. Tumor response was assessed by RECISTv1.0. The primary efficacy endpoint was investigator-assessed overall response rate (ORR). At the FDA’s behest, the sponsor retrospectively collected patient scans for a blinded independent review committee (BIRC) assessment of ORR. The sponsor was able to transfer scans for BIRC review on 153 of the 163 patients in the FAS population. Two patients did not consent to transfer of scans, and eight patients received the first dose of ceritinib less than 18 weeks prior to the analysis cut-off date and thus could not have confirmation of best response. Discordance between investigator and BIRC assessment was 21%. Duration of Response (DOR) was an additional efficacy outcome. Efficacy data for the FAS by investigator and BIRC is presented in Table 2.

Table 2: ORR and DOR in patients with ALK+ NSCLC who previously received crizotinib (Data cut-off: October 31, 2013)

Efficacy Parameter	Investigator Assessment (N=163)	BIRC Assessment (N=163)
ORR (95% CI)	54.6% (47, 62)	43.6% (36, 52)
CR	1.2%	2.5%
PR	53.4%	41.1%
DOR, median (months) (95% CI)	7.4 (5.4, 10.1)	7.1 (5.6, NE)
CR, complete response; NE, not estimable; PR, partial response.		

Subgroup analysis revealed higher point estimates for ORR in the Asian population compared to Caucasians and in ECOG PS 0 patients versus PS \geq 1. Among 14 patients with brain metastases identified as target lesions by investigators, 1 patient had a confirmed CR and 6 patients had confirmed PRs in the brain. In an exploratory analysis, Dr. Khozin did not find an association between length of time since stopping crizotinib and response to ceritinib. In addition, there appeared to be no association between % ALK positivity in the tumor specimen and best response.

Primary Reviewer Conclusions:

The primary clinical and statistical reviewers concluded that the benefit-risk of ceritinib in patients with ALK-positive metastatic NSCLC who progressed on or are intolerant to crizotinib is favorable for accelerated approval, and that the magnitude and duration of ORR are reasonably likely to predict clinical benefit.

7. Safety

I concur with the clinical reviewer's (Dr. Sean Khozin) conclusions regarding the safety of ceritinib.

The safety profile of ceritinib was primarily evaluated in 255 ALK-positive patients (246 patients with NSCLC and 9 patients with other cancers who received ceritinib at a dose of 750 mg daily) in study X2101. The median duration of exposure to ceritinib was 6 months. A summary of the key safety findings based on the data cut-off date of October 31, 2013 safety update is listed below.

- Dose reductions due to adverse reactions occurred in 59% of patients. The most frequent adverse reactions, reported in at least 10% of patients, that led to dose reductions or interruptions were: increased ALT (29%), nausea (20%), increased AST (16%), diarrhea (16%), and vomiting (16%).
- Serious adverse drug reactions reported in 2% or more of patients were convulsion, pneumonia, ILD/pneumonitis, dyspnea, dehydration, hyperglycemia, and nausea.
- Fatal adverse reactions occurred in 5% of patients, consisting of: pneumonia (4 patients), respiratory failure, ILD/pneumonitis, pneumothorax, gastric hemorrhage, general physical health deterioration, pulmonary tuberculosis, cardiac tamponade, and sepsis (1 patient each).
- Discontinuation of therapy due to adverse reactions occurred in 10% of patients treated with ceritinib. The most frequent adverse drug reactions that led to discontinuation in 1% or more patients in were pneumonia, ILD/pneumonitis, and decreased appetite.
- Common all grade treatment emergent adverse events (TEAE) of >20% incidence: diarrhea (86%), nausea (80%), vomiting (60%), abdominal pain (54%), fatigue (52%), decreased appetite (34%), and constipation (29%).
- Common grade 3-4 TEAE of > 3% incidence: diarrhea (6%), fatigue (5%), nausea (4%), vomiting (4%).
- Common all grade laboratory abnormalities of > 25% incidence: ALT increased (80%), AST increased (75%), creatinine increased (58%), glucose increased (49%), phosphate decreased (36%), lipase increased (28%).
- Common grade 3-4 laboratory abnormalities of > 10% incidence: ALT increased (27%), AST increased (13%), glucose increased (13%), lipase increased (10%).
- Review of adverse events of special interest revealed the following:
 - Severe and persistent gastrointestinal (GI) toxicity: Diarrhea, nausea, vomiting or abdominal pain (all grades) occurred in 96% of patients and Grade 3-4 in 14% of patients. Does modification due to diarrhea, nausea, vomiting or abdominal pain occurred in 38% of patients. The toxicity may be in part due to local GI toxicity. Whether a meal or snack could attenuate this toxicity is not known. In addition,

- the recommended dose of ceritinib with a meal or a snack warrants further study in the post-marketing setting.
- Hepatotoxicity: Elevations in ALT > 5 times ULN occurred in 27% of patients. One patient required permanent discontinuation due to drug induced liver injury potentially meeting Hy's law criteria with transaminase elevation followed by total bilirubin rise and jaundice.
 - Interstitial Lung Disease/Pneumonitis: occurred in 4% of patients (all grades), 3% (grade 3-4), and 0.4% grade 5.
 - QT Interval Prolongation: QTc increase > 500 msec occurred in one patient (0.3%), and 60 msec increase over baseline occurred in 10 patients (3%).
 - Hyperglycemia: Grade 3-4 (based on lab values) occurred in 13% of patients. There was a 6-fold increase in the risk of CTCAE Grade 3-4 hyperglycemia in patients with diabetes or glucose intolerance and a 2-fold increase in patients taking corticosteroids.
 - Bradycardia: sinus bradycardia with a heart rate of less than 50 beats per minute occurred as a new finding in a review of ECGs in 1% of patients. Bradycardia was reported as an adverse drug reaction in 3% of patients. Four patients developed syncope, however a relation between syncope and bradycardia or bradyarrhythmia could not be established.
 - Acute pancreatitis: a possible signal may exist based on elevations in pancreatic enzymes and gastrointestinal toxicity. However, the Applicant's and Reviewer's analysis did not establish a clear association between ceritinib and acute pancreatitis based on the available data. Routine post-marketing pharmacovigilance and analysis of the randomized studies are warranted.
 - Convulsions: Occurred in 4% of patients. However, review of the 22 events in 16 patients showed that all of these patients likely developed convulsions due to underlying brain metastasis. It is not known whether ceritinib lowers the seizure threshold in patients with underlying brain metastases. Routine post-marketing pharmacovigilance and analysis of the randomized studies are warranted.

8. Advisory Committee Meeting

The NDA for this new molecular entity was not presented to the Oncologic Drugs Advisory Committee (ODAC) because the application did not raise significant efficacy or safety issues for the proposed indication. The application did not raise significant public health questions on the role of ceritinib for the indication, and outside expertise from ODAC was not necessary since there were no controversial issues that would benefit from advisory committee discussion.

On March 27, 2014, individual teleconferences were held with Special Government Employees (SGEs) Arun Rajan, MD of the Thoracic Malignancies Branch of the National Cancer Institute (NCI) and Pamela Moffitt, a patient representative and lung cancer survivor.

Prior to these individual teleconferences, the SGEs reviewed a summary document of the safety and efficacy data and draft product labeling. Overall, both Dr. Rajan and Ms. Moffitt felt that the benefit-risk of ceritinib for the treatment of patients with ALK-positive metastatic NSCLC who progressed on or are intolerant to crizotinib was favorable. Both SGEs were concerned about the gastrointestinal toxicity of the drug, but felt that the response rates and duration of response were clinically meaningful. Dr. Rajan was supportive of further study of an exposure-matched strategy of lower doses of ceritinib with food in the post-marketing setting to better inform product labeling and to potentially mitigate against persistent or serious gastrointestinal toxicity.

9. Pediatrics

Ceritinib is exempt from the pediatric study requirements of the Pediatric Research Equity Act in accordance with the provisions of 21 CFR 314.55. Ceritinib was granted Orphan Drug Designation by the Office of Orphan Products Development for the treatment of patients with NSCLC that is ALK-positive on September 27, 2013.

10. Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP):** No issues
- **Exclusivity or Patent Issues of Concern:** No issues. Refer to exclusivity review.
- **Financial Disclosures:** No issues. With respect to financial disclosure information for study X2101, 96% of 127 US clinical investigators responded, and 100% of 164 Non US clinical investigators responded. For study X1101, 100% of 66 clinical investigators responded. Two US investigators in study X2101 received >\$25,000 for research grants from the Applicant. However, bias was minimized by independent data monitoring by Novartis, multiple investigators and clinical study sites in the trial, and independent central radiologic review of ORR and duration of response.
- **Other GCP Issues:** None
- **Office of Scientific Investigation (OSI) Audits:** OSI inspections of Dr. Alice Shaw (Massachusetts General Hospital, Site 0504), Dr. Raneeh Mehra (Fox Chase Cancer Center, Site 0505), Dr. Dong-Wan Kim (Seoul Korea, Site 0201), Novartis Pharmaceuticals, and (b) (4) (Independent Radiologic CRO) found no issues.

The following is excerpted the OSI executive summary of findings (3/24/14):

“Based on the review of preliminary inspectional findings for clinical investigators Dr. Alice Shaw (Site 0504), Dr. Raneeh Mehra (Site 0505), the Sponsor, Novartis Pharmaceuticals Corporation, and the blinded independent radiological review committee

(BIRC, CRO [REDACTED] (b) (4)) the Study CLDK378X2101 data appear reliable based on available information. No preliminary inspectional findings information is available for Prof. Dongwan Kim (Site 0201) at this time. The inspection of Dr. Dongwan Kim is currently ongoing and expected to be completed no later than March 28, 2014.”

Update Email from OSI’s Matthew R. McNew to Lauren Iacono-Connor regarding Prof Dong-Wan Kim of Seoul Korea (Site 0201) (3/27/14):

“I have completed the inspection and have found no observations. I recommend classification as NAI. The dates of inspection were 3/17-26/14, excluding the weekend. There were 82 subjects screened and 62 enrolled. I reviewed a total of 31 subject records. Three SAE’s were not reported within the protocol’s 24 hour timeframe requirement, but were reported shortly thereafter.”

- **Other Discipline Consults:** None
- **Other Outstanding Regulatory Issues:** None

11. Labeling

- **Proprietary name:** On March 24, 2014, OSE/DMEPA concluded that the proposed proprietary name, Zykadia is acceptable.
- **OSE/ Division of Risk Management (DRISK):** concluded that based on the available data and the potential benefits and risks of treatment, a REMS is not necessary for ceritinib.
- **OSE/ Division of Medication Error Prevention and Analysis (DMEPA):** DMEPA participated in the labeling discussions and provided recommendations for the container labels, carton and insert labeling.
- **Patient Labeling Team:** The patient labeling team participated in labeling discussions.
- **Office of Prescription Drug Promotion (OPDP):** OPDP participated in labeling discussions. Refer to OPDP review in DARRTS for OPDP labeling recommendations.
- **Maternal Health:** Concurred that a pregnancy category D is the appropriate classification for ceritinib based on its mechanism of action and findings of embryofetal toxicity observed in animal studies. Maternal Health also participated in labeling discussions with respect to ‘Warnings and Precautions’ (Embryofetal Toxicity), ‘Use in Special Populations’ (Pregnancy, Nursing Mothers, Females and Males of Reproductive Potential), and ‘Patient Counseling Information’.

12. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action: Approval
- Risk Benefit Assessment

Patients with ALK-positive metastatic NSCLC who have progressed on crizotinib have a serious and life-threatening illness, with an overall poor prognosis and limited effective available therapies. The efficacy and safety results in clinical trial CLDK378X2101 demonstrate a favorable benefit-risk profile for ceritinib in patients with ALK-positive mNSCLC previously treated with crizotinib. All review team members recommend approval.

The basis of the approval recommendation is the demonstration of a large magnitude of ORR (44% by BIRC, 55% by investigator) of long duration (median of roughly 7 months) in a patient population (ALK-positive mNSCLC refractory to crizotinib) where limited treatment options exist in a serious and life threatening disease. A large magnitude of effect on ORR of suitable duration is a surrogate endpoint that is reasonably likely to predict clinical benefit. Response rate of large magnitude and long duration have been observed in trials with other TKIs targeting specific genetic aberrations (such as EGFR kinase domain mutations and ALK-rearrangements) in mNSCLC, which have subsequently in randomized confirmatory trials demonstrated improvements in progression-free survival of large magnitude when compared to chemotherapy.

Section 21 CFR 314.510 addresses approval based on a clinical endpoint other than survival or irreversible morbidity. Accelerated approval is subject to the requirement that the Applicant study the drug further to confirm clinical benefit. As a condition of accelerated approval, the Applicant is required to perform a randomized, multicenter post marketing study or studies to confirm the superiority of ceritinib over standard therapy in ALK-positive metastatic NSCLC. The Applicant has identified X2301 and X2303 as the studies to be used to confirm clinical benefit. Both of these studies use chemotherapy in the control arm, rather than an ALK inhibitor, and study X2301 in particular will be difficult to enroll patients in the United States, given that the standard of care is to treat patients initially with crizotinib. Nevertheless, the results of either study could potentially be used to confirm clinical benefit if the results are statistically robust and clinically meaningful. Although the Applicant has discussed with the Agency the possibility of a randomized trial comparing ceritinib to crizotinib, no such trial has been submitted under IND.

The risks of ceritinib are acceptable relative to the benefits. The main risks, as highlighted in the 'Warnings and Precautions' section of the prescriber information, include severe and persistent gastrointestinal (GI) toxicity, hepatotoxicity, interstitial lung disease/ pneumonitis, QT interval prolongation, hyperglycemia, bradycardia, and embryofetal toxicity.

The dose and schedule of 750 mg daily in the fasted state used in study X2101 is acceptable. However, there remains some concern and uncertainty regarding the severe and persistent gastrointestinal toxicity associated with this dosing strategy. In study X2101, 38% of patients required dose modification due to diarrhea, nausea, vomiting, or abdominal pain, and severe cases occurred in 14% of patients. Anecdotal reports from investigators and patients suggest that in the event of severe or intolerable gastrointestinal toxicity, patients are reducing the dose and taking ceritinib with food in an attempt to reduce local GI symptoms.

The concerns with this approach are two-fold. First, the food effect study in healthy volunteers suggested that a dose of 600 mg or above with meals (either high fat or low fat) could lead to exposures exceeding that of ceritinib 750 mg taken in the fasted state and therefore could increase the risk of severe adverse reactions such as liver toxicity, pneumonitis, hyperglycemia, and QTc prolongation. Second, the current starting dose recommendations to administer in the fasting state and, in the event of severe or intolerable GI toxicity, to continue taking in the fasting state with dose reduction after recovery, could lead to diminished compliance, underexposure, and compromised efficacy.

Based on the single dose food effect study in healthy volunteers, ceritinib 450 mg taken with a meal (either high fat or low fat) is expected to result in a similar exposure to ceritinib 750 mg taken in the fasted state. Given the safety and potential compliance issues with the current dosing regimen, FDA and the Applicant agreed to a postmarketing study to investigate the safety and exposure of ceritinib 450 mg taken with meals compared to 750 mg taken in the fasting state.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

The Applicant did not propose a REMS and the review teams did not identify the need for a REMS at this time to ensure the safe use of ceritinib.

- Recommendation for other Postmarketing Requirements and Commitments

I agree with the postmarketing requirements and commitments proposed by the review teams and agreed upon with the Applicant. Please note that some of the milestone dates may be modified with finalization of the action letter.

ACCELERATED APPROVAL REQUIREMENTS

2146-1 Conduct and submit the results of a multicenter, randomized study or studies 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.

Study/Trial Completion: 04/30/2019
Final Report Submission: 10/31/2019

POSTMARKETING REQUIREMENTS UNDER 505(o)

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

Draft protocol submission: 7/31/2014
Final protocol submission: 9/30/2014
Trial completion: 2/28/2017
Interim Analysis Report Submission: 7/6/2016
Final report submission: 8/31/2017

2146-3 Complete a pharmacokinetic trial to determine the appropriate dose of 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.”

Study/Trial Completion: 01/31/2016
Final Report Submission: 06/30/2016

2146-4 Conduct a clinical trial to evaluate the effect of repeat doses of 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.”

Final Protocol Submission: 09/30/2014
Study/Trial Completion: 08/31/2016
Final Report Submission: 02/28/2017

2146-5 Conduct a clinical trial to evaluate the effect of repeat doses of 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.”

Final Protocol Submission: 09/30/2014
Study/Trial Completion: 08/31/2016
Final Report Submission: 02/28/2017

2146-6 Conduct a clinical trial to evaluate if proton pump inhibitors, H₂-receptor antagonists, and antacids alter the bioavailability of ceritinib and to determine how to dose ceritinib with regard to concomitant gastric acid reducing agents.

Final Protocol Submission: 01/31/2015
Study/Trial Completion: 08/31/2015
Final Report Submission: 02/29/2016

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

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.

Final Report Submission: 4/30/2014

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).

Final Report Submission: 5/16/2014

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

/s/

GIDEON M BLUMENTHAL
04/11/2014