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APPLICATION NUMBER:

205755Orig1s000

MEDICAL REVIEW(S)

Clinical Investigator Financial Disclosure
Review Template

Application Number: NDA 205755

Submission Date(s): 12/24/13

Applicant: Novartis

Product: Ceritinib

Reviewer: Sean Khozin, MD, MPH

Date of Review: 4/17/14

Covered Clinical Study (Name and/or Number): X2101

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: 318 (127 US and 164 non-US)		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>2</u>		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____</p> <p>Significant payments of other sorts: <u>2</u></p> <p>Proprietary interest in the product tested held by investigator: _____</p> <p>Significant equity interest held by investigator in sponsor of covered study: _____</p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>316</u>		
Is an attachment provided with the reason:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*. Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

Upon review of the applicant's Financial Disclosure Certification, it was noted initially that 5 out of the 127 financial disclosures were not collected. FDA issued an IR on January 22, 2014 for an amendment to the Financial Disclosure Certification confirming that the applicant acted with due diligence to obtain financial disclosure information but was unable to do so for all the investigators in Study X2101 and to state the reason(s) why 5 out of 127 financial disclosures were not collected. In their response, the applicant provided two additional financial disclosures from investigators not declaring any financial interests and provided adequate rationale on why the other 3 investigator disclosures could not be collected, confirming due diligence in the process. The two investigators that had disclosable financial interests (both due to having received research grants) were at sites that recruited only (b) (6), minimizing potential bias on the overall study results. Furthermore, the study results were robust and clinically meaningful when tumor response (the study's primary endpoint) was analyzed according to a blinded independent review committee assessment.

Overall, the applicant adequately disclosed financial arrangements with the clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators* and the arrangements did not raise questions about the integrity of the data.

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/s/

SEAN N KHOZIN
04/17/2014

GIDEON M BLUMENTHAL
04/17/2014

CLINICAL/ STATISTICAL REVIEW

Application Type	NDA
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Division / Office	DOP2/OHOP/CDER
Reviewer Name(s)	Sean Khozin, MD, MPH (Clinical; efficacy and safety) Lijun Zhang, PhD (Statistics; efficacy)
Review Completion Date	March 25, 2014
Established Name	Ceritinib
(Proposed) Trade Name	ZYKADIA
Therapeutic Class	NME
Applicant	Novartis
Formulation(s)	Oral
Dosing Regimen	750 mg PO once a day
Indication(s)	ALK-positive metastatic non-small cell lung cancer
Intended Population(s)	Patients who have progressed on, or are intolerant to, crizotinib

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Based on a favorable risk-benefit assessment of data submitted from the single arm clinical trial X2101, reviewers recommend accelerated approval of ceritinib (Zykadia) for the following indication:

Treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.

This indication differs from the applicant's proposed indication in that it limits the intended population to patients with ALK-positive metastatic (b) (4) NSCLC who have been specifically treated with crizotinib (b) (4)

1.2 Risk Benefit Assessment

The recommendation for approval is based on the results of a single arm clinical trial (X2101) titled "A phase I, multicenter, open-label dose escalation study of ceritinib, administered orally in adult patients with tumors characterized by genetic abnormalities in anaplastic lymphoma kinase (ALK)." The trial enrolled a total of 163 patients with metastatic ALK-positive NSCLC who had progressed on or were intolerant to crizotinib. All patients received ceritinib at a dose of 750 mg once daily. The primary endpoint was overall response rate (ORR) according to RECIST 1.0 as evaluated by investigators and a Blinded Independent Central Review Committee (BIRC). Duration of response (DOR) was an additional outcome measure. The study population characteristics were: median age 52 years, age < 65 (87%), female (54%), White (66%), Asian (29%), never or former smoker (97%), ECOG PS 1 (64%), progression on previous crizotinib (91%), number of prior therapies >3 (35%), and adenocarcinoma histology (93%). Sites of extra-thoracic metastasis included brain (60%), liver (42%) and bone (42%). ALK-positivity was verified retrospectively by review of local test results for 99% of patients.

As of the data cut-off date of October 31, 2013, ORR was 55% (95% CI 47 to 62) and 44% (95% CI 36 to 52) per investigator and BIRC assessment, respectively. DOR was 7.4 and 7.1 months per investigator and BIRC assessment, respectively.

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 other supportive studies. The median duration of exposure to ceritinib was 6 months. The most common adverse events (>10%) 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 (>10%) were increased alanine transaminase (ALT) (80%), increased aspartate

transaminase (AST) (75%), increased creatinine (58%), increased glucose (51%), increased lipase (29%), and increased bilirubin (16%). Dose reductions due to adverse events occurred in 59% of patients. The most frequent adverse events that led to dose reductions or interruptions were: increased ALT (29%), nausea (20%), increased AST (16%), diarrhea (16%), and vomiting (16%). Serious adverse reactions reported in at least 2% of patients included convulsion, pneumonia, pneumonitis, dyspnea, hyperglycemia, and nausea. Fatal adverse reactions in patients treated with ceritinib occurred in 5% of patients and included one case of pneumonitis. Discontinuation of therapy due to adverse reactions occurred in 10%. The most frequent adverse reactions that led to discontinuation in at least 1% of patients included pneumonia, pneumonitis, and decreased appetite.

Based on the data submitted, ceritinib can provide meaningful therapeutic benefit to patients over existing treatments and the drug has demonstrated a favorable risk-benefit profile in the treatment of patients with ALK-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib. The primary treatment effect of ORR of large magnitude and duration is considered to represent a substantial improvement over available therapies (e.g., pemetrexed and docetaxel). Demonstration of such a treatment effect is reasonably likely to predict clinical benefit in patients with metastatic NSCLC and has been used as the basis for accelerated approval for other agents in metastatic NSCLC which in subsequent confirmatory randomized trials have shown significant improvements in time-to-event endpoints such as progression-free survival (PFS) compared with available therapy. Although at the recommended dose, most patients taking ceritinib in X2101 required dose reductions due to adverse events, discontinuation rate due to adverse events was low and the toxicity profile appears to be manageable.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations for Postmarket Requirements and Commitments

The applicant has discussed with FDA two confirmatory trials (Table 1) as required to confirm clinical benefit for drugs approved under subpart H [505(b) of the Federal Food, Drug, and Cosmetic Act]. At the time of this review, the two trials are ongoing and are recommended for designation as Post Marketing Requirements (PMR).

The reviewers also agree with FDA's clinical pharmacology PMR investigating gastrointestinal tolerability and the efficacy, and pharmacokinetics of 450 mg and 600 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. This PMR relates to the observations that administration of ceritinib with a meal may improve gastrointestinal toxicity; however, it can also increase exposure, which may in turn increase non-gastrointestinal toxicity.

Table 1. Confirmatory trials for ceritinib as discussed with the applicant

Study number and title	Description	No of patients as of October 31, 2013
A2303: 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	Phase 3 Ongoing, enrolling patients	14
A2301: 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	Phase 3, Ongoing, enrolling patients	8

2 Introduction and Regulatory Background

Lung cancer is the leading cause of cancer deaths in the United States with an estimated number of new cases of approximately 220,000 and 160,000 deaths in 2012.¹ About 85% of cases are non-small cell lung cancer (NSCLC), the majority of which present as advanced disease (stage IIIB or stage IV) at the time of diagnosis.¹ The median survival of patients with advanced unselected NSCLC with supportive care alone is about 3 to 6 months.² Standard first-line systemic treatment of unselected patients consists of platinum-based doublet chemotherapy with response rates of about 30% and a median survival of about 10 months.^{3, 4, 5}

Following progression on first-line treatment, available therapies for second-line treatment are associated with ORR of about 10% and small improvements in survival (Table 2).

In recent years, clinically relevant molecular subsets of NSCLC with “driver mutations” have been identified. Gene fusion of the Anaplastic Lymphoma Kinase (ALK) with upstream partners (most commonly EML4) is thought to represent an oncogenic event resulting in constitutive activation of the ALK kinase domain. ALK gene rearrangement is found in about 5% of patients with NSCLC⁶ and is thought to be mutually exclusive with EGFR and KRAS mutations⁷ and associated younger age, nonsmoking status, and adenocarcinoma histology.⁸

Crizotinib, an orally available small-molecule inhibitor of ALK and MET tyrosine kinases, received accelerated approval by FDA on August 26, 2011. The approval was based on the results of two single arm studies enrolling a total of 255 ALK-positive advanced NSCLC patients with overall response rates of 50 and 61%, corresponding to a median duration of response (DOR) of 42 and 48 weeks, respectively.⁹ Crizotinib received regular approval on November 20, 2013 based on a randomized trial (n=347) demonstrating superior progression-free survival (PFS) and ORR for crizotinib-treated patients compared to chemotherapy (pemetrexed or docetaxel) in patients with ALK-positive NSCLC with disease progression after platinum-based doublet chemotherapy. Efforts are underway to characterize mechanisms of acquired resistance to crizotinib, including identification of secondary resistance mutations.¹⁰

2.1 Product Information

International non-proprietary name (INN): Ceritinib

Chemical name(s):

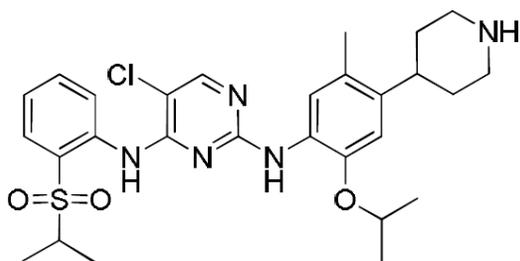
IUPAC

5-Chloro-2-N-{5-methyl-4-(piperidin-4-yl)-2-[(propan-2-yl)oxy]phenyl}-4-N-[2-(propane-2-sulfonyl)phenyl]pyrimidine-2,4-diamine

CAS

5-Chloro-N4-[2-[(1-methylethyl)sulfonyl]phenyl]-N2-[5-methyl-2-(1-methylethoxy)-4-(4-piperidinyl)phenyl]-2,4-pyrimidinediamine

Structural formula



Molecular formula

$C_{28}H_{36}ClN_5O_3S$

Relative molecular mass

558.14

Physical state

White to almost white or light yellow or light brown powder.

Dosage strength

150 mg

Hard gelatin capsule, size 00

Blue opaque (cap), white opaque (body) capsule, imprinted with “LDK 150MG” (cap) and “NVR” (body)



2.2 Tables of Currently Available Treatments for Proposed Indications

In the US, crizotinib is considered standard therapy for treatment of NSCLC patients whose tumors harbor ALK gene rearrangements. Further-line treatment involves standard platinum-

based doublet chemotherapy (if not previously administered as first-line treatment for metastatic disease) or standard single agent therapy as shown in Table 2.

Table 2. Available therapies for second-line treatment of non-small cell lung cancer

	Median PFS/TTP (months)	Median OS (months)	ORR % (95% CI)
Docetaxel (n=125) vs Vinorelbine/Ifosfamide (n=123)	TTP 2.0 (1.6, 2.7) vs 1.8 (1.5, 2.3)	5.7 (5.1, 7.1) vs 5.6 (4.4, 7.9); p = 0.13	5.7 (2.3, 11.3) vs 0.8 (0.0, 4.5)
Docetaxel (n=55) vs BSC (n=49)	TTP 2.8 (2.1, 4.2) vs 1.6 (1.4, 2.1)	7.5 (5.5, 12.8) vs 4.6 (3.7, 6.1); p = 0.01	5.5 (1.1, 15.1) vs N/A
Docetaxel in metastatic ALK+ NSCLC* (n=72)			5.9 (2.3, 15.5)
Pemetrexed (n=283) vs docetaxel (n=288) (non-inferiority) <i>Nonsquamous subset (N=399)</i>	PFS 2.9 (2.4-3.1) vs 2.9 (2.7-3.4) HR 0.97 (0.82-1.16)	8.3 (7.0-9.4) vs 7.9 (6.3-9.2) HR 0.99 (0.82-1.20) 9.3 (7.8-9.7) vs 8.0 (6.3-9.3) HR 0.89 (0.71-1.13)	8.5 (5.2-11.7) vs 8.3 (5.1-11.5)
Pemetrexed metastatic ALK+ NSCLC* (n=99)			29.3 (20.6, 39.3)
Erlotinib (n=438) vs placebo (n=451)	2.8 (2.8, 3.1) vs 2.6 (1.9, 2.7) HR 0.71 (0.62, 0.82) p < 0.0001	12.0 (10.6, 13.9) vs 11.0 (9.9, 12.1) HR 0.81 (0.70, 0.95) P = 0.0088	8.9 vs <1
*Versus crizotinib (n=172, ORR 65.7%) in a randomized trial against chemotherapy (docetaxel or pemetrexed). The results showed significant improvement in the primary endpoint of PFS with crizotinib.			
BSC, best supportive care; ORR, overall response rate; OS, overall survival; PFS, progression free survival; TTP, time to tumor progression			

2.3 Availability of Proposed Active Ingredient in the United States

Ceritinib is currently not marketed in the U.S.

2.4 Important Safety Issues With Consideration to Related Drugs

The current label for crizotinib, the only approved and available ALK-inhibitor in the US as of the time of this review, describe gastrointestinal disorders as the most common adverse events associated with the drug. Adverse events of special interest include hepatotoxicity (including fatal cases), pneumonitis (including fatal cases), QT prolongation, bradycardia (usually asymptomatic), and vision disorders including visual impairment, photopsia, vision blurred, vitreous floaters, photophobia, and diplopia. These events may represent a class effect of ALK tyrosine kinase inhibitors. It should be noted that crizotinib is also an inhibitor of c-MET and ROS1.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

On March 6, 2013, Breakthrough Therapy Designation was granted for ceritinib for the treatment of (b) (4) ALK-positive NSCLC patients who have progressed on or are intolerant to (b) (4) crizotinib (b) (4) based on early evidence of clinical activity as demonstrated by ORR of long duration and an acceptable safety profile.

On May 20, 2013, FDA issued Written Responses to Novartis in response to Novartis' February 22, 2013 meeting request to discuss the content and format of the NDA submission for ceritinib in the treatment of patients with (b) (4) NSCLC who have (b) (4) with crizotinib based on the results of X2101. FDA stated that the primary analysis in X2101 should be based on the full analysis set (FAS) consisting of all patients who receive at least one full or partial dose of ceritinib.

On November 22, 2013, a pre-NDA meeting was held with FDA to discuss the X2101 trial. FDA agreed to the content of the NDA as outlined in the Novartis' proposed eCTD table of contents and that data from X2101 and the supportive studies appear to be adequate to allow a substantive benefit-risk evaluation of ceritinib for the proposed indication of (b) (4) ALK-positive NSCLC patients who have progressed on crizotinib. FDA emphasized that the final indication will be assessed by examining the submitted data in a benefit-risk analysis at the time of review. FDA also reiterated its previous response from a July 18, 2013 meeting that the primary analysis should best be based on the FAS, consisting of all patients who receive at least one full or partial dose of ceritinib, not the efficacy analysis [sub]set (EAS), as proposed by Novartis. FDA stated that the EAS should be submitted as supportive evidence and that 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.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The overall organization, ease of finding information, responses to request additional information from the applicant (including final reports or datasets/data files/analyses), completeness of the submitted information were acceptable by the reviewers.

3.2 Compliance with Good Clinical Practices

The applicant stated that all studies were conducted in full compliance with current Good Clinical Practices and were closely monitored by Novartis personnel or a contract research organization for compliance to the protocol, Novartis SOPs and applicable regulatory guidance. On February 4, 2014, the applicant notified FDA that upon locking of the clinical database for study X2101 on January 24, 2014 for the Safety and Efficacy Update with the cut-off date of October 31, 2013, it was found that adverse event data (serious and non-serious) with onset on or prior to the NDA cut-off date of August 2, 2013 were not included in the original NDA database.

These were comprised of 8 SAEs and 112 AEs which were submitted to the Agency with the applicant's correspondence, along with an updated benefit-risk assessment maintaining a favorable profile. The applicant conducted a root cause assessment concluding that human error during the last cycle of reconciliation was largely responsible for the gap and stated plans for the following corrective actions:

1. The Novartis QC process was amended to require a re-check of the 5 latest SAEs entered into the Novartis global pharmacovigilance safety database in addition to the standard reconciliation of a random sample of 5% of all SAEs.
1. Updating the SAE Reconciliation Tracking template to make it easier to verify that 100% of SAEs have been accurately reconciled;
2. Requiring a secondary consistency check between the clinical and safety databases to ensure no events are missed in either database; and
3. Providing remedial training to all data managers, clinical monitors, and CROs on "lessons learned" and the process improvements being implemented to prevent recurrences.
4. Reinforcing the importance of on-going data entry and data collection with both sites and Field Monitors.

FDA's Office of Scientific Investigations (OSI) inspected select clinical investigator sites in addition to Novartis Pharmaceuticals Corporation and BIRC (CRO (b) (4)) for study X2101 and concluded that the data in support of the application appeared reliable based on the available information.

3.3 Financial Disclosures

Upon review of the applicant's Financial Disclosure Certification, it was noted that 5 out of the 127 financial disclosures were not collected. FDA issued an IR on January 22, 2014 for an amendment to the Financial Disclosure Certification confirming that the applicant acted with due diligence to obtain financial disclosure information but was unable to do so for all the investigators in Study X2101 and to state the reason(s) why 5 out of 127 financial disclosures were not collected. In their response, the applicant provided two additional financial disclosures from investigators not declaring any financial interests and provided adequate rationale on why the other 3 investigator disclosures could not be collected, confirming due diligence in the process.

Overall and taking into account the above amendment to the applicant's Financial Disclosure Certification, the applicant adequately disclosed financial arrangements with the clinical investigators as recommended in the guidance for industry Financial Disclosure by Clinical Investigators and the arrangements did not raise questions about the integrity of the data.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

No significant issues identified as of the time of this review.

4.3 Preclinical Pharmacology/Toxicology

No significant issues identified as of the time of this review.

4.4 Clinical Pharmacology

At the recommended dose of 750 mg once daily taken under the recommended fasted conditions, the majority of patients treated with ceritinib had gastrointestinal (GI) adverse reactions in X2101. Administration of ceritinib with food may theoretically improve GI tolerability, but would lead to exposure-related toxicities such as AST/ALT elevations, hyperglycemia, and QTc prolongation as the food effect study showed 73% increased exposures with a high-fat meal and 58% increased exposures with a low-fat meal as compared to a fasted state. This issue may warrant further investigation via a PMR to investigate the safety and efficacy of ceritinib administered in lower than recommended doses with a meal.

4.4.1 Mechanism of Action

Ceritinib is an orally available drug that based on the available information primarily inhibits ALK kinase. It also has activity against ROS1, INSR, and IGF1R.

4.4.2 Pharmacodynamics

(b) (4)

4.4.3 Pharmacokinetics

Absorption

- The absolute bioavailability of ceritinib was not determined in clinical studies, but was estimated to be about 40% to 60% in various preclinical species when administered as a solution or suspension under fasted conditions. The lower limit for the extent of ceritinib oral absorption is estimated to be approximately 25% in humans based on the percentage of metabolites recovered in feces.
- T_{max}
 - Median (range) for parent: 6 h (individual range: 4 to 24 h) at 750 mg after a single dose in patients; 6 h (individual range: 0 to 23 h) at 750 mg at steady-state (Cycle 2 Day 1) in patients.
 - Median (range) for metabolites: Not determined as metabolite levels were too low.

Distribution

- V_d/F or V_d
 - Geometric mean (%CV): V_d/F: 4230 L (164%) at 750 mg after a single dose in patients.
 - % bound: Mean (%CV): 97.2% (1.75%) bound to plasma protein.

Elimination

- Primary route: The primary route of elimination of ceritinib is via the feces (mean: 91% of an oral dose) with 68% being excreted as unchanged ceritinib and the remainder eliminated as metabolites. The applicant states that evidence from preclinical studies

suggests that hepatic metabolism and potentially biliary excretion and gastrointestinal secretion may all contribute to the fecal elimination of ceritinib.

- Other routes: Only 1.3% of the single administered oral dose is recovered in the urine.
- Terminal $t_{1/2}$
 - Geometric mean (%CV) for parent: 40.6 h (34.7%) at 750 mg after a single dose in patients.
 - Geometric mean (%CV) for metabolites: Not determined as metabolite levels were too low.
- CL/F or CL
 - Geometric mean (%CV): CL/F: 88.5 L/h (162.5%) at 750 mg after a single dose in patients; 33.2 L/h (37.1%) at 750 mg at steady state (Cycle 2 Day 1) in patients.

Intrinsic factors

- Age: The C_{max} and AUC_{tau} at steady state in patients ≥ 65 years were estimated to be 1.04- fold higher than in the reference population (age < 65 years).
- Sex: The C_{max} and AUC_{tau} at steady state in female patients were estimated to be 1.14- fold higher than in male patients.
- Race: The C_{max} and AUC at steady state in Asian patients were estimated to be 1.1-fold higher than in non-Asian patients.

Extrinsic factors

- CYP3A was identified as the major CYP isozyme responsible for the metabolism of ceritinib.
- Food effects: Compared to the fasted state, a low-fat meal increased C_{max} and AUC_{inf} following a single 500 mg oral dose of ceritinib in healthy subjects by 43% and 58%, respectively, whereas a high fat meal increased C_{max} and AUC_{inf} by 41% and 73% respectively (Study A2101).

5 Sources of Clinical Data

The primary source of clinical data for this NDA is the single arm clinical trial X2101, a first in human trial of ceritinib conducted in 304 adult patients with advanced tumors confirmed to have genetic abnormalities in ALK (ALK-positive). The trial enrolled both ALK inhibitor naïve patients and patients previously treated with an ALK inhibitor and was comprised of a dose-escalation phase to determine the maximum tolerated dose (MTD) and recommended dose (RD), and an expansion phase to better characterize the efficacy, safety and pharmacokinetics (PK) of ceritinib. Enrollment in this study was closed on July 31, 2013. The data cut-off dates for the present submission for this trial and all other ongoing trials of ceritinib are August 2, 2013 and October 31, 2013 (updated cut-off). The other trials in support of this application are shown in Section 5.1. The original protocol for X2101 was dated August 19, 2010 and was amended 6 times as shown in Table 4. The rationale for the amendments appears reasonable.

Table 4. Summary of protocol amendments to X2101

Amendment	Major changes
June 20, 2011	<ul style="list-style-type: none"> Specify that patients with NSCLC are only eligible if they have evidence of ALK translocation in $\geq 15\%$ of tumor cells, as assessed by FISH Failure to deliver $\geq 75\%$ of the planned doses in a treatment cycle due to ceritinib-related toxicity is considered a DLT. Clarify in Section that AEs occurring after cycle 1 may be considered in dose escalation decisions.
March 22, 2012	<ul style="list-style-type: none"> Expansion arm 1 was split into two arms: 1A and 1B, for the purposes of separating the ALK-refractory patients from the ALK non-refractory. Allowed for temporary interruption of ceritinib for local CNS therapy in patients who developed progressive disease in the CNS, but also experienced clinical benefit outside of the CNS. These patients could subsequently continue treatment with ceritinib on study. Clarified the exclusion of patients with CNS metastases, who are unstable or need intervention.
July 4, 2012	<ul style="list-style-type: none"> Increase the sample size of the expansion arms 1A, 1B, and 2 by an additional 75 patients in each. Reduced the required interval between the last dose of crizotinib and the first dose of ceritinib from 2 weeks to 1 week. Increased the number of allowed dose reductions from 2 to 3.
January 16, 2013	<ul style="list-style-type: none"> Facilitated collection of imaging data for independent review by an imaging CRO designated by Novartis. Allowed for continued treatment with ceritinib after disease progression has been documented outside of the CNS, when in the opinion of the investigator the patient was thought to derive clinical benefit from continued therapy.
April 10, 2013	<ul style="list-style-type: none"> Defined the analysis cutoff point for the primary clinical study report, to specify that the primary analyses of antitumor activity will be performed in patients with NSCLC who had previously received crizotinib and were treated with ceritinib at a dose of 750 mg qd. Provided additional details on the statistical analyses that will be performed for tumor response data both based on investigator assessment and an independent review of imaging.
August 29, 2013	<ul style="list-style-type: none"> Updated the available safety and efficacy information, adding guidance for treatment of patients who develop pneumonitis/interstitial lung disease that is considered related to ceritinib.

5.1 Tables of Studies/Clinical Trials

	Trial	Description	Primary endpoint	No of patients	ceritinib dose
Efficacy and safety	X2101(ongoing; enrollment complete)	Phase 1, multicenter, dose-escalation trial in patients with ALK positive tumors; prior ALK inhibitor therapy was allowed	Escalation phase: MTD Efficacy endpoint: ORR per RECIST 1.0	Escalation phase: 59 Expansion phase: 245 Total at 750 mg: 255*	Escalation phase: 50 to 750 mg Expansion phase: 750 mg
	X1101 (enrollment complete for dose-escalation, ongoing for expansion)	Phase 1, multi-center, dose-escalation trial in Japanese patients with ALK positive tumors; prior ALK inhibitor therapy was allowed	Escalation phase: MTD Efficacy endpoint: ORR per RECIST 1.1	Escalation phase: 19** Expansion phase: 0 Total at 750 mg: 6**	Escalation phase 300 to 750 mg Expansion phase: 750 mg

Safety	X2102 (enrolling patients, FPFV Jun-2013)	Phase Ib, open-label, dose-escalation trial of ceritinib and AUY922 in patients with ALK positive NSCLC previously treated with ALK inhibitor	Escalation phase: MTD	Escalation phase: 4 of 24	ceritinib 600 mg AUY922 40 mg/m2/week
	A2201 (enrolling patients, FPFV Nov-2012)	Phase 2, multi-center, single-arm trial in adult patients with ALK activated NSCLC previously treated with chemotherapy and crizotinib	ORR by per RECIST 1.1	107 of 137	750 mg
	A2203 (enrolling patients, FPFV Dec-2012)	Phase 2, multi-center, single-arm trial in crizotinib naïve adult patients with ALK-activated NSCLC	ORR per RECIST 1.1	26 of 105	750 mg
	A2303 (enrolling patients, FPFV Jun-2013)	Phase 3, multi-center, randomized, open-label study of ceritinib vs. standard second-line chemotherapy (pemetrexed or docetaxel) in patients previously treated with chemotherapy and crizotinib; patients had to have progressed on crizotinib.	PFS by BIRC per RECIST 1.1	2 of 236	750 mg
<p>As of August 2, 2013 ORR: Overall response rate; PFS: progression-free survival; BIRC: Blinded Independent Review Committee; FPFV: First Patient First Visit * 246 patients with NSCLC and 9 patients with another malignancy ** 18 patients with NSCLC (5 treated at 750 mg) and 1 patient with another malignancy (treated at 750 mg) The applicant states that following trials were open for enrollment but no patient was treated as of August 2, 2013:</p> <ul style="list-style-type: none"> • X2103, a Phase 1 dose-finding study of ceritinib in pediatric patients with ALK-positive malignancies • A2301, a Phase 3 multi-center, randomized, open-label study of ceritinib vs. chemotherapy (pemetrexed plus cisplatin) in previously untreated patients with advanced ALK-positive NSCLC • A2402, an open-label, multi-center, expanded treatment protocol of ceritinib in adult patients with ALK positive NSCLC previously treated with an ALK inhibitor 					

5.2 Review Strategy

The review strategy included close examination of the clinical study reports, supportive analyses, and the risk-benefit assessment submitted by the applicant. Important safety and efficacy datasets were re-analyzed by the clinical and/or statistical reviewer. Additional exploratory analyses were also conducted. The reliability of the data was assessed based on review of conflict of interest

reports, protocol deviations, and random cross-validation of datasets with CRF forms. Sensitivity and subgroup analyses were performed as necessary.

5.3 Discussion of Individual Studies/Clinical Trials

CLDK378X2101 (X2101)

This is a single arm trial to investigate the MTD and clinical activity of ceritinib in patients with ALK-positive malignancies. This trial is closed to enrollment with 304 patients and comprised of:

- a dose-escalation phase to determine the MTD/RD
- an expansion phase to further characterize efficacy, safety and PK in the following cohorts of patients treated at RD:
 - Arm 1A: Patients with ALK-positive NSCLC who had disease progression during treatment with an ALK inhibitor or within 2 weeks of the last dose of an ALK inhibitor and planned initiation of ceritinib within 60 days of the last dose of the prior ALK inhibitor.
 - Arm 1B: Patients with ALK-positive NSCLC who were previously treated with an ALK inhibitor and did not meet the criteria for Arm 1A.
 - Arm 2: Patients with ALK-positive NSCLC who were not previously treated with an ALK inhibitor.
 - Arm 3: Patients with tumors other than NSCLC with a genetic abnormality in ALK

Table 5. Objectives and endpoints of trial X2101

	Objective	Endpoint
Primary	To determine the MTD of ceritinib as a single agent when administered orally to adult patients with tumors characterized by genetic abnormalities in ALK	MTD: Incidence rate and category of Dose Limiting Toxicities (DLT) during the first cycle (including the PK run-in) of ceritinib treatment.
Secondary	To characterize the safety and tolerability of ceritinib, including both acute and chronic toxicities	Adverse drug reactions and serious adverse drug reactions, changes in hematology and blood chemistry values, assessments of physical examinations, vital signs and electrocardiograms.
	To characterize single and multiple-dose PK of ceritinib	Plasma concentration of ceritinib and PK parameters, including but not limited to AUC_{0-last} , $AUC_{0-\tau}$, C_{max} , T_{max} , the apparent elimination half-life [$T_{1/2}$], accumulation ratio (AR_{acc})
	To assess anti-tumor activity of ceritinib as a single agent when administered orally to adult patients with tumors characterized by genetic abnormalities in ALK at MTD by CT/MRI	Overall response (complete response (CR) or partial response (PR)) rate defined according to RECIST v1.0, duration of response (DOR), PFS using both local and central evaluations of tumor assessments
Exploratory	To identify mutations in the ALK gene or other molecular abnormalities in tumor samples associated with clinical progression after treatment with an ALK inhibitor	Mutations in the ALK gene and other molecular alterations in tumor samples, and relationship between these alterations and anti-tumor activity
	To assess overall survival (OS) in patients treated with ceritinib	Death

Abbreviations: AE, adverse event; ALK, anaplastic lymphoma kinase; AUC_{0-tlast}, area under the concentration-time curve (AUC) from time zero to the last measurable concentration sampling time; C_{max}, maximum concentration; CR, complete response; CT, computed tomography; DLT, dose-limiting toxicity; EORTC, European Organization for Research and Treatment of Cancer; MRI, magnetic resonance imaging; MTD, maximum tolerated dose; PFS, progression-free survival; PK, pharmacokinetic; PR, partial response; R_{acc}, accumulation ratio; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious adverse event; t_{1/2}, half-life; T_{max}, time to reach maximum plasma concentration.

To be eligible for X2101, patients' tumors had to harbor an ALK translocation in $\geq 15\%$ of cells, as measured by FISH. In patients with diseases other than NSCLC, identification of an ALK translocation was not required, and overexpression of ALK protein could be considered.

Key inclusion criteria as stated in the protocol

- Patients must be diagnosed with a locally advanced or metastatic malignancy that has progressed despite standard therapy, or for which no effective standard therapy exists. Only patients with tumors characterized by genetic abnormalities in ALK will be enrolled. For NSCLC an ALK translocation must be detected by FISH in $\geq 15\%$ of tumor cells. In patients with diseases other than NSCLC ALK translocation is not required, and overexpression of ALK protein may be considered indicative of a genetic abnormality in ALK.
- Measurable disease:
 - Escalation phase: Patients with measurable or non-measurable disease as determined by modified RECIST version 1.0
 - Expansion phase: Presence of at least one measurable lesion as determined by modified RECIST version 1.0
- Age ≥ 18 years
- Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2
- Life expectancy ≥ 12 weeks
- Organ function and laboratory results obtained within 14 days of enrollment:
 - Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9/L$
 - Hemoglobin (Hgb) ≥ 9 g/dL (≥ 90 g/L)
 - Platelets $\geq 100 \times 10^9/L$
 - Serum total bilirubin $\leq 1.5 \times$ upper limit of normal (ULN), except for patients with Gilbert's syndrome who may be included if total bilirubin $\leq 3.0 \times$ ULN and direct bilirubin $\leq 1.5 \times$ ULN
 - AST (SGOT) and ALT (SGPT) - $2.5 \times$ ULN, except for patients with tumor involvement of the liver who must have AST and ALT $\leq 5 \times$ ULN
 - Calculated creatinine clearance (CrCL) ≥ 50 mL/min (≥ 0.835 mL/s) (Cockcroft Gault formula)
 - Serum amylase \leq ULN (if amylase $>$ ULN but there is no evidence of pancreatic disease, the patient may be enrolled)
 - Serum lipase \leq ULN (if lipase $>$ ULN but there is no evidence of pancreatic disease, the patient may be enrolled)
 - Fasting plasma glucose ≤ 200 mg/dL (≤ 11.1 mmol/L)
- Prior treatment with an ALK inhibitor
 - Prior treatment with ceritinib is not permitted.

- Escalation phase: Patients previously treated with an ALK inhibitor, and patients not previously treated with an ALK inhibitor may be included.
- Expansion phase
 - Arm 1A: Patients must have NSCLC and disease progression during treatment or within 2 weeks of the last dose of a previous ALK inhibitor, and the first dose of ceritinib is expected to be ≤ 60 days since the last dose of the prior ALK inhibitor.
 - Arm 1B: Patients must have NSCLC that has progressed since prior therapy with an ALK inhibitor, but that need not have been the last prior therapy, and do not meet the criteria for Arm 1A.
 - Arm 2: Patients must have NSCLC that has not been previously treated with an ALK inhibitor.
 - Arm 3: Patients must have a malignancy other than NSCLC, and there is no requirement regarding prior therapy with an ALK inhibitor.
- If an archival tumor sample is available, there must be a plan in place to obtain it prior to completion of the first cycle of ceritinib therapy. If an archival tumor sample is not available the patient must agree to a biopsy prior to starting ceritinib therapy if it is feasible. For patients who were previously treated with an ALK inhibitor, the archival tumor sample or biopsy must have been obtained after disease progression following the ALK inhibitor, if available.

Key inclusion criteria as stated in the protocol

- Patients with symptomatic central nervous system (CNS) metastases who are neurologically unstable or require increasing doses of steroids to control their CNS disease. If a patient requires steroids for management of CNS symptoms, the steroid dose must have been stable for the two weeks preceding study entry. Patients with controlled CNS metastases or asymptomatic CNS metastases that do not require local antineoplastic therapy, such as radiotherapy or surgery, may participate in the trial.
- Patients with unresolved nausea, vomiting or diarrhea $>$ CTCAE grade 1
- Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of ceritinib (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection)
- History of pancreatitis or history of increased amylase or lipase that was due to pancreatic disease
- Acute or chronic liver disease. Evidence of active viral hepatitis, including Hepatitis A, B or C (testing for viral hepatitis not mandatory).
- Known diagnosis of human immunodeficiency virus (HIV) infection (HIV testing not mandatory)
- Patients with a prior or current history of a second malignancy (except adequately treated in situ carcinoma of the cervix or non-melanoma carcinoma of the skin, or any other curatively treated malignancy that has not been treated or recurred in the prior 3 years).
- Clinically significant cardiac disease or impaired cardiac function including congestive heart failure (New York Heart Association Class III or IV), arrhythmia or conduction abnormality requiring medication, or cardiomyopathy; or clinically uncontrolled

hypertension (systolic blood pressure >140 mmHg or diastolic blood pressure > 90 mmHg)

- Patients who have been treated with chemotherapy or biologic therapy or other investigational agent < 2 weeks prior to starting study drug for compounds with a half-life \leq 3 days, and < 4 weeks prior to starting study drug for compounds with a prolonged half-life. Patients whose immediate prior treatment was crizotinib may start treatment with ceritinib one week after the last dose of crizotinib.
- Patients receiving treatment with medications that are known to be strong inhibitors or inducers of CYP3A4/5 that cannot be discontinued at least a week prior to start of treatment with ceritinib and for the duration of the study.
- Patients receiving medications that are mainly metabolized by CYP3A4/5 and have low therapeutic index, that cannot be discontinued at least a week prior to start of treatment with ceritinib, and for the duration of the study
- CYP2C9: patients receiving warfarin and phenytoin that cannot be discontinued at least a week prior to start of treatment with ceritinib and for the duration of the study.
- Medications with a known risk of prolonging the QT interval or inducing Torsades de Pointes
- Patients receiving coumarin-type anticoagulants who cannot discontinue at least a week prior to start of treatment and for the duration of the study.
- Pregnant or nursing (lactating) women

In X2101, an adaptive Bayesian logistic regression model (BLRM) with 2 parameters, guided by the escalation with overdose control (EWOC) principle, was used to make dose recommendations and estimate the MTD/RDE during the escalation phase of the trial.

In the dose-escalation phase X2101, 59 patients were treated at dose levels of 50 to 750 mg. Eight dose-limiting toxicities (DLTs) at Cycle 1 were observed in 6 patients:

- At 400 mg: grade 3 hypophosphatemia in one patient, and grade 3 transaminase increase evolving from grade 2 ALT increased in one patient.
- At 600 mg: grade 3 diarrhea and grade 3 dehydration in one patient each
- At 750 mg: grade 3 diarrhea with grade 3 vomiting in one patient and intolerable grade 2 diarrhea in one patient

Based on the BLRM used to guide dose-escalation, the probability of overdose (>25% probability that the DLT rate \geq 33%) at Cycle 1 was 3.3% at the 750 mg dose level. However, during the dose-escalation discussion between the Investigators and Novartis, the applicant states that further dose-escalation was considered to be medically inappropriate due to the increasing frequency of persistent grade 1-2 nausea, vomiting and diarrhea, and occurrence of grade 3-4 ALT and AST increases with prolonged treatment. The applicant states that additional information for confirmation of the 750 mg dose as the appropriate recommended dose came from the incidence of DLTs in Cycle 1 in the first 10 patients treated at this dose in the expansion phase of the study where there were no first-cycle DLTs in these 10 patients. The applicant also states that they did not note any major differences in the frequency of AEs with the 750mg and the immediate lower doses (400-700 mg). Furthermore, based on the preliminary

efficacy data, the applicant states that although tumor responses were observed at doses of 400 mg and above, the response duration appeared to be shorter at lower doses and nonclinical data from ALK-positive NSCLC xenograft models indicated that ceritinib should be dosed at the MTD to maximize efficacy, in particular against crizotinib resistant tumor models.

X2101's protocol outlined the following key analysis sets:

- **The Full Analysis Set (FAS)** consisting of all patients who receive at least one full or partial dose of ceritinib. Patients will be classified according to the assigned treatment (dose-level and schedule planned).
- **The Efficacy Analysis Set (EAS)** as the primary data set used for the analysis of tumor response data (ORR, DOR, and PFS based on investigator assessments) and for the analysis of OS. This data set is a subset of the FAS and consists of patients who received the first dose of ceritinib at least 18 weeks prior to the analysis cutoff date.
- **The Central Efficacy Analysis Set (CEAS)** to be used for the analysis of tumor response data based on independent central review assessments. This data set is a subset of the EAS and consists of patients
 - who received the first dose of ceritinib at least 18 weeks prior to the analysis cutoff date, and
 - for whom EITHER the baseline scan and at least one post-baseline scan are available and can be evaluated by the Blinded Independent Review Committee (BIRC) OR no post baseline scan was performed in the study due to early death or discontinuation.
- **The Safety Set** consisting of all patients who receive at least one dose of study drug classified according to treatment received.

In the protocol for X2101, it was stated that the primary clinical study report (CSR) will be produced based on an analysis cutoff date defined to ensure that a minimum of 120 NSCLC patients in the 750 mg dose group (from dose escalation or dose expansion) who have received prior treatment with crizotinib, have received the first dose of ceritinib at least 18 weeks prior to the analysis cutoff date. The protocol stated that the primary evaluation of the anti-tumor activity of ceritinib will be based on investigator assessment of response (Overall Response Rate and Duration of Response) using the EAS for the population of ALK-translocated NSCLC patients who have previously received crizotinib and were assigned to the 750 mg dose of ceritinib. The protocol specified that the incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by primary system organ class, severity based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, type of adverse event, and relationship to the study drug by treatment group.

6 Review of Efficacy

Efficacy Summary

The efficacy of ceritinib in patients with ALK-positive metastatic NSCLC was established by demonstration of ORR of large magnitude and duration in a single arm trial (X2101) titled "A phase I, multicenter, open-label dose escalation study of ceritinib, administered orally in adult

patients with tumors characterized by genetic abnormalities in anaplastic lymphoma kinase (ALK).” The trial enrolled a total of 163 patients with metastatic ALK-positive NSCLC who had progressed on or were intolerant to crizotinib. All patients received ceritinib at a dose of 750 mg once daily. The primary endpoint was ORR according to RECIST 1.0 as evaluated by investigators and a Blinded Independent Central Review Committee (BIRC). Duration of response (DOR) was an additional outcome measure. The study population characteristics were: median age 52 years, age < 65 (87%), female (54%), White (66%), Asian (29%), never or former smoker (97%), ECOG PS 1 (64%), progression on previous crizotinib (91%), number of prior therapies >3 (35%), and adenocarcinoma histology (93%). Sites of extra-thoracic metastasis included brain (60%), liver (42%) and bone (42%). ALK-positivity was verified retrospectively by review of local test results for 99% of patients.

As of the data cut-off date of October 31, 2013, ORR was 55% (95% CI 47 to 62) and 44% (95% CI 36 to 52) per investigator and BIRC assessment, respectively. DOR was 7.4 and 7.1 months per investigator and BIRC assessment, respectively. In exploratory subgroup analyses of response by BIRC assessment, ORR was 64% (95% CI 49 to 77) in Asian patients and 36% (95% CI 27 to 46) in White patients. Median DOR was 6.9 and 7.1 months in Asian and White patients, respectively. Similar results were observed by investigator assessment.

6.1 Indication

The applicant’s proposed indication is as follows:

“[ZYKADIA] is a kinase inhibitor indicated for the treatment of patients with [REDACTED] (b) (4) metastatic non-small cell lung cancer (NSCLC) who have [REDACTED] (b) (4) [REDACTED]”

6.1.1 Methods

The primary efficacy endpoint was the overall response rate (ORR = complete response [CR]+ partial response [PR]) by investigator assessment per RECIST version 1.0. Response was also evaluated by BIRC. Exact 2-sided 95% confidence intervals were calculated for all proportion estimates.

Estimates of time-to-event endpoints were obtained using the Kaplan-Meier method. Duration of response and time to response were described using Kaplan-Meier method among patients with a confirmed objective response.

6.1.2 Demographics

Of the 304 patients enrolled in X2101, there were 255 patients treated at 750mg of ceritinib (246 patients with NSCLC and 9 non-NSCLC). Baseline demographics and disease characteristics for the NSCLC patients are shown in

Table 6 and

Table 7. The majority of the patients in X2101 were female, never or non-smoker, with adenocarcinoma history, findings that are consistent with existing data on the clinicopathologic characteristics of NSCLC patients with ALK positive tumors. The majority of patients previously treated with crizotinib had brain metastasis at baseline, which is consistent with the brain being a common primary site of relapse in patients with ALK-positive NSCLC treated with crizotinib.

Table 6. Baseline demographics in trial X2101

	Prior crizotinib (n=163)	Crizotinib naïve n=83	All patients n =246
Sex, n (%)			
Male	75 (46.0)	39 (47.0)	114 (46.3)
Female	88 (54.0)	44 (53.0)	132 (53.7)
Age (years)			
Mean (SD)	51.5 (11.6)	53.9 (12.0)	52.3 (11.8)
Median	52.0	55.0	53.0
Range	24.0, 80.0	22.0, 80.0	22.0, 80.0
Age in category, n (%)			
<65 years	141 (86.5)	66 (79.5)	207 (84.2)
≥65 years	22 (13.5)	17 (20.5)	39 (15.8)
Race, n (%)			
White	108 (66.3)	48 (57.8)	156 (63.4)
Black	4 (2.5)	0	4 (1.6)
Asian	47 (28.8)	35 (42.2)	82 (33.3)
Other	4 (2.4)	0	4 (1.6)
Region, n (%)			
North America	86 (52.8)	15 (18.1)	101 (41.1)
Europe	36 (22.1)	32 (38.6)	68 (27.6)
Asia Pacific	41 (25.2)	36 (43.4)	77 (31.3)
Smoking classification, n (%)			
Never smoked	109 (66.9)	44 (53.0)	153 (62.2)
Ex-smoker	49 (30.1)	38 (45.8)	87 (35.4)
Smoker	5 (3.1)	1 (1.2)	6 (2.4)
ECOG PS, n (%)			
0	38 (23.3)	25 (30.1)	63 (25.6)
1	104 (63.8)	51 (61.5)	155 (63.0)
>1	21 (12.9)	7 (8.4)	28 (11.4)
BMI (kg/m2)*			
Mean (SD)	25.1 (4.6)	23.6 (3.9)	24.6 (4.4)
Median	24.6	23.0	24.3
Range	16.6, 42.5	16.7, 41.8	16.6, 42.5
Body weight (kg)			
Mean (SD)	71.3 (16.0)	65.7 (14.1)	69.4 (15.6)
Median	70.0	61.8	68.0
Range	42.1, 123.5	43.0, 103.0	42.1, 123.5

*One patient in the prior crizotinib treated group had BMI value missing.
Source: Applicant's analysis. Verified by reviewers.

Table 7. Baseline disease characteristics in trial X2101

	Prior crizotinib (n=163)	Crizotinib naïve n=83	All patients n =246
Baseline disease burden (INV), cm			
N	163	83	246
Mean (SD)	9.2 (6.8)	8.7 (6.1)	9.0 (6.6)
Median	8.0	6.6	7.6
Range	1.0, 42.4	1.3, 25.1	1.0, 42.4
Baseline disease burden (IRC), cm			
N	146	74	220
Mean (SD)	9.8 (7.4)	10.7 (7.4)	10.1 (7.4)
Median	8.1	8.3	8.2
Range	1.3, 34.3	1.5, 34.2	1.3, 34.3
Number of metastasis sites at baseline, n (%)			
1	9 (5.5)	3 (3.6)	12 (4.9)
2	19 (11.7)	14 (16.9)	33 (13.4)
3	32 (19.6)	19 (22.9)	51 (20.7)
4	37 (22.7)	21 (25.3)	58 (23.6)
>4	64 (39.3)	25 (30.1)	89 (36.2)
Missing	2 (1.2)	1 (1.2)	3 (1.2)
Brain metastasis at screening, n (%)			
Yes	98 (60.1)	26 (31.3)	124 (50.4)
No	65 (39.9)	57 (68.7)	122 (49.6)
Number of prior regimens, n (%)			
0	0	16 (19.3)	16 (6.5)
1	26 (16.0)	38 (45.8)	64 (26.0)
2	45 (27.6)	16 (19.3)	61 (24.8)
3	35 (21.5)	7 (8.4)	42 (17.1)
>3	57 (34.9)	6 (7.2)	63 (25.6)
ALK positive by FISH, using Vysis probe and positivity definition $\geq 15\%$, n (%)			
Yes	128 (78.5)	52 (62.7)	180 (73.2)
No	35 (21.5)	29 (34.9)	64 (26.0)
PD on last ALK inhibitor treatment*, n (%)			
Yes	149 (91.4)		
No	14 (8.6)		

Time from last dose of prior ALK-inhibitor treatment to first dose of study drug (months), n (%)			
N	163		
Mean (SD)	2.0 (2.8)		
Median	0.8		
Range	0.1, 16.6		
Tumor histology/cytology – n(%)			
Adenocarcinoma	152 (93.3)	76 (91.6)	228 (92.7)
Squamous cell carcinoma	3 (1.8)	0	3 (1.2)
Adenosquamous cell carcinoma	2 (1.2)	1 (1.2)	3 (1.2)
Large cell carcinoma	2 (1.2)	0	2 (0.8)
Spindle cell	0	1 (1.2)	1 (0.4)
Other	2 (1.2)	5 (6.0)	7 (2.8)
Missing	2 (2.1)	0	2 (2.1)
*Disease progression during treatment with (or within 2 weeks of last dose of) last prior ALK inhibitor Source: Applicant’s analysis. Verified by reviewers.			

All 163 ALK-positive NSCLC patients at 750 mg treated with prior ALK inhibitors had received crizotinib. In addition, 5 of these patients were also treated with another investigational ALK inhibitor, CH5424802, as the last prior ALK inhibitor. For all 5 patients, their tumors had progressed during prior crizotinib therapy, and also during treatment with CH5424802.

6.1.3 Subject Disposition

A total of 304 patients with advanced ALK-positive tumors were enrolled in the dose-escalation (n=59) and expansion phases (n=245) of X2101. Among these were 290 patients with ALK-positive NSCLC; of these, 246 patients were treated at the RD of ceritinib 750mg PO QD (Table 8). There were a total of 54 screen failures (source: VISSF dataset) with a median patient age of 51 (24-79). Reasons for screen failures reported by the applicant were reviewed and appeared reasonable and included unresolved toxicity from previous therapy, poor performance status, and elevated LFTs.

ALK status was collected retrospectively in X2101 with least one report available for 244 of the 246 NSCLC patients treated at 750 mg. Of the 244 patients with available reports, ALK positivity was confirmed in 243 patients (99.6%): by FISH in 236 patients (96.7%), by RT-PCR in 5 patients (2.0%), by IHC in 1 patient (0.4%), and by other method in 1 patient (0.4%). 180 patients (73.8%) had an ALK positive test by FISH that used the Vysis probe and $\geq 15\%$ of positive cells as cut-off for positivity. The reviewer finds ALK status confirmation in X2101 acceptable noting that the proposed indication for ceritinib in this NDA is in the post-crizotinib setting and that crizotinib is currently only indicated in ALK-positive NSCLC patients.

At the time of the initial data cut-off August 2, 2013, treatment for 142 of the 246 patients (57.7%) was ongoing. The most frequent reasons for discontinuation of treatment were disease progression (26.8%) and AE (8.9%). Treatment continuation rate were lower for those who had

received prior ALK inhibitor (50.9%) than those who were ALK-inhibitor naïve (71.1%). Updated disposition based on data cut-off of October 31, 2013 is shown in Table 8.

Table 8. NSCLC patient disposition in X2101 as of October 31, 2013

Source: SCE-Update Table 2-3	Prior crizotinib, n=163 n (%)	Crizotinib naïve, n=83 n (%)	All patients, n =246
Treatment discontinued	89 (54.6)	29 (34.9)	118 (48.0)
Disease progression	59 (36.2)	18 (21.7)	77 (31.3)
Adverse events	17 (10.4)	7 (8.4)	24 (9.8)
Consent withdrawal	10 (6.1)	1 (1.2)	11 (4.5)
Death	3 (1.8)	3 (3.6)	6 (2.4)
Treatment ongoing	74 (45.4)	54 (65.1)	128 (52.0)

6.1.4 Analysis of Primary Endpoint(s)

The reviewers based the primary assessment of efficacy on the FAS dataset (Table 9) and patients previously treated with crizotinib (n=163). Results showed ORR of large magnitude (54.6%) and long duration (median DOR 7.4 months) based on investigators' assessment. Median time to response (in weeks) based on investigator's assessment was: 6.1 (4.6, 24.1) for patients with prior crizotinib, 6.1 (3.0, 24.1) for crizotinib-naïve patients and 6.1 (3.0, 24.1) for all NSCLC patients treated at the recommended dose.

Table 9. Response rate and duration of response, NSCLC patients in X2101 (FAS; cutoff: October 31, 2013)

	Prior crizotinib n=163	Crizotinib naïve n=83	All patients n=246
Per INV-Assessment			
ORR, n (%)	89 (54.6)	55 (66.3)	144 (58.5)
95% CI	(46.6, 62.4)	(55.1, 76.3)	(52.1, 64.8)
Complete Response, n (%)	2 (1.2)	1 (1.2)	3 (1.2)
Partial Response, n (%)	87 (53.4)	54 (65.1)	141 (57.3)
Stable Disease, n (%)	32 (19.6)	19 (22.9)	51 (20.7)
Progressive Disease, n (%)	16 (9.8)	0	16 (6.5)
Unknown, n (%)	26 (16.0)	9 (10.8)	35 (14.2)
Duration of Response			
Median (95% CI), in months	7.4 (5.4, 10.1)	NE (9.6, NE)	9.7 (7.0, 11.4)
Per BIRC-Assessment			
ORR, n (%)	71 (43.6)	50 (60.2)	121 (49.2)
95% CI	(35.8, 51.5)	(48.9, 70.8)	(42.8, 55.6)
Complete Response, n (%)	4 (2.5)	1 (1.2)	5 (2.0)
Partial Response, n (%)	67 (41.1)	49 (59.0)	116 (47.2)
Stable Disease, n (%)	41 (25.2)	20 (24.1)	61 (24.8)
Progressive Disease, n (%)	20 (12.3)	5 (6.0)	25 (10.2)
Unknown, n (%)	31 (19.0)	8 (9.6)	39 (15.9)
Duration of Response			
Median (95% CI), in months	7.1 (5.6, NE)	NE	NE (7.1, NE)
Source: Reviewer analysis			

Assessment of ORR and DOR by BIRC was slightly lower, but still clinically meaningful. ORR was 43.6% (35.8, 51.5) with median duration of response of 7.1 months (Table 9). Table 10 shows response assessments by investigator and BIRC in EAS and CEAS. Response assessments of 10 patients were not included in CEAS. As BIRC review was introduced via an amendment based on FDA’s recommendations, two patients did not provide consent for transfer to BIRC and did not have their scans reviewed. Furthermore, 8 patients received the first dose of ceritinib <18 weeks prior to the analysis cut-off date and did not meet the inclusion criteria for CEAS. Response assessment of the 10 patients not in CEAS is as follows (PR, 2 patients; SD 4 patients; unknown, 4 patients).

Discordance between investigator and BIRC assessment was 20.5% and 22.9% for all NSCLC patients and those with prior crizotinib treatment, respectively. This degree of discordance is acceptable to the reviewers. In X2101, most of the discordance (16.3%) in the cohort previously treated with crizotinib was in cases where the BIRC review indicated “non-responder” versus investigators’ assessment of “responder,” which may indicate a slight investigator bias in response assessment.

Table 10. Response rate and duration of response, NSCLC patients in X2101 (EAS, CEAS; cutoff: October 31, 2013)

	Prior crizotinib	Crizotinib naïve	All patients
Per INV-Assessment, in EAS-NSCLC 750 mg			
Number of patients, n	155	77	232
ORR, n (%)	85 (54.8)	53 (68.8)	138 (59.5)
95% CI	(46.7, 62.8)	(57.3, 78.9)	(52.9, 65.9)
Complete Response, n (%)	2 (1.3)	1 (1.3)	3 (1.3)
Partial Response, n (%)	83 (53.5)	52 (67.5)	135 (58.2)
Stable Disease, n (%)	29 (18.7)	15 (19.5)	44 (19.0)
Progressive Disease, n (%)	16 (10.3)	0	16 (6.9)
Unknown, n (%)	25 (16.1)	9 (11.7)	34 (14.7)
Duration of Response			
Median (95% CI), in months	7.4 (5.4, 10.1)	NE (9.6, NE)	9.7 (7.0, 11.4)
Per BIRC-Assessment, in CEAS-NSCLC 750 mg			
Number of patients, n	153	77	230
ORR, n (%)	69 (45.1)	47 (61.0)	116 (50.4)
95% CI	(37.1, 53.3)	(49.3, 72.0)	(43.8, 57.1)
Complete Response, n (%)	4 (2.6)	1 (1.3)	5 (2.2)
Partial Response, n (%)	65 (42.5)	46 (59.7)	111 (48.3)
Stable Disease, n (%)	37 (24.2)	17 (22.1)	54 (23.5)
Progressive Disease, n (%)	20 (13.1)	5 (6.5)	25 (10.9)
Unknown, n (%)	27 (17.7)	8 (10.4)	35 (15.2)
Duration of Response			
Median (95% CI), in months	7.1 (5.6, NE)	NE	NE (7.1, NE)
Source: SCE Update tables 2-8 and 2-12			

Table 11. Discordance between investigator and BIRC-assessed ORR, in CEAS (cutoff: October 31, 2013)

	Prior crizotinib n=163	Crizotinib naïve n=83	All patients n =246
Number of patients, n	153	77	230
Overall discordance rate of overall response status, n (%)	35 (22.9)	12 (15.6)	47 (20.5)
BIRC-responder vs. INV-non-responder, n (%)	10 (6.5)	3 (3.9)	13 (5.7)
BIRC-non-responder vs. INV-responder, n (%)	25 (16.3)	9 (11.7)	34 (14.8)
Source: SCE Update table 2-16			

Study X2101 allowed for administration of ceritinib post-RECIST disease progression if the patient, in the opinion of the investigator, were to derive clinical benefit. Per investigator assessment of disease progression, 67/163 (41.1%) of prior crizotinib, 19/83 (22.9%) of crizotinib-naïve, and 86/246 (35.0%) of all NSCLC patients treated at the recommended dose received ceritinib post-RECIST progression for a median (in days) of 29, 23, and 28 days, respectively (Table 12).

Table 12. Treatment of patients post-RECIST disease progression in X2101 [reviewer analysis]

	Prior crizotinib (n=163)	Crizotinib naïve (n=83)	All patients (n=246)
Per BIRC-assessment			
Receiving ceritinib post disease progression	64	17	81
Time of treatment post PD Median (range), in days	49 (1, 402)	81 (2, 374)	49 (1, 402)
Per INV assessment			
Receiving ceritinib post disease progression	67	19	86
Time of treatment post PD Median (range), in days	29 (1, 366)	23 (1, 219)	28 (1, 366)

6.1.5 Analysis of Secondary Endpoints(s)

In X2101, OS and PFS were evaluated as secondary endpoints and the results are shown in Table 13. Considering that time-to-event endpoints are difficult to interpret in single arm trials, implications of OS and PFS in trial X2101 are not clear and no conclusions can be made based on the results.

Table 13. Progression-free survival (PFS) and overall survival (OS) in X2101

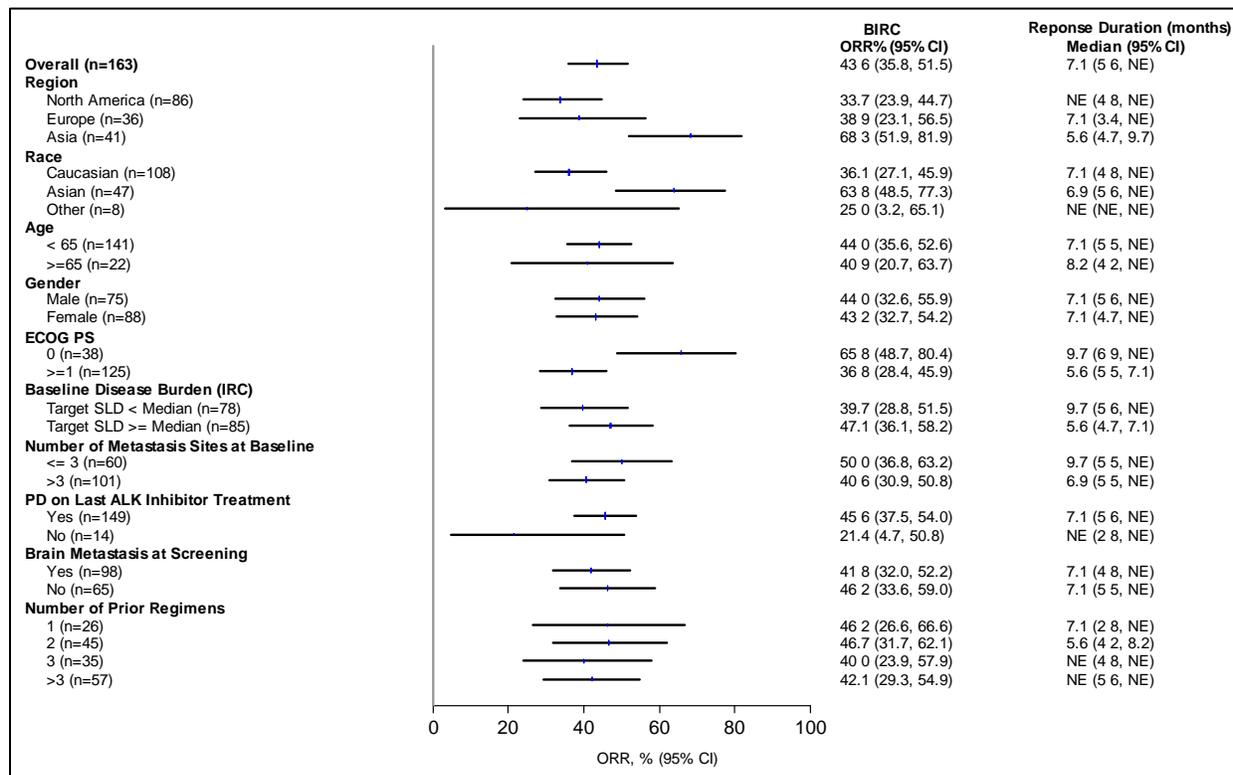
	Prior crizotinib n=163	Crizotinib naïve n=83	All patients n =246
Progression-Free Survival, IRC			
Number of events, n(%)	84 (51.5)	22 (26.5)	106 (43.1)
Median (95% CI), months	6.74 (5.52, 7.69)	NE (13.73, NE)	8.21 (6.93, 9.76)
Progression-Free Survival, INV			
Number of events, n(%)	89 (54.6)	26 (31.3)	115 (46.8)
Median (95% CI), months	6.90 (5.39, 8.41)	NE (8.31, NE)	8.21 (6.70, 10.12)
Overall Survival			
Number of deaths, n (%)	44 (27.0)	11 (13.3)	55 (22.4)
Median (95% CI), months	NE (14.75, NE)	NE	NE
Source: Reviewer analysis			

6.1.7 Subpopulations

Exploratory analyses of ORR were conducted in clinically relevant subgroups in X2101 per BIRC assessment in patients who had received prior crizotinib therapy (Figure 1). Overall, higher point estimates for ORR with non-overlapping confidence intervals were seen in Asian versus White and ECOG PS 0 versus ECOG PS ≥ 1 patients. Factors contributing to the higher ORR in the Asian patients in X2101 are not entirely clear but may be partly related to the higher exposure seen in these patients (see 7.5.3 Drug-Demographic Interactions). The role of ECOG PS in NSCLC has been previously illustrated with reports showing that patients with lower scores may have better prognosis and response to therapy.

In X2101, there were 14 patients with brain metastasis that were considered to be target lesions by the investigators. Among these patients, 1 patient had a confirmed CR and 6 patients had confirmed PRs in the brain. In X2101, there were a total of 131 NSCLC patients with PD in the study, including 100 NSCLC patients in the 750 mg dose group. Of the 100 NSCLC patients in the 750 mg dose group who had a PD, CNS was a site of progression at the time of the first PD in 32 of the 77 (42%) patients who had prior crizotinib therapy and in 5 of the 23 (22%) crizotinib-naïve patients. In 26 of the 77 (34%) patients who had prior crizotinib therapy, CNS was the only site of disease progression. Therefore, the CNS appeared a relatively common primary site of disease progression, especially in patients previously treated with crizotinib. The available data at this time is limited and does not allow an adequate assessment of the activity of ceritinib in the CNS.

Figure 1. Subgroup analyses of ORR per BIRC assessment in patients who received prior crizotinib in X2101 [reviewer analysis]



6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Analyses exploring dose- and exposure-response relationships in X2101 were conducted. These analyses were exploratory and conducted to generate hypotheses. No conclusions were drawn as a result of these analyses. Exposure analyses were based on average trough concentrations.

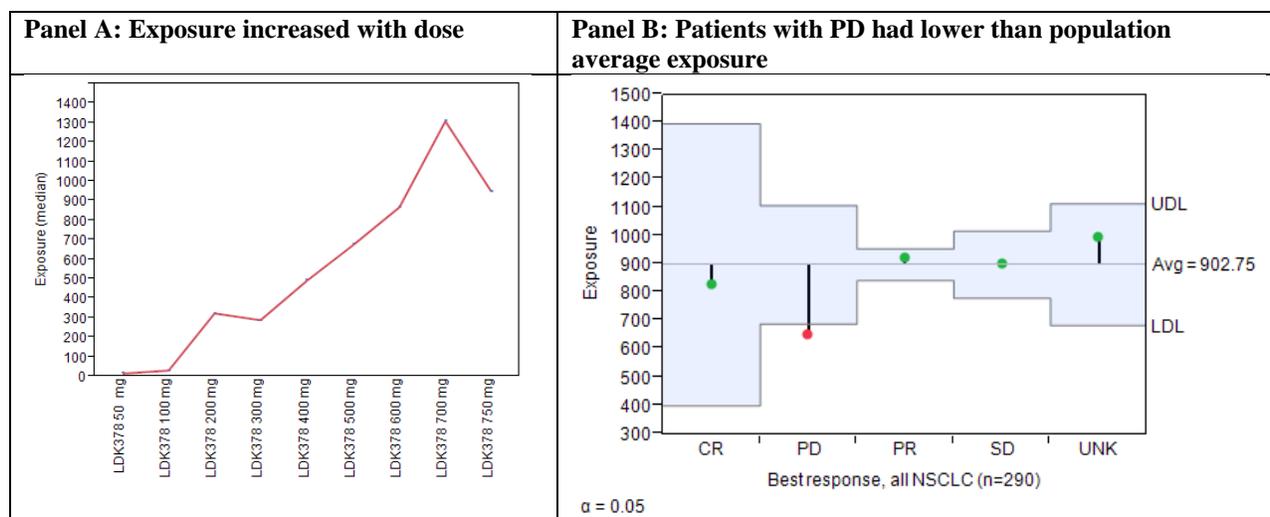
In X2101, the majority of patients the NSCLC patients were treated at the recommended dose of 750mg daily (n=246), making comparisons with the lower doses (n=44) difficult. Although the point estimates for ORR were slightly higher in patients treated at 750 mg versus <750mg, the confidence intervals were overlapping and the results can be considered to be similar in both groups (Table 14).

In X2101, there was an increase in exposure (as measured by average trough concentrations of ceritinib) with every dose level increase in ceritinib (Figure 2, panel A). Patients with PD as best response had exposures that were significantly lower than the population average (Figure 2, panel B). It should be noted that factors other than dose were shown to increase exposure (e.g., Asian race and food intake, see clinical pharmacology review). The exposure threshold to attain maximal probability of response is not clear.

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

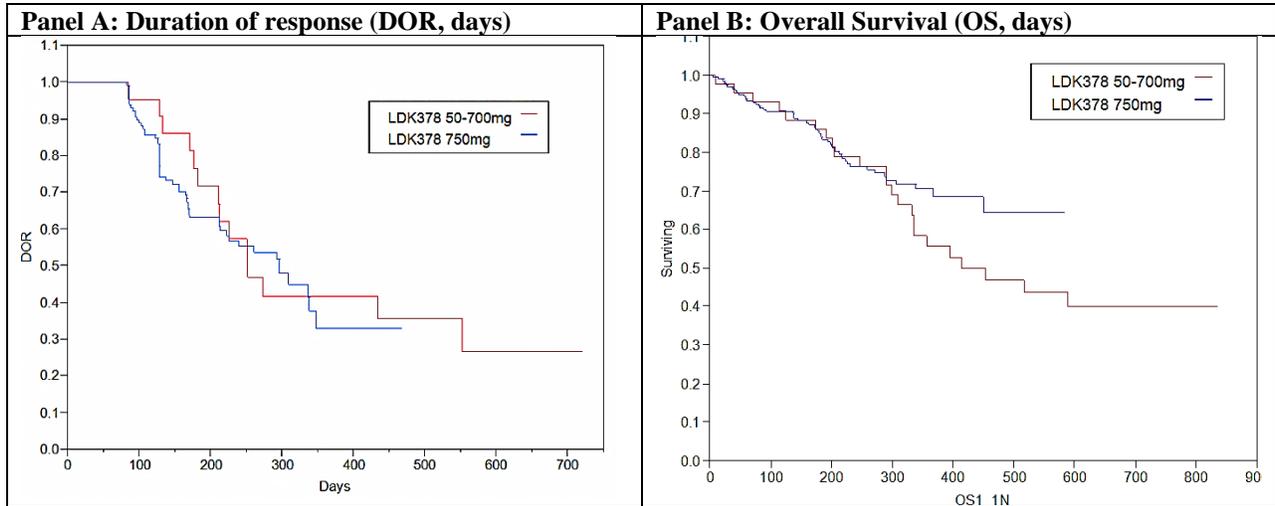
	Ceritinib 750mg (n=246)	Ceritinib <750mg (n=44)
Investigator assessment		
ORR, n (%)	144 (58.5%)	22 (50.0%)
(95% CI)	(52.1%, 64.8%)	(34.6%, 65.4%)
Duration of response		
Median (95% CI), in months	9.7 (7.0, 11.4)	8.2 (5.9, 18.1)
BIRC assessment		
ORR, n (%)	121 (49.2%)	17 (38.6%)
(95% CI)	(42.8%, 55.6%)	(24.4%, 54.5%)
Duration of response		
Median (95% CI), in months	NE (7.1, NE)	8.3 (7.0, 18.6)

Figure 2. Dose, exposure, and response in X2101 [reviewer analysis]



Whereas exposure increased with dose and patients with PD showed the lowest exposure average in X2101, DOR and OS were comparable in patients treated at 750mg versus <750mg (Figure 3). It should be noted that the OS curves started to separate around day 300 (Figure 3, panel B) and the median OS in the 750 mg has not yet been reached, however, due to the small number of patients, and the fact that this is not a randomized comparison, no conclusions can be made regarding improvements in OS as a function of dose (750mg versus <750mg).

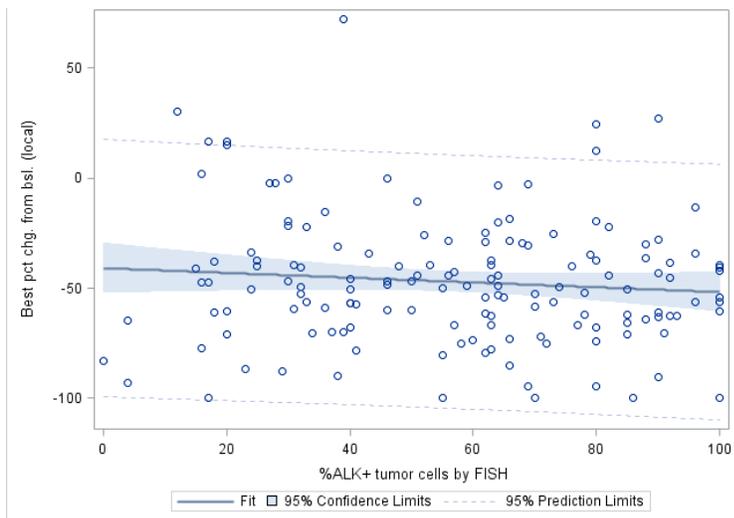
Figure 3. DOR (investigator assessment) and OS in 750mg versus lower doses in X2101 [reviewer analysis]



6.1.10 Additional Efficacy Issues/Analyses

Reviewers found no correlation between percent ALK-positivity by FISH and best response in X2101. In an exploratory analysis of percent change at the time of best response (excluding patients whose best response was unknown), a total of 149 patients with percent ALK-positivity reported on their FISH test and percent best change from baseline tumor measurement from the FAS-NSCLC 750 mg daily cohort were identified (data cut-off October 31, 2013). There was no correlation between the percent change at the time of best response and degree of ALK positivity (Figure 4)

Figure 4. Correlation between percent ALK positivity by FISH and response in X2101 [review analysis]



7 Review of Safety

Safety Summary

The safety evaluation primarily focused on the single arm study X2101, in which 304 patients were evaluable for safety. Several supportive studies were also considered in the safety evaluation. In study X2101, 255 ALK-positive patients (246 patients with NSCLC and 9 patients with other cancers) received ceritinib at a dose of 750 mg daily. The median duration of exposure was 6 months. The study population characteristics were: median age 53 years, age <65 (84%), female (53%), White (63%), Asian (34%), NSCLC adenocarcinoma histology (90%), never or former smoker (97%), ECOG PS 1 (63%), brain metastasis (49%), and number of prior therapies 2 or more (67%).

The most common adverse events (>10%) 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 majority of the gastrointestinal adverse events were grade 1-2.

The most common laboratory abnormalities (>10%) were increased ALT (80%), increased AST (75%), increased creatinine (58%), increased glucose (51%), increased lipase (29%), and increased bilirubin (16%). Grade 3-4 laboratory increases in ALT and AST occurred in 27% and 13%, respectively. Grade 3-4 increased glucose occurred in 13% and the risk was greater in patients on corticosteroids and those with diabetes at baseline. The most common serious adverse events (SAEs) in study X2101 included convulsion (4%), pneumonitis (4%) and hyperglycemia (2%).

Adverse events of interest likely to be a class effect of ALK inhibitors included QT prolongation, bradycardia, visual disturbance, pneumonitis, and hepatotoxicity. Adverse events of interest unique to ceritinib included amylase and lipase elevations and hyperglycemia. There was one case of acute pancreatitis in an ongoing supportive study, where the datasets were not submitted to the NDA.

Dose reductions due to adverse events occurred in 59% of patients in X2101 with discontinuation of ceritinib due to adverse events occurring in 10%. Adverse events leading to dose reductions or interruptions included increased ALT (29%), nausea (20%), increased AST (16%), diarrhea (16%), and vomiting (16%). Frequent adverse events that led to discontinuation included pneumonia, pneumonitis, and decreased appetite.

Fatal adverse events in patients treated with ceritinib occurred in 5% of patient comprised of pneumonia (4 patients), respiratory failure, pneumonitis, pneumothorax, gastric hemorrhage, general physical health deterioration, pulmonary tuberculosis, cardiac tamponade, and sepsis (one patient each).

The tolerability of ceritinib at the recommended dose of 750 mg daily was limited primarily due to hepatic and GI toxicity; however, the overall safety profile is favorable in light of the observed

treatment effect in the proposed population. Exploration of a lower dose with food in the post-marketing setting is recommended.

7.1 Methods

7.1.1 Clinical Trials Used to Evaluate Safety

Table 15. Clinical trials used to evaluate safety

Study number and title	Description	No of patients as of October 31, 2013	Comments
X2101: A phase I, multicenter, open-label dose escalation study of ceritinib, administered orally in adult patients with tumors characterized by genetic abnormalities in ALK	Phase 1 Ongoing, enrollment closed	Total = 304 50-700 mg/day (N=49) 750 mg/day (N=255)	Primary assessment of safety data
X1101: A phase I, multicenter, open label dose escalation study of ceritinib, administered orally in Japanese patients with tumors characterized by genetic alterations in ALK	Phase 1 Ongoing Enrolling patients in expansion phase of the study only	Total =19 300-600 mg/day (N=13) 750 mg/day (dose escalation) (N=6)	Supportive analyses
A2201: A phase II, multicenter, single-arm study of oral ceritinib in adult patients with ALK-activated NSCLC previously treated with chemotherapy and crizotinib	Phase 2 Ongoing, enrollment closed	140	SAE and death listings, narratives from the Novartis global pharmacovigilance safety database, AEs leading to study drug discontinuation and AEs requiring dose adjustment or study drug interruption
A2203: A phase II, multicenter, single-arm study of oral ceritinib in crizotinib naïve adult patients with ALK-activated NSCLC	Phase 2 Ongoing, enrolling patients	82	
A2303: 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	Phase 3 Ongoing, enrolling patients	14	SAE and death listings, and narratives from the Novartis global pharmacovigilance safety database
X2102: A Phase Ib, open-label, dose escalation study of ceritinib and AUY922 in patients with ALK rearranged NSCLC	Phase 1b Ongoing, enrolling patients	6	
A2301: 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	Phase 3, Ongoing, enrolling patients	8	

cancer			
A2402: An open-label, multi-center, Expanded Treatment Protocol (ETP) of oral ceritinib in adult patients with non-small cell lung cancer (NSCLC) characterized by ALK(+) rearrangements in patients previously treated with an ALK inhibitor	Expanded Treatment Protocol Ongoing, enrolling patients	4	
X2103: A Phase I, open-label, dose escalation study of ceritinib in pediatric patients with malignancies that have a genetic alteration in anaplastic lymphoma kinase (ALK)	Phase 1 Ongoing, enrolling patients	5	

7.1.2 Categorization of Adverse Events

Medical history and current medical conditions and adverse events were coded using the Medical dictionary for regulatory activities (MedDRA) terminology version 16.0. The PT terms and the corresponding verbatim terms included in the datasets were reviewed to check for accuracy of MedDRA coding for a random selection of about 20% of the events. Comparison of the Applicant’s MedDRA PTs to the verbatim terms did not show major discrepancies. The review focused on coding accuracy including “splitting” (coded terms too narrow) or “lumping” (coded terms too broad) and whether the intensity of the adverse events were coded appropriately.

Adverse events severity and laboratory value abnormalities were graded using on the National Cancer Institute’s Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

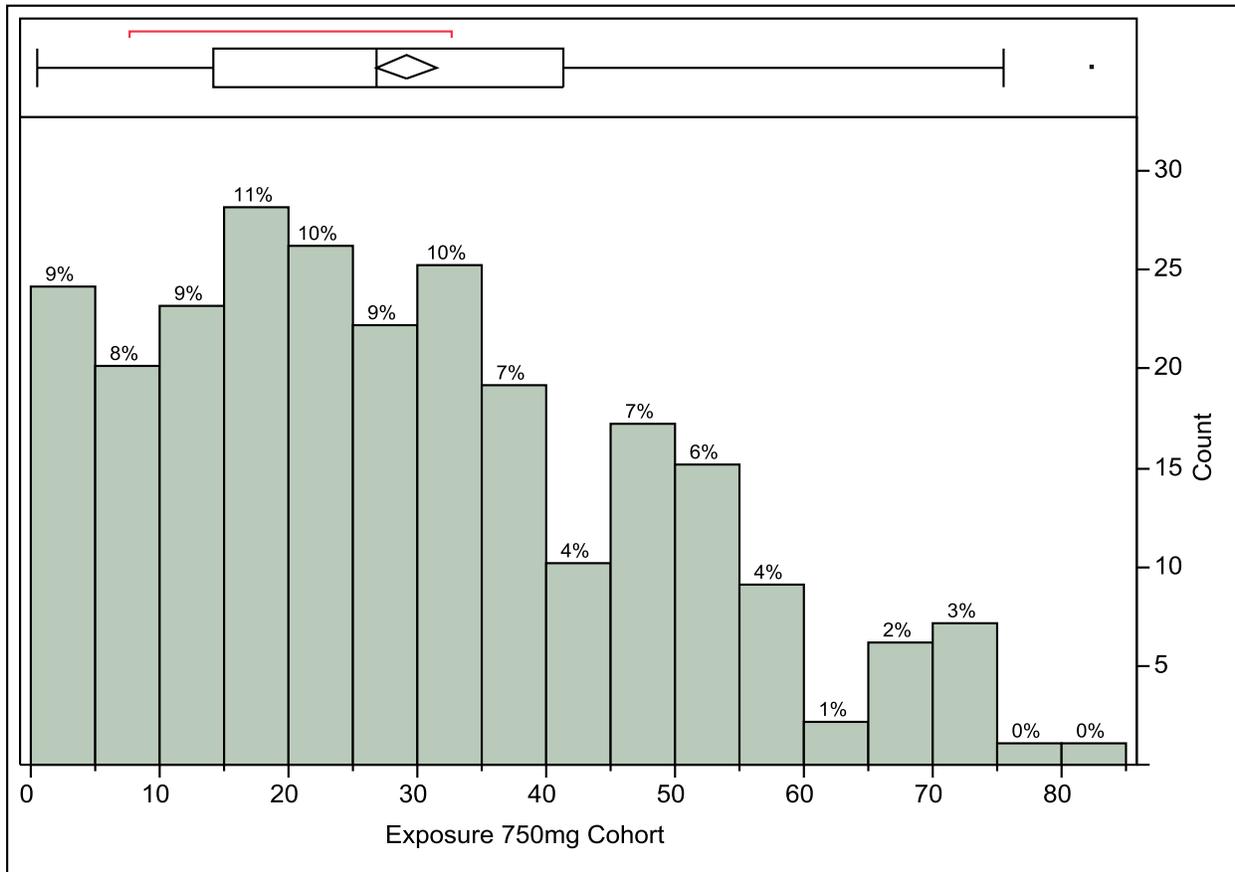
No safety data was pulled. Refer to Table 15 for a list of primary and supportive safety studies.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

In study X2101, the median duration of exposure to ceritinib as of October 31, 2013 in all 304 patients was 27.3 weeks (range 0.4 to 119.0 weeks, Figure 5). For the 255 patients treated at the recommended dose of 750 mg, the median duration of exposure was 26.9 weeks (range 0.4 to 82.3 weeks). The median duration of exposure was 3.7 months (range 0.1 to 10.0 months) in Study A2201, and 2.3 months (range 0 to 9.3 months) in Study A2203.

Figure 5. Patient exposure in study X2101as of October 31, 2013, patients treated at 750mg, n=255 [reviewer analysis, dataset ADRGEXP]



The applicant calculated the median relative dose intensity (RDI) across all ceritinib doses as 87.2% (range 30.2% to 121.1%), with 75.7% of all patients having an RDI \geq 75%. The median RDI at 750 mg was 84.8% (range 30.2% to 100.0%).

Baseline patients characteristics in the different dose cohorts in study X2101 is shown in Table 16.

Overall, a reasonable number of subjects were exposed to the drug for an adequate duration to allow for assessment of safety in the proposed patient population. The majority of the patients were treated at the recommended dose of 750 mg. Given that most patients were White and Asian, extrapolation of the safety findings to other race groups may be limited.

Table 16. Baseline patient characteristics per dose cohort in study X2101, as of October 31, 2013

	ceritinib 50-300 mg	ceritinib 400-700 mg	ceritinib 750 mg	All patients^[1]
Demographic variable	N=10	N=39	N=255	N=304
Age (years)				
n	10	39	255	304
Mean (SD)	49.1 (14.95)	52.8 (14.06)	51.9 (12.08)	52.0 (12.41)
Median	51.0	53.0	53.0	53.0
Min-Max	22.0 - 66.0	22.0 - 78.0	22.0 - 80.0	22.0 - 80.0
Age category (years) – n				
< 65	9 (90.0)	31 (79.5)	215 (84.3)	255 (83.9)
≥ 65	1 (10.0)	8 (20.5)	40 (15.7)	49 (16.1)
Sex – n (%)				
Male	3 (30.0)	12 (30.8)	119 (46.7)	134 (44.1)
Female	7 (70.0)	27 (69.2)	136 (53.3)	170 (55.9)
Race – n (%)				
White	8 (80.0)	31 (79.5)	160 (62.7)	199 (65.5)
Black	0	0	4 (1.6)	4 (1.3)
Asian	1 (10.0)	7 (17.9)	87 (34.1)	95 (31.3)
Native American	0	0	1 (0.4)	1 (0.3)
Pacific Islander	1 (10.0)	0	0	1 (0.3)
Other	0	1 (2.6)	3 (1.2)	4 (1.3)
Ethnicity – n (%)				
Hispanic/Latino	1 (10.0)	5 (12.8)	26 (10.2)	32 (10.5)
Chinese	0	2 (5.1)	17 (6.7)	19 (6.3)
Indian (Indian)	0	0	6 (2.4)	6 (2.0)
Mixed ethnicity	0	2 (5.1)	1 (0.4)	3 (1.0)
Other	9 (90.0)	30 (76.9)	205 (80.4)	244 (80.3)
BMI (kg/m²)				
n	10	38	254	302
Mean (SD)	22.6 (5.16)	24.3 (4.82)	24.5 (4.40)	24.4 (4.48)
Median	23.2	23.3	24.2	24.2
Min-Max	16.7 - 33.0	17.5 - 36.5	14.7 - 42.5	14.7 - 42.5
ECOG performance status – n (%)				
1	3 (30.0)	8 (20.5)	65 (25.5)	76 (25.0)
2	7 (70.0)	25 (64.1)	161 (63.1)	193 (63.5)
> 2	0	6 (15.4)	28 (11.0)	34 (11.2)
Smoking history – n (%)				
Ex-smoker	0	0	1 (0.4)	1 (0.3)
Current smoker	6 (60.0)	27 (69.2)	159 (62.4)	192 (63.2)
Ex-smoker	4 (40.0)	12 (30.8)	88 (34.5)	104 (34.2)
Current smoker	0	0	8 (3.1)	8 (2.6)

This table presents data for all patients (NSCLC and non-NSCLC) who received at least one dose of ceritinib (FAS).
[1] All patients include 14 non-NSCLC patients (50-300 mg: 2 patients, 400-700 mg: 3 patients, and 750 mg: 9 patients).

Source: X2101-Table 14.1-3.1a and X2101 Table 11-2

7.2.3 Special Animal and/or In Vitro Testing

Target organs in nonclinical animal models included the pancreas, biliopancreatic/bile ducts, gastrointestinal tract, and liver. Pancreatic atrophy was observed in monkeys and rats at 15% and 1.5-fold, respectively, of the human exposure by AUC at the recommended dose. Biliopancreatic duct and bile duct necrosis was observed in rats at exposures equal to or greater than 5% of the human exposure by AUC at the recommended dose. Bile duct hemorrhage and inflammation was also noted in monkeys at exposures equal to or greater than 50% of the human exposure by AUC at the recommended dose. Necrosis and hemorrhage of the duodenum was exhibited in monkeys at 50% of the human exposure by AUC, and in rats at an exposure similar to that observed clinically.

7.2.4 Routine Clinical Testing

Safety assessments in study X2101 consisted of monitoring and recording all AEs, including SAEs, the regular monitoring of hematology, serum chemistry, urinalysis, routine monitoring of vital signs (respiratory rate, sitting pulse, sitting blood pressure, and body temperature), weight, ECOG PS, chest CT scans, and physical condition. Assessments were usually performed at baseline/screening, pre-dose on PK run-in Day 1 in the dose-escalation phase and Cycle 1 Day 1 in the expansion phase, and varying frequencies in every treatment cycle as relevant to the parameter being assessed, and at the end of treatment (EOT).

Hematology, basic metabolic blood chemistry, liver function tests (AST, ALT, total bilirubin, and alkaline phosphatase), serum amylase, and lipase were analyzed at:

- Baseline/screening
- PK run-in Day 1 (prior to first dose in escalation phase)
- Cycle 1 Day 1 (within 3 days prior to the administration of ceritinib)
- Cycle 1 Day 8
- Cycle 1 Day 15
- Day 1 and Day 15 of Cycle 2 to Cycle 6 (\pm 3 days)
- Day 1 of Cycle 7 and subsequent cycles thereafter (\pm 3 days)
- End of treatment

A standard 12 lead ECG was performed at the following time points:

- Baseline/screening, single ECG within 14 days prior to first dose of ceritinib
- PK run-in Day 1 in the dose-escalation phase and Cycle 1 Day 1 in expansion phase, three serial ECGs at least 5 to 10 minutes apart prior to the first dose of ceritinib and single ECGs 4, 8 and 24 hours post-dose
- Cycle 1 Day 8 in the dose-escalation phase, single ECG pre-dose and 4 hours post-dose

- Day 1 of Cycle 2 to Cycle 6, single ECG pre-dose
- After Cycle 6, ECGs should only be performed if clinically indicated
- End of treatment (EOT), single ECG

The routine clinical testing in study X2101 appears to have been sufficient to elicit adequate adverse event data.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The applicant’s efforts to detect specific adverse events that have been seen with other ALK TKIs (e.g., QT prolongation, hepatotoxicity) were reasonable appeared adequate.

7.3 Major Safety Results

7.3.1 Deaths

In study X2101, a total of 45 (14.8%) on treatment deaths were reported. There were a total of 86 (28.3%) deaths up to the data cutoff data of October 31, 2013 (Table 17).

Table 17. Causes of death in X2101[reviewer analysis] →

The following are excerpts from the review of deaths in study X2101:

X2101-0101-90028: Death (euthanasia)

Patient also had SAE (headache)

Phase: Expansion

Arm: 1A

Trial drug dose: 750 mg qd

This 48-year-old Caucasian female with metastatic ALK+NSCLC was in the Netherlands. The patient received the first dose of the study medication on 14-Sep-2012 (Day 1). On Day 119 (10 Jan-2013), the patient’s MRI showed slight progression of brain and leptomeningeal metastases. On Day 127 (18-Jan-2013), an MRI scan (with contrast) revealed new lesions in the brain and the patient was diagnosed with disease progression. The study medication was permanently discontinued due to patient’s withdrawal of informed consent. The patient received the last dose of the study medication

Cause of death (MedDRA PT)	N
Acute Respiratory Failure	1
Alveolar Rhabdomyosarcoma	1
Breast Cancer	1
Cardiac Tamponade	1
Death	4
Disease Progression	14
Euthanasia	1
Gastric Hemorrhage	1
General Physical Health Deterioration	2
Inflammatory Carcinoma Of The Breast	1
Inflammatory Myofibroblastic Tumour	1
Interstitial Lung Disease	1
Invasive Ductal Breast Carcinoma	1
Lung Adenocarcinoma	1
Lung Cancer Metastatic	1
Lung Neoplasm Malignant	8
Malignant Neoplasm Progression	5
Malignant Pleural Effusion	1
Neoplasm	2
Non-Small Cell Lung Cancer	25
Non-Small Cell Lung Cancer Metastatic	2
Pneumonia	3
Pneumonia Aspiration	1
Pneumothorax	1
Pulmonary Tuberculosis	1
Respiratory Failure	3
Sepsis	1
Septic Shock	1

on (b) (6). On (b) (6), (b) (6) after the last dose of the study medication, the patient experienced headache (grade 3) and was hospitalized. The patient was treated with dexamethasone. On (b) (6) the event (headache) resolved. On (b) (6) after the last dose of the study medication, the patient died due to what was reported as “euthanasia.”

X2101-0081-90176: Death (interstitial lung disease)

Patient also had: SAE (interstitial lung disease), discontinuation due to AE (interstitial lung disease)

Phase: Expansion

Arm: 1B

Trial drug dose: 750 mg qd

This 48-year-old Caucasian male with metastatic ALK+ NSCLC was at a site in Italy. The patient received the first dose of the study medication on 30-May-2013 (Day 1). On Day (b) (6), a CT scan of the chest was performed due to rapidly progressing dyspnea associated with lowering of oxygen saturation (pO₂ 80%). The CT scan showed a reduction of the lung lesions in the right lung and the development of interstitial lung disease in the left lung. The patient was diagnosed with interstitial lung disease in the left lung (grade 4; the analysis of sputum showed presence of *Klebsiella pneumoniae*), which resulted in hospitalization. The study medication was permanently discontinued on Day (b) (6) due to the event (interstitial lung disease).

X2101-0505-00001: Death (breast cancer)

Phase: Escalation

Cohort: 3

Trial drug dose: 200 mg qd

This 48-year-old Caucasian female had metastatic ALK+ breast cancer. The study medication was permanently discontinued due to disease progression and the patient received the last dose of study medication on Day 40 (23-Jul-2011). On (b) (6) after the last dose of the study medication, the patient died likely due to disease progression.

X2101-0062-90006: Death (gastric bleeding)

Also had SAE (hypercalcemia, ileus, constipation, nausea)

Phase: Expansion

Arm: 1A

Trial drug dose: 750 mg qd

This 37-year-old Caucasian male with metastatic ALK+ NSCLC was enrolled at a site in Germany. The patient’s relevant past medical history included appendectomy, pleurectomy, and diarrhea. Relevant active medical conditions and symptoms at enrollment included tumor pain and anemia. On Day 31 (29-May-2013), the study medication was interrupted due to event of hypercalcemia (grade 3). The patient was also treated with metoclopramide for nausea. On (b) (6) the patient rapidly deteriorated with sudden vomiting which turned into

hematemesis and increased abdominal pain. On [REDACTED] (b) (6) the patient died due to gastric bleeding. The patient had received the last dose of the study medication on Day 30 (28-May-2013). The Investigator reported that hypercalcemia was indicative of tumor progression and the patient died of rapidly progressing intra-abdominal metastases which caused bowel obstruction and acute bleeding.

Overall, the reviewer agrees with the assessment of deaths based on the MedDRA PTs in Table 17. In studies X2102, A2201, A2203, and A2303, the applicant reported 17 deaths as of October 31, 2013. Review of the cases suggests that the majority were due to the underlying malignancy/disease progression.

7.3.2 Serious Adverse Events

In X2101, serious adverse events (SAEs) were defined as one of the following:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
 - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
 - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
 - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
 - Social reasons and respite care in the absence of any deterioration in the patient's general condition
 - Any SAEs that are expected due to the condition being treated, including if the SAE is a primary outcome measure, and whether there has been a clear agreement with regulators not to consider these as SAEs, provided the information is collected elsewhere

The reviewer's analysis of X2101 showed that of the 304 patients treated at any dose of ceritinib, SAEs were reported in 133 (43.8%) of patients. The applicant's analysis showed a similar result with SAEs in 41.4% with SAEs reported in $\geq 2\%$ of all patients as follows: pneumonia (3.6%), convulsion (3.6%), dyspnea (2.6%), pneumonitis (2.6%), hyperglycemia (2.0%), and respiratory failure (2.0%). SAEs were reported in 40.4% of patients in the 750 mg and 51.3% in the 400-700 mg dose groups.

Table 18. Serious adverse events occurring in > 1 patient in study X2101, all patients, n=304 [reviewer's analysis, dataset AAEV]

Preferred term	N (% , n=304)
Convulsion	12 (3.9%)
Pneumonia	12 (3.9%)
Dyspnea	10 (3.3%)
Pneumonitis	8 (2.6%)
Dehydration	6 (2.0%)
Hyperglycemia	6 (2.0%)
Pericardial Effusion	6 (2.0%)
Respiratory Failure	6 (2.0%)
Nausea	5 (1.6%)
Pneumothorax	5 (1.6%)
Vomiting	5 (1.6%)
Alanine Aminotransferase Increased	4 (1.3%)
Pericarditis	4 (1.3%)
Anemia	3 (1.0%)
Asthenia	3 (1.0%)
Back Pain	3 (1.0%)
Bronchitis	3 (1.0%)
Constipation	3 (1.0%)
Diarrhea	3 (1.0%)
General Physical Health Deterioration	3 (1.0%)
Headache	3 (1.0%)
Non-Cardiac Chest Pain	3 (1.0%)
Pain	3 (1.0%)
Pleural Effusion	3 (1.0%)
Pulmonary Embolism	3 (1.0%)
Pyrexia	3 (1.0%)
Abdominal Pain	2 (0.7%)
Acute Respiratory Failure	2 (0.7%)
Anxiety	2 (0.7%)
Arthralgia	2 (0.7%)
Aspartate Aminotransferase Increased	2 (0.7%)
Atrial Fibrillation	2 (0.7%)
Decreased Appetite	2 (0.7%)
Empyema	2 (0.7%)
Fatigue	2 (0.7%)
Gastroenteritis	2 (0.7%)
Hypoxia	2 (0.7%)
Ileus	2 (0.7%)
Interstitial Lung Disease	2 (0.7%)
Lung Infection	2 (0.7%)
Metastases To Central Nervous System	2 (0.7%)
Pleuritic Pain	2 (0.7%)

Pneumonia Aspiration	2 (0.7%)
Respiratory Distress	2 (0.7%)
Respiratory Tract Infection	2 (0.7%)
Sepsis	2 (0.7%)
Septic Shock	2 (0.7%)
Urinary Tract Infection	2 (0.7%)

As shown in Table 18, convulsions (SAEs) occurred in about 4% of the patients in X2101. Overall, the reviewer’s analysis showed 22 events of convulsions (all grades based on MedDRA PTs) in 16 (5%) of patients in study X2101. A review of these events (Table 19) showed that all of these patients developed convulsions likely due to brain metastasis. About 60% of the patients in X2101 entered the trial with brain metastasis, which is likely due to the fact that about half of the patients on crizotinib progress in the brain as the primary site of relapse.

Table 19. Review of patients with convulsions in X2101.

Patient ID [SID1A]	Reviewer’s comments*	ceritinib starting dose	Prior crizotinib?	Sex	Age
0175_90033	History of brain radiotherapy. Narrative provided for SAEs of convulsion and death. Patient had dose interruption on day 36 for elevated LFTs and resumes on day 50 at 600mg. Had another reduction to 450mg for rash on day 126. Day 141 progression in brain lesions. Patient experienced convulsion on day (b) (6). On day (b) (6), patient died, assessed as “disease progression.” At the time of death, a second episode of convulsion was ongoing.	750 mg	Yes	Female	62
0201_90017	Patient had multiple brain metastases at baseline.	750 mg	Yes	Female	66
0201_90035	Patient had multiple brain metastases at baseline.	750 mg	Yes	Female	33
0201_90036	Patient with metastatic brain lesions at base line status post radiotherapy. Narrative provided for SAEs of death, diarrhea, abdominal pain, dehydration, convulsion, pneumonia, pulmonary tuberculosis, septic shock, and respiratory failure. On day (b) (6), patient experienced convulsion and was hospitalized. No action was taken with study medication and patient was treated with dexamethasone, and levetiracetam. On day (b) (6) the event (convulsion) resolved. Patient presented with pneumonia on day (b) (6) indicated as TB (had diagnostic bronchoscopy) and hospitalized. On day (b) (6) patient died, assessed as “TB induced pneumonia.” Last day of study medication was day 55.	750 mg	No	Male	48
0201_90044	Likely due to brain metastasis.	750 mg	Yes	Female	37
0502_90015	Patient with brain lesions at baseline. Narrative provided for SAE of death. Past medical history included muscle spasms and convulsion. On Day 85, patient was diagnosed with disease progression due to new lesions in the central nervous system. The study medication was temporarily interrupted from day (b) (6) and the patient underwent radiotherapy (gamma knife) for the new brain	750 mg	Yes	Female	48

	lesions on day (b) (6). The study medication was restarted on day 114 and on day (b) (6), patient experienced convulsions. Treatment with study drug continued and patient was treated with levetiracetam. On day 177, the study medication was permanently discontinued due to disease progression and (b) (6) days later patient died, assessed due to “disease progression.”				
0502_90023	Brain with CNS metastasis at baseline. Narrative provided for SAE of convulsion. On day (b) (6), patient was diagnosed with disease progression (+31.25% change in SLD from nadir) and on day experienced left sided numbness, and with aphasia and developed convulsions, resulting in hospitalization. The study medication was temporarily interrupted on day 200 and patient was treated with dexamethasone, levetiracetam and acetylsalicylic acid. On Day 201, the study medication was restarted at the same dose. On day 213 a spiral CT scan revealed further worsening of target lesions (+56.25% change in SLD from nadir) and study medication was permanently discontinued due to disease progression. Patient received the last dose of study medication on Day 224.	750 mg	Yes	Male	50
0504_00020	Patient with brain metastasis at baseline status post radiotherapy. Narrative provided for SAE of convulsion and musculoskeletal pain. On Day 380, spiral CT scan revealed worsening of the target lesion (hilar adenopathy, portal adenopathy, liver dome and liver) with SLD = 15.3 cm and a new lesion in brain, and liver. On day (b) (6) patient developed convulsions and musculoskeletal pain and was hospitalized. The patient received the last dose of study medication on day and (b) (6) later died, assessed as “disease progression.”	600 mg	Yes	Male	42
0504_00025	Patient with brain metastasis at baseline. Narrative provided for SAEs of convulsion, spinal cord compression and dose limiting toxicity of diarrhea. On day 130, patient was diagnosed with disease progression with new lesions in brain. Study medication was temporarily interrupted from day 140 and the patient underwent treatment with stereotactic proton beam radiotherapy. Study medication was restarted on Day 150 at the dose of 600mg qd as per the protocol. Another study interruption occurred day 194 for whole brain radiotherapy. On day (b) (6), patient experienced convulsion and was hospitalized. No action was taken with the study medication and patient was treated with levetiracetam. Patient recovered but on day (b) (6) experienced spinal cord compression and was hospitalized. Patient had temporary interruption of study medication and resumption on day 222. On day 234, a CT scan revealed a worsening of non-target lesion in the liver and study medication was permanently discontinued due to disease progression.	750 mg	Yes	Male	58
0504_90037	Patient with CNS metastasis at baseline status post	750 mg	Yes	Female	45

	radiotherapy. Narrative provided for SAEs of spinal fracture, convulsion, and urinary tract infection. Patient had dose reduction to 600mg qd on day 42 for fatigue. On day (b) (6) the patient was hospitalized due to convulsion and was noted to have “slight” hypernatremia (blood sodium 130 mmol/L [normal values 135-145 mmol/L]). On the same day, a CT scan of brain performed was negative for new metastasis and noted stable for known metastases. The study medication was permanently discontinued due to withdrawal of consent by the patient. The patient received the last dose of study medication on day 58.				
0505_00005	Patient with baseline brain metastasis status post radiotherapy. On day 148, patient was diagnosed with disease progression with worsened non-target lesions and new lesions in brain. On day (b) (6), patient experienced convulsion and was hospitalized. No action was taken with the study medication. The patient was treated with levetiracetam. On day (b) (6), the event (convulsion) resolved. On day (b) (6), the patient developed new non-target lesions in the brain (disease progression), and the study medication was permanently discontinued. Death was assessed as “disease progression.”	400 mg	Yes	Female	40
0505_90033	Patient with baseline lesion in the brain status post radiotherapy. Other baseline lesions included a pelvic mass. Narrative provided for SAEs of asthenia, back pain, pain, convulsion, arthralgia and intra-abdominal hemorrhage on lovenox. On day 1, patient experienced convulsions. A brain CT scan performed on the same day showed disease progression with enlarging brain metastases and intra-lesional hemorrhage, hydrocephalus with leptomeningeal carcinomatosis. Patient was treated with levetiracetam and dexamethasone and event (convulsion resolved).	750 mg	Yes	Female	30
0505_90043	Normal MRI of brain at baseline. Narrative provided for SAE of convulsion. Study medication discontinued on day 191 due to disease progression and (b) (6) days after the last dose of the study medication, the patient experienced convulsion and was hospitalized. A CT scan of the head performed on the same day revealed multiple brain metastases.	750 mg	Yes	Female	31
0505_90044	Patient with baseline brain metastasis status post left craniotomy with temporal metastatic resection. SAE narrative provided for death, empyema, and two episodes of convulsions days (b) (6). Brain imaging after first episode of convulsion showed metastatic disease in brain with “petechial bleed.” The patient was treated with levetiracetam and continued therapy. Brain imaging at second episode of convulsions showed CNS disease progression. Patient taken off study drug on day 113 and (b) (6) days later died due to a stated reason of “disease progression.” Last day of study medication was on day 183 due to disease progression. Patient died (b) (6).	750 mg	Yes	Female	51

	days after the last dose of the study medication due to unknown reason.				
0505_90046	Patient had baseline brain lesions status post radiotherapy with history of seizures. Narrative provided for SAEs central nervous system lesion, convulsion, diabetic ketoacidosis, acute respiratory failure, respiratory failure, urinary tract Infection. According to the narrative, convulsion occurred before start of study medication on day -56. The study medication was permanently discontinued due to respiratory failure on day 58 and patient died ^{(b) (6)} days later.	750 mg	Yes	Male	29
*Comments focus on convulsion-related events. Cases were identified according to MedDRA PTs in the overall safety population (n=304)					

In study A2201, 37 SAEs were reported in 26/140 (18.6%) patients. In study A2203, 18 SAEs were reported in 10/82 (12.2%) patients. In study A2301, 1 SAE was reported in 1 patient and in study A2303, 1 SAE was reported in 1 patient. There was 1 (0.7) case of pancreatitis in study A2201 (n=140). No other new safety signals were noted in the supportive safety trials.

7.3.3 Dropouts and/or Discontinuations

Discontinuations due to adverse events occurred in 29/304 (9.5%) of all patients in X2101 and 26/255 (10.1%) of patients treated at 750 mg (Table 20). The 39 AEs leading to discontinuation in the 29 patients were grade 1 (n=2, 5.1%), grade 2 (n=8, 20.5%), grade 3 (n=20, 51.3%) and grade 4 (n=9, 2.31%) and 35 (89.7%) occurred in the 750 mg cohort. Excluding the 3 patients where the primary reason for discontinuation was assessed to be due to disease progression, discontinuation due to AEs as *the primary reason* was seen in 26 (8.6%) of all patients.

Table 20. Adverse events leading to dose discontinuation in study X2101 [reviewer analysis, dataset AAEV]

Patient ID	Preferred Term (PT)	Grade	ceritinib dose	Reviewer comments
0002_90002	Pneumonia Aspiration	4	750 mg	Patient had also experienced SAE of pyrexia. Primary reason for discontinuation appears disease progression as assessed by investigator. Reviewer agrees.
0041_90028	Corneal Infiltrates	3	750 mg	On Day 22, study medication was reduced to 600 mg qd due to persistent vomiting and diarrhea. Also grade 3 increased AST/ALT. Last dose day 316. No details on presentation of corneal infiltrates.
0041_90045	Malignant Neoplasm Of Thorax	4	750 mg	Primary reason for discontinuation appears disease progression as assessed by investigator. Reviewer agrees.
0062_90004	General Physical Health Deterioration	3	750 mg	Patient had also experienced SAE of

				gait disturbance. Primary reason for discontinuation appears disease progression as assessed by investigator. Reviewer agrees.
0064_90003	Hemoptysis	3	750 mg	On Day (b) (6) patient was noted with blood in sputum and was hospitalized. Bronchoscopy revealed tumor as probably cause of bleeding. Day 84, study drug discontinued due to PD.
0064_90004	General Physical Health Deterioration	3	750 mg	On Day (b) (6) patient was noted with general physical health deterioration (grade 3, PS not reported), and was hospitalized. On the same day the study medication was permanently discontinued due to the event (general physical health deterioration). No treatment was reported. Day of death and for this patient unknown.
0064_90006	Pneumonia	3	750 mg	Last day of drug day (b) (6). Patient hospitalized with pneumonia and also pulmonary embolus. Best response ORR. Died due to what investigator noted as progression in the liver.
0081_90176	Interstitial Lung Disease	4	750 mg	Symptoms on day (b) (6) with hypoxia. CT evidence of ILD. Sputum had Klebsiella pneumonia. Unclear if fever, cough. The patient had noninvasive ventilation placed and was treated with dexamethasone, duragesic, imipenem, and fluconazole. Patient's condition worsened and he died with chest xray showing worsening interstitial lung disease.
0082_00014	Sepsis	4	750 mg	On day (b) (6) patient presented with hyperglycemia and fever. Patient had been on steroids for brain metastasis which could have worsened infection. Patient treated with broad spectrum antibiotics. Died due to sepsis.
0121_90014	Respiratory Failure	4	750 mg	Day 42 dose of study medication was reduced to 600 mg qd due to events of nausea and vomiting (both grade 2). On Day (b) (6) patient was diagnosed with respiratory tract infection (grade 3) and was hospitalized. A CT scan performed on the same day showed pleural effusion. Patient treated and improved. Day (b) (6) patient had embolism (likely pulmonary although not clear) On Day (b) (6) patient was hospitalized with respiratory failure (grade 4) and died shortly after.
0121_90022	Pneumothorax	4	750 mg	Event on day (b) (6) Patient eventually

				died due to event. Had pleural effusion on imaging and underwent thoracentesis, which can cause pneumothorax.
0121_90026	Hemorrhage Intracranial	2	750 mg	Event on day 4. Patient with history of brain metastasis.
0121_90027	Cardiac Tamponade	4	750 mg	On Day (b)(6) patient experienced chest pain and was hospitalized and diagnosed with acute pericarditis (grade 2). SAE of cardiac tamponade occurred on day (b)(6) and patient died the following day.
0141_90035	Alanine Aminotransferase Increased	3	750 mg	Appears to be a case of DILI. 55 year-old white female. At study entry, no liver metastasis reported. Study drug discontinued on day 37 due to increased transaminases and alkaline phosphatase. On Day 43, patient was diagnosed with jaundice (grade 3) with total bilirubin of 74 µmol/L (grade 3). Jaundice resolved day 70 and transaminases and alkaline phosphatase returned to normal range by approximately day 100. Concomitant potentially hepatotoxic medication at the time of event: cetirizine.
	Aspartate Aminotransferase Increased	3		
	Blood Alkaline Phosphatase Increased	2		
	Hepatitis Cholestatic	3		
0175_00017	Depressed Level Of Consciousness	3	600 mg	Patient had diarrhea which may have resulted in hypovolemic hyponatremia.
	Hyponatremia	4		
0201_90020	Pneumonitis	2	750 mg	Patient with 3 episodes of pneumonitis. Occurred post rechallenge with the study drug until permanently discontinued on day 154.
		3		
0201_90080	Renal Failure Acute	3	750 mg	On Day (b)(6) patient was noted with elevated serum creatinine at 451 µmol/L, BUN at 20.7 mmol/L, decreased urine output (< 100 mL/day); and was diagnosed with acute renal failure (grade 3), due to which the patient was hospitalized. On the next day a renal ultrasound showed no focal lesions or hydronephrosis; and negative Autoantibodies (b)(6) days after the last dose of the study medication, patient's serum creatinine was normal at 0.9 mg/dL and the event (renal failure acute) was considered resolved. Not clear if patient was have any GI symptoms causing fluid loss while on the study drug.
0502_00006	Cauda Equina Syndrome	3	750 mg	Patient with CNS disease. Patient status fall and trauma to likely the

				spine at the time of diagnosis with Cauda Equina Syndrome.
0502_90030	Decreased Appetite	2	750 mg	Study drug discontinued on day 15 and (b) (6) days after the last dose of the study medication, the patient died due to “malignant pleural effusion” likely secondary to disease progression. Best response unknown.
	Dyspnea	2		
	Fatigue	3		
0504_90052	Pneumonitis	3	750 mg	On Day 175 patient presented with dyspnea and was diagnosed with possible pneumonitis with ground glass opacities on CT but study drug continued and patient treated with Lasix and prednisone. On Day 188 patient experienced dyspnea and study medication discontinued.
0504_90054	Pneumonia	3	750 mg	On Day (b) (6) patient was diagnosed with disease progression (new lesions in brain) and admitted with fever and pneumonia. Drug discontinued on day (b) (6). Patient died (b) (6) days later. Disease progression likely causing pulmonary infection and leading to drug discontinuation.
0505_00002	Blood Alkaline Phosphatase Increased	3	400 mg	Patient also with elevated AST/ALT. Unclear day of drug discontinuation. No detailed history provided.
0505_90046	Respiratory Failure	4	750 mg	On day 22, patient with diabetic ketoacidosis and acute respiratory failure. Patient intubated and treated with metformin, pioglitazone hydrochloride, insulin glargine and glucose. On Day 36 the events (diabetic ketoacidosis, acute respiratory failure) resolved. Day (b) (6) drug discontinued due to respiratory failure with evidence of infection, hospitalized and given antibiotics. Died (b) (6) days later. Best response SD. May have died secondary to PD.
0506_90016	Decreased Appetite	3	750 mg	Multiple events occurred that may have contributed to patient’s deterioration, including dyspnea secondary to pleural effusion on day 1 requiring thoracentesis and VATS pleurodesis complicated by pneumothorax. Patient died due to disease progression. Best response SD.
0507_00008	Pain In Extremity	2	600 mg	Event started on day 87. May have been neuropathic. Treated with gabapentin and had dose reduction. Last dose day 214, 5 days later, event resolved.

0507_90010	Pneumonia	3	750 mg	Diagnosed day 61 and medication discontinued day (b) (6) and (b) (6) days later patient died. Best response SD.
0507_90033	Monoplegia	3	750 mg	Study drug discontinued day 34. Patient withdrew informed consent. Unknown if improved. Best response SD and alive as of last report.
	Performance Status Decreased	3		
0507_90035	Pleural Effusion	2	750 mg	Patient with (pleural effusion, pericardial effusion, pleuritic pain). May have been due to underlying disease. Known survival status. Best response PR.
	Pleuritic Pain	2		
0507_90038	Nausea	1	750 mg	Last dose on day 22 and 3 days later events resolved. Patient alive as of last report.
	Weight Decreased	1		

7.3.4 Significant Adverse Events

Dose interruptions or adjustments

Of the 304 patients treated at any dose of ceritinib, AE requiring dose adjustment or interruption were reported in 70.7% of patients. The reviewer’s analysis showed a median dose delay of 7.5 days (range 1 to 90) (Figure 6). About 3% of the events were grade 4 (Figure 7). The most frequent AEs requiring a dose adjustment or interruption ($\geq 5\%$ of patients) were: ALT increased (27.0%), nausea (18.1%), AST increased (15.5%), vomiting (15.1%), diarrhea (14.1%), and fatigue (7.6%); abdominal pain (5.6%). Grade 3-4 AEs requiring dose adjustment or interruption were reported in 48.4% of all patients. The most frequent grade 3-4 AEs requiring dose adjustment or interruption ($\geq 3\%$ of patients) were: ALT increased (24.3%), AST increased (8.2%), diarrhea (3.9%), lipase increased (3.6%), vomiting (3.3%) and nausea (3.0%). The incidence of AEs requiring dose adjustment or interruption was higher in the 750 mg (74.1%) than the 400-700 mg (61.5%) dose group and largest difference ($>10\%$) was seen for diarrhea.

Figure 6. Dose delays in study X2101, all patients (n=304), [reviewer’s analysis, dataset ADRGEXP]

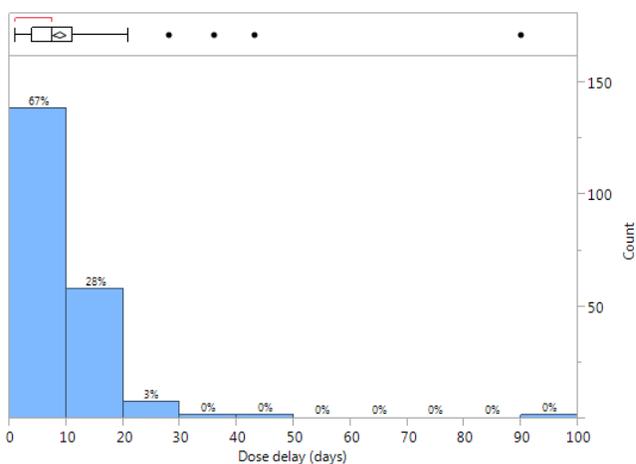
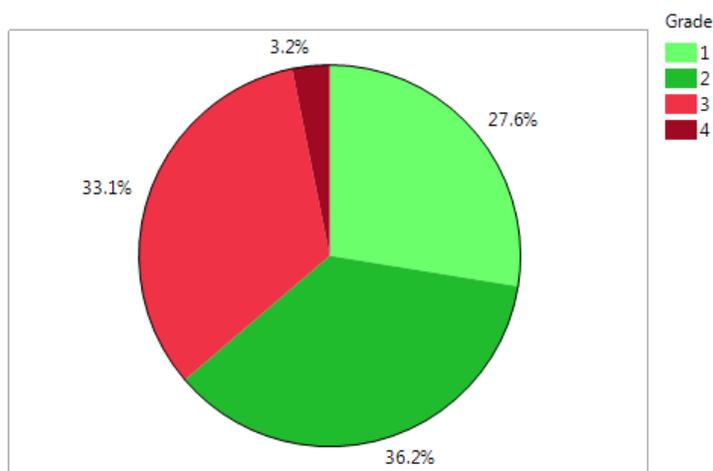


Figure 7. CTCAE grades of adverse events leading to dose interruption/adjustment in study X2101 [reviewer analysis, dataset AAEV]



Dose reductions

Of the 304 patients treated at any dose of ceritinib, 166 patients (54.6%) had at least one dose reduction. 107 patients (35.2%) had 1 dose reduction, 47 patients (15.5%) had 2 dose reductions, and 12 patients (3.9%) had ≥ 3 dose reductions during the study. In the 750 mg dose group, 150 patients (58.8%) had at least one dose reduction and 99 patients (38.8%) had 1 dose reduction. Among patients treated at 400-700 mg, the number of patients with dose reduction was 15 (38.5%).

Adverse events requiring additional therapy

Of the 304 patients treated at any dose of ceritinib, AE requiring additional therapy were reported in 99.0% of patients (all grades), and grade 3-4 AEs in 43.8% of patients.

Hepatotoxicity

ALT and AST elevations were the 4th and 8th most common reported adverse events in patients treated at 750 mg in study X2101 (Table 21) with about 1% SAEs (Table 18). One patient [X2101-0141-90035] discontinued due to hepatotoxicity (Table 20). Ceritinib was interrupted for this patient due to jaundice and drug-induced liver injury (DILI) and the patient later discontinued therapy. The applicant's analysis did not show any cases of Hy's law and the reviewer's analysis revealed 1 case that almost met the criteria (section 7.4.2). In study A2201, there were 3 cases of hepatotoxicity SAEs. Overall, hepatotoxicity and DILI can be caused by ceritinib, with the potential for more severe cases as more patients are exposed to the drug. This risk appears to be generally consistent with the profile of other approved TKIs.

Bradycardia

Of the 304 patients treated at any dose of ceritinib, the applicant conducted an analysis of a group of AEs associated with bradycardia, which was reported in 25 patients (8.2%). The search

terms the applicant used to retrieve bradycardia-associated events also included QT prolongation and syncope-associated events.

The reviewer's analysis found the following related events in safety database:

- Bradycardia (PT, all grades) in 5 (2%) patients
- Syncope (PT, all grades) in 4 (1%) patients
- Bradyarrhythmias (including conduction defects and disorders of sinus node function) as per broad SMQ analysis: 28 events in 17 (6%) patients.

Hyperglycemia

In study X2101, AEs associated with hyperglycemia (based on PTs) were reported in 32 patients (10.5%). The following AEs were reported: hyperglycemia (22 patients; 7.2%), diabetes mellitus (9 patients; 3.0%), blood glucose increased (2 patients; 0.7%), diabetic ketoacidosis (1 patient; 0.3%), and glucose tolerance impaired (1 patient; 0.3%). Grade 3-4 AEs were reported in 16 (5.3%) patients, all of whom were treated at 750 mg. These included hyperglycemia (14 patients, 4.6%), glucose tolerance impaired (1 patient, 0.3%), and diabetic ketoacidosis (1 patient, 0.3%). In study A2203, there was 1 case of hyperglycemia associated SAE requiring insulin treatment (resolved).

In study X2101, glucose laboratory values in the 304 patients treated at any dose of ceritinib showed 150 patients (49.3%) had post-baseline > grade 0 values for glucose (including patients with missing baseline). The most frequent elevations from grade 0 were to grade 1 (27.4%, 65/237). Elevations in glucose from baseline grade 0 to post-baseline > grade 0 were reported for 14/30 patients (46.7%) in the 400-700 mg and for 89/197 patients (45.2%) in the 750 mg dose groups. Elevations to newly occurring grade 3-4 values were reported for 1/38 patients (2.6%) in the 400-700 mg and for 32/255 patients (12.5%) in the 750 mg dose groups. SAE of hyperglycemia occurred in 2.0% (Table 18).

Overall, it appears that ceritinib can cause hyperglycemia, likely due to inhibition of IGF-1R/INSR. The reviewer's analysis showed that in the 22 patients that had hyperglycemia (according to MedDRA PT), steroid use was common, probably due to the fact that many patients had brain metastasis in study X2101. Fourteen (63.6%) of the patients who developed hyperglycemia (according to MedDRA PT) were taking methylprednisone, prednisone, or prednisolone as concomitant medications, which can cause, exacerbate, or reduce the threshold for developing hyperglycemia. No hyperglycemia AEs leading to discontinuation were reported.

Neuropathy

Of the 304 patients treated at any dose of ceritinib in study X2101, AE associated with neuropathy were reported in 50 patients (16.4%). The following AEs were reported: paraesthesia (17 patients; 5.6%), muscular weakness (11 patients; 3.6%), gait disturbance and neuropathy peripheral (6 patients each; 2.0%), hypoaesthesia (5 patients; 1.6%) peripheral sensory neuropathy (4 patients; 1.3%), dysaesthesia (2 patients, 0.7%), neuralgia (2 patients, 0.7%), peripheral motor neuropathy (2 patients, 0.7%), and hypotonia, muscle atrophy and polyneuropathy were each reported in 1 patient. All events were grade 1 or 2 in severity, except

for 3 patients in whom a grade 3 event was reported (muscle atrophy, muscular weakness and gait disturbance). No grade 4 events were reported.

Serum creatinine increased

Of 304 patients treated at any dose of ceritinib, AEs associated with creatinine elevation or renal function included the following events: blood creatinine increased (41 patients, 13.5%), renal failure acute (4 patients, 1.3%), azotaemia (3 patients, 1.0%), renal failure (3 patients, 1.0%), glomerular filtration rate decreased (2 patients, 0.7%), glomerular filtration rate abnormal (1 patient, 0.3%), and renal impairment (1 patient, 0.3%). The majority of AEs occurred at the 750 mg dose. AEs were reported in the following patients who were treated at lower doses: blood creatinine increased (500 mg, 1 patient; 400 mg, 1 patient), renal failure (500 mg, 1 patient) (also see section 7.4.2 Laboratory Findings). No cases of renal cyst, renal cyst hemorrhage, renal cyst infection, or renal cyst ruptured were reported in study X2101.

Visual disorders

Of the 304 patients treated at any dose of ceritinib, AEs associated with visual disorders were reported in 30 patients (9.9%). The following AEs were reported: visual impairment (13 patients; 4.3%) and vision blurred (8 patients; 2.6%), photopsia (5 patients; 1.6%), and diplopia (3 patients; 1.0%), and accommodation disorder, presbyopia and visual acuity reduced were each reported in 1 patient. One grade 3 event (diplopia) was reported in a patient treated at 500 mg. No grade 4 AEs, SAEs or AEs requiring dose adjustment or interruption, discontinuation or deaths associated with visual disorders were reported.

Edema

Of the 304 patients treated at any dose of ceritinib, AEs associated with edema were reported in 33 patients (10.9%), all of which were grade 1-2. The following AEs were reported: peripheral edema (27 patients; 8.9%), edema (5 patients; 1.6%), and face edema (1 patient; 0.3%). As of No SAEs associated with edema were reported, and none of the AEs led to study drug discontinuation.

Photosensitivity

Of the 304 patients treated at any dose of ceritinib in study X2101, AEs associated with photosensitivity (all grade 1) were reported in 6 patients (sunburn in 3 patients, photosensitivity reaction in 3 patients); all patients were treated at 750 mg.

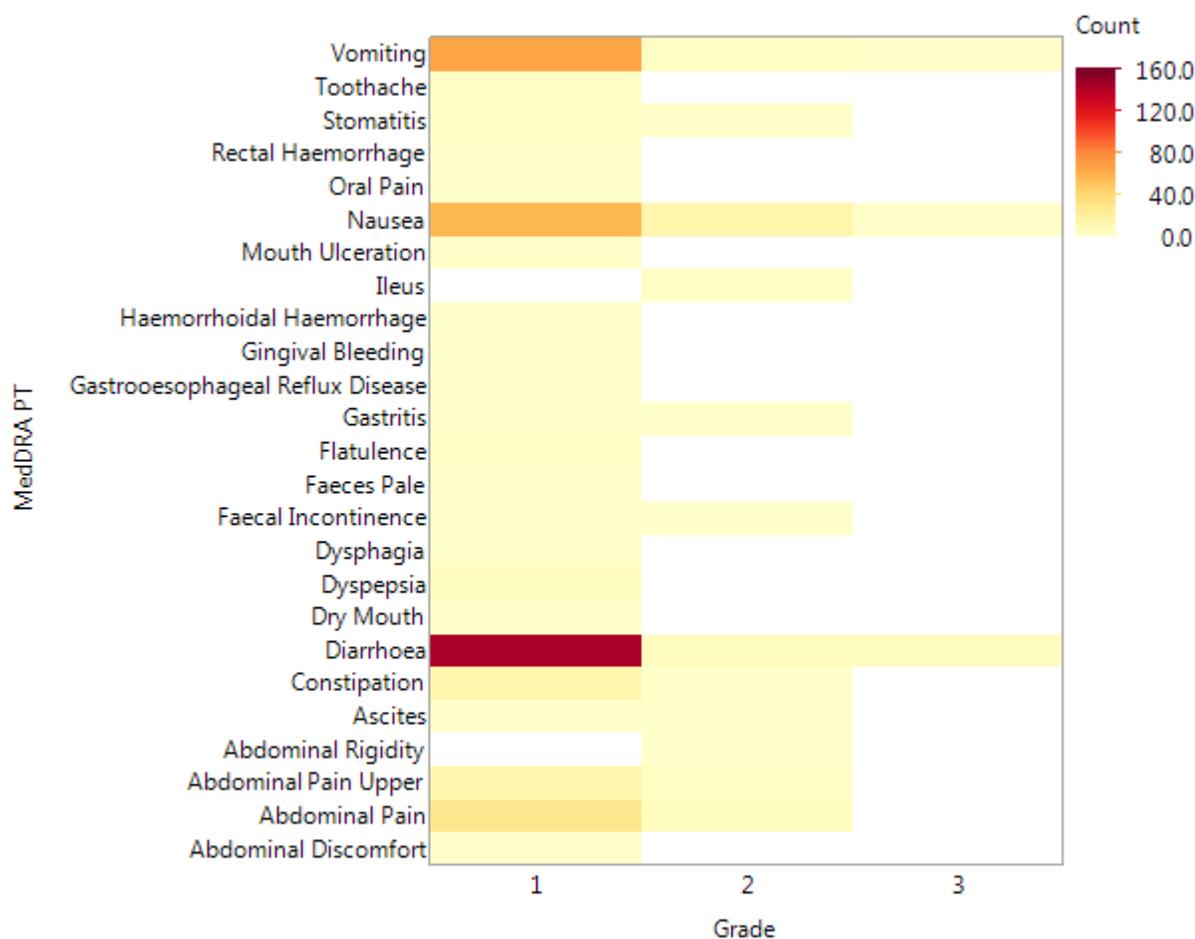
7.3.5 Submission Specific Primary Safety Concerns

Acute pancreatitis

Ceritinib has been shown to increase amylase and lipase levels (see adverse events and laboratory sections in this review). Positive de-challenge and re-challenge was seen in a subset of patients with amylase/lipase elevations. Reviewer's algorithmic SMQ analysis showed 38 (13%) cases consistent with possible acute pancreatitis, however these were not reported as such by the investigator. As expected, the incidence of GI symptoms such as diarrhea, nausea, vomiting, and abdominal pain was high in these patients but closer inspection of the timing of events did not clearly show a clinical picture consistent with acute pancreatitis and the majority of the GI events

were grade 1 (Figure 8). In the fully-acrued study A2201 (n=140), there was one case of acute pancreatitis as of October 31, 2013. An information request was sent to the applicant to perform an assessment of the association between the use of ceritinib and acute pancreatitis. Both the reviewer’s and the applicant’s analyses did not establish a clear association between ceritinib and acute pancreatitis based on the available data.

Figure 8. Gastrointestinal events in the 38 patients with possible acute pancreatitis based on algorithmic SMQ analysis [reviewer’s analysis, AAEV dataset, count refers to number of events]



7.4 Supportive Safety Results

7.4.1 Common Adverse Events

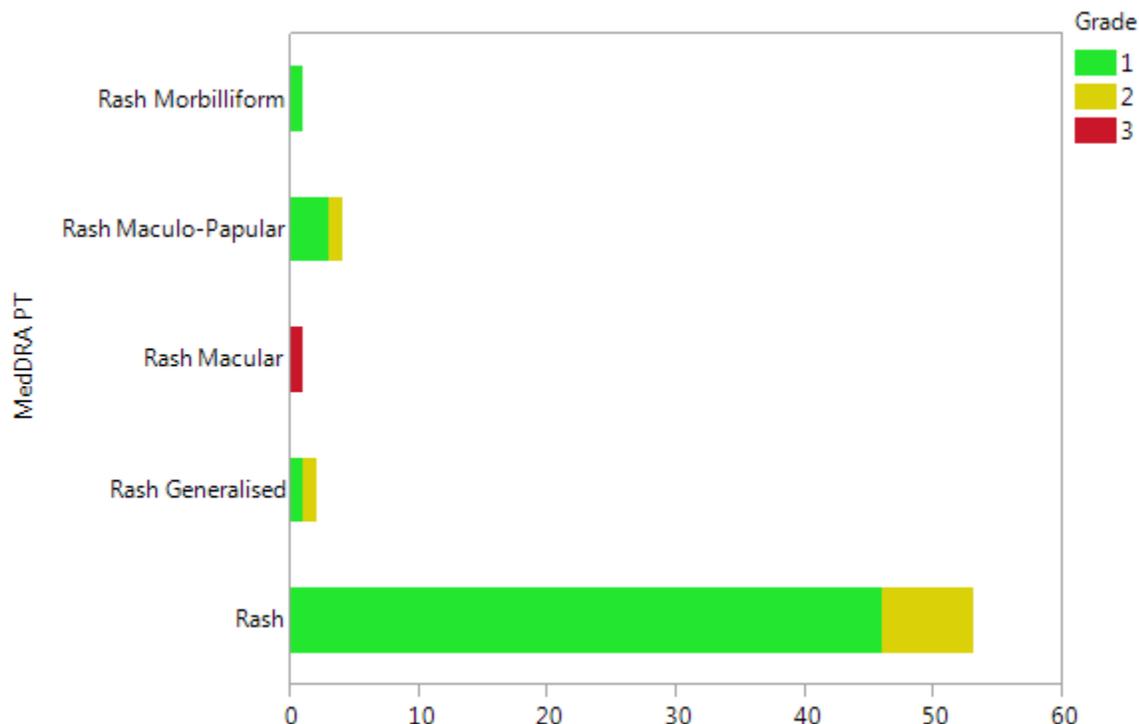
The most common adverse events in study X2101 are listed in Table 21. Gastrointestinal events were the most common.

Table 21. Common adverse events ($\geq 10\%$) in study X2101 as of October 31, 2013 in patients treated at 750mg, n=255 [reviewer analysis, dataset AAEV]

<i>PT</i>	<i>ceritinib 750 mg (N = 255)</i>		
	<i>Events</i>	<i>Number of subjects</i>	<i>Proportion (%)</i>
Diarrhea	669	220	86.27
Nausea	421	209	81.96
Vomiting	400	154	60.39
Alanine aminotransferase increased	336	112	43.92
Fatigue	177	107	41.96
Abdominal pain	185	94	36.86
Decreased appetite	138	91	35.69
Aspartate aminotransferase increased	187	80	31.37
Constipation	99	76	29.8
Cough	99	69	27.06
Abdominal pain upper	97	60	23.53
Dyspnea	72	54	21.18
Asthenia	71	48	18.82
Back pain	62	48	18.82
Blood alkaline phosphatase increased	91	47	18.43
Headache	60	44	17.25
Blood creatinine increased	75	41	16.08
Pyrexia	67	41	16.08
Weight decreased	51	39	15.29
Rash	44	32	12.55
Insomnia	33	31	12.16
Anemia	53	27	10.59
Dizziness	33	27	10.59
Dyspepsia	30	27	10.59
Edema peripheral	29	27	10.59
Hypokalemia	31	26	10.2
Musculoskeletal pain	29	26	10.2

In study X2101, HLT adverse events of “rashes, eruptions and exanthems NEC” were reported in 42/304 (14%) of all patients. The majority of the events at the PT level were grade 1 and “rash” (Figure 9).

Figure 9. , HLT adverse events of “rashes, eruptions and exanths NEC” in study X2101 as of October 31, 2013 [reviewer’s analysis, dataset AAEV, x axis=number of events]



7.4.2 Laboratory Findings

Alanine aminotransferase (ALT); serum glutamic-pyruvic transaminase (SGPT)

Of the 304 patients treated at any dose of ceritinib, 237 patients (78.0%) had a post-baseline grade ALT value that was > grade 0. The most frequent elevations from grade 0 were to grade 1 (35.2%, 90/256). Elevations in ALT from baseline grade 0 to post-baseline > grade 0 were reported for 25/34 patients (73.5%) in the 400-700 mg and for 168/215 patients (78.1%) in the 750 mg dose groups. Elevations to newly occurring grade 3-4 values were reported for 10/39 patients (25.6%) in the 400-700 mg and for 69/255 patients (27.1%) in the 750 mg dose groups.

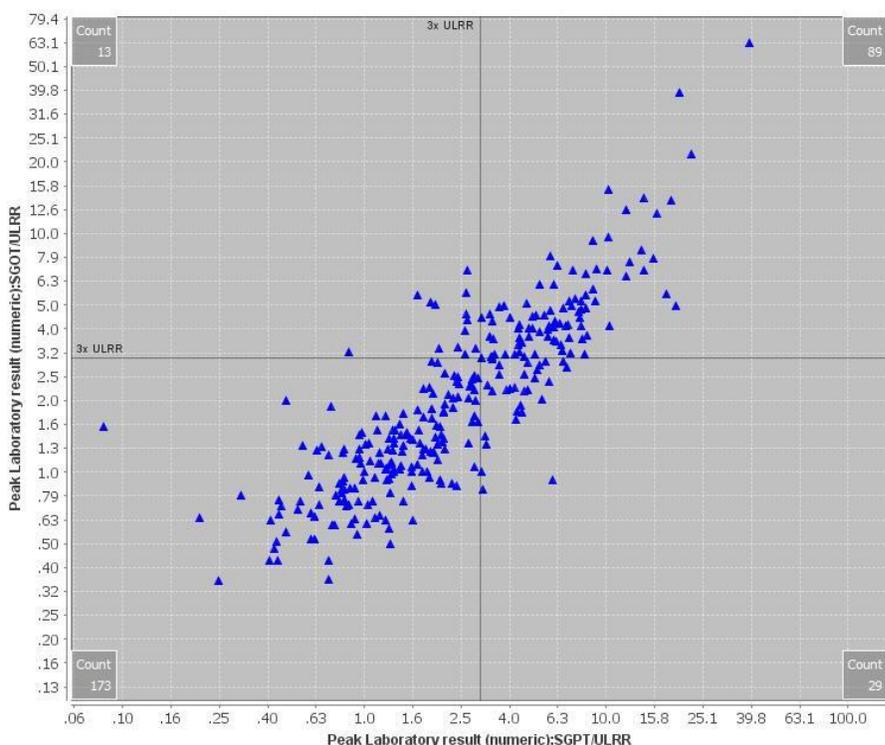
Aspartate aminotransferase (AST); serum glutamic oxaloacetic transaminase (SGOT)

Of the 304 patients treated at any dose of ceritinib, 225 patients (74.0%) had post-baseline grade AST value that was > grade 0. The most frequent elevations from grade 0 were to grade 1 (39.8%, 104/261). Elevations in AST from baseline grade 0 to post-baseline > grade 0 were reported for 24/33 patients (72.7%) in the 400-700 mg and for 161/220 patients (73.2%) in the 750 mg dose groups. Elevations to newly occurring grade 3-4 values were reported for 7/39 patients (17.9%) in the 400-700 mg and for 34/255 patients (13.3%) in the 750 mg dose groups.

Reviewer’s analysis showed that 131 (43.1%) of the 304 patients had peak AST or ALT elevations of ≥ 3 times the upper limit of normal on at least one occasion (Figure 10). There were

114/255 (44.7%) and 17/49 (34.7%) of patients with such measurements in the 750 mg and lower dose groups, respectively.

Figure 10. Peak serum glutamic-pyruvic transaminase (SGPT) and serum glutamic oxaloacetic transaminase (SGOT) elevations in study X2101, all dose groups (n=304; lines represent 3 x upper limit of normal) [reviewer's analysis, dataset ALRS]



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Alkaline phosphatase (ALP)

Of the 304 patients treated at any dose of ceritinib, 229 patients (75.3%) had a post-baseline grade ALP value that was > grade 0. The most frequent elevations from grade 0 were to grade 1 (38.7%, 77/199). Elevations in ALP from baseline grade 0 to post-baseline > grade 0 were reported for 13/21 patients (61.9%) in the 400-700 mg and for 113/172 patients (65.7%) in the 750 mg dose groups. Elevations to newly occurring grade 3 values were reported for 4/39 (10.3%) in the 400-700 mg and for 26/253 patients (10.3%) in the 750 mg dose groups.

Total bilirubin

Of the 304 patients treated at any dose of ceritinib, 41 patients (13.5%) had post-baseline grade total bilirubin value that was > grade 0. Elevations from baseline grade 0 to post-baseline > grade 0 were reported for 2/38 patients (5.3%) in the 400-700 mg and for 35/249 patients (14.1%) in the 750 mg dose groups. Elevations to newly occurring grade 3 values were reported for none of the patients in the 400-700 mg and for 2/255 patients (0.8%) in the 750 mg dose groups. No elevations to grade 4 values were observed.

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Hy's law analysis

The reviewer's initial analysis showed 3 potential cases of Hy's law (Figure 11). Upon further review of the treatment pattern, timing of the laboratory abnormalities, and concomitant medications, only one subject remained a probable case (Figure 12), although this patient had a rise in total bilirubin levels during treatment discontinuation and as AST and ALT levels were trending down. Early during treatment, this patient had an elevated ALP, which is more consistent with cholestasis.

Figure 11. Hy's law analysis in study X210, all patients, n=304. Three cases met criteria (upper right) [reviewer's analysis, dataset ALRS]

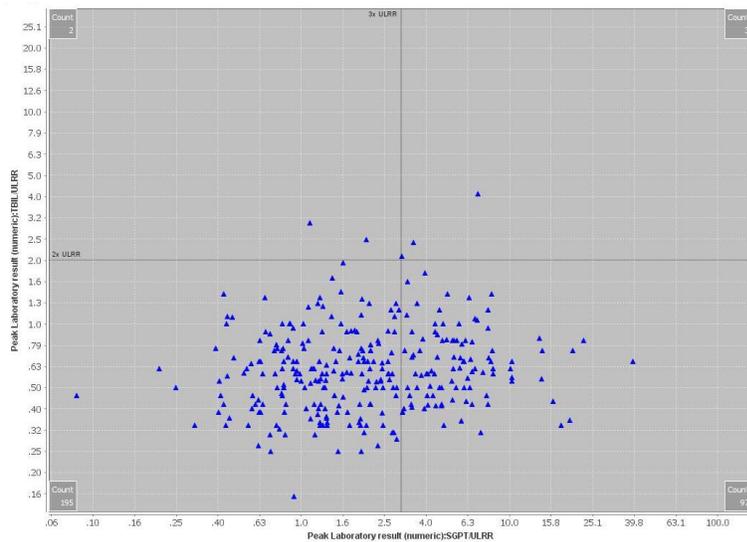
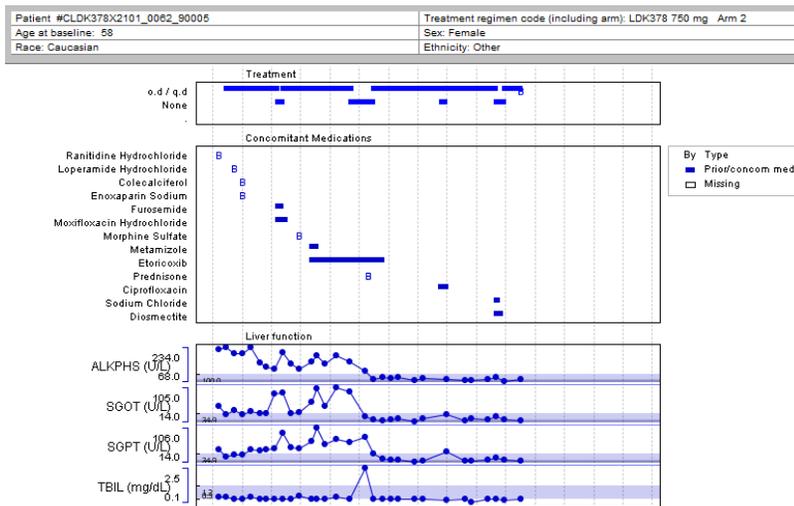


Figure 12. Treatment pattern, concomitant medications and laboratory trends a potential case of Hy's law in study X2101 [reviewer's analysis]



Glucose

Of the 304 patients treated at any dose of ceritinib, 150 patients (49.3%) had post-baseline > grade 0 values for glucose (including patients with missing baseline). The most frequent elevations from grade 0 were to grade 1 (27.4%, 65/237). Elevations in glucose from baseline grade 0 to post-baseline > grade 0 were reported for 14/30 patients (46.7%) in the 400-700 mg and for 89/197 patients (45.2%) in the 750 mg dose groups. Elevations to newly occurring grade 3-4 values were reported for 1/38 patients (2.6%) in the 400-700 mg and for 32/255 patients (12.5%) in the 750 mg dose groups.

A risk ratio analysis was conducted by the applicant at the reviewer's request to assess the risk of grade 3 and 4 hyperglycemia in patients taking corticosteroids and those with history of diabetes or other glucose intolerance based on medical history records with Preferred Terms matching any of the following: "Type 2 Diabetes Mellitus", "Diabetes Mellitus", "Blood Glucose Increased", "Hyperglycemia", or "Impaired Fasting Glucose". The estimated risk of grade 3/4 hyperglycemia was 5.7 times higher (95% CI: 3.18, 10.08) for patients with a history of diabetes or other glucose intolerance versus all other patients and 2.4 times higher (95% CI: 1.21, 4.75) for patients with concomitant use of corticosteroids versus all other patients.

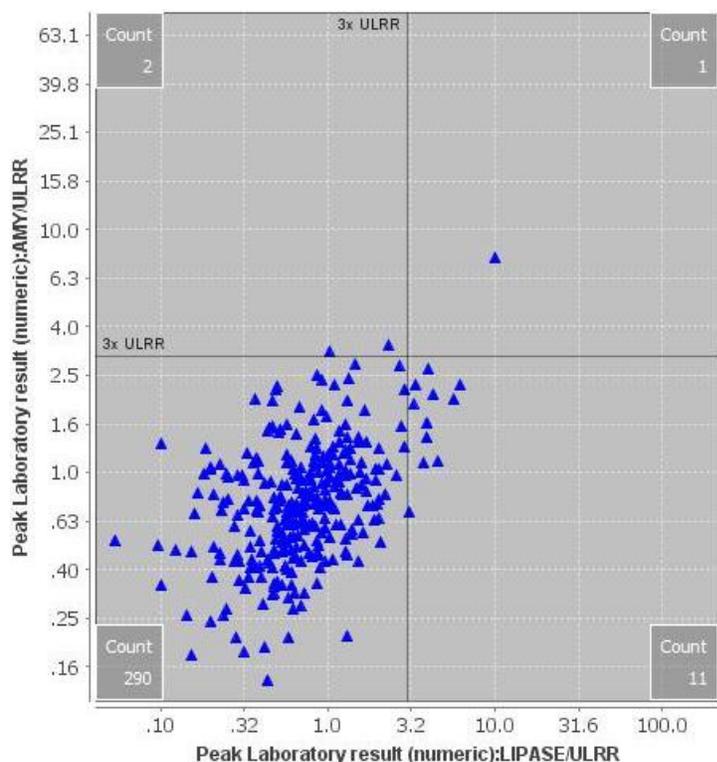
Amylase and Lipase

Of the 304 patients treated at any dose of ceritinib, 80 patients (26.3%) had post-baseline > grade 0 values for amylase. The most frequent elevations from grade 0 were to grade 1 (14.9%, 40/269). Elevations in amylase from baseline grade 0 to post-baseline > grade 0 were reported for 5/37 patients (13.5%) in the 400-700 mg and for 45/222 patients (20.3%) in the 750 mg dose groups. Elevations to newly occurring grade 3-4 values were reported for 1/39 patients (2.6%) in the 400-700 mg and for 14/255 patients (5.5%) in the 750 mg dose groups.

Of the 304 patients treated at any dose of ceritinib, 91 patients (29.9%) had post-baseline > grade 0 values for lipase. The most frequent elevations from grade 0 were to grade 1 (14.7%, 43/292). Elevations in lipase (hyper) from baseline grade 0 to post-baseline > grade 0 were reported for 15/38 patients (39.5%) in the 400-700 mg and for 66/244 patients (27.0%) in the 750 mg dose groups. Elevations to newly occurring grade 3-4 values were reported for 3/39 patients (7.7%) in the 400-700 mg and for 26/255 patients (10.2%) in the 750 mg dose groups.

Reviewer's analysis showed that 14/304 (4.6%) of patients had peak amylase or lipase elevations of ≥ 3 times the upper limit of normal on at least one occasion (Figure 13)

Figure 13. Peak amylase and lipase elevations in study X2101, all dose groups (n=304; lines represent 3 x upper limit of normal) [reviewer's analysis, dataset ALRS]



Creatinine

Of the 304 patients treated at any dose of ceritinib, 173 patients (56.9%) had post-baseline creatinine (hyper) values that were > grade 0. Elevations were observed from grade 0 to grade 1 (17.6%, 52/296), grade 0 to grade 2 (36.8%, 109/296) and grade 1 to grade 2 (75.0%, 6/8). Elevations in creatinine from baseline grade 0 to post-baseline > grade 0 were reported for 22/38 patients (57.9%) in the 400-700 mg and for 140/248 patients (56.5%) in the 750 mg dose groups. Elevations to newly occurring grade 3 values were reported for none of the patients in the 400-700 mg and for 4/255 patients (1.6%) in the 750 mg dose groups.

Hematology

Decreased lymphocytes: Post-baseline grade 3-4 values were reported for 88/304 patients (28.9% overall, and for 15/39 (35.9%) in the 400-700 mg and for 71/255 (27.8%) in the 750 mg dose groups.

Decreased neutrophils: Post-baseline grade 3-4 values were reported for 6/304 patients (2.0% overall, none of the patients in the 400-700 mg and for 6/255 (2.4%) in the 750 mg dose groups.

Decreased hemoglobin: Post-baseline grade 3-4 values were reported for 15/304 patients (4.9% overall, and for 1/39 (2.6%) in the 400-700 mg and for 13/255 (5.1%) in the 750 mg dose groups.

Decreased WBC: Post-baseline grade 3-4 values were reported for 4/304 patients (1.3%) overall, none of the patients in the 400-700 mg and for 4/255 (1.6%) in the 750 mg dose groups.

Testosterone

Among the 76 patients with available baseline testosterone values, 31 patients had a low baseline value, 43 had a normal value and 2 had a high baseline value. For the 31 patients with a low baseline value, testosterone remained low for 18 patients, shifted to normal for 11 patients and shifted to high in 1 patient. For the 43 patients with a normal baseline value, 8 patients shifted to low, 2 shifted to high, and 32 patients maintained a normal testosterone level. For the 2 patients with high baseline value, post-baseline testosterone was available only in 1 patient and it was also high.

FSH

Among the 71 patients (53.0%) with available baseline FSH values, 6 patients had a low baseline value, 33 had a normal value and 32 had a high baseline value. For the 6 patients with a low baseline value, FSH remained low for the 3 patients with available post-baseline value. For the 33 patients with a normal baseline value, 2 shifted to low, 23 maintained abnormal FSH level, and 7 shifted to high. For the 32 patients with high baseline value, FSH shifted to normal for 1 patient and remained high in 29 patients.

LH

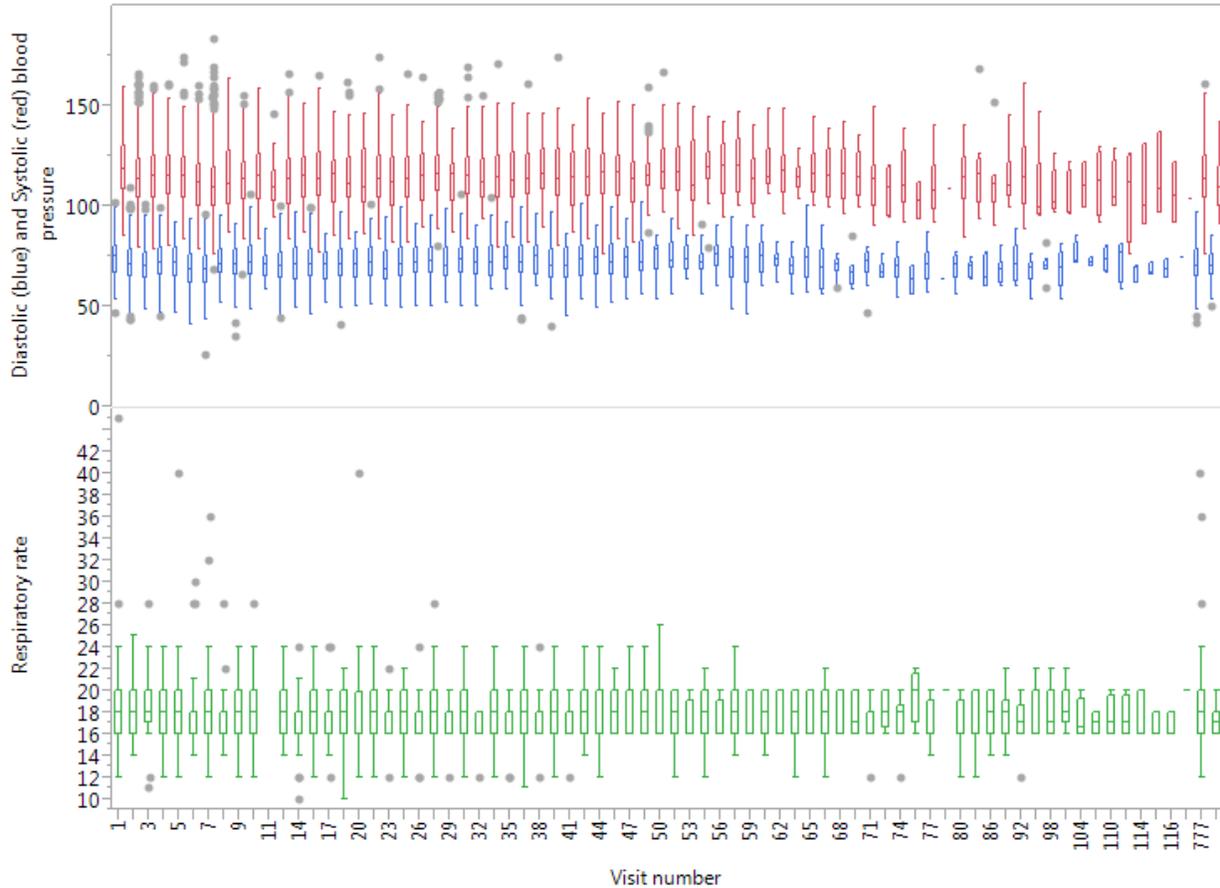
Among the 71 patients (53.0%) with available baseline LH values, 6 patients had a low baseline value, 52 had a normal value and 13 had a high baseline value. For the 6 patients with a low baseline value, LH remained low for 2 patients and shifted to normal for 1 of the patients with available post-baseline value. For the 52 patients with a normal baseline value, 3 shifted to low, 32 maintained a normal LH level, and 14 shifted to high. For the 13 patients with high baseline value, LH shifted to normal for 2 patients and remained high in 10 patients.

Overall, adequate evaluation of the anti-androgenic effects with ceritinib treatment is not possible based on the limited data provided. Ceritinib was shown to lower testosterone, FSH, and LH in a minority of the patients tested.

7.4.3 Vital Signs

Overall, no general effects on blood pressure and respiratory rate were seen over time in study X2101 as of October 31, 2013 (Figure 14).

Figure 14. Trends overtime in blood pressure and respiratory rate in study X210 as of October 31, 2013, all patients (n=304) [reviewer’s analysis, dataset AVSN]



Sitting pulse over time in study X2101 is shown in Figure 15. The reviewer’s analysis showed an overall lowering of sitting pulse in the study (Figure 16) with the majority of patients having a decline in sitting pulse as compared to baseline corresponding to 85/304 (27.9%) new cases of bradycardia (where baseline >60 but minimum rate of <60bpm on at least one occasion) with the majority between 50-60 bpm (Figure 17).

Clinical/Statistical Review
Sean Khozin, MD, MPH and Lijun Zhang, PhD
NDA 205755
Ceritinib (Zykadia, LDK378)

Figure 15. Sitting pulse over time in study X2101, all patients (n=304) [reviewer's analysis, dataset AVSN]

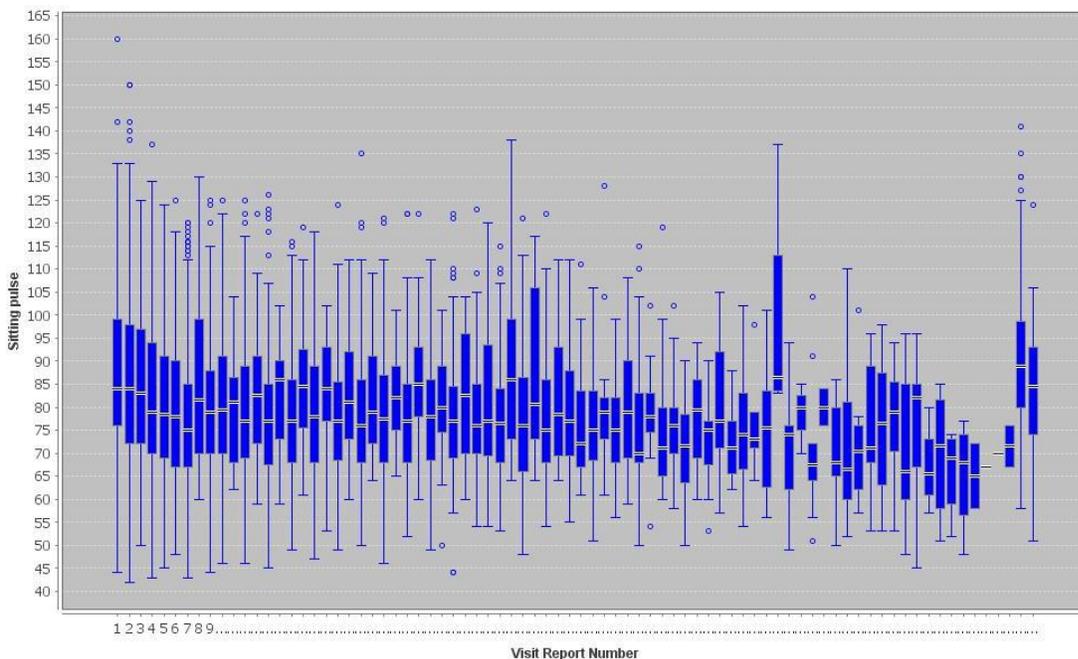


Figure 16. Change in sitting pulse from baseline in study X2101, all patients (n=304) [reviewer's analysis, dataset AVSN]

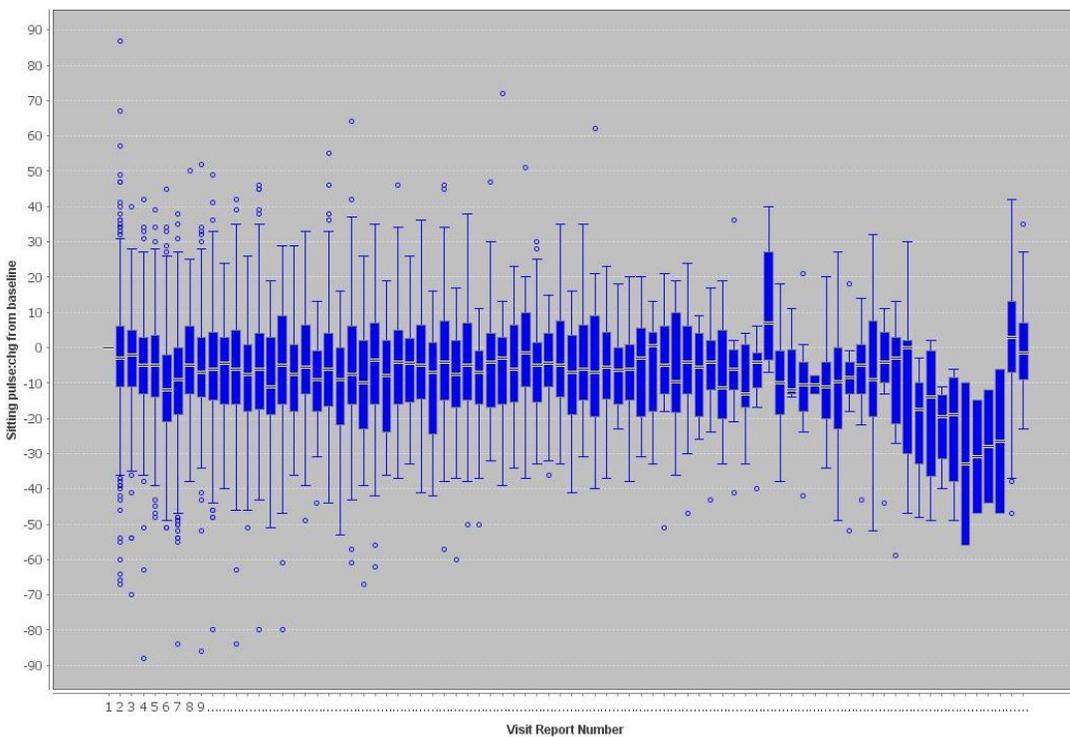
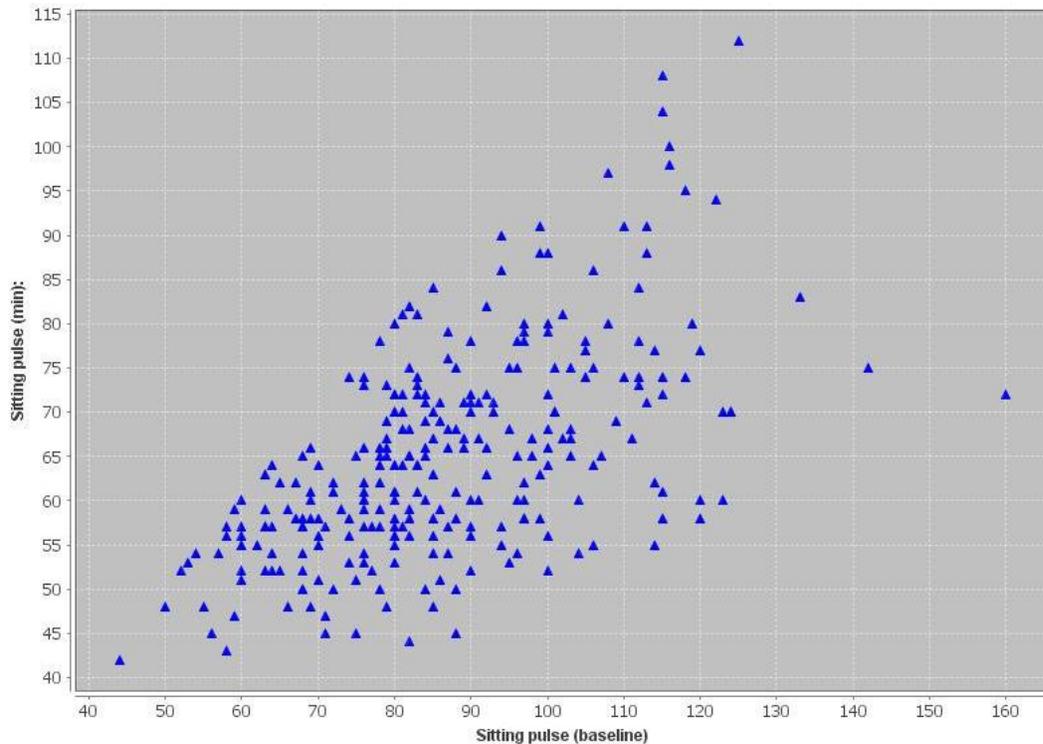


Figure 17. Minimum sitting pulse versus baseline measurements in study X2101, all patients (n=304) [reviewer's analysis, dataset AVSN]



7.4.4 Electrocardiograms (ECGs)

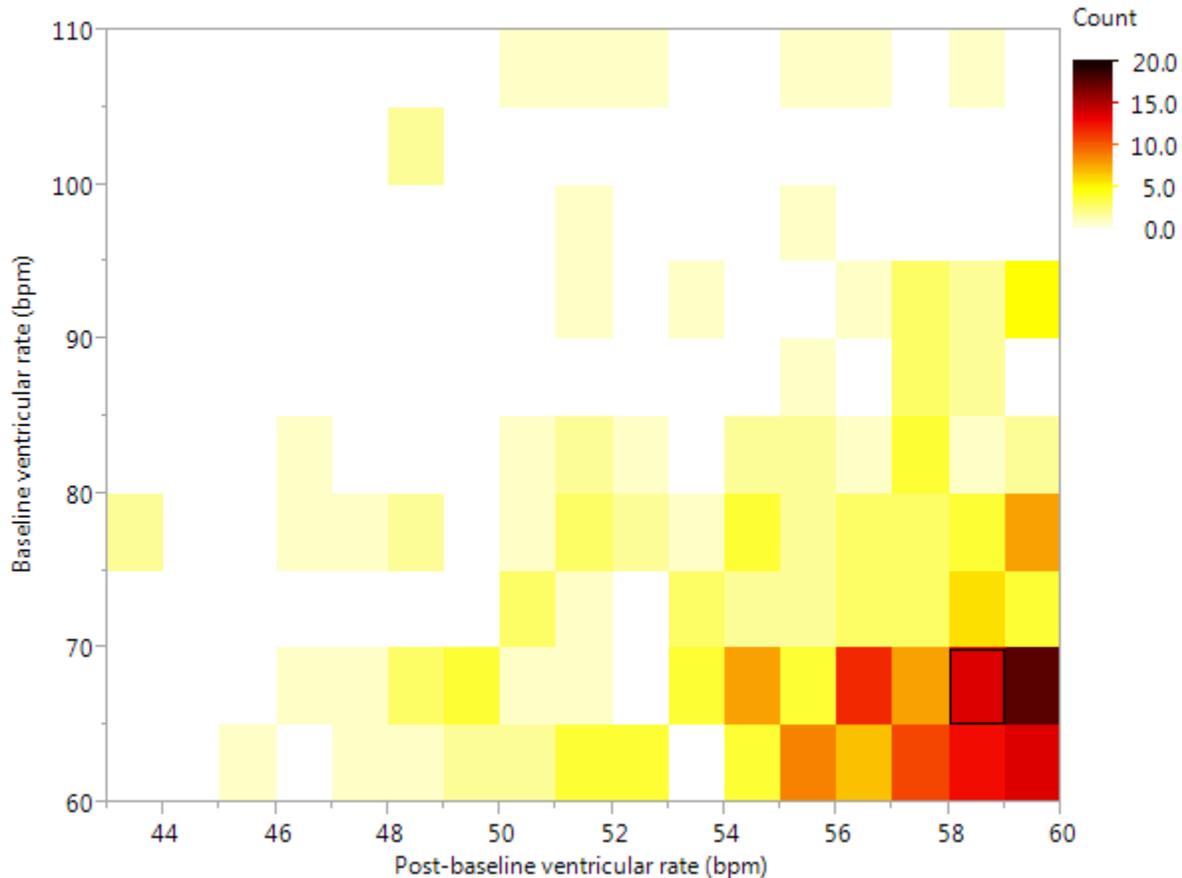
Evaluable patients for analyses based on changes from baseline are those with a baseline ECG and at least one post-baseline ECG.

Heart rate

Of the 303 evaluable patients with ECG data, the applicant reported 9 patients (3.0%) had a >25% decrease in heart rate from baseline to < 50 bpm (the applicant's cutoff for bradycardia) and at steady state (pre-dose on Cycle 2 Day 1, 260 evaluable patients in any treatment group) there was an average decrease in heart rate of -8.9 bpm (SD = 12.95). Sinus bradycardia was noted as a newly occurring abnormal finding in 2 patients (0.7%, 750 mg/day treatment dose group).

The reviewer's analysis defining bradycardia as a ventricular rate (VR) < 60 bpm showed that 86 (28.4%) patients with baseline VR > 60 bpm had bradycardia at least on one measurement. Most of these post baseline VR's in this group clustered between 50-60 bpm in patients with a baseline VR of 60 to 80 bpm (Figure 18). The median absolute change in VR (multiple measurements per patient) in the new cases of bradycardia was -14 bpm (range -58.3 to -1). These results are consistent with heart rate measurements based on sitting pulse described previously.

Figure 18. Ventricular rate in new cases of bradycardia (rate <60 bmp): baseline vs post baseline [reviewer's analysis, dataset AECG, count refers to number of events]



QT interval

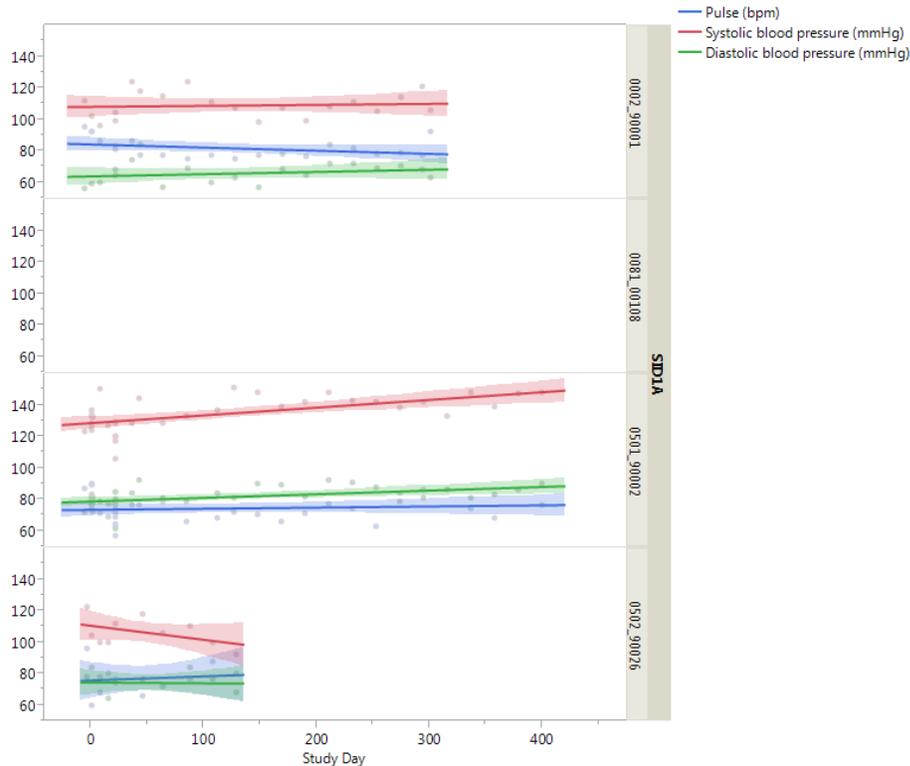
The applicant's analysis showed 10 patients (3.3%) out of 299 evaluable patients had a new QTcP > 480 ms post baseline, 1 (0.3%) patient had a new QTcP > 500ms, and 7 patients (2.3%) had a QTcP change from baseline > 60 ms (Table 12-19). At steady-state (pre-dose on Cycle 2 Day 1, 260 evaluable patients in any treatment group), there was an average increase from baseline in QTcP of 12.9 ms (SD = 16.53).

The reviewer's analysis of ECG data based on corrected QTc using Bazett's formula is shown in Figure 20. In this analysis, 5 patients had new QTc elevation >500 ms. It should be noted that Bazett's correction overcorrects at elevated heart rates and under corrects at heart rates below 60 beats per minute. The reviewer's analysis of QTc using Fridericia's formula showed 1 case above 500ms. There were 4 single events of syncope in the following patients, none with significant ECG changes:

- X2101-0081-00108: Grade 3 syncope.
- X2101-0002-90001: Grade 3 syncope.
- X2101-0501-90002: Grade 3 syncope.

- X2101-0502-90026: Grade 1 syncope.

Figure 19. Pulse, systolic and diastolic blood pressure in patients with syncope in X2101 [reviewer's analysis, dataset AVSN] (SIDIA=patient ID; data on vitals not found for 0081-0018 in AVSN)

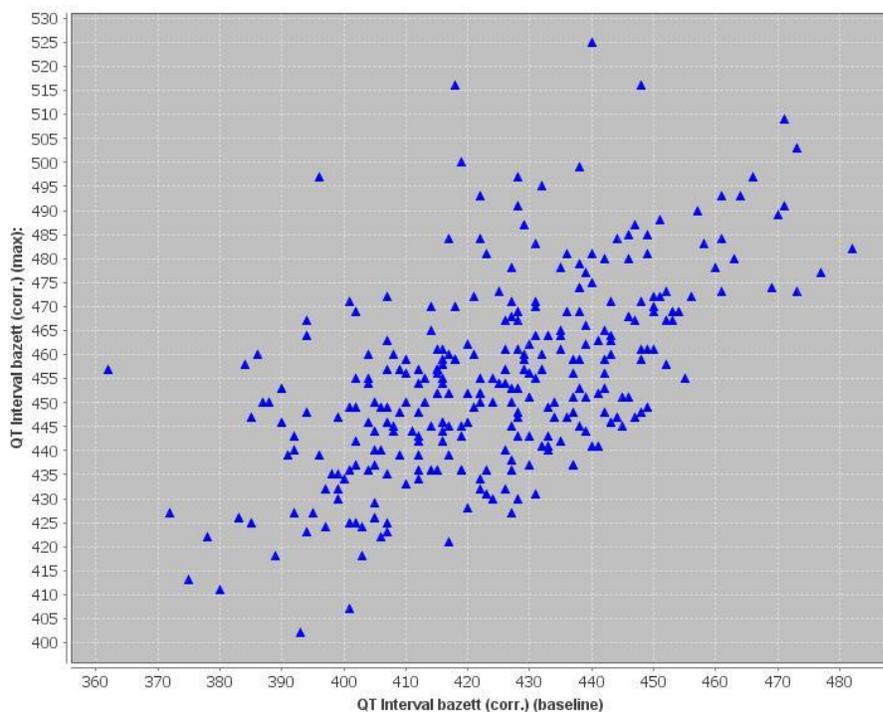


Vitals for patients with syncope remained stable throughout the trial (Figure 19). Narratives for the cases of syncope were requested and reviewed and did not show a clear association between the use of ceritinib and syncope. For patient 0081-0018, for whom no vitals were found in dataset AVSN, heart rate was generally in the 52-80 bpm range. Systolic blood pressure was in the 90-120 mmHg range, and the diastolic blood pressure was in the 50-80 mmHg range. On ECGs throughout the study, the QT interval remained <450 ms; heart rate was 54-101 bpm; and there were no abnormalities aside from one episode of sinus tachycardia at baseline. All 4 patients had syncope in an unmonitored setting, i.e., no vitals captured during episodes.

Overall, ceritinib has the potential to increase the QT interval. In study X2101, no discontinuation due to QT interval occurred and in 4 cases (1.3%), dose adjustments/interruptions were needed. None appeared to be clearly associated with clinically significant symptoms.

Figure 20. QTc interval analysis based on Bazett's formula [reviewer's analysis, ECG dataset]

Baseline vs Max Value Scatter Plot - All Patients



PR interval

Of the 302 evaluable patients, 27 patients (8.9%) had a newly occurring PR > 200 ms. The mean increase in PR from baseline at steady-state was 3.1 ms (SD = 12.47). First degree AV block was noted as a newly occurring abnormal finding in 19/298 evaluable patients (6.4%).

QRS interval

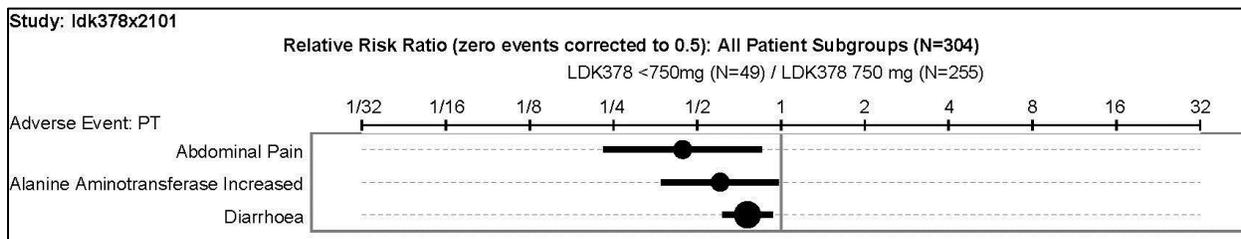
Of the 303 evaluable patients, 5 patients (1.7%) had a newly occurring QRS > 110 ms, and none had QRS > 120 ms.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

At the recommended dose of 750 mg, the majority of the patients in X2101 had dose interruption/reduction, primarily due to gastrointestinal adverse events or hepatotoxicity. In an exploratory analysis of dose dependency for adverse events in study X2101, abdominal pain, diarrhea, and ALT increase occurred significantly more frequently in the 750mg dose group (n=255) compared with the 50-700mg dose cohort (n=49) (Figure 21).

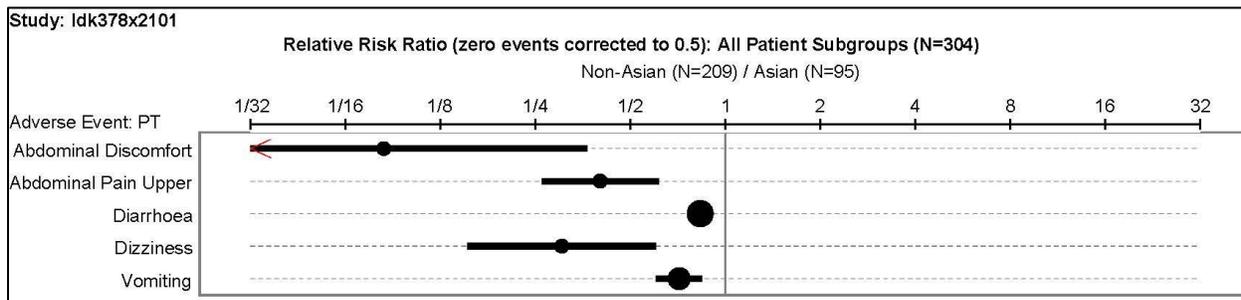
Figure 21. Dose dependency for adverse events in study X210, October 31, 2013 cutoff data [reviewer's analysis, AAEV dataset]



7.5.3 Drug-Demographic Interactions

Subgroup analysis of safety by age, race and gender, assessed by the incidence of AEs did not reveal relevant clinically meaningful differences. The applicant's analysis suggested that the Asian population was predicted to have approximately 10% higher steady-state exposure (as assessed by C_{max} , AUC_{tau} and C_{min}) compared to non-Asian population. This race difference in ceritinib exposures was explained by the applicant likely due to the difference in body weight (mean body weight for Asians vs. non-Asians: 61.3 kg vs. 72.3 kg). The reviewer's exploratory analysis showed that diarrhea, vomiting, abdominal pain/discomfort, and dizziness may be significantly increased in the Asian population (Figure 22). The results are limited by the small number of patients in the AE subgroups.

Figure 22. Adverse events in study X2101 in Asian vs Non-Asian subjects, October 31, 2013 update [reviewer's analysis, AAEV dataset]



7.5.5 Drug-Drug Interactions

CYP3A contributes to the majority of the hepatic microsomal oxidative metabolism of ceritinib. Exposure of ceritinib may therefore be influenced by co-administered agents that affect CYP3A. In healthy subjects, co-administration of a single 450 mg ceritinib dose with ketoconazole (200 mg twice daily for 14 days), a strong CYP3A inhibitor, resulted in 2.9-fold and 1.2-fold increase in ceritinib AUC_{inf} and C_{max} , respectively, compared to when ceritinib was given alone. Co-administration of ceritinib with strong CYP3A inhibitors increases ceritinib plasma concentrations. Concomitant use of strong CYP3A inhibitors should be avoided. Co-administration of ceritinib with moderate CYP3A inhibitors should be carefully monitored.

In healthy subjects, co-administration of a single 750 mg ceritinib dose with rifampin (600 mg daily for 14 days), a strong CYP3A inducer, resulted in 70% and 44% decreases in ceritinib AUC_{inf} and C_{max}, respectively, compared to when ceritinib was given alone. Co-administration of ceritinib with strong CYP3A inducers decreases ceritinib plasma concentrations. Concomitant use of strong CYP3A inducers should be avoided.

7.6 Additional Safety Evaluations

7.6.2 Human Reproduction and Pregnancy Data

There are no clinical data with ceritinib in pregnant women.

8. Postmarketing Experience

None

9 Appendices

9.1 Literature Review/References

See “References” at the end of this review.

9.2 Labeling Recommendations

The review teams did not object to the trade name of [ZYKADIA]. Major labeling recommendations are as follows:

- Limit indication to metastatic patients since all enrolled patients in X2101 had been treated with crizotinib for advanced disease.
- Limit indication to patients who have progressed on or are intolerant to crizotinib to reflect the treated population in X2101.
- Include exploratory efficacy analyses of ORR in Asian versus non-Asian patients
- Add gastrointestinal toxicity, bradycardia, hyperglycemia to Warning and Precautions.

9.3 Advisory Committee Meeting

No advisory committee meeting was held. A special government employee (SGE) and patient representative are scheduled to be consulted for this application. They will be asked to comment on the proposed label and the benefit-risk profile of ceritinib for the proposed indication.

References

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- ¹ Siegel R, Naishadham D, Jemal A (2012) Cancer Statistics 2012. *CA Cancer J Clin*; 62(1):10-29
 - ² Marino P, Pampallona S, Preatoni A, et al. Chemotherapy vs supportive care in advanced non-small-cell lung cancer. Results of a meta-analysis of the literature. *Chest* 1994; 106(3): 861-865.
 - ³ Kelly K, Crowley J, Bunn PA, et al. Randomized Phase III Trial of Paclitaxel Plus Carboplatin Versus Vinorelbine Plus Cisplatin in the Treatment of Patients With Advanced Non-Small-Cell Lung Cancer: A Southwest Oncology Group Trial. *JCO*. 2001;19(13):3210–3218.
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 - ⁵ Fossella F, Pereira JR, Pawel J von, et al. Randomized, Multinational, Phase III Study of Docetaxel Plus Platinum Combinations Versus Vinorelbine Plus Cisplatin for Advanced Non-Small-Cell Lung Cancer: The TAX 326 Study Group. *JCO*. 2003;21(16):3016–3024.
 - ⁶ Pao W, Girard N. New driver mutations in non-small-cell lung cancer. *The Lancet Oncology*. 2011;12(2):175–180.
 - ⁷ Gainor JF, Varghese AM, Ou SH, et al. ALK rearrangements are mutually exclusive with mutations in EGFR or KRAS: an analysis of 1,683 patients with non-small cell lung cancer. *Clin Cancer Res*. 2013 Aug 1;19(15):4273-81
 - ⁸ Kwak EL, Bang YJ, Camidge DR, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. *N Engl J Med*; 363:1693-703.
 - ⁹ FDA News Release. <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm269856.htm>. Accessed March 24, 2014.
 - ¹⁰ Katayama R, Shaw AT, Khan TM, et al. Mechanisms of Acquired Crizotinib Resistance in ALK-Rearranged Lung Cancers. *Sci Transl Med*. 2012;4(120):120ra17–120ra17.

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/s/

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CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 205755

Applicant: Novartis

Stamp Date: December 24, 2013

Drug Name: Ceritinib (LDK378) NDA Type: NME, Priority Review

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			Cross referenced to Summary of Clinical Safety in 2.7.4 with ISS appendices in section 5.3.5.3.
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			X	Results are from a single trial summarized in 2.7.3: Summary of Clinical Efficacy
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				The Application is a 505(b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Study Number: CLDK378X2101 Study 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)	X			

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Sample Size: 304 Location in submission: Section 5.3.5.2 .				
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?	X			Claim is based on a one single arm study (CLDK378X2101) in addition to a supportive single arm study (CLDK378X1101)
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			Efficacy based on single arm studies that appear adequate.
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	CLDK378X2101 was conducted in U.S.
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (<i>e.g.</i> , QT interval studies, if needed)?	X			
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and	X			

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	adverse dropouts (and serious adverse events if requested by the Division)?				
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (<i>e.g.</i> , label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			X	The drug has been granted orphan drug designation by FDA.
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	CLDK378X2101 was conducted in U.S.
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? YES

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Reviewing Medical Officer

Date

Clinical Team Leader

Date

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/s/

SEAN N KHOZIN
01/21/2014

GIDEON M BLUMENTHAL
01/21/2014