CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205755Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 205755 (**Priority Review**)	**Reviewer:** Okpo Eradiri, PhD	
Division:	DOP2		
Applicant:	Novartis	**Biopharmaceutics Team Leader:** Angelica Dorantes, PhD	
Trade Name:	Zykadia Capsules, 150 mg	**Acting Biopharmaceutics Supervisory Lead:** Richard Lostritto, PhD	
Generic Name:	Ceritinib Capsules, 150 mg	**Date Assigned:**	1/8/2014
Indication	Treatment of patients with (b) (4) metastatic non small cell lung cancer (NSCLC) who have (b) (4)	**Date of Review:**	3/25/2014
Formulation/ Strength	Capsule/ 150 mg		
Route of Administration	Oral		

SUBMISSIONS REVIEWED IN THIS DOCUMENT		
Submission Dates	**Date of Informal/Formal Consult**	**Primary Review due in DARRTS**
11/27/2013		3/25/2014

Type of Submission:	505 (b)(1) Application (NME)
Key review points:	- Dissolution method and acceptance criteria - Bridging of three manufacturing sites

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I) SUMMARY OF BIOPHARMACEUTICS FINDINGS

This is a rolling NDA submission with Priority Review status and Breakthrough Therapy designation. The drug molecule, an NME, has been granted an Orphan designation.

Ceritinib (also referred to as LDK378 by the Applicant) is an ATP-competitive inhibitor of anaplastic lymphoma kinase (ALK) activity. The drug product has been formulated as a single-entity immediate-release 150 mg capsule (hard gelatin capsule, size 00) for oral use. Ceritinib is said to inhibit *in-vitro* and *in-vivo* autophosphorylation of ALK, ALK-mediated phosphorylation of downstream signaling proteins, and proliferation of ALK-dependent cancer cells. The drug substance is achiral.

The definitive clinical study in the NDA is a Phase 1 open-label, dose-escalation study that investigated the safety, PK, PD and anti-tumor activity of the drug in patients with tumors confirmed to have genetic abnormalities in ALK. The Application also contains a dose-escalation phase of a study in Japanese patients with tumors characterized by genetic alterations in ALK. The Biopharmaceutics review is focused on the evaluation and acceptability of the following:

- Adequacy of the dissolution method;
- Adequacy of the proposed dissolution acceptance criterion;
- Acceptability of the data supporting the bridging of the sites used to manufacture the clinical batches.

The electronic links associated with biopharmaceutics are as follows:

Pharmaceutical Development: \\cdsesub1\evsprod\nda205755\0002\m3\32-body-data\32p-drug-prod\ldk378-hard-gelatin-capsule-01\32p2-pharm-dev\pharmaceutical-development.pdf

Specifications Table: \\cdsesub1\evsprod\nda205755\0002\m3\32-body-data\32p-drug-prod\ldk378-hard-gelatin-capsule-01\32p5-contr-drug-prod\32p52-analyt-proc\specifications-tm-150mg.pdf

1) Dissolution Method and Acceptance Criterion:

The Applicant's proposed dissolution method and acceptance criterion are:

USP Apparatus/RPM	Medium/Temperature	Volume	Acceptance Criterion
II/60 rpm	0.01M HCl, pH 1 at 37 °C	900 mL	Q = (b) (4) % at (b) (4) min

The proposed dissolution method is acceptable. However, the proposed acceptance criterion is not acceptable for the following reasons:

Based on the provided dissolution data, an acceptance criterion of Q = (b) (4)% at 15 min is recommended.

2) Bridging of the sites used to manufacture the clinical batches

The comparative dissolution data of representative batches from three different manufacturing sites exhibited similar in-vitro drug release profiles. Bridging of the manufacturing sites has therefore been established and is acceptable.

II) RECOMMENDATION

The ONDQA/Biopharmaceutics team has reviewed NDA 205-755 and its amendments submitted on March 4, 2014 and March 21, 2014, and find the biopharmaceutics data/information acceptable. In a teleconference on March 24, 2014, the Applicant accepted FDA's recommended acceptance criterion of Q = (b) (4)% at 15 min Therefore, from the Biopharmaceutics perspective, APPROVAL is recommended for NDA 205-755 for Ceritinib Capsules, 150 mg.

The following dissolution method and acceptance criterion should be implemented for release and on stability:

Apparatus/RPM	Medium	Volume	Acceptance Criteria
USP Apparatus 2 at 60 rpm	0.01M HCl, pH 1	900 mL	Q = (b) (4)% at 15min

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III) QUESTION BASED REVIEW – BIOPHARMACEUTICS EVALUATION

A) GENERAL ATTRIBUTES

1 What are the highlights of the chemistry and physico-chemical properties of the drug substance (e.g. solubility) and formulation of the drug product?

Drug Substance

Ceritinib is an NME; its chemical structure is displayed in Figure 1.

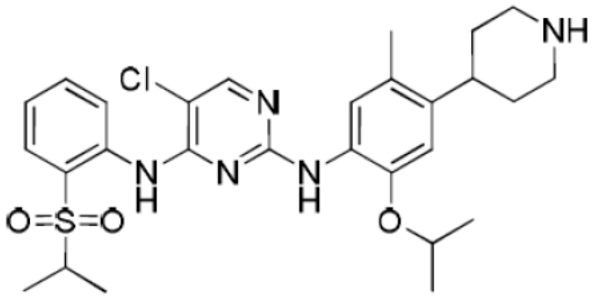

Figure 1: Structural formula of Ceritinib (C28H36ClN5O3S; M.Wt = 558.14)

Ceritinib is practically insoluble in water (0.02 mg/mL) but very soluble in methanol (18 mg/mL). The drug molecule is also soluble in 0.01M - 0.1M hydrochloric acid. The solubility of ceritinib over the physiologic pH range and in different solvents is presented in Table 1. In general, solubility of ceritinib decreases with increasing pH; the pKa values are 9.7 and 4.1.

The drug substance is achiral and non-hygroscopic. (b) (4)

Table 1: Solubility of ceritinib in different solvents and at different pH values.

Solvent	Solubility (mg/mL) at 25°C
Water	0.02
Ethanol	4.3
Methanol	18.3
Isopropanol	3.9
Acetonitrile	3.3
Water/Acetonitrile/Trifluoroacetic acid 800:200:1 (v/v/v)	8.4
Water/Acetonitrile 1:1 (v/v)	2.4
0.1N HCl	11.9
0.01N HCl	5.5
0.001N HCl	0.64
pH 4.5	0.03
pH 5.0	0.04
pH 6.0	0.01
pH 6.8	0.01
pH 8.0	0.003
pH 9.0	0.1

Drug Product

The proposed drug product is formulated as a 150 mg size 00 hard gelatin capsule, weighing approximately 493 mg. The composition of the drug product is presented in Table 2.

Table 2: Quantitative composition of Ceritinib Capsules, 150 mg.

Ingredient	Amount per 150 mg Capsule (mg)	Function	Reference to standards
Capsule fill			
LDK378	150.00	Active ingredient	Novartis monograph
Microcrystalline Cellulose	(b) (4)	(b) (4)	USP / NF
(b) (4) Hydroxypropyl Cellulose			USP / NF
Sodium Starch Glycolate			USP / NF
Magnesium Stearate [1]			USP / NF
Colloidal (b) (4)			USP / NF
Capsule fill weight			
Empty capsule shell, pre-printed			
Capsule shell (theoretical weight)			Novartis monograph
Ink – black [2]			
Total capsule weight (approx.)	**493.00**	**--**	

[1]

2 Is there any information on BCS classification? What claim did the applicant make based on BCS classification? What data are available to support this claim?

The Applicant performed permeability experiments to compare Ceritinib to mannitol (a low permeability marker) and propranolol (high permeability marker) and classified the API as a low permeability drug. The drug also exhibits low aqueous solubility at neutral to high pH values. The Applicant therefore designates Ceritinib as a BCS Class 4 compound. The Applicant also designates Ceritinib as a substrate for the apical efflux transporter, P-glycoprotein.

B.1. DISSOLUTION INFORMATION

3 What is the proposed dissolution method?

The Applicant's proposed dissolution method testing conditions can be summarized as follows:

Apparatus:	USP 2 (Paddle)
Medium:	900 mL 0.01M HCl
Temperature:	37 ± 0.5 ˚C
Rotation speed:	60 (b) (4)
Proposed Spec Sampling Time:	(b) (4) min
Analysis:	(b) (4)

4 What data are provided to support the adequacy of the proposed dissolution method (e.g medium, apparatus selection, etc.)?

4.1 *Dissolution Medium Selection*

The following media were used to perform dissolution testing of 150 mg Ceritinib Capsules (batch # 1010000958) in USP (b) (4) 2 (paddle):

0.01M HCl, (b) (4)

A rotation speed of (b) (4) rpm was used in (b) (4) while 60 rpm was used for Apparatus 2; in addition, (b) (4) UV was used for the paddle. The Applicant

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Based on the data submitted with the original Application and the new data sets provided on March 20, 2014, the most appropriate acceptance criterion for this putative formulation of Ceritinib is:

Q = (b) (4) % at 15 min.

C) DRUG PRODUCT FORMULATION DEVELOPMENT AND BRIDGING ACROSS PHASES

11 What are the highlights of the drug product formulation development?

No rigorous formulation development has been undertaken by the Applicant at this stage of clinical development of the drug product. The manufacturing process involves (b) (4)

(b) (4) Although several strengths were made and used in the early phase of development, only the 150 mg strength is currently submitted for approval.

12 Are all the strengths evaluated in the pivotal clinical trials? What data are available to support approval of lower strengths?

The Applicant is seeking approval for only one dosage strength, 150 mg.

13 Are there any manufacturing changes implemented (e.g. formulation changes, process changes, site change, etc.) to the clinical trial formulation? What information is available to support these changes?

There are no manufacturing changes to be assessed in the NDA. However, three different sites (one in the United States and two in Switzerland) were used to manufacture the clinical batches. In the February 18, 2014 IR Letter, the following comment was included to request bridging data for the 3 manufacturing sites:

> The clinical batches of your proposed drug product were manufactured at two manufacturing sites in Switzerland and the United States. Submit to the NDA, comparative dissolution data of representative batches from the two sites demonstrating similarity in dissolution profiles between the two manufacturing sites.

In the March 4, 2014 response, the Applicant submitted dissolution data that demonstrate unequivocally that batches of the product manufactured at the three sites showed similar dissolution profiles (Figure 6).

(b) (4)

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/s/

OKPONANABOFA ERADIRI
03/25/2014

ANGELICA DORANTES
03/25/2014

Clinical Pharmacology NDA Review	
NDA/SDN	NDA 205755 \\CDSESUB1\evsprod\NDA205755\0002
Type/Category	NME (Priority)
	Granted Breakthrough Therapy and Orphan Drug Designation
Brand Name	ZYKADIA
Generic Name	Ceritinib (LDK378)
Receipt Date	Part 1: November 27, 2013 Part 2: December 12, 2013 Part 3: December 24, 2013
Target Action Date	April 17, 2014
PDUFA Date	August 24, 2014
Proposed Indication	Treatment of Patients with (b) (4) Metastatic Non-Small Cell Lung Cancer (NSCLC) who Have (b) (4)
Dosage Form	150 mg Capsule
Route of Administration	Oral
Dosing Regimen and Strength	750 mg Once Daily
Applicant	Novartis Pharmaceuticals
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OND Division	Division of Oncology Products 2
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1 EXECUTIVE SUMMARY

The Applicant seeks accelerated approval of ceritinib for the treatment of patients with [redacted] metastatic non-small cell lung cancer (NSCLC) who have [redacted] The proposed dosing regimen is 750 mg taken once daily (QD) on an empty stomach at least 2 hours before or 2 hours after food.

The efficacy and safety of ceritinib was established in an open-label, single-arm study that enrolled patients with metastatic ALK-positive NSCLC who progressed while receiving or were intolerant to crizotinib. The objective response rate (ORR) evaluated by a Blinded Independent Central Review Committee (BIRC) was 44% (95% CI: 36, 52) and the median duration of response was 7.1 months (95% CI: 5.6, NE) at the recommended dose of 750 mg ceritinib once daily (n=163). The most common adverse reactions (incidence ≥25%) were diarrhea, nausea, vomiting, abdominal pain, fatigue, decreased appetite, and constipation. The most common Grade 3-4 adverse reactions (incidence ≥5%) were alanine transaminase (ALT) elevation, aspartate transaminase (AST) elevation, hyperglycemia, lipase (blood) increase, diarrhea, and fatigue. Approximately 60% of patients initiating treatment at 750 mg required at least one dose reduction. Gastrointestinal (GI) disorders were reported in 98% of patients receiving ceritinib and resulted in dose modification in 42% of patients.

The Clinical Pharmacology Section of the NDA is supported by food effect, ADME (absorption, distribution, metabolism, excretion), and two drug-drug interaction studies in healthy subjects; single and repeat dose pharmacokinetics (PK) studies in cancer patients; and in vitro studies to assess the drug interaction potential of ceritinib with cytochrome P450 (CYP) and transporters. Population pharmacokinetic (PopPK) analyses using data from ALK-positive cancer patients enrolled in the registration trial did not identify clinically important covariates influencing ceritinib PK. There were no evident exposure-response (E-R) relationships for effectiveness (ORR and progression-free survival [PFS]). Higher exposure appears to be associated with higher incidence and earlier safety events including overall Grade 3-4 adverse events (AEs), time to first dose reduction/interruption, and individual AEs such as AST/ALT elevations and hyperglycemia. No significant relationships were identified between systemic exposure and gastrointestinal (GI) tract AEs, possibly because the high drug concentration in the GI tract leads to GI tract AEs directly. Ceritinib prolonged the QTc interval in a concentration dependent manner.

1.1 RECOMMENDATIONS

The NDA 205755 is acceptable from a clinical pharmacology perspective provided that the Applicant and the FDA come to an agreement regarding the labeling language and the identified clinical pharmacology trials to be conducted as postmarketing requirements. The adequacy of the clinical pharmacology program in the overall drug development plan of ceritinib is summarized in the table below.

Drug Development Decision	Sufficiently Supported?	Recommendations and Comments
Proposed dosing regimen of 750 mg QD in the fasted state	☐ Yes ☒ No Refer to **Section 2.2.4.4**	**PMR:** Clinical trial to evaluate the gastrointestinal tolerability, efficacy, and PK of 450 mg ceritinib taken with a meal as compared with that of 750 mg ceritinib taken in the fasted state in metastatic ALK-positive NSCLC patients. Refer to **Section 1.2.1**. **Labeling Recommendation:** For severe or intolerable nausea or vomiting or diarrhea despite optimal antiemetic or anti-diarrheal therapy, withhold until improved and resume ceritinib with a 150 mg dose reduction OR take with meals as instructed below: • If receiving 750 mg daily, reduce the dose to 450 mg daily; • If receiving 600 mg daily, reduce the dose to 300 mg daily.
Dose adjustment in patients with organ impairment	☐ Yes ☒ No Refer to **Section 2.3.1**	**Labeling Recommendation:** Dose adjustment is not recommended in patients with mild hepatic impairment. The recommended dose has not been determined in patients with moderate and severe hepatic impairment. **PMR:** Hepatic impairment study. Refer to **Section 1.2.1**.
Dose adjustment in patients with comedications that affect the PK of ceritinib	☐ Yes ☒ No Refer to **Section 2.4.2.7** and **2.4.2.8**	**Labeling Recommendation:** CYP3A Inhibitors and Inducers: Avoid concurrent use of strong CYP3A inhibitors and inducers. If concomitant use of a strong CYP3A inhibitor is unavoidable, reduce the ceritinib dose by approximately one-third, rounded to the nearest 150 mg dosage strength. After discontinuation of a strong CYP3A inhibitor, resume the ceritinib dose that was taken prior to initiating the strong CYP3A4 inhibitor. Acid Reducing Agents: Gastric acid reducing agents (e.g., proton pump inhibitors, H_2-receptor antagonists, antacids) may alter the solubility of ceritinib and reduce its bioavailability as ceritinib demonstrates pH-dependent solubility and becomes poorly soluble as pH increases in vitro. **PMR:** Drug-drug interaction study with gastric acid reducing agents. Refer to **Section 1.2.1**.
Dose adjustment in patients with comedications whose PK are affected by ceritinib	☐ Yes ☒ No Refer to **Section 2.4.2.3**	**Labeling Recommendation:** Avoid concurrent use of CYP3A or CYP2C9 substrates with narrow therapeutic indices. If concurrent use of these medications is unavoidable, consider dose reduction of these comedications. **PMR:** Drug-drug interaction studies with CYP3A and CYP2C9 sensitive substrates. Refer to **Section 1.2.1**.

1.2 PHASE 4 REQUIREMENTS AND COMMITMENTS

1.2.1 Postmarketing Requirements (PMR)

The Applicant is required to conduct the following clinical pharmacology studies under postmarketing requirements (PMRs). These PMRs will be included in the Approval letter with milestones agreed upon after negotiation with the Applicant.

Drug Development Question	Rationale	PMR
What is the exposure-matched dose of ceritinib taken with food to improve GI tolerability and compliance without compromising efficacy?	98% of patients experienced GI adverse reactions. Ceritinib is proposed to be taken in the fasted state, but taking ceritinib with food may alleviate GI toxicities and improve patients' compliance.	Conduct a clinical trial to evaluate the gastrointestinal tolerability, efficacy, and pharmacokinetics of 450 mg ceritinib taken with a meal as compared with that of 750 mg ceritinib taken in the fasted state in metastatic ALK-positive NSCLC patients. Final Protocol Submission: To be determined Trial Completion: To be determined Final Report Submission: To be determined
Should the dose of ceritinib be reduced in patients with moderate and severe hepatic impairment?	92% of the administered dose is recovered in the feces, indicating that hepatic elimination is the major elimination pathway.	Complete a pharmacokinetic trial to determine the appropriate dose of ceritinib in patients with hepatic impairment. Final Protocol Submission: Submitted Trial Completion: January 2016 Final Report Submission: June 2016
What is the effect of gastric acid reducing agents on the PK of ceritinib?	Ceritinib's solubility is pH-dependent, with a solubility of 11 mg/mL at pH=1 and 0.0002 mg/mL at pH=6.8.	Conduct a clinical trial to evaluate if proton pump inhibitors, H_2-receptor antagonists, and antacids alter the bioavailability of ceritinib. The trial results should allow for a determination on how to dose ceritinib with regard to concomitant gastric acid reducing agents. Final Protocol Submission: January 2015 Trial Completion: August 2015 Final Report Submission: February 2016
What is the effect of ceritinib on the PK of sensitive CYP3A substrates?	Ceritinib inhibits CYP3A4 in vitro (R_1 value of 7.0-8.5).	Conduct a clinical trial evaluating the effect of repeat doses of ceritinib on the single dose pharmacokinetics of midazolam (CYP3A4 substrate). The results of this clinical trial should allow for a determination on how to dose ceritinib with regard to concomitant sensitive CYP3A4 substrates and CYP3A4 substrates with narrow therapeutic indices. Final Protocol Submission: September 2014 Trial Completion: August 2016 Final Report Submission: February 2017

Drug Development Question	Rationale	PMR
What is the effect of ceritinib on the PK of sensitive CYP2C9 substrates?	Ceritinib inhibits CYP2C9 in vitro (R_1 value of 6.0).	Conduct a clinical trial evaluating the effect of repeat doses of ceritinib on the single dose pharmacokinetics of warfarin (CYP2C9 substrate). The results of this clinical trial should allow for a determination on how to dose ceritinib with regard to concomitant sensitive CYP2C9 substrates and CYP2C9 substrates with narrow therapeutic indices. Final Protocol Submission: September 2014 Trial Completion: August 2016 Final Report Submission: February 2017

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DCPV: DDD – B Booth; Office of Clinical Pharmacology Director – I Zineh

A mid-cycle Clinical Pharmacology briefing was presented by Ruby Leong, Yuzhuo Pan, and Pengfei Song on February 21, 2014 with the following participants: Brian Booth, Julie Bullock, Vicky Hsu, Sean Khozin, Fang Li, Qi Liu, Nitin Mehrotra, Young-Jin Moon, Olanrewaju Okusanya, NAM Atiqur Rahman, Vikram Sinha, Yaning Wang, Gene Williams, Ping Zhao, and Issam Zineh.

1.3 SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY FINDINGS

Unresolved Dosing Issue with Regard to GI Tolerability

The proposed dosing regimen for ceritinib with regard to food is 750 mg daily on an empty stomach at least 2 hours before or 2 hours after food. At the recommended dose under fasted conditions, the majority of patients experienced gastrointestinal (GI) adverse reactions including diarrhea (86%), nausea (80%), vomiting (60%), and abdominal pain (54%). The absolute bioavailability of ceritinib has not been studied but is expected to be low. The food effect study

showed that a high-fat, high-calorie meal increased ceritinib AUC by 73% and C_{max} by 41%; a low-fat meal increased ceritinib AUC by 58% and C_{max} by 43% as compared to fasted conditions. Administration of ceritinib at 750 mg with food may improve GI tolerability and compliance, but could lead to exposure-related toxicities such as AST/ALT elevations, hyperglycemia, and QTc prolongation. The Applicant proposed to conduct a clinical trial to evaluate the effect of a (b) (4) (b) (4) on the PK of ceritinib in healthy subjects based on the hypothesis that the magnitude of increase in ceritinib exposure would be smaller with (b) (4) than that observed with low-fat or high-fat full meals while alleviating GI adverse events. FDA recommends determination of an exposure-matched dose of ceritinib taken with food to improve GI tolerability and compliance in patients without compromising efficacy. A postmarketing trial should be conducted to evaluate the GI tolerability, efficacy, and PK of 450 mg ceritinib taken with a meal as compared with that of 750 mg ceritinib taken in the fasted state in metastatic ALK-positive NSCLC patients.

Exposure-Response Relationships

No significant exposure-response relationships were identified for the primary efficacy endpoint ORR and secondary efficacy endpoint PFS in ALK-positive NSCLC patients who received prior treatment with an ALK inhibitor. Based on the analysis results, it is unclear whether the plateau of the exposure-efficacy curve has been reached or not.

Higher systemic exposure appears to be associated with more frequent and earlier overall Grade 3 or worse (G3+) adverse events (AEs), as well as with higher incidence of individual AEs such as G3+ ALT/AST elevation, and G2+ hyperglycemia. No significant relationships were identified between systemic exposure and gastrointestinal (GI) tract AEs, possibly because the high drug concentration in the GI tract leads to GI tract AEs directly. Higher systemic exposure also appears to be associated with earlier and more frequent dose reductions or dose interruption. Given that the permanent discontinuation due to AEs occurred in only 10% patients, the management of AEs via dose reductions and interruptions is effective in maintaining patients on study drug.

Population concentration-QTc analyses using time-matched ECG and PK data from the clinical trial showed that ceritinib prolonged the QTc interval in a concentration dependent manner. Following repeat daily doses of 750 mg ceritinib, large changes (i.e., >20 ms) in the QTc interval were detected at steady-state (Cycle 2 Day 1 and beyond). The largest mean change from baseline was 19.3 ms with the upper bound of the 2-sided 90% confidence interval (CI) of 22.2 ms, observed at Cycle 6 Day 1.

ADME and Potential DDIs

Following oral administration of ceritinib, C_{max} was reached at 4-6 hours, with a terminal half-life ($t_{1/2}$) of 41 hours. Inter-patient variability following repeat doses of 750 mg ceritinib is 74% for AUC and 76% for C_{max}. Ceritinib exhibits nonlinear time-dependent PK, with exposures that are dose proportional after a single dose, but greater than dose proportional after repeat doses in the dose range of 50 to 750 mg. Following ceritinib 750 mg QD, steady state is achieved within

15 days with 6-fold accumulation. Apparent clearance (CL/F) at steady-state (33 L/h) is lower than that after a single dose (89 L/h), likely due to auto-inhibition of CYP3A.

Ceritinib is primarily metabolized by CYP3A, and is also a reversible and time-dependent inhibitor of CYP3A in vitro. Coadministration of ketoconazole (a strong CYP3A inhibitor) 200 mg twice daily for 14 days and a single dose of 450 mg ceritinib increased ceritinib AUC by 2.9-fold and C_{max} by 20% in healthy subjects. Coadministration of rifampin (a strong CYP3A inducer) 600 mg daily for 14 days and a single dose of 750 mg ceritinib decreased ceritinib AUC by 70% and C_{max} by 44% in healthy subjects. Given that the drug-drug interaction (DDI) studies were conducted using single doses of ceritinib, the effect of strong CYP3A modulators on the steady-state PK of ceritinib in patients is unclear due to nonlinear, time-dependent PK of ceritinib. Physiologically-based pharmacokinetic modeling (PBPK) predicted that ketoconazole can increase the steady-state ceritinib exposure (AUC) by 51%; rifampin can decrease steady-state ceritinib AUC by 67%. Therefore, it is recommended to avoid concomitant use of strong CYP3A inhibitors and inducers given the magnitude of exposure change in the context of the exposure-response curves for safety and effectiveness observed with ceritinib. If avoiding concomitant strong CYP3A inhibitors is not possible, the ceritinib dose should be reduced by approximately one-third, rounded to the nearest 150 mg dosage strength. After discontinuation of a strong CYP3A inhibitor, the ceritinib dose that was taken prior to initiating the strong CYP3A4 inhibitor should be resumed.

In addition to CYP3A, ceritinib also inhibits CYP2C9 in vitro. PMRs will be requested to evaluate the effect of repeat doses of ceritinib on the single dose PK of a sensitive CYP3A4 substrate (e.g., midazolam) and CYP2C9 substrate (e.g., warfarin).

Given that the aqueous solubility of ceritinib is pH-dependent with lower solubility (<750 mg/250 mL) at higher pH, gastric acid reducing agents may decrease the solubility of ceritinib and subsequently reduce its bioavailability. A PMR will be requested to evaluate the effect of gastric acid reducing agents on the PK of ceritinib.

Organ Dysfunction Studies

The ADME study showed that hepatic elimination is the major route of elimination (92% of the administered radiolabeled dose was recovered in the feces), indicating that hepatic impairment may increase the systemic exposure of ceritinib. The Applicant is requested to submit the results of an ongoing hepatic impairment study under a PMR to determine the appropriate ceritinib dose given that AEs including AST/ALT elevations, QTc prolongation, and hyperglycemia are exposure-related. No dose adjustment is recommended for mild hepatic impairment because PK (popPK estimated steady-state AUC), effectiveness (ORR), and safety (overall Grade 3-4 AEs) are similar between patients with mild hepatic impairment and patients with normal hepatic function.

The ADME study showed that the renal pathway contributed minimally to ceritinib elimination (1.3% of the administered radiolabeled dose was recovered in the urine). Dose adjustments are not recommended for patients with mild or moderate renal impairment because there are no clinically important differences in PK (popPK estimated steady-state AUC), effectiveness

(ORR), and safety (overall Grade 3-4 AEs) between patients with mild or moderate renal impairment and patients with normal renal function. Patients with severe renal impairment were not enrolled in the clinical study.

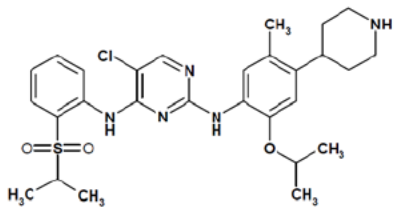
2 QUESTION-BASED REVIEW

2.1 General Attributes

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

The molecular weight of ceritinib is 558 g/mol (**Figure 1**). The proposed drug product is available as 150 mg capsules.

Figure 1. Chemical structure of ceritinib



Ceritinib solubility in aqueous media is pH-dependent with decreased solubility at higher pH (**Table 1**). Ceritinib is completely soluble at acidic pH=1 (dose/250 mL=3 mg/mL), but 55,000-fold less soluble at pH=6.8. Therefore, an in vivo study to assess the effect of gastric acid reducing agents on the PK of ceritinib is warranted and will be requested as a PMR (refer to **Section 1.2.1**).

Table 1. Solubility of ceritinib

Solvent	Solubility (mg/mL)
Water	0.21
Acidic media (pH=1)	11
Neutral or alkaline media (pH=6.8)	0.0002*
	(b) (4)

Source: Summary of Biopharmaceutic Studies and Associated Analytical Methods, Table 1-1, Page 5.

Ceritinib showed low permeability across Caco-2 cells (refer to **Section 2.5.1**). The Applicant claims that ceritinib is a BCS Class 4 compound with low permeability and low solubility.

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Ceritinib is an inhibitor of anaplastic lymphoma kinase (ALK). ALK translocation leads to expression of a fusion protein, resulting in aberrant ALK signaling and proliferation of ALK-dependent cancer cells. In the majority of NSCLC cases, EML4 is the translocation partner for

ALK. Ceritinib inhibited EML4-ALK kinase activity in a NSCLC cell line (H2228) (IC_{50}: 11 nM) in vitro and induced tumor regression in H2228 derived xenografts in mouse and rat.

The proposed indication is for the treatment of patients with [redacted] (b) (4) metastatic non-small cell lung cancer (NSCLC) who have [redacted] (b) (4).

2.1.3 What are the proposed dosage(s) and route(s) of administration?

The Applicant's proposed dosing regimen is 750 mg orally once daily (QD) on an empty stomach at least 2 hours before or 2 hours after food.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Table 2 lists the relevant clinical pharmacology and clinical studies included in the application.

Table 2. Summary of clinical pharmacology and clinical studies

Study Number	Study Design	Study Population	Assessment	Dosing regimen
A2105	Open label, single dose	Healthy subjects (n=6)	ADME	750 mg [^{14}C]-ceritinib oral capsule containing 300 µCi radioactivity
A2101	Open label, randomized, crossover with 7-day washout	Healthy subjects (n=28)	Food effect with FMI capsule	Single 500 mg dose in the fasted state or administered with a high-fat, high-calorie meal or low-fat meal
A2104	Open label, single dose	Healthy subjects (n=19)	DDI	Single 450 mg dose and in combination with ketoconazole
A2106	Open label, single dose	Healthy subjects (n=19)	DDI	Single 750 mg dose and in combination with rifampin
X1101	Open label dose escalation and expansion phase	Japanese cancer patients with genetic alterations of ALK (n=19)	PK in Japanese patients	Single and multiple-dose: 300, 450, 600 and 750 mg QD
X2101	Open label dose escalation and expansion phase	ALK-positive cancer patients (n=59 for dose escalation phase; n=245 for expansion phase)	Efficacy, safety, popPK	Single and multiple-dose: 50, 100, 200, 300, 400, 500, 600, 700 and 750 mg QD

ADME: Absorption, distribution, metabolism, excretion; ALK: Anaplastic lymphoma kinase; DDI: Drug-drug interaction; FMI: Final market image; PK: Pharmacokinetics; PopPK: Population pharmacokinetics; QD: Once daily

In addition, ceritinib plasma concentration data from Study X2101 were used to develop a PopPK model to assess the potential influence of covariates on inter-patient variability in ceritinib PK parameters, and explore exposure-response relationships for efficacy and safety endpoints.

2.2.2 What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical studies?

The primary efficacy outcome measures of the registration trial X2101 were overall response rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST) as evaluated by investigators and a Blinded Independent Central Review Committee (BIRC). Duration of response (DOR) and progression-free survival were additional outcome measures.

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure-response relationships?

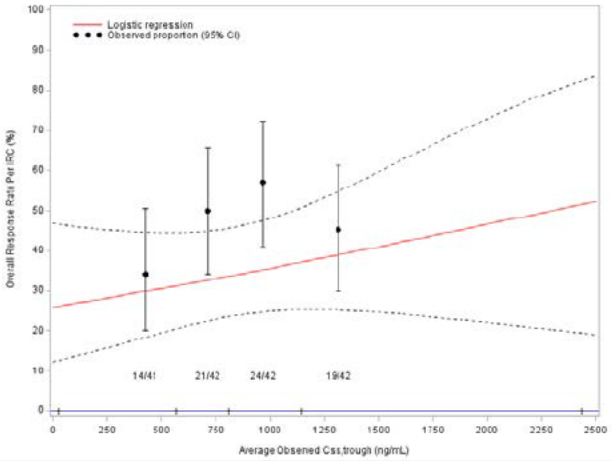
Yes. Ceritinib was the major component in human plasma after oral administration and it was appropriately identified and measured to assess PK parameters (refer to **Section 2.6**).

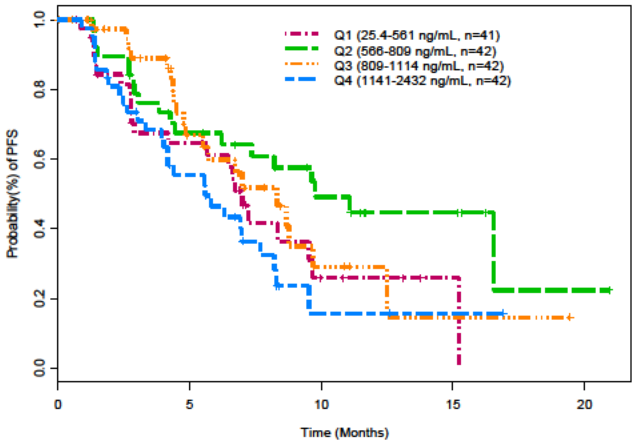
2.2.4 Exposure-response

2.2.4.1 *What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?*

The Pharmacometrics review concluded that there were no significant exposure-response (E-R) relationships for the primary efficacy endpoint ORR and for the secondary efficacy endpoint PFS (**Figure 2**), based on data from Study X2101 that included dose levels ranging from 50 mg to 750 mg in patients with ALK-positive NSCLC (n=167) who have received treatment of an ALK inhibitor (refer to Pharmacometrics review in **Section 4.1**). Based on the ORR analysis results, it is unclear whether the plateau of the exposure-efficacy curve has been reached, which may be due to two possible reasons: (1) the distribution of the available exposure data (primarily driven by the data from patients who received 750 mg daily dose) may not be enough to adequately characterize the full exposure-efficacy curve for ORR, and (2) the small sample size may limit the robustness for the predicted exposure-efficacy relationship. Furthermore, there was no clear trend observed with PFS curves stratified by $C_{ss,trough}$ quartiles.

Figure 2. Relationship between average observed steady-state trough concentration ($C_{trough,ss}$) and proportion of patients with ORR (left) and PFS (right) stratified by $C_{trough,ss}$ quartiles in ALK-positive NSCLC patients (n=167) who received prior treatment with an ALK inhibitor





On the left figure, the solid black symbols represent the observed ORR per central radiology review in each quartile of average observed $C_{ss,trough}$ for all subjects, regardless of the prognostic factors. The vertical black bars represent the 95% confidence interval (CI). The solid line and the dashed lines represent the multivariate logistic regression model predicted mean and 95% CI of the probability of ORR by average observed $C_{ss,trough}$ for Caucasian patients with brain metastasis, ECOG status of 1, and a baseline sum of longest diameter of 8.1 cm. (Please note that the predictions are not for all patients, therefore do not fit the solid black symbols which represent the observed ORR in each $C_{ss,trough}$ quartile for all patients, regardless of the prognostic factors. The logistic regression model prediction is generated as follows: numeric covariates at the median, categorical covariates at the highest frequency level). The exposure range in each quartile of $C_{ss,trough}$ is denoted by the horizontal blue line along with the number of responders/total number of patients in each quartile.

The right figure shows Kaplan-Meier curve of progression free survival (PFS) per central radiology review by $C_{ss,trough}$ quartiles in ALK+ NSCLC patients who were previously treated with ALK inhibitors.

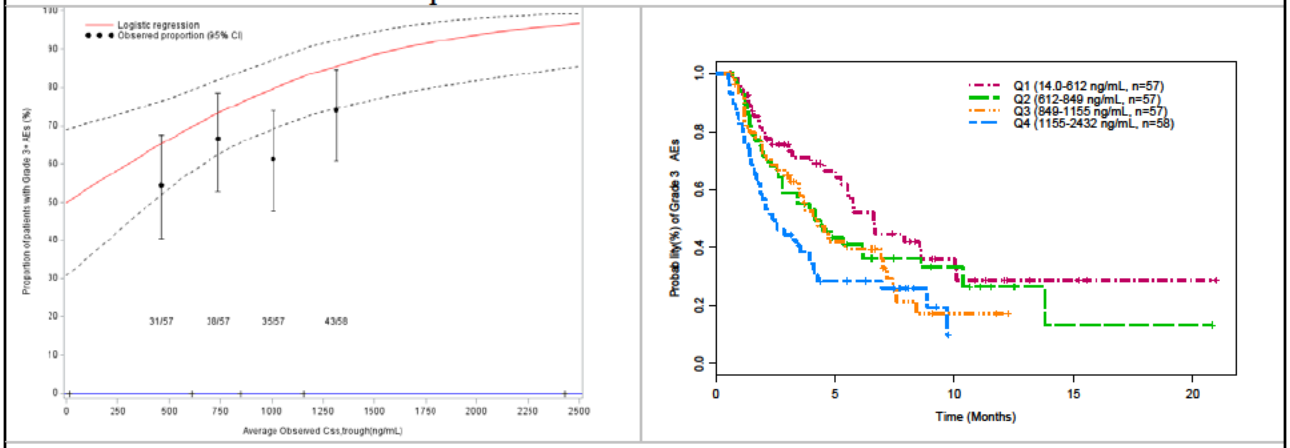
Source: Pharmacometrics review, Figures 1 and 2.

2.2.4.2 *What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?*

The Pharmacometrics review concluded that higher systemic exposure appears associated with more frequent and earlier overall Grade 3/4 AEs (**Figure 3**). There were also higher incidences of individual AEs such as Grade 3/4 aspartate aminotransferase (AST) and alanine aminotransferase (ALT) elevations, and Grade 2 or worse hyperglycemia with increased ceritinib systemic exposure (**Figure 4a, 4b, 4c**). Based on these E-R analyses for safety, reducing the dose may decrease certain exposure-related toxicities such as AST/ALT elevations and hyperglycemia.

No significant E-R relationships were identified between $C_{ss,trough}$ and overall Grade 3-4 gastrointestinal (GI) tract AEs (**Figure 4d**) or Grade 2 or worse diarrhea, possibly because plasma concentration is not a good predictor for GI tract AEs as high drug concentrations in the GI tract may lead to GI tract AEs directly (refer to Pharmacometrics review in **Section 4.1**). Dose reduction due to severe or intolerable GI toxicity occurred in the clinical trial and is recommended in the proposed product labeling (refer to **Section 3**).

Figure 3. The relationship between average observed $C_{ss,trough}$ and Grade 3 or worse (G3+) AEs in patients with ALK-positive tumors who were treated with ceritinib

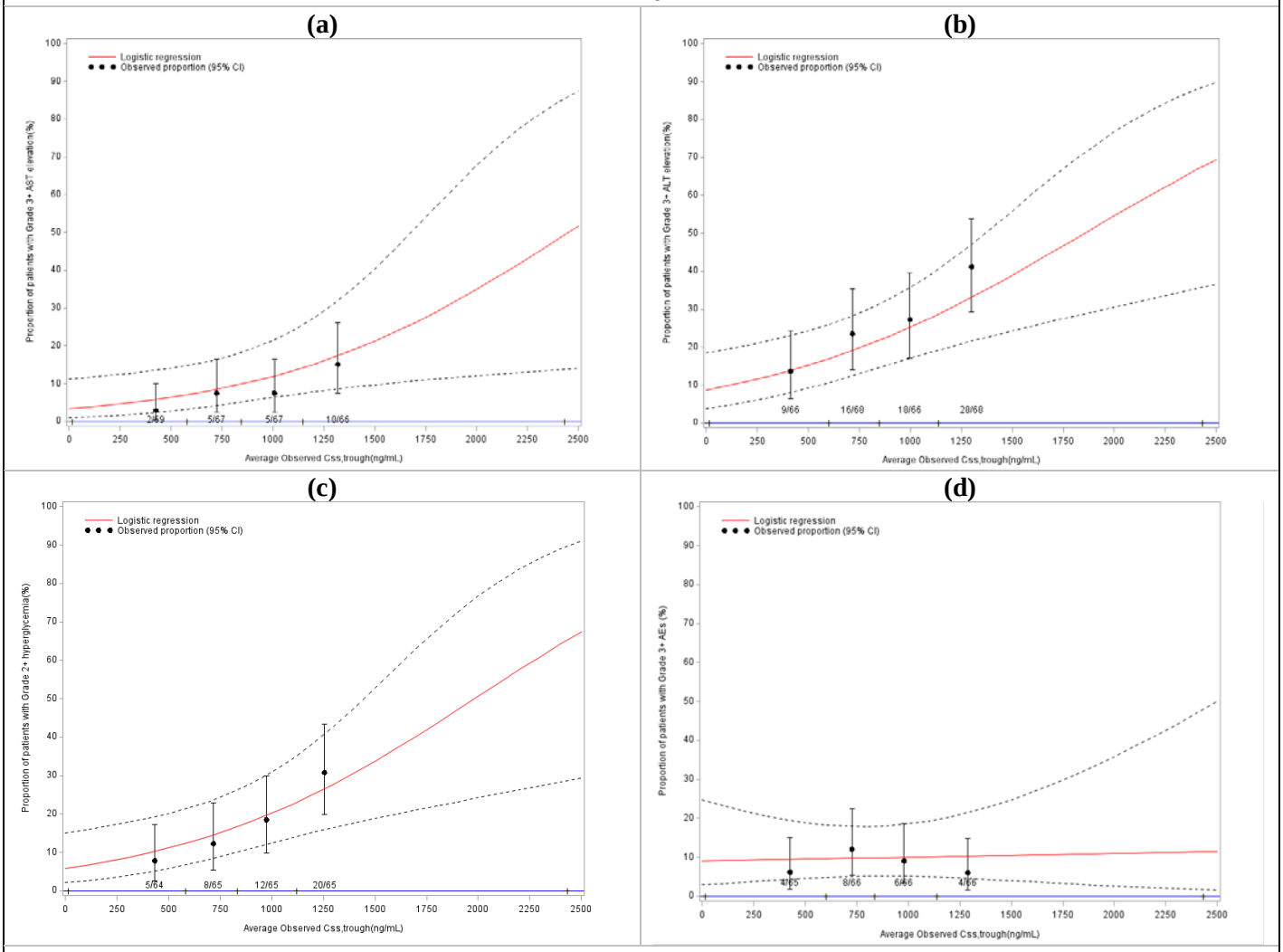


In the left figure, the solid black symbols represent the observed incidence of G3+ AEs in each quartile of average observed $C_{ss,trough}$ for all subjects, regardless of the prognostic factors. The vertical black bars represent the 95% confidence interval (CI). The solid and dotted lines represent the multivariate logistic regression model predicted mean and 95% CI of incidence of G3+ AE of concern by average observed $C_{ss,trough}$ for Caucasian patients with brain metastasis, ECOG status of 1, and prior treatment with ALK inhibitors. The exposure range in each quartile of average observed $C_{ss,trough}$ is denoted by the horizontal blue line along with the number of patients who experienced AE of concern/total number of patients in each quartile.

The right figure shows Kaplan-Meier curve of time to first G3+ AEs by quartiles of observed average $C_{ss,trough}$ in patients with ALK-positive tumors who were treated with ceritinib.

Source: Pharmacometrics review, Figures 3 and 4.

Figure 4. Relationship between average observed $C_{trough,ss}$ and individual AEs including (a) G3+ AST elevation, (b) G3+ ALT elevation, (c) G2+ hyperglycemia, and (d) G3+ GI tract AEs in patients with ALK-positive tumors in trial X2101

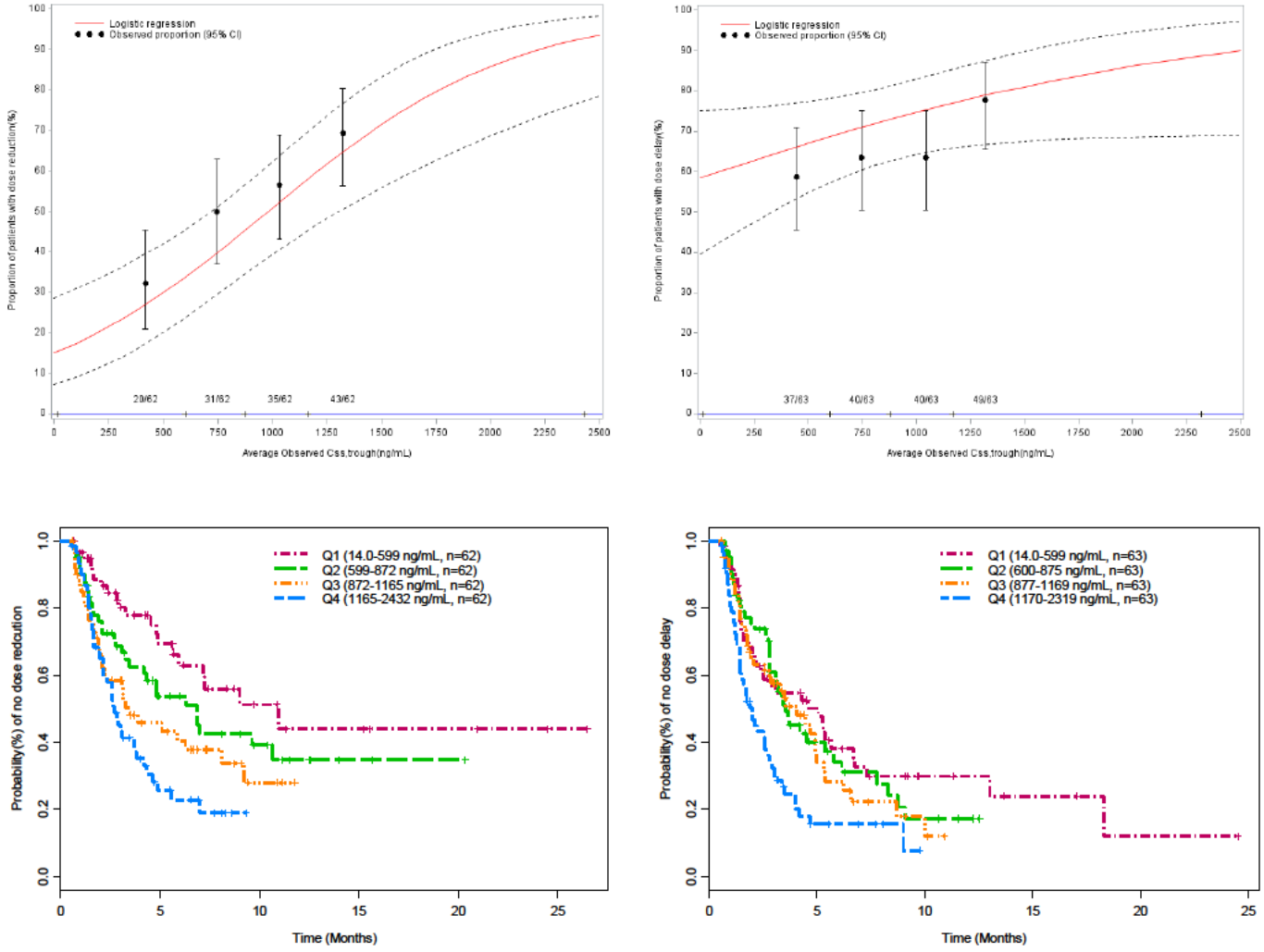


In each figure above, the solid black symbols represent the observed incidence of AEs of concern in each quartile of average observed $C_{ss,trough}$ for all subjects, regardless of the prognostic factors. The vertical black bars represent the 95% confidence interval (CI). The solid and dotted lines represent the multivariate logistic regression model predicted mean and 95% CI of incidence of AE of concern by average observed $C_{ss,trough}$ for Caucasian patients with brain metastasis, ECOG status of 1, and prior treatment with ALK inhibitors. The exposure range in each quartile of average observed $C_{ss,trough}$ is denoted by the horizontal blue line along with the number of patients who experienced AE of concern/total number of patients in each quartile.

Source: Pharmacometrics review, Figures 5, 6, and 7.

Results of logistic regression analyses also suggested that higher exposure may be associated with more frequent dose reductions and dose interruptions (**Figure 5**). Higher exposures also appear to be associated with earlier time to first dose reduction and interruption as shown by Kaplan-Meier analyses (**Figure 5**).

Figure 5. Relationship between average observed $C_{trough,ss}$ and proportion of patients with dose reduction (left) and dose interruption (right) in patients with ALK-positive tumors in trial X2101



In the upper panel, the solid black symbols represent the observed incidence of dose reduction (left, upper) or interruption (right, upper) in each quartile of average observed $C_{ss,trough}$ for all subjects, regardless of the prognostic factors. The vertical black bars represent the 95% confidence interval (CI). The solid and dotted lines represent the multivariate logistic regression model predicted mean and 95% CI of incidence of dose reduction or interruption by average observed $C_{ss,trough}$ for Caucasian patients with brain metastasis, ECOG status of 1, and prior treatment with ALK inhibitors. The exposure range in each quartile of average observed $C_{ss,trough}$ is denoted by the horizontal blue line along with the number of patients who experienced dose reduction or interruption/total number of patients in each quartile.

Lower panel figures show Kaplan-Meier curves of time to first dose reduction (left, lower) and dose interruption (right, lower) by quartiles of average observed $C_{ss,trough}$ in patients with ALK-positive tumors who were treated with ceritinib

Source: Pharmacometrics review, Figures 9 and 10.

2.2.4.3 *Does this drug prolong the QT or QTc interval?*

In Study X2101, time-matched ECG and PK samples were collected at pre-dose, 4, 8, and 24 hours post-dose on days 1 and 8 of cycle 1, pre-dose on day 1 of cycles 2-6, and end of treatment during the dose escalation phase; pre-dose, 4, 8, and 24 hours post-dose on day 1 of cycle 1, pre-dose on day 1 of cycles 2-6, and end of treatment during the expansion phase.

The relationship between ΔQTcF and ceritinib concentrations was determined by pooling data from Cycle 2 Day 1 and beyond in patients who received doses of 50 mg to 750 mg (**Table 3**).

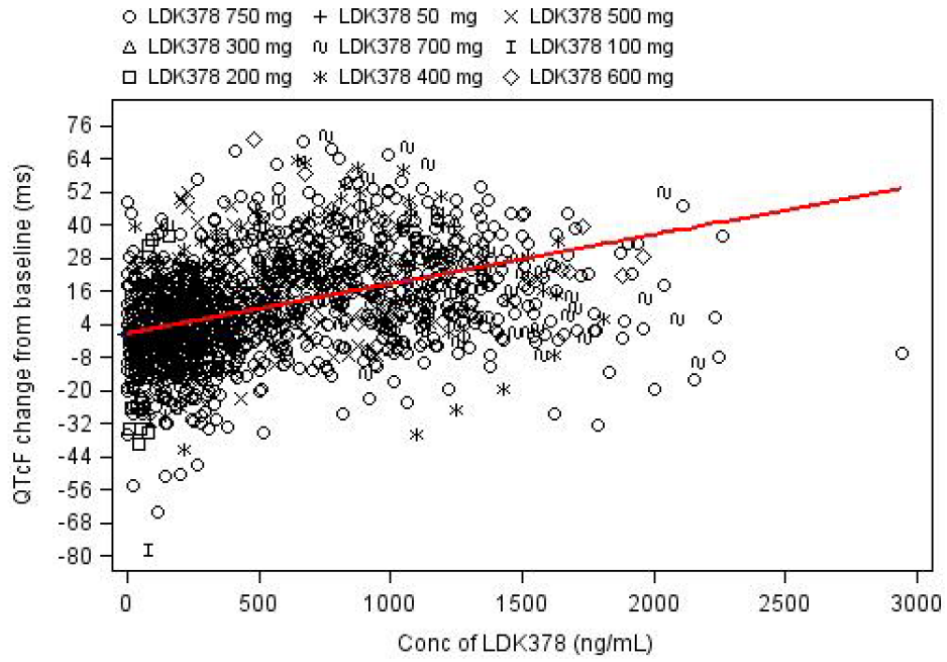
Table 3. ΔQTcF for ceritinib at doses of 50 to 750 mg from Cycle 2 Day 1 and beyond

Treatment	N	Mean (ms)	90% CI for Mean (ms)
50 mg	2	1.5	(-3.8, 6.8)
100 mg	3	-3.0	(-5.6, -0.4)
200 mg	50	-8.0	(-11.5, -4.5)
300 mg	18	13.7	(7.9, 19.4)
400 mg	91	15.3	(11.6, 19.0)
500 mg	83	18.8	(15.7, 21.8)
600 mg	60	21.2	(17.6, 24.8)
700 mg	45	16.3	(11.6, 21.0)
750 mg	955	18.2	(17.2, 19.2)

Source: QT-IRT Review, Table 2. N=304 patients.

The QT-IRT review concluded that ceritinib prolonged the QTc interval in a concentration-dependent manner based on population concentration-QTc analyses using a linear mixed effects model (**Figure 6**).

Figure 6. Concentration-ΔQTcF relationship using a linear mixed effects model



Source: QT-IRT review, Figure 3.

Following repeat daily doses of 750 mg ceritinib, large changes (i.e., >20 ms) in the QTc interval were detected at steady-state (Cycle 2 Day 1 and beyond). The largest mean change from baseline was 19.3 ms with the upper bound of the 2-sided 90% confidence interval (CI) of 22.2 ms, observed at Cycle 6 Day 1 (**Table 4**).

Table 4. ΔQTcF for ceritinib at the 750 mg dose

Treatment	Visit	Time (h)	N	Mean	90% CI for Mean
750 mg	Cycle 1 Day 1	4	236	1.0	(-0.6, 2.6)
		8	215	1.5	(-0.2, 3.2)
		24	222	2.0	(0.3, 3.7)
	Cycle 2 Day 1	0	216	18.7	(16.7, 20.6)
	Cycle 3 Day 1	0	184	16.5	(14.1, 18.8)
	Cycle 4 Day 1	0	169	17.7	(15.3, 20.2)
	Cycle 5 Day 1	0	149	18.7	(15.9, 21.4)
	Cycle 6 Day 1	0	138	19.3	(16.5, 22.2)

Source: QT-IRT Review, Table 1. N=255 patients.

It is recommended in the labeling for patients with QTc interval >500 ms on at least 2 separate ECGs, to withhold ceritinib until QTc interval <481 ms or recovery to baseline; if baseline QTc is >481 msec, resume with a 150 mg dose reduction.

2.2.4.4 *Is the dose and dosing regimen selected by the applicant consistent with the known relationship between dose-concentration-response, and is there any unresolved dosing or administration issue?*

The Pharmacometrics review concluded that based on currently available data, the proposed dose of 750 mg QD is acceptable. The results of E-R analyses for efficacy did not show a clear relationship between systemic exposure and ORR or PFS (refer to **Section 2.2.4.1**). However, the ORR of 44% (95% CI: 36, 52) and median duration of response of 7.1 months (95% CI: 5.6, NE) suggested that the proposed dose of 750 mg is effective. Higher systemic exposure is associated with more frequent and earlier overall Grade 3-4 AEs, and higher incidence of individual AEs including Grade 3-4 AST/ALT elevations and Grade 2 or worse hyperglycemia. Higher systemic exposure is also associated with earlier and more frequent dose reductions or dose interruptions (refer to **Section 2.2.4.2**). Given that permanent discontinuation due to AEs occurred in only 10% of patients, the proposed dose of 750 mg with management of AEs via dose reductions or interruptions appears acceptable.

Although the current proposed dosing regimen is acceptable, there may be alternative ways to administer ceritinib that may lead to better tolerability and compliance. At the recommended dose of 750 mg QD, the majority of patients experienced GI adverse reactions including diarrhea (86%), nausea (80%), vomiting (60%), and abdominal pain (54%). No significant E-R relationships were identified between systemic exposure and overall Grade 3/4 GI tract AEs or Grade 2 or worse diarrhea, possibly because systemic exposure is not a good predictor for GI tract AEs as high drug concentrations in the GI tract may lead to GI tract AEs directly. The absolute bioavailability of ceritinib has not been studied, but is expected to be low. The food effect study showed that a high-fat, high-calorie meal increased ceritinib AUC by 73% and C_{max} by 41%; a low-fat meal increased ceritinib AUC by 58% and C_{max} by 43% as compared to fasted conditions (refer to **Section 2.5.3**). Administration of ceritinib 750 mg with food may improve GI tolerability and compliance, but could lead to exposure-related toxicities such as AST/ALT elevations, hyperglycemia, and QTc prolongation (refer to **Sections 2.2.4.2** and **2.2.4.3**). To address this unresolved issue, the Applicant proposed to conduct a clinical trial to evaluate the effect of a (b) (4) on the PK of ceritinib in healthy subjects based on the hypothesis that the magnitude of increase in ceritinib exposure would be smaller with concomitant intake of a (b) (4) than that observed with low-fat or high-fat full meals while alleviating GI adverse events. FDA recommends a postmarketing trial be conducted to evaluate the GI tolerability, efficacy, and PK of 450 mg ceritinib taken with a meal as compared with that of 750 mg ceritinib taken in the fasted state in metastatic ALK-positive NSCLC patients. Given an expected increase of exposures by 58% to 73% when ceritinib is administered with meals, exposures following a 450 mg dose of ceritinib taken with a meal would be similar to exposures following 750 mg ceritinib taken in the fasted state.

Additional unresolved dosing and administration issues with ceritinib to be addressed under PMRs include potential dose adjustment in patients with hepatic impairment and in patients receiving acid reducing agents.

2.2.5 What are the PK characteristics of the drug?

2.2.5.1 *What are the single dose and multiple dose PK parameters?*

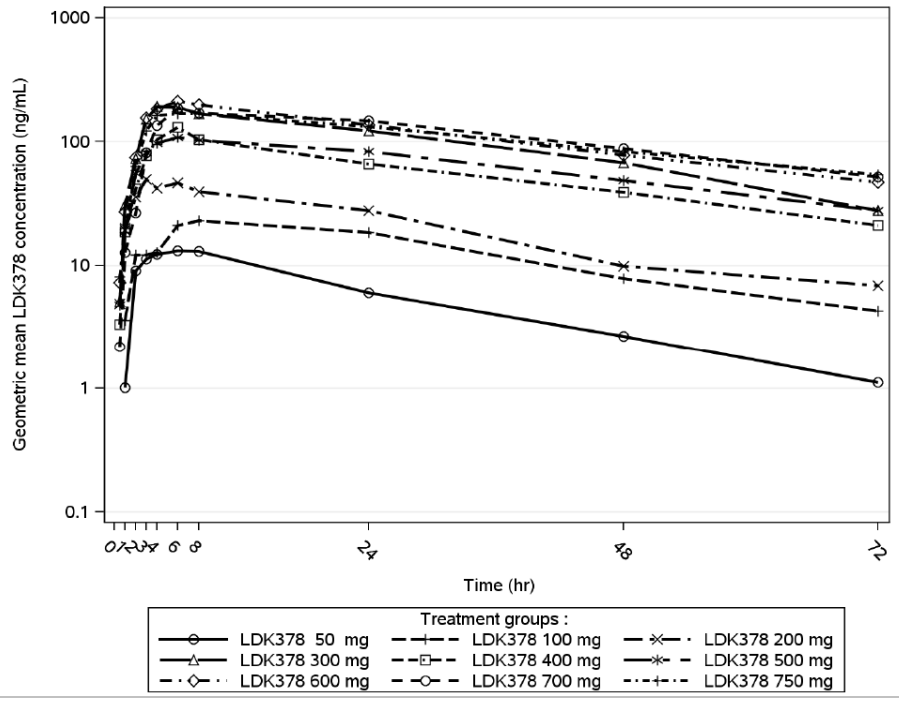
The single dose PK of ceritinib have been evaluated in four clinical pharmacology studies in healthy subjects (A2101, A2104, A2105, A2106), in patients in Study X2101, and in Japanese patients (X1101). The multiple-dose PK of ceritinib has been evaluated in patients in Study X2101, and in Japanese patients (X1101).

Ceritinib exhibits nonlinear time-dependent PK, with exposures that are dose proportional after a single dose, but greater than dose proportional after repeat doses in the dose range of 50 to 750 mg. Following ceritinib 750 mg QD, steady state is achieved by approximately 15 days with 6-fold accumulation after three weeks. Apparent clearance (CL/F) at steady-state (33 L/h) is lower than that after a single dose (89 L/h), likely due to auto-inhibition of CYP3A. The terminal half-life ($t_{1/2}$) at the 750 mg dose is 41 hours.

During the dose escalation phase in Study X2101, intensive PK samples were collected at pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 24, 48, 72 hours post-dose during PK run-in; at pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 24 hours post-dose on cycle 1 day 8; at pre-dose on day 15 of cycles 1 and 2; day 1 of cycle 3 and subsequent cycles; at pre-dose, 1, 2, 4, 6, 8, and 24 hours post-dose on cycle 2 day 1 in only those patients enrolled in the 50, 100, and 200 mg dose levels. During the expansion phase, intensive PK samples were collected at pre-dose, 1, 2, 4, 6, 8, 24 hours post-dose on day 1 of cycles 1 and 2; pre-dose on day 15 of cycles 1 and 2 and day 1 of cycles 3 and 4.

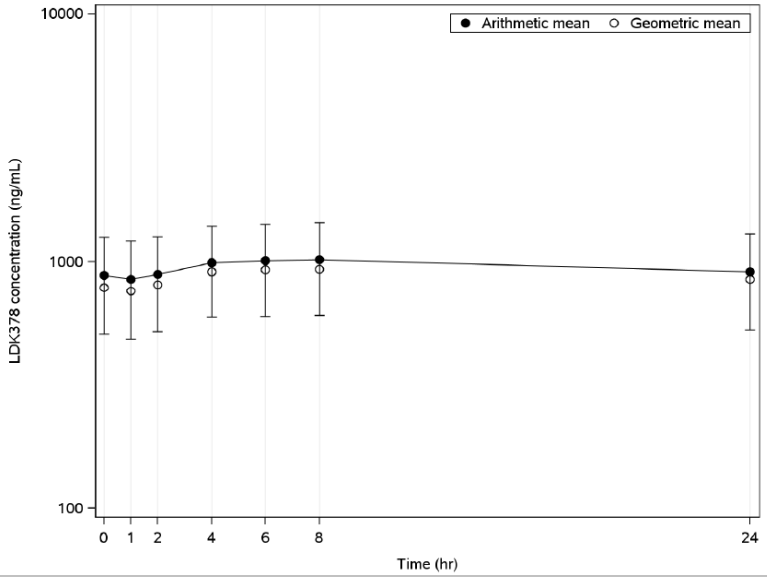
Mean concentration-time profiles after a single dose of 50 to 750 mg ceritinib are shown in **Figure 7** and after 750 mg QD doses in **Figure 8**.

Figure 7. Mean concentration-time profiles after single doses of ceritinib (day 1)



Source: Summary of Clinical Pharmacology Studies, Figure 2-2, Page 22.

Figure 8. Mean concentration-time profiles after repeat doses of ceritinib (cycle 2 day 1)



Source: Summary of Clinical Pharmacology, Figure 2-3, Page 23.

Single dose and multiple dose PK parameters of ceritinib were determined using noncompartmental analysis and summarized in **Table 5** and **Table 6**, respectively.

Table 5. PK parameters following single doses of ceritinib on cycle 1 day 1 during PK-run-in period of dose escalation phase

Dose (mg)	T1/2 (h)	Tmax (h)	Cmax (ng/mL)	AUC0-24h (ng*h/mL)	AUClast (ng*h /mL)	Vz/F (L)	CL/F (L/h)
50	19.5	5.95	13.1	226	366	3540	126
	n=1	n=1	n=1	n=1	n=1	n=1	n=1
100	19.4	15.0 (6.00-24.0)	29.3 (10.1)	467 (10.7)	938 (24.3)	3250	116
	n=1	n=2	n=2	n=2	n=2	n=1	n=1
200	33.2	5.08 (4.17-6.00)	40.2 (88.5)	703 (55.6)	1460 (62.9)	3720	77.5
	n=1	n=2	n=2	n=2	n=2	n=1	n=1
300	30.1 (10.0)	4.00 (4.00-5.95)	198 (41.5)	3440 (44.7)	7470 (46.5)	1880 (50.7)	44.5 (36.8)
	n=3	n=3	n=3	n=3	n=3	n=2	n=2
400	30.7 (39.1)	4.99 (2.97-6.73)	120 (80.9)	1920 (78)	4070 (81.8)	3470 (74.4)	95.9 (58.6)
	n=10	n=12	n=12	n=12	n=12	n=5	n=5
500	31.1 (11.1)	3.98 (3.00-23.5)	153 (86.5)	2350 (87.9)	5140 (142)	6230 (219)	147 (170)
	n=7	n=8	n=8	n=8	n=8	n=3	n=3
600	37.6 (24.6)	6.00 (3.00-24.1)	212 (59.7)	3590 (53.4)	8180 (57.4)	1990 (4.30)	46.3 (9.60)
	n=6	n=9	n=9	n=9	n=9	n=2	n=2
700	38.9 (98.4)	6.00 (4.00-25.0)	206 (146)	3450 (138)	9210 (112)	2340 (56.5)	66.6 (35.8)
	n=3	n=4	n=4	n=4	n=4	n=2	n=2
750	40.6 (34.7)	6.02 (3.95-23.8)	186 (127)	3390 (121)	7870 (127)	4230 (164)	88.5 (163)
	n=9	n=10	n=10	n=10	n=10	n=3	n=3

Source: Summary of Clinical Pharmacology, Table 2-1, Page 24.

Table 6. PK parameters following repeat doses of ceritinib on cycle 1 day 8 of dose escalation phase

Dose (mg)	Tmax (h)	Cmax (ng/mL)	AUC0-24h (ng*h/mL)	AUClast (ng*h /mL)	Cmin (ng/mL)	CLss/F (L/h)	Racc
50	2.46 (2.00-2.92) n=2	25.1 (37.5) n=2	435 (42.1) n=2	425 (47.0) n=2	12.6 (73.9) n=2	115 (42.1) n=2	2.56 n=1
100	3.49 (3.00-3.98) n=2	76.7 (20.9) n=2	1520 (41.1) n=2	1530 (40.8) n=2	52.9 (63.8) n=2	65.8 (41.1) n=2	3.25 (53.5) n=2
200	3.00 (2.98-7.95) n=3	212 (18.0) n=3	4150 (32.2) n=3	4150 (32.3) n=3	116 (21.5) n=3	48.2 (32.2) n=3	6.62 (17.6) n=2
300	4.00 (3.00-7.18) n=3	381 (168) n=3	7660 (403) n=2	5000 (252) n=3	295 (152) n=3	39.2 (403) n=2	1.83 (216) n=2
400	6.08 (2.98-24.0) n=13	419 (69.7) n=13	7680 (77.4) n=9	8330 (74.3) n=13	298 (72.2) n=14	52.1 (77.4) n=9	3.80 (125) n=7
500	3.95 (1.93-6.00) n=9	641 (40.0) n=9	12300 (37.4) n=9	12300 (37.2) n=9	456 (54.7) n=8	40.7 (37.4) n=9	6.08 (71.5) n=7
600	4.00 (0-23.6) n=9	688 (68.3) n=9	14700 (71.7) n=7	13100 (70.5) n=9	397 (124) n=9	40.8 (71.7) n=7	3.55 (51.7) n=6
700	5.97 (2.00-24.0) n=5	1140 (37.7) n=5	35200 (0.800) n=2	19600 (97.3) n=5	896 (38.7) n=4	19.9 (0.800) n=2	6.84 (89.4) n=2
750	5.03 (3.00-7.95) n=8	674 (76.2) n=8	13900 (74.8) n=8	14000 (74.2) n=8	496 (78.6) n=8	53.9 (74.8) n=8	4.68 (72.1) n=8

n: number of patients with non-missing values.
Values are median (range) for Tmax, geometric mean (CV% of geometric mean) for all others.
Racc: Accumulation ratio calculated based on AUC0-24h

Source: Summary of Clinical Pharmacology, Table 2-2, Page 25.

Steady-state trough concentrations of ceritinib by dose are summarized in **Table 7**.

Table 7. Steady-state trough concentrations of ceritinib

Dose	Cycle 2 day 1 pre-dose ceritinib concentrations (ng/mL)	Average steady-state trough concentrations (ng/mL)
50	16.2 n=1	15.1 (11.2) n=2
100	30.3 n=1	43.6 (50.0) n=2
200	88.0 (300) n=2	149 (213) n=3
300	418 (119) n=3	414 (113) n=3
400	466 (92.4) n=10	463 (77.5) n=14
500	524 (35.3) n=7	680 (50.7) n=8
600	646 (88.6) n=7	733 (57.6) n=9
700	417 (267) n=2	1231 (34.2) n=3
750	773 (66.0) n=207	871 (46.5) n=203

Source: apkconc.xpt; values are for geometric mean (CV% of geometric mean) where applicable
Average steady-state trough concentration is defined as the geometric mean of all evaluable steady-state trough concentrations for each patient.

PK parameters following 750 mg ceritinib on day 1 of cycles 1 and 2 of the expansion phase are summarized in **Table 8**.

Table 8. PK parameters following 750 mg ceritinib on day 1 of cycles 1 and 2 of the expansion phase

Parameter[a]	Cycle 1 Day 1	Cycle 2 Day 1
Tmax (h)	6.00 (1.13-24.0) n=208	6.00 (0-22.6) n=133
Cmax (ng/mL)	203 (101) n=208	1010 (44.8) n=133
Cmin (ng/mL)	- -	828 (48.4) n=169
AUC0-24h (ng*h/mL)	3340 (112) n=73	22600 (37.1) n=23
AUC0-8h (ng*h/mL)[b]	- -	7090 (43.4) n=77
AUClast (ng*h/mL)	2040 (175) n=208	8900 (76.1) n=133
CLss/F (L/h)	- -	33.2 (37.1) n=23
Racc	- -	6.20 (58.5) n=9

n: number of patients with non-missing values.

[a] Values are median (range) for Tmax, geometric mean (CV% of geometric mean) for all others.

[b] AUC0-8h is calculated at Cycle 2 Day 1 in the expansion phase. A 24h sample was collected at Cycle 2 Day 1 for some patients enrolled in the expansion phase after Amendment 4 was implemented; for these patients AUC0-24h were also calculated.

Source: Summary of Clinical Pharmacology, Table 2-3, Page 26.

2.2.5.2 *How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?*

After oral administration of ceritinib capsules, median T_{max} ranged from 4 to 6 hours in patients across 400 to 750 mg dose groups, and approximately 6 to 8 hours in healthy subjects. The mean terminal $t_{1/2}$ ranged from 31 to 41 hours across 400 to 750 mg dose groups in patients, and 36 to 48 hours across 450 to 750 mg dose groups in healthy subjects.

2.2.5.3 *What are the characteristics of drug absorption?*

Following oral administration of ceritinib, C_{max} was reached approximately 4-6 hours under fasting conditions. Administration of a single 500 mg dose of ceritinib with a high-fat, high-calorie meal in healthy subjects resulted in a 73% increase in AUC and 41% increase in C_{max} as compared with fasted conditions while a low-fat meal increased AUC by 58% and C_{max} by 43% as compared to fasted conditions.

An absolute bioavailability study was not conducted. Based on the mean percentage of the dose recovered as metabolites in the excreta in the ADME study [A2105], a lower limit on the extent of oral absorption is estimated to be approximately 25%. Given that apparent passive permeability of ceritinib is low and ceritinib is a substrate for P-glycoprotein (P-gp), ceritinib

absorption is likely limited.

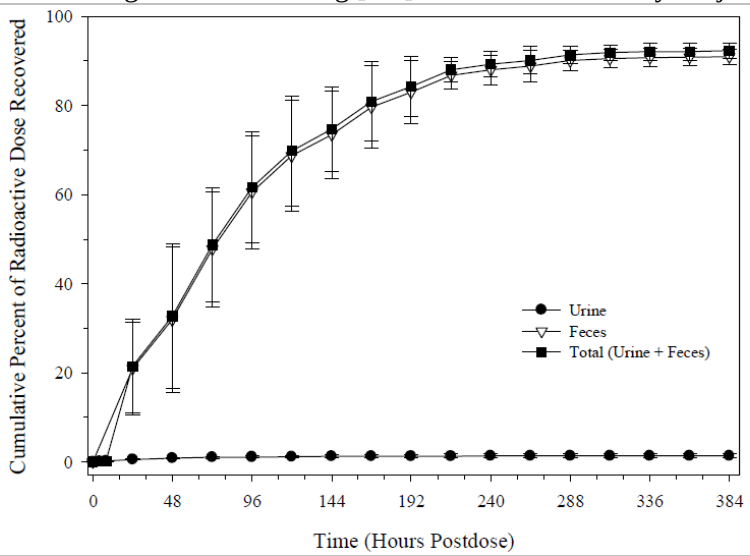
2.2.5.4 *What are the characteristics of drug distribution?*

The geometric mean apparent volume of distribution (V_d/F) ranged from 1990 to 6230 L across 400 to 750 mg dose groups. Ceritinib is 97.2% bound to human plasma proteins (type of plasma proteins, albumin or alpha glycoprotein, is unspecified) independent of concentration over the concentration range of 50 to 10,000 ng/mL [Study 900777]. The mean blood to plasma ratio in human blood in vitro is 1.35.

2.2.5.5 *Does the mass balance study suggest renal or hepatic as the major route of elimination?*

The ADME study (A2105) in 6 healthy subjects who received a single dose of 750 mg [^{14}C]-ceritinib with blood samples collected up to 336 hours and urine and feces samples collected up to 384 hours post-dose, suggests hepatic as the major route of elimination. The mean recovery of the administered dose was 92.3% (68% as unchanged parent compound) in the feces and 1.3% in the urine (**Figure 9**). The major circulating component in plasma was unchanged ceritinib, which constituted 81.6% of plasma radioactivity.

Figure 9. Mean radioactive dose recovered in urine and feces after a single dose of 750 mg [^{14}C]-ceritinib in 6 healthy subjects

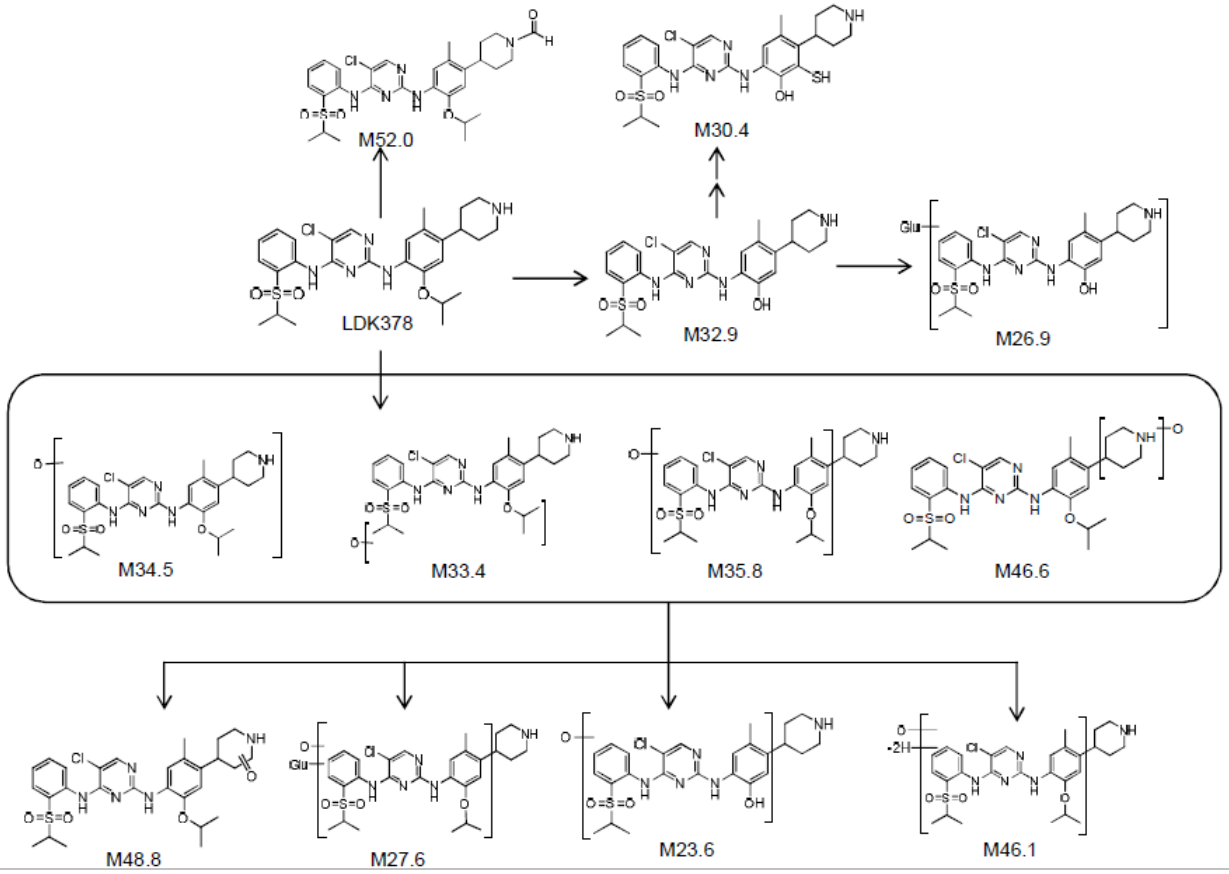


Source: A2105 Final Study Report, Figure 11-10, Page 69

2.2.5.6 *What are the characteristics of drug metabolism?*

Hepatic oxidative metabolism of ceritinib is primarily mediated by CYP3A (>90%) as shown in an in vitro study using human liver microsomes [Study R0900839]. The metabolic pathway in humans is shown in **Figure 10**.

Figure 10. The metabolism of ceritinib after a single dose of 750 mg [^{14}C]-ceritinib in 6 healthy subjects



Source: A2105 Final Study Report, Figure 11-9, Page 66

After a single oral 750 mg dose of [^{14}C]-ceritinib, plasma samples were collected at pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 10, 12, 24, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264, 288, 312, and 336 hours post-dose in 6 healthy subjects [Study A2105]. Unchanged [^{14}C]-ceritinib accounted for 81.6% of plasma radioactivity. Eleven metabolites were identified in plasma, with no metabolite contributing >2.3% to the mean radioactivity AUC or >5.8% to the radioactivity AUC in any individual subject (**Table 9**). Unchanged [^{14}C]-ceritinib accounted for 68% of the recovered dose in the feces with ten metabolites identified (no metabolite contributing >6.5% of the administered dose) (**Table 9**). Urine was not profiled for metabolites due to the low levels of radioactivity recovered in urine. Ceritinib (parent compound) accounted for >90% of $AUC_{0\text{-}24h}$ of total drug related material in patients (Study X2101).

Table 9. Components of plasma, urine, and feces after a single dose of 750 mg [^{14}C]-ceritinib in healthy subjects (n=6)

	Mean % of total AUC in plasma (Range)	Mean % of dose in feces (Range)
Parent	81.6 (75.9-89.1)	68.0 (59.7-79.2)
M23.6	1.2 (0.5-2.5)	3.9 (1.6-5.3)
M26.9	1.1 (0.3-1.6)	-
M27.6	1.4 (0.1-2.7)	-
M30.4	-	2.1 (1.0-2.8)
M32.9	1.9 (0.8-5.8)	1.8 (1.3-2.4)
M33.4	1.6 (0.5-2.7)	1.4 (0.7-3.5)
M34.5	1.9 (0.1-4.5)	1.2 (0.6-1.7)
M35.8	1.8 (0.8-2.9)	6.5 (4.5-7.6)
M46.1	2.3 (1.5-3.7)	1.6 (0.9-2.8)
M46.6	1.7 (0.4-5.1)	1.1 (0.6-1.7)
M48.8	1.7 (1.1-2.2)	1.4 (0.9-2.1)
M52.0	2.0 (0.7-4.0)	2.2 (1.1-3.7)
Source: A2105 Final Study Report, Table 11-8, Page 61; Table 11-9, Page 65.		

2.2.5.7 *What are the characteristics of drug excretion?*

The ADME study (A2105) showed that 92.3% (68% unchanged parent compound) of the [^{14}C]-ceritinib oral dose was recovered in the feces and 1.3% in the urine. Non-metabolic elimination such as biliary excretion and gastrointestinal secretion in humans cannot be ruled out. Biliary excretion of unchanged ceritinib accounted for 34.9% of the intravenous dose in bile-duct cannulated rats, while direct GI secretion accounted for 12.1% of the dose, indicating that 50% of the clearance in rats is mediated through non-metabolism pathways [Study 900773a].

Elimination

Apparent clearance (CL/F) at steady-state (33 L/h) is lower than that after a single dose (89 L/h), likely due to auto-inhibition of CYP3A. The terminal half-life ($t_{1/2}$) at the 750 mg dose is 41 hours.

2.2.5.8 *Based on PK parameters, what is the degree of linearity or non-linearity based in the dose-concentration relationship?*

Ceritinib exhibits nonlinear, time-dependent PK in humans. After a single dose, exposures are dose proportional in the range of 50 to 750 mg with an estimated slope of 0.99 (90% CI: 0.68, 1.30) for $AUC_{0\text{-}24h}$ and 0.97 (90% CI: 0.65, 1.29) for C_{max} using a power model. After repeat doses of 50 to 750 mg, exposures (C_{trough} on Cycle 2 Day 1) are greater than dose proportional with an estimated slope of 1.47 (90% CI: 1.10, 1.84).

2.2.5.9 *How do the PK parameters change with time following chronic dosing?*

The mean accumulation ratio for $AUC_{0\text{-}24h}$ is 4.7 (day 8/day 1 of cycle 1) and 6.2 (day 1 of cycle 2/cycle 1). Refer to **Table 5** and **Table 6** for single and multiple dose PK parameters, respectively.

2.2.5.10 *What is the inter- and intra-subject variability of the PK parameters in volunteers and patients and what are the major causes of variability?*

The inter-subject variability as estimated by geometric mean CV% in healthy subjects administered single oral doses of 450 to 750 mg was determined to be 42-74% for AUC_{inf} and 35-94% for C_{max}. Inter-patient variability in steady state AUC and C_{max} at the dose of 750 mg is 74% and 76%, respectively.

The population PK (popPK) analysis assessed the influence of covariates including body weight, gender, race, age, hepatic function (baseline ALT, total bilirubin, albumin), renal function (baseline eGFR), ECOG performance status, prior crizotinib treatment, and concomitant medications (CYP3A inhibitors and inducers, pH-elevating agents). Body weight and baseline albumin were found to be statistically significant covariates impacting CL/F of ceritinib. However, the effects of these covariates on ceritinib PK were not considered to be clinically important.

2.3 INTRINSIC FACTORS

2.3.1 What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on effectiveness or safety responses?

No formal studies have been conducted to assess the effect of age, race, weight, height, or organ dysfunction on exposure and response to ceritinib. The Applicant's popPK analysis, verified by our pharmacometrics review, did not identify clinically important effects of body weight, age, gender, mild and moderate renal impairment, and mild hepatic impairment as covariates on clearance or volume of distribution of ceritinib (refer to Pharmacometrics review in **Section 4.1**).

Relationship between Age and Exposure

The popPK analysis showed that age (<65 years, ≥65 years) is not a statistically significant covariate influencing ceritinib PK.

Relationship between Gender and Exposure

The popPK analysis showed that gender is not a statistically significant covariate influencing ceritinib PK. Exposures of ceritinib in women (n=170) were 12% higher than that observed in men (n=132), which is not considered to be a clinically important difference requiring dose modification.

Relationship between Race and Exposure

The effect of race on ceritinib PK was evaluated in Caucasian (n=197, 65.2%), Asian (n=95, 31.5%), Black (n=4, 1.3%), and other races (n=6, 2.0%). The popPK analysis suggested that exposures were 10% higher in Asians as compared to non-Asians, most likely explained by the

lower body weight in Asians (mean body weight for Asians is 61 kg versus non-Asians of 72 kg). This difference in exposure is not considered to be a clinically important and does not require dose modification.

Relationship between Weight and Exposure

PopPK analyses identified body weight as a significant covariate influencing ceritinib PK. Patients with lower body weight (<60 kg) had 20% higher systemic exposures and those with higher body weight (>80 kg) had 15% lower exposures as compared to patients with body weight of 60-80 kg. However, these differences are not considered to be clinically important.

Relationship between Renal Impairment and Exposure

The Applicant did not conduct a dedicated renal impairment study. Renal function was not retained as a covariate in the final population PK model (**Figure 12**). The AUC_{ss} in patients with mild or moderate renal impairment were predicted to have a 1.09-fold (90% CI: 0.97-1.25) and 1.19-fold (90% CI: 0.95-1.49) increase in AUC_{ss} compared to patients with normal renal function. These potential PK differences are not considered to be clinically important because additional analyses suggested that baseline renal function has no apparent influence on effectiveness (ORR) and safety (any Grade 3-4 AEs) (**Table 10**).

Therefore, no dose adjustment in patients with mild and moderate renal impairment is recommended. Patients with severe renal impairment were excluded from enrollment in the clinical studies. A severe renal impairment study is not recommended as renal excretion is a minor route of elimination (1.3% of the orally administered dose was recovered in the urine) and based on discussion with the Clinical reviewer, lung cancer does not typically metastasize to the kidneys and the patient population is not intrinsically renally compromised.

Table 10. Proportion of patients with ORR or any Grade 3-4 AEs based on renal function

	Normal Renal Function	Mild Renal Impairment	Moderate Renal Impairment
Any Grade 3-4 AEs[1]	113/160 (71%)	60/79 (76%)	12/16 (75%)
ORR[2]	58/108 (54%)	25/46 (54%)	6/9 (67%)

[1] ITT Safety Population, data cut-off of October 31, 2013, n=255
[2] NSCLC patients with prior ALK inhibitor who received 750 mg ceritinib, data cut-off of October 31, 2013, n=163

Relationship between Hepatic Impairment and Exposure

Because ADME study results showed that 92% of the oral administered dose was recovered in the feces, hepatic impairment is likely to increase the systemic exposure of ceritinib. Therefore, a PMR will be requested to submit the results from the ongoing single dose hepatic impairment study in otherwise healthy subjects. PopPK analyses showed similar ceritinib exposures between patients with mild hepatic impairment (total bilirubin ≤ULN and AST >ULN or total bilirubin >1-1.5 × ULN and AST any value, n=48) and patients with normal hepatic function (total

bilirubin ≤ULN and AST ≤ULN, n=254). In addition, the data suggested that baseline hepatic function (mild hepatic impairment) has no apparent influence on effectiveness (ORR) and safety (any Grade 3-4 AEs) (**Table 11**). Dose adjustment in patients with mild hepatic impairment is not recommended. Patients with moderate and severe hepatic impairment were excluded from enrollment in the clinical study and dose recommendations have not been determined in patients with moderate and severe hepatic impairment.

Table 11. Proportion of patients with ORR or any Grade 3-4 AEs based on hepatic function

	Normal Hepatic Function	Mild Hepatic Impairment
Any Grade 3-4 AEs[1]	155/215 (73%)	30/40 (75%)
ORR[2]	74/136 (54%)	15/27 (56%)

[1] ITT Safety Population, data cut-off of October 31, 2013, n=255
[2] NSCLC patients with prior ALK inhibitor who received 750 mg ceritinib, data cut-off of October 31, 2013, n=163

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups?

No clinically important PK differences have been identified in specific patient populations. Therefore, no dosage regimen adjustments are currently recommended for specific patient populations. The Applicant is requested to conduct a hepatic impairment study under a PMR to determine the recommended dose in patients with moderate or severe hepatic impairment (refer to **Section 1.2.1**).

2.3.2.1 *Elderly*

Age was not identified as a significant covariate influencing ceritinib PK based on a popPK analysis which included patients 22-80 years of age.

2.3.2.2 *Pediatric*

A study has not been conducted in pediatric patients. As ceritinib received orphan drug designation for the treatment of patients with NSCLC that is ALK-positive, a study in pediatric patients is not required for this indication.

2.3.2.3 *Gender*

The popPK analysis showed that gender is not a statistically significant covariate influencing ceritinib PK. Exposures of ceritinib in women (n=170) were 12% higher than that observed in men (n=132), which is not considered to be a clinically important difference requiring dose modification based on gender.

2.3.2.4 *Race/Ethnicity*

The popPK analysis in Caucasian (n=197, 65.2%), Asian (n=95, 31.5%), Black (n=4, 1.3%), and other races (n=6, 2.0%) showed that exposures were 10% higher in Asians as compared to non-Asians, most likely explained by the lower body weight in Asians (mean body weight for Asians is 61 kg versus non-Asians is 72 kg). This difference in exposure is not considered to be clinically important and does not require dose modification.

2.3.2.5 *Renal Impairment*

Refer to **Section 2.3.1**. PopPK analyses showed 9% and 19% higher ceritinib exposures in patients with mild renal impairment (CLcr 60 to <90 mL/min, n=97) and moderate renal impairment (CLcr 30 to <60 mL/min, n=22), respectively, as compared to those with normal renal function (CLcr ≥90 mL/min, n=183). These PK differences are not considered to be clinically important because data suggested that baseline renal function has no apparent influence on effectiveness (ORR) and safety (any Grade 3-4 AEs); therefore patients with mild and moderate renal impairment do not require dose modification.

2.3.2.6 *Hepatic Impairment*

Refer to **Section 2.3.1**. PopPK analyses showed that ceritinib exposures were similar between patients with mild hepatic impairment (total bilirubin ≤ULN and AST >ULN or total bilirubin >1-1.5 × ULN and AST any value, n=254) and patients with normal hepatic function (total bilirubin ≤ULN and AST ≤ ULN, n=48). In addition, data suggested that baseline mild hepatic impairment has no apparent influence on effectiveness (ORR) and safety (any Grade 3-4 AEs). No dose modification in patients with mild hepatic impairment is recommended. The Applicant is requested to conduct a clinical trial under a PMR to determine the appropriate ceritinib dose in patients with moderate and severe hepatic impairment.

2.3.2.7 *What pregnancy and lactation use information is there in the application?*

The proposed labeling states that ceritinib can cause fetal harm when administered to a pregnant woman based on its mechanism of action, and lists ceritinib under pregnancy category D.

It is not known whether ceritinib is present in human milk. The proposed labeling states that (b) (4) (b) (4) discontinue nursing (b) (4) taking into account the importance of the drug to the mother.

2.4 EXTRINSIC FACTORS

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or dose-response and what is the impact of any differences in exposure on response?

The effect of extrinsic factors including concomitant medications (CYP3A inhibitors and inducers) were evaluated in vivo and prior crizotinib treatment was evaluated using popPK analyses.

2.4.2 Drug-drug interactions?

2.4.2.1 *Is there an in vitro basis to suspect in vivo drug-drug interactions?*

Yes. See below.

2.4.2.2 *Is the drug a substrate of CYP enzymes?*

Yes. CYP3A4 was identified as the primary CYP enzyme (>90%) responsible for the hepatic oxidative metabolism of ceritinib in human liver microsomes (**Table 12**).

Table 12. Inhibition of [^{14}C]-ceritinib metabolism by selective CYP inhibitors

Substrate/Inhibitor (main inhibited P450)	Concentration range used (μM)	Median reported K_i or IC_{50} value (μM)[a]	IC_{50} (μM)	% maximal inhibition[b]
Ketoconazole (3A)	0-1	0.100	~ 0.03	90.5
Azamulin (3A)	0-5	0.150	~ 0.01	100
Ticlopidine (2B6/2C19)	0-10	1.70	>10	10.9
S-mephenytoin (CYP2C19)	0-250	95.5	>250	18
Montelukast (2C8)	0-2	0.0140 (0.18-0.71)[c]	>2	16.5
Furafylline (1A2)	0-10	2.00	>10	19.1
Quinidine (2D6)	0-1	0.0605	>1	17.9
Sulfaphenazole (2C9)	0-5	0.510	>5	11.9
Fluvastatin (2C9)	0-5	0.525	>5	21.6

[a] median values were calculated from (DMPK R0400785). If a range of values was reported for a study an average value was taken. The K_i or IC_{50} values used in the calculations corresponded to inhibition of one enzyme (or subfamily, in the case of CYP3A).

[b] percent maximal inhibition of total [^{14}C]LDK378 metabolism at the concentrations of inhibitor examined

Source: Report R0900839, Table 6-7, Page 25.

2.4.2.3 *Is the drug an inhibitor and/or an inducer of CYP enzymes?*

Inhibitor

Yes. Ceritinib reversibly inhibits CYP2A6, CYP2B6, CYP2C9, CYP2D6, and CYP3A4 in vitro. Ceritinib is also time-dependent inhibitor of CYP3A4/5 but not CYP1A2, CYP2C9, or CYP2D6 at ceritinib concentrations of up to 50 μM.

The potential of ceritinib to inhibit CYP enzymes was evaluated using human liver microsomes [Study 900796]. As shown by the R_1 values >1.1 calculated assuming clinical concentrations (maximal steady-state concentration of 1010 ng/mL or 1.8 μM) (**Table 13**), ceritinib reversibly inhibits CYP2A6, CYP2B6, CYP2C9, CYP2D6, and CYP3A4 in vitro. In vivo studies to evaluate the drug interaction potential of ceritinib with coadministered drugs that are CYP3A4 and CYP2C9 sensitive substrates or those with narrow therapeutic indices are warranted and will be requested as PMRs. If these in vivo studies show no drug interaction, in vivo evaluation of a CYP2D6 substrate will not be needed because the R_1 value for CYP2D6 is smaller than those for CYP3A4 and CYP2C9 and only slightly >1.1. An in vivo study to evaluate the drug interaction potential of ceritinib with coadministered drugs that are CYP2A6 substrates is not necessary because CYP2A6 is not among those CYP enzymes requiring routine assessment as recommended in the 2012 Drug Interaction draft FDA Guidance for Industry.

Table 13. IC_{50} and calculated R_1 values for ceritinib inhibition of CYP activities in human liver microsomes

CYP Enzyme	Substrate	ceritinib IC_{50} (unbound) µM	Ki value (unbound) µM	R_1 value $(1+I/K_i)$
CYP1A2	Phenacetin	> 100 (2.5)	-	1.0
CYP2A6	Coumarin	5 (1.5)	0.03 (0.009)	61.0
CYP2B6	Bupropion	2 (0.3)	5.3 (0.780)	1.3
CYP2C8	Paclitaxel	25 (0.6)	-	1.1
CYP2C8	Amodiaquine	2 (0.6)	16.7 (4.86)	1.1
CYP2C9	Diclofenac	2 (0.6)	0.24 (0.0701)	8.5
CYP2C19	S-mephenytoin	70 (1.8)	-	1.0
CYP2D6	Bufuralol	20 (2.9)	-	1.2
CYP2E1	Chlorzoxazone	30 (4.4)	-	1.1
CYP3A4/5	Midazolam	0.2 (0.06)	0.16 (0.0469)	12.3
CYP3A4/5	Testosterone	0.2 (0.06)	-	19.0

Calculation of R_1 values based on maximal steady-state concentration of 1010 ng/mL or 1.8 µM [I]
K_i assumed to be $IC_{50}/2$ for competitive inhibition for those CYP enzymes without an experimental K_i value

Inducer

Yes. There was dose-dependent induction of CYP3A4 mRNA. The potential of ceritinib (0.25-2.5 µM) to induce CYP enzymes was evaluated using human hepatocytes from three donors [Study 200856]. Results showed that there was no induction of CYP1A2, CYP2B6, or CYP2C9 mRNA (<4-fold) relative to vehicle control (**Table 14**). There was dose-dependent induction of CYP3A4 mRNA with 3.2-, 8.7-, and 6.1-fold change in the three human hepatocyte lots, respectively. Ceritinib did not induce CYP1A2 or CYP2B6 activity (<2-fold) relative to vehicle control. Marginal induction of CYP2C9 activity (2.3-fold) was observed at 1 µM in one of the three human hepatocyte lots. Marginal induction of CYP3A activity (2.1-fold) was observed at 2.5 µM in one of the human hepatocyte lots. The inconsistency in magnitude of change between CYP3A mRNA and activity levels may be due to ceritinib-mediated time-dependent inhibition of CYP3A [Study R0700696].

Table 14. Ceritinib induction of mean mRNA and activity levels of CYP enzymes

	CYP1A2		CYP2B6		CYP2C9		CYP3A4	
Ceritinib (μM)	mRNA	Activity	mRNA	Activity	mRNA	Activity	mRNA	Activity
0.25	1.01	1.15	1.02	1.05	1.12	1.27	1.27	0.98
1.0	1.14	1.22	1.17	1.20	1.15[d]	1.77	2.73	1.43
2.5	1.07	1.01	0.96	0.92	1.18	1.10	6.03[b]	1.33[c]
Known positive inducer[a]	32.1	31.7	10.2	4.65	2.34	3.50	31.1	8.81

[a] Omeprazole 50 μM for CYP1A2, phenobarbital 1000 μM for CYP2B6 and CYP2C9, rifampin 10 μM for CYP3A4
[b] Mean of 3.24-, 8.74-, and 6.12-fold change relative to vehicle control in the three human hepatocyte lots
[c] Mean of 0.936-, 0.983-, 2.06-fold change relative to vehicle control in the three human hepatocyte lots
[d] Mean of 1.75-, 1.24-, and 2.31-fold change relative vehicle control in the three human hepatocyte lots

The potential of PXR transcriptional activation of the CYP3A4 promoter by ceritinib was evaluated in Study R0700559. Ceritinib was not an activator of PXR in vitro up to 1 μM (the highest concentration tested in which the cells were viable). However, maximal steady-state concentrations in humans (1.8 μM) exceed the concentration of ceritinib used in this in vitro study.

2.4.2.4 *Is the drug an inhibitor and/or an inducer of transporters?*

Ceritinib is not a P-gp (P-glycoprotein) inhibitor or BCRP (breast cancer resistance protein) inhibitor. Ceritinib inhibited OATP1B1 (organic anion transporting polypeptide 1B1) or OATP1B3 activity (organic anion transporting polypeptide 1B3) by 31.8% and 24.1%, respectively. Ceritinib inhibited OAT1 (organic anion transporter) activity by 16.3% and did not inhibit OAT3 activity. Ceritinib inhibited OCT2 (organic cation transporter) activity by 35.4% and did not inhibit OCT1 activity. There are no in vitro studies to evaluate ceritinib as an inducer of transporters.

Inhibitor

P-gp and BCRP: The potential for ceritinib to inhibit P-gp and BCRP was evaluated by assessing the effect of increasing concentrations of ceritinib (0.0-1.5 μM) on the efflux of probe fluorescent substrates for P-gp and BCRP, Rhodamine 123 (Rho123) and Bodipy FL prazosin (BDP), respectively in vitro [Study R0900229]. Maximal steady-state concentrations in humans (1.8 μM) slightly exceed the highest ceritinib concentration of 1.5 μM tested due to low solubility of ceritinib. Given that the efflux of probe substrates Rho123 and BDP did not appear to decrease considerably with increasing concentrations of ceritinib as measured by fluorescence (**Table 15**), an in vivo DDI study with a P-gp or BCRP substrate is considered unnecessary.

Table 15. Effect of ceritinib on P-gp-mediated Rho123 efflux (left) and BCRP-mediated BDP efflux (right)

[LDK378] (μM)	Rho123 fluorescence (geometric mean)
0	12.6
0.001	14.2
0.01	14.4
0.05	15.3
0.1	18.2
0.25	10.9
0.5	18.0
1	15.7
1.5	16.5
CsA (10 μM)	250.3
CsA (10 μM)	258.5

CsA: Cyclosporin A, positive control inhibitor of P-gp

Source: Report R0900229, Table 6-2, Page 16.

[LDK378] (μM)	BDP fluorescence (geometric mean)
0	18.2
0.001	15.8
0.01	17.8
0.05	16.8
0.1	18.0
0.25	15.5
0.5	15.2
1	17.3
1.5	17.2
FTC (10 μM)	130.1
FTC (10 μM)	120.3

FTC: Fumitremorgin C, positive control inhibitor of BCRP

Source: Report R0900229, Table 6-1, Page 16.

OATP1B1 and OATP1B3: The potential for ceritinib to inhibit OATP1B1 or OATP1B3 transporters was evaluated by assessing the effect of increasing concentrations of ceritinib (0.05-5 μM) on the accumulation of the OATP substrate, [^{3}H]estradiol-17ß-glucuronide, and percent inhibition of OATP activity in human embryonic kidney (HEK) cells in vitro [Study R1300170]. Ceritinib inhibited OATP1B1 and OATP1B3 activity by 31.8% and 24.1%, respectively. The IC_{50} values of OATP1B1 or OATP1B3 inhibition were determined to be >5 μM (concentrations were limited up to 5 μM due to low solubility of ceritinib). Given that the calculated R-value is <1.25 (**Table 16**), an in vivo DDI study with a sensitive substrate of OATP1B1 or OATP1B3 is considered unnecessary.

Table 16. IC_{50} and calculated R values for ceritinib inhibition of OATP transporters

Transporter	**Substrate**	**Ceritinib IC_{50} (μM)**	**C_{max}[a]/IC_{50}**	**R value[b] (1+ (fu × $I_{in,max}$/IC_{50})**
OATP1B1	Estradiol 17β-D-glucuronide	> 5	< 0.36	1.06
OATP1B3	Estradiol 17β-D-glucuronide	> 5	< 0.36	1.06

[a] Plasma maximal steady-state concentration (C_{max}) of 1010 ng/mL or 1.8 μM

[b] $I_{in,max}$ is the estimated maximum inhibitor concentration at the inlet to the liver and is equal to C_{max} + (k_a × Dose × F_a F_g/Q_h). F_a F_g (fraction of the dose of inhibitor which is absorbed) = 1; k_a (absorption rate constant of the inhibitor) = 0.1 min^{-1}; Q_h (estimated hepatic blood flow) = 1500 mL/min.

OAT1 and OAT3: The potential for ceritinib to inhibit organic anion transporters (OAT1 and OAT3) was evaluated by assessing the effect of increasing concentrations of ceritinib (0.05-5 μM) on the accumulation of the OAT1 substrate ([^{3}H]cidofovir) and the OAT3 substrate ([^{3}H]estrone-3-sulfate) and percent inhibition of OAT activity in HEK cells in vitro [Study R1200913]. Ceritinib inhibited OAT1 activity by 16.3% and did not inhibit OAT3 activity. The

IC_{50} value of OAT1 inhibition was determined to be >5 μM (concentrations were limited up to 5 μM due to low solubility of ceritinib). Given that the unbound C_{max}/IC_{50} for OAT1 is <0.1 and ceritinib did not inhibit OAT3 (**Table 17**), an in vivo DDI study with a sensitive substrate of OAT1 or OAT3 is considered unnecessary.

Table 17. IC_{50} and calculated unbound C_{max}/IC_{50} values for ceritinib inhibition of OAT and OCT transporters

Transporter	Substrate	Ceritinib IC_{50} (μM)	Unbound C_{max}[a]/IC_{50}
OAT1	Cidofovir	> 5	< 0.01
OAT3	Estrone-3-sulfate	ND[b]	-
OCT1	MPP+	ND[b]	-
OCT2	Metformin	> 5	< 0.01

[a] C_{max} of 1.8 μM; 3% unbound ceritinib - unbound C_{max} of 0.05 μM
[b] Not determined; ceritinib did not inhibit transporter in vitro

OCT1 and OCT2: The potential for ceritinib to inhibit OCT1 and OCT2 was evaluated by assessing the effect of increasing concentrations of ceritinib (0.05-5 μM) on the accumulation of the OCT1 substrate ([^{3}H]MPP^+) and the OCT2 substrate ([^{14}H]metformin) and percent inhibition of OCT activity in HEK cells in vitro [Study R1300023]. Ceritinib inhibited OCT2 activity by 35.4% and did not inhibit OCT1 activity. The IC_{50} value of OCT2 inhibition was determined to be >5 μM (concentrations were limited up to 5 μM due to low solubility of ceritinib). Given that the unbound C_{max}/IC_{50} for OCT2 is <0.1 and ceritinib did not inhibit OCT1 (**Table 17**), an in vivo DDI study with a sensitive substrate of OCT1 or OCT2 is considered unnecessary.

Inducer

There are no in vitro studies to evaluate ceritinib as an inducer of transporters.

2.4.2.5 *Are there other metabolic/transporter pathways that may be important?*

Ceritinib is a P-gp and BCRP substrate in vitro; however their contribution to ceritinib absorption is considered limited. Ceritinib is not a substrate for the hepatic uptake transporters OCT1, OAT2, OATP1B1, and OATP2B1.

Ceritinib is a P-gp substrate in vitro as the net flux ratio is ≥2 (182 at 3.0 μM and 19.5 at 14 μM ceritinib) in Caco-2 cells and LY335979 (a P-gp inhibitor) reduced the efflux ratio (>50%) to approximately 6 at both 3.0 and 14 μM [Study R1000083]. Sensitivity analyses of effective permeability (P_{eff}) were conducted during the PBPK review to determine P-gp contribution to oral absorption of ceritinib. If the intestinal efflux transporter P-gp significantly contributed to the oral absorption of ceritinib, an inhibition of P-gp would result in increased P_{eff} of ceritinib. Sensitivity analyses showed that an increase in P_{eff} led to a similar increase of AUC and C_{max} with a 50% increase in P_{eff} resulting in 34% and 36% increase in ceritinib AUC and C_{max}, respectively, and a 2-fold increase in P_{eff} resulting in 61% and 66% increase in ceritinib AUC and

C_{max}, respectively.

The in vivo DDI study showed that ketoconazole (a strong CYP3A4/P-gp inhibitor) coadministration resulted in an increase of ceritinib AUC and C_{max} that was not in the same magnitude (2.8-fold in AUC and 22% in C_{max}). These simulation and in vivo results suggest that ketoconazole did not increase P_{eff} or affect intestinal efflux transport of ceritinib. Given that the observed effect of ketoconazole on ceritinib exposure is most likely due to CYP3A inhibition and not P-gp inhibition, an in vivo DDI study with a P-gp inhibitor is considered unnecessary.

Ko143 (a BCRP inhibitor) had a smaller effect on the reduction of efflux ratio to 121 at 3 μM ceritinib, indicating that an in vivo DDI study with a BCRP inhibitor is not necessary.

Ceritinib is not a substrate for the hepatic uptake transporters OCT1, OAT2, OATP1B1 and OATP2B1 as shown by <2-fold uptake in cells expressing transporters as compared to control cells [Study R1000482] (**Table 18**).

Table 18. Transport of ceritinib by OCT1, OAT2, OATP1B1, OATP2B1

Substrate	[^{14}C]LDK378 concentration, μM	Transporter being tested	Cellular uptake (pmol mg protein^{-1}·min^{-1})		Fold stimulation in uptake caused by transporter[a]
			Control cells	expressing cells	
[^{14}C]LDK378	5.0	OCT1	396 ± 30	386 ± 26	-
	5.6	OAT2	360 ± 35	517 ± 9.4	1.44
	5.6	OATP1B1	360 ± 35	463 ± 27	1.29
	6.3	OATP2B1	466 ± 5.7	470 ± 51	1.01

[a] The fold stimulation in uptake caused by the respective transporters was calculated by dividing uptake in the transporter expressing cells from the uptake in the HEK Flp-In control cells.

Source: Report R1000482, Table 5-2, Page 13.

2.4.2.6 *Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?*

No, ceritinib is recommended as monotherapy for this marketing application.

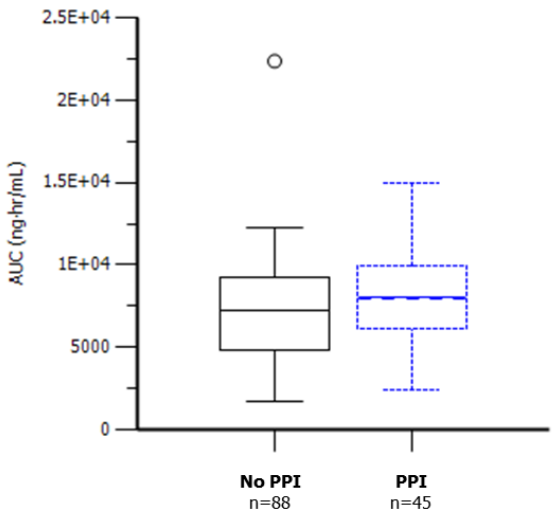
2.4.2.7 *What other co-medications are likely to be administered to the target population?*

Concomitant medications used by ≥20% of the 304 patients (NSCLC, n=290 and non-NSCLC, n=14) treated with any dose of ceritinib in the clinical trial included anti-diarrheal therapy (primarily loperamide, 55%), antiemetics (metoclopramide, 37%), serotonin ($5HT_3$) antagonists (ondansetron, 38%), glucocorticoids (primarily dexamethasone and prednisone, 39%), opioids (primarily oxycodone and morphine, 37%), proton pump inhibitors (PPI, primarily omeprazole and pantoprazole, 30%), acetaminophen (33%), laxatives (primarily lactulose, polyethylene glycol, and magnesium oxide, 24%), benzodiazepines (primarily lorazepam, 22%), and fluoroquinolones (primarily levofloxacin, 22%).

Coadministration of gastric acid reducing agents such as PPIs may lead to decreased drug absorption, leading to decreased effectiveness of ceritinib as ceritinib exhibits pH-dependent

solubility (refer to **Section 2.1.1**). Concomitant administration of acid reducing agents (e.g., H_2-receptor antagonists and PPIs) was significantly associated with a decrease in the absorption rate (k_a) of ceritinib in the popPK analysis, while exposures were similar in patients who received PPIs as compared to that in patients who did not receive PPIs (**Figure 11**). However, these analyses are limited and should be interpreted in the context that the timing of coadministration of a PPI was not taken into consideration in the PK sampling plan. Given that approximately 30% of patients in the clinical trial received PPIs, an appropriate dosing strategy with regard to gastric acid reducing agents should be determined. A PMR will be requested to conduct a clinical trial to determine how to dose ceritinib with regard to concomitant gastric acid reducing agents (refer to **Section 1.2.1**).

Figure 11. Effect of PPI coadministration on ceritinib steady-state exposure (AUC on cycle 2 day 1)



2.4.2.8 *Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?*

Yes. Coadministration of ketoconazole (a strong CYP3A inhibitor) 200 mg twice daily for 14 days and a single dose of 450 mg ceritinib increased ceritinib AUC by 2.9-fold (90% CI: 2.5, 3.3) and C_{max} by 22% (90% CI: 7.0%, 39%) in 19 healthy subjects. Coadministration of rifampin (a strong CYP3A inducer) 600 mg QD for 14 days and a single dose of 750 mg ceritinib decreased ceritinib AUC by 70% (90% CI: 61%, 77%) and C_{max} by 44% (90% CI: 24%, 59%) in 19 healthy subjects.

DDI with Strong CYP3A Modulators

The effect of ketoconazole (a strong CYP3A inhibitor) on ceritinib PK was evaluated in a single dose, two period crossover study in 19 healthy subjects under fasted conditions (Study 2104). Coadministration of ketoconazole 200 mg twice daily for 14 days with a single dose of 450 mg ceritinib increased ceritinib AUC by 2.9-fold and C_{max} by 22% as compared to ceritinib alone (**Table 19**). Clearance (CL/F) of ceritinib decreased by 65% from 78.1 L/h to 27.1 L/h with coadministration of ketoconazole.

Table 19. Comparative analysis of ceritinib PK parameters on day 1 (without ketoconazole) and day 18 (with ketoconazole) (n=19)

Exposure parameter	Geometric Mean Ratio* (90% CI)		
	Ceritinib alone (450 mg)	**Ceritinib (450 mg) with ketoconazole (200 mg BID for 14 days)**	**Geometric Mean Ratio* (90% CI)**
$AUC_{0\text{-}336h}$ (ng·hr/mL)	5640 (44.3) n=18	16300 (47.0) n=19	2.86 (2.45-3.34)
$AUC_{0\text{-}inf}$ (ng·hr/mL)	5760 (43.4) n=18	16600 (47.2) n=19	2.86 (2.46-3.33)
C_{max} (ng/mL)	133 (34.9) n=18	164 (40.3) n=19	1.22 (1.07-1.39)

* ceritinib 450 mg alone vs. ceritinib 450 mg and ketoconazole 200 mg BID for 14 days

The effect of rifampin (a strong CYP3A inducer) on ceritinib PK was evaluated in a single dose, two period crossover study in 19 healthy subjects under fasted conditions (Study 2106). Coadministration of rifampin 600 mg QD for 14 days with a single dose of 750 mg ceritinib decreased ceritinib AUC by 70% and C_{max} by 44% (**Table 20**). Clearance (CL/F) of ceritinib increased by 3.3-fold from 70.6 L/h to 234 L/h with coadministration of rifampin.

Table 20. Comparative analysis of ceritinib AUC and C_{max} on day 1 (without rifampin) and day 21 (with rifampin) (n=19)

Exposure parameter	Geometric Mean Ratio* (90% CI)		
	Ceritinib alone (750 mg)	Ceritinib (750 mg) with rifampin (600 mg QD for 14 days)	Geometric Mean Ratio* (90% CI)
$AUC_{0\text{-}168h}$ (ng·hr/mL)	10100 (74.2) n=17	3130 (87.8) n=17	0.31 (0.24-0.40)
$AUC_{0\text{-}inf}$ (ng·hr/mL)	10600 (72.1) n=17	3210 (85.4) n=17	0.30 (0.23-0.39)
C_{max} (ng/mL)	219 (93.6) n=17	122 (85.1) n=17	0.56 (0.41-0.76)
* ceritinib 750 mg alone vs. ceritinib 750 mg and rifampin 600 mg QD for 14 days			

Given that the drug-drug interaction studies were conducted using single doses of ceritinib, the magnitude of the effect of strong CYP3A modulators on the steady-state PK of ceritinib after repeat dosing in patients is unknown due to nonlinear, time-dependent PK of ceritinib. PBPK modeling predicted that ketoconazole can increase the steady-state ceritinib exposure (AUC) by 51% and that rifampin can decrease steady-state AUC by 67%. Given the magnitude of exposure change in the context of the exposure-response curves for safety and effectiveness observed with ceritinib (refer to **Section 2.2.4.1** and **2.2.4.2**), the following recommendations are provided with regard to concomitant use of strong CYP3A inhibitors:

- Avoid concomitant use of strong CYP3A inhibitors with ceritinib.
- If avoiding concomitant strong CYP3A inhibitors is not possible, the ceritinib dose should be reduced by approximately one-third, rounded to the nearest 150 mg dosage strength. After discontinuation of the strong CYP3A inhibitor, the ceritinib dose that was taken prior to initiating the strong CYP3A4 inhibitor should be resumed.

With regard to concomitant administration of strong CYP3A inducers, the recommendation is avoidance of concurrent use of strong CYP3A inducers. In order to compensate for the 70% decrease in exposure caused by a strong CYP3A inducer, approximately 8-9 capsules would have to be administered to achieve a dose of 1275 mg ceritinib, which is likely not feasible for patients.

DDI with Moderate CYP3A Modulators

PBPK modeling predicted that fluconazole, a moderate CYP3A4 inhibitor, can increase ceritinib exposure by 37% and efavirenz, a moderate CYP3A4 inducer, can decrease ceritinib exposure by 43% (**Table 21**). A clinical trial to further evaluate the effect of a moderate CYP3A4 inhibitor or

inducer on ceritinib PK is considered unnecessary given the magnitude of predicted changes in steady-state exposures after coadministration with a moderate CYP3A4 inhibitor and inducer. It is not recommended to restrict the concomitant use of moderate CYP3A4 inhibitors and inducers.

Table 21. PBPK model simulated ceritinib steady-state AUC and C_{max} following coadministration of ceritinib 750 mg daily with CYP3A modulators

	Sponsor's model		FDA's model	
Dosing of CYP3A modulators	**AUC Ratio (90% CI)**	**C_{max} Ratio (90% CI)**	**AUC Ratio (90% CI)**	**C_{max} Ratio (90% CI)**
Strong CYP3A inhibitor ketoconazole 200 mg twice daily	1.35 (1.27, 1.42)	1.32 (1.26, 1.39)	1.51 (1.43, 1.59)	1.47 (1.40, 1.54)
Moderate CYP3A inhibitor fluconazole 200 mg once daily	1.15 (1.12, 1.19)	1.14 (1.11, 1.17)	1.37 (1.31, 1.42)	1.32 (1.28, 1.37)
Strong CYP3A inducer rifampin 600 mg once daily	0.51 (0.45, 0.57)	0.54 (0.49, 0.60)	0.33 (0.30, 0.36)	0.37 (0.34, 0.40)
Moderate CYP3A inducer efavirenz 600 mg once daily	NA	NA	0.57 (0.52, 0.62)	0.61 (0.56, 0.65)

Source: PBPK review, Table A6.

2.4.2.9 *Is there a known mechanistic basis for pharmacodynamic drug-drug interactions?*

No. Pharmacodynamic data were not collected in the clinical study.

2.4.2.10 *Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions or protein binding?*

The Applicant is requested to conduct DDI studies with CYP3A and CYP2C9 sensitive substrates and gastric acid reducing agents under PMRs. Refer to **Section 1.2.1**.

2.4.3 What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?

Refer to **Section 2.2.4.4** on unresolved dosing and administration issues with regard to GI intolerability.

2.5 GENERAL BIOPHARMACEUTICS

2.5.1 Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

The Applicant classifies ceritinib as BCS class 4 based on data showing that ceritinib has low permeability in Caco-2 cells [Study R1000083] and poor aqueous solubility (refer to **Section 2.1.1**). The apparent passive permeability of ceritinib in the presence of LY335979 (a P-gp

inhibitor) was 0.27×10^{-5} cm·min^{-1} at 3.0 µM and 0.98×10^{-5} cm·min^{-1} at 14.0 µM, which were lower than that of the low permeability marker mannitol (4.0×10^{-5} cm·min^{-1}).

2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the clinical trial formulation?

The proposed drug product has been available as 25, 50, and 150 mg capsules during ceritinib development. The 150 mg capsule is the only capsule strength intended for commercialization. There were minor differences between the 150 mg capsules used in the clinical trials and the commercial product as listed below:

- Compounds for starting materials
- Color of capsules
- (b) (4) processes
- Manufacturing sites

These differences are not expected to alter the bioavailability of the to-be-marketed capsule. Refer to the Biopharmaceutics review.

2.5.3 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

The effect of food on ceritinib PK was evaluated in a single 500 mg dose, randomized, three-treatment, two period crossover study (A2101) with a 14-day washout period in 28 healthy subjects who received the to-be-marketed formulation of 150 mg capsules plus one 50 mg clinical trial capsule. Given that ceritinib exhibits linear PK in the dose range of 50 to 750 mg following a single dose, the use of a single 500 mg dose that is lower than the clinical dose of 750 mg appears reasonable. The high-fat meal consisted of approximately 1000 total calories with a composition of 50% fat, 35% carbohydrates, and 15% protein as recommended in the Food Effect FDA Guidance for Industry; the low-fat meal consisted of approximately 330 total calories with a composition of 25% fat, 60% carbohydrates, and 15% protein. Refer to **Table 22** for representative high- and low-fat meals.

Table 22. Representative high-fat (left) and low-fat meals (right)

Food item	Calories (kcal)	Fat (g)	Carbohydrate (g)	Protein (g)
2 eggs fried	184	13.8	1.3	12.5
2 slices of bread	134	1.8	25	4.1
1 tablespoon butter	102	11.5	Trace	0.1
1 tablespoon jelly	54	Trace	13	trace
3 strips of bacon	109	9.4	0.1	5.8
4 ounces of hash brown potato	252	13.4	32.6	3.7
8 fluid ounces of whole milk	150	8.2	11.4	8.0
Total calories (kcal)	1000	510	336	139
% of total calories	100	52	34	14

Food item	Calories (kcal)	Fat (g)	Carbohydrate (g)	Protein (g)
2 slices of white bread toast	134	1.7	25	3.8
1 tablespoon light fat margarine*	59	6.6	Trace	Trace
1 tablespoon jelly	55	Trace	14	Trace
8 fluid ounces of skim milk	86	0.4	11.8	8.4
Total calories (kcal)	334	78	206	50
% of total calories	100	23	62	15

* Margarine spread: approximately 48% fat. Source: USDA National Nutrient Database for Standard reference, 2010

Source: A2101 Final Study Report, Tables 7-3 and 7-4, Page 260

At the recommended dose of 750 mg QD, the majority of patients experienced GI adverse reactions. Taking ceritinib with food may improve GI tolerability, but would increase exposures. Administration of a single 500 mg dose of ceritinib with a high-fat, high-calorie meal in healthy subjects resulted in a 73% increase in AUC and 41% increase in C_{max} with no effect on t_{max} as compared with fasted conditions; a low-fat meal increased AUC by 58% and C_{max} by 43% and decreased t_{max} by a median of 2 hours as compared to fasted conditions (**Table 23**).

Table 23. PK parameters of a single dose of ceritinib after a high-fat or a low-fat meal compared to fasted conditions

	Geometric Mean (%CV)			Geometric Mean Ratio (90% CI)	
PK Parameter	High-fat high-calorie meal (n=14)	Low-fat low-calorie meal (n=14)	Fasted (n=27)	High-fat/fed	Low-fat/fed
AUC_{inf}	12002 (32)	10941 (23)	6929 (42)	1.73 (1.46, 2.05)	1.58 (1.34, 1.86)
$AUC_{0\text{-}168h}$	11419 (32)	10564 (23)	6650 (42)	1.71 (1.45, 2.03)	1.59 (1.35, 1.87)
C_{max}	225 (29)	229 (20)	160 (44)	1.41 (1.18, 1.68)	1.43 (1.21, 1.71)
Source: Study 2101 final study report, Table 11-3, Page 48; Listing 16.2.6-1.1, Pages 555-558					

In order to determine an exposure-matched dose of ceritinib taken with food to improve GI tolerability and compliance without compromising efficacy, a postmarketing trial will be requested to evaluate the GI tolerability, efficacy, and PK of 450 mg of ceritinib taken with a meal as compared with that of 750 mg ceritinib taken in the fasted state in metastatic ALK-positive NSCLC patients. Refer to **Section 2.2.4.4**.

2.5.4 When would a fed BE study be appropriate and was one conducted?

Not applicable.

2.5.5 How do dissolution conditions and specifications ensure in vivo performance and quality of the product?

Refer to Biopharmaceutics review.

2.5.6 If different strength formulations are not bioequivalent based on standard criteria, what clinical safety and efficacy data support the approval of various strengths of the to-be-marketed product?

Not applicable as only one strength of 150 mg capsules will be marketed. Refer to CMC review.

2.5.7 If the NDA is for a modified release formulation of an approved immediate product without supportive safety and efficacy studies, what dosing regimen changes are necessary, if any, in the presence or absence of PK-PD relationship?

Not applicable.

2.5.8 If unapproved products or altered approved products were used as active controls, how is BE to the 'to-be-marketed' product? What is the basis for using either in vitro or in vivo data to evaluate BE?

Not applicable.

2.5.9 What other significant, unresolved issues in relation to in vitro dissolution of in vivo BA and BE need to be addressed?

None.

2.6 ANALYTICAL SECTION

2.6.1 How are the active moieties identified and measured in the plasma and the other matrices?

Ceritinib was measured in human plasma using a validated liquid chromatography-mass spectrometry (LC-MS/MS) method [Validated Report No. R1100240, R1100240-01]. In the mass balance study, total radioactivity in blood, plasma, urine, and feces were measured by liquid scintillation counting.

2.6.2 Which metabolites have been selected for analysis and why?

Concentrations of ceritinib metabolites were not measured as there were no major circulating metabolites. Eleven metabolites were identified in plasma, with no metabolite contributing >2.3% to the mean radioactivity AUC or >5.8% to the radioactivity AUC in any individual subject.

2.6.3 For all moieties measured is free, bound or total measured?

Given that ceritinib is 97.2% bound to human plasma proteins, total plasma concentrations were measured.

2.6.4 What bioanalytical methods are used to assess concentrations?

Ceritinib concentrations in human plasma were measured by LC-MS/MS using validated methods [Validated Report No. R1100240, R1100240-01].

2.6.4.1 *What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?*

The standard curve was generated using seven calibration samples in the concentration range of 1.0 ng/mL (LLOQ) to 500 ng/mL and weighted ($1/x^2$) linear regression. A 100-fold dilution of human plasma samples has been validated. This standard curve range was adequate for the purposes of determining plasma concentrations of ceritinib in the clinical studies.

2.6.4.2 *What are the lower and upper limits of quantification?*

See **Section 2.6.4.1**.

2.6.4.3 *What are the accuracy, precision and selectivity at these limits?*

The mean %bias and %CV of calibration standards and quality controls for validation of the

bioanalytical method were ≤15%, and are acceptable based on the 2013 FDA Guidance for Industry *Bioanalytical Method Validation*. Acceptance criteria for QC samples in each run were met (%bias within ±15% of the nominal concentration for at least 2/3 of QC samples and QC samples at a minimum of three concentrations) (**Table 24**).

Table 24. Summary of accuracy and precision of calibration standards and quality controls used in clinical studies

Report No.	Study	Calibration standards		Quality controls	
		Mean accuracy (%Bias)	Mean precision (%CV)	Mean accuracy (%Bias)	Mean precision (%CV)
RCLDK378X2101	X2101[a]	-6.4-3.6 [a]	0.9-6.6 [a]	-1.2-0.8 [b]	2.7-7.4 [b]
RCLDK378A2101	A2101	-5.6-5.0	4.7-10.4	-8.0-2.4	8.6-11.3
RCLDK378A2104	A2104	-5.0-4.8	2.5-7.5	-4.8-1.2	2.3-6.8
RCLDK378A2105	A2105	-2.8-1.8	1.0-4.9	-2.0 to -0.3)	1.4-4.8
RCLDK378A2106	A2106	-5.2-3.0	2.5-4.3	-4.8-0.0	2.5-4.4

[a] **Source:** DMPK RCLDK378X2101 Report Tables 5-6, 5-7, 5-8, 5-9, 5-10 for data on Cs. Data from Cs obtained on five different instruments.
[b] **Source:** DMPK RCLDK378X2101 Report Tables 5-11, 5-12, 5-13, 5-14, 5-15 for data on QCs. Data from QCs obtained on five different instruments.

The selectivity/specificity of the method was established using blank plasma from six sources. Selectivity was ensured at the LLOQ.

2.6.4.4 *What is the sample stability under the conditions used in the study? (long-term, freeze-thaw, sample-handling, sample transport, autosampler)*

The stability of ceritinib in human plasma under the following conditions is summarized:
- Short-term stability in spiked human plasma: 24 hours at room temperature.
- Post-preparative stability in extracts on the autosampler set at 10°C: 137 hours.
- Long-term stability in incurred human plasma: 21 months at ≤ -65°C, 39 days at ≤ -15°C.
- Three freeze-thaw cycles ≤ -70°C at concentrations of 3.0 and 400 ng/mL.
- Stability in solution stored between 2 and 8°C: 13 months.

2.6.4.5 *What is the QC sample plan?*

Four QC samples at concentrations of 3.0 ng/mL (low, 3 × LLOQ), 25.0 ng/mL (mid), 250 ng/mL (mid), and 400 ng/mL (high) were prepared in duplicate in each run.

3 DETAILED LABELING RECOMMENDATIONS

Only relevant clinical pharmacology sections are included. The Agency's suggested changes to the proposed labeling are shown in underline blue text and removal of content shown by ~~red strikethroughs~~. Of note, the Agency's labeling modifications have not been agreed upon by the Applicant as of the date of this review.

2 DOSAGE AND ADMINISTRATION

2.1 [redacted] Dosing and Administration

The recommended dose of ZYKADIA is 750 mg [redacted] orally once daily [redacted] until disease progression or unacceptable toxicity. Take ZYKADIA ~~on an empty stomach, i.e.,~~ at least 2 hours before [redacted] or 2 hours after [redacted] food *[see* [redacted] *Clinical Pharmacology (12.3)]*.

A recommended dose has not been determined for patients with moderate to severe hepatic impairment *[see Use in Specific Populations (8.6)]*.

2.2 Dose Modifications

Table 1: ZYKADIA Dose Interruption, Reduction, or Discontinuation Recommendations [redacted]

Criteria	ZYKADIA Dosing
Severe or intolerable nausea or vomiting or diarrhea despite optimal antiemetic or anti-diarrheal therapy	Withhold until improved then: Resume ZYKADIA with a 150 mg dose reduction **OR** **Take with meals** as instructed below: • If receiving 750 mg daily, reduce the dose to 450 mg daily; • If receiving 600 mg daily, reduce the dose to 300 mg daily.

2.3 Dose Modification for Strong CYP3A4 Inhibitors

Avoid concurrent use of strong CYP3A inhibitors during treatment with ZYKADIA *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*.

If concomitant use of a strong CYP3A inhibitor is unavoidable, reduce ZYKADIA dose by approximately one-third, rounded to the nearest 150 mg dosage strength. After discontinuation of a strong CYP3A inhibitor, resume ZYKADIA dose that was taken prior to initiating the strong CYP3A4 inhibitor.

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on Ceritinib [redacted]

Ceritinib is primarily metabolized by CYP3A4 and is a substrate of the efflux transporter P-glycoprotein (P-gp).

Strong CYP3A Inhibitors

Ketoconazole (a strong CYP3A4/P-gp inhibitor) increased the systemic exposure of ceritinib [redacted] *[see Clinical Pharmacology (12.3)]*. Avoid concurrent [redacted] use of strong CYP3A inhibitors during treatment with ZYKADIA. If concomitant use of strong CYP3A inhibitors including [redacted] certain antivirals (e.g., ritonavir), [redacted] macrolide antibiotics (e.g., telithromycin), antifungals (e.g., ketoconazole), [redacted] and nefazodone is unavoidable, reduce ZYKADIA dose by approximately one-third, rounded to the nearest 150 mg dosage strength. After discontinuation of a strong CYP3A inhibitor, resume ZYKADIA dose that was taken prior

to initiating the strong CYP3A4 inhibitor. (b) (4)

Avoid grapefruit and grapefruit juice as they may inhibit CYP3A.

(b) (4)

(b) (4)

Strong CYP3A Inducers

Rifampin (a strong CYP3A4/P-gp inducer) decreased the systemic exposure of ceritinib (b) (4) *[see Clinical Pharmacology (12.3)]*. Avoid concurrent (b) (4) use of strong CYP3A inducers (b) (4) (e.g., carbamazepine, (b) (4) phenytoin, (b) (4) rifampin, and St. John's Wort) (b) (4)

7.2 (b) (4) Effect of Other Drugs on Ceritinib (b) (4)

Ceritinib inhibits CYP3A and CYP2C9 (b) (4) at clinical (b) (4) concentrations *[see Clinical Pharmacology (12.3)]*. Avoid concurrent use of CYP3A and CYP2C9 substrates known to have narrow therapeutic indices or substrates primarily metabolized by CYP3A and CYP2C9 during treatment with ZYKADIA. If use of these medications is unavoidable, consider dose (b) (4) reduction (b) (4) of (b) (4) CYP3A substrates with (b) (4) narrow therapeutic indices (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, (b) (4) pimozide, (b) (4) quinidine, sirolimus, tacrolimus) and CYP2C9 substrates with (b) (4) narrow therapeutic indices (e.g., phenytoin, warfarin).

(b) (4)

8 USE IN SPECIFIC POPULATIONS

8.6 Hepatic Impairment

(b) (4) As ceritinib is eliminated primarily via the liver, patients with hepatic impairment may have increased exposure (b) (4) Dose adjustment is not recommended for patients with mild hepatic impairment (total bilirubin ≤ULN and AST >ULN or total bilirubin >1.0 to 1.5 × ULN and any AST) based on results of the population pharmacokinetic

analysis *[see Clinical Pharmacology (12.3)]*. A recommended dose has not been determined for patients with moderate to severe hepatic impairment.

(b) (4)

12.2 Pharmacodynamics

Cardiac Electrophysiology

(b) (4) Serial ECGs were collected following a single dose and at steady-state to evaluate the effect of ceritinib on the QT interval in an open-label, dose-escalation, and expansion study. A total of 304 patients were treated with ZYKADIA doses ranging from 50 to 750 mg with 255 patients treated with ZYKADIA 750 mg. One of 304 patients (<1%) were found to have QTcF (corrected QT by the Fridericia method) >500 msec and 16 patients (5.3%) had an increase from baseline QTcF >60 msec. A central tendency analysis of the QTcF data at steady-state demonstrated that the highest upper bound of the two-sided 90% CI for QTcF was 22 msec at ZYKADIA 750 mg. (b) (4) pharmacokinetic/pharmacodynamic analysis suggested (b) (4) concentration-dependent (b) (4) QTc interval prolongation *[see Warnings and Precautions (5.3)]*.

Based on central review of ECG data, 2 of 304 patients (0.7%) had (b) (4) bradycardia defined as less than 50 beats per minute. Bradycardia was reported as an adverse drug reaction in 3 (b) (4)% of patients in Study 1. (b) (4)

12.3 Pharmacokinetics

Absorption

After single oral administration of ZYKADIA in patients, peak (b) (4) plasma levels (C_{max}) of ceritinib were (b) (4) achieved at approximately 4 to 6 hours, and AUC and C_{max} increased dose proportionally over 50 to 750 mg. (b) (4) The absolute bioavailability of ZYKADIA (b) (4) has not been determined.

Following ZYKADIA 750 mg once daily dosing, steady-state was reached by approximately 15 days with a geometric mean accumulation ratio of 6.2 after 3 weeks. Systemic exposure increased in a greater than dose proportional manner after repeat doses of 50 to 750 mg once daily.

Systemic exposure (b) (4) of ceritinib was (b) (4) increased when administered with (b) (4). A high-fat meal increased ceritinib AUC by 73% and C_{max} by 41% and a low-fat meal increased ceritinib AUC by 58% and C_{max} by 43% as compared with the fasted state *[see Dose Modifications (2.2)]* (b) (4) .

(b) (4)

(b) (4)

Distribution

(b) (4) Ceritinib is 97% bound to human plasma proteins. (b) (4) independent of drug concentration (b) (4) The apparent volume of distribution (V_d/F) is 4230 L following a single dose of ZYKADIA 750 mg. Ceritinib also has a slight preferential distribution to red blood cells, relative to plasma, with a mean *in vitro* blood-to-plasma ratio of 1.35. (b) (4)

(b) (4)

Elimination

Following a single dose of 750 mg ZYKADIA (b) (4) the geometric mean apparent plasma terminal half-life (b) (4) ($t_{1/2}$) of ceritinib was (b) (4) 41 hours in patients. (b) (4)

Ceritinib demonstrates nonlinear PK over time. The geometric mean apparent clearance (CL/F) of ceritinib was lower at steady-state (33.2 L/h (b) (4)) after 750 mg daily (b) (4) -dosing than that after a single 750 mg (b) (4) dose (88.5 L/h (b) (4)) (b) (4)

Metabolism: In vitro studies demonstrated that CYP3A was the major enzyme involved in the metabolic clearance of ceritinib. Following oral administration of a single 750 mg radiolabeled ceritinib dose, ceritinib as the parent compound was the main circulating component (82%) in human plasma.

Excretion: Following oral administration of a single 750 mg radiolabeled ceritinib dose, 92.3% of the administered dose was recovered in the feces (b) (4) (with 68% as unchanged parent compound) (b) (4) while 1.3% of the administered (b) (4) dose was (b) (4) recovered in the urine.

(b) (4)

(b) (4)

Specific Populations

Age, Gender, Race, and Body Weight: Age, gender, race, and body weight had no clinically important effect on the systemic exposure of ceritinib based on population pharmacokinetic analyses.

Hepatic Impairment: (b) (4) As ceritinib is eliminated primarily via the liver, patients with hepatic impairment may have increased exposure. A pharmacokinetic trial in patients with hepatic impairment has not been conducted. Based on a population pharmacokinetic analysis of 48 patients with mild hepatic impairment (total bilirubin ≤ULN and AST >ULN or total bilirubin >1.0 to 1.5 × ULN and any AST) and 254 patients with normal hepatic function (total bilirubin ≤ULN and AST ≤ULN), ceritinib exposures were similar in patients with mild hepatic impairment and normal hepatic function. (b) (4) The pharmacokinetics of ceritinib have not been studied in patients with moderate or severe hepatic impairment *[see Use in Specific Populations (8.6)]*.

Renal Impairment: (b) (4) -A pharmacokinetic trial in patients with renal impairment has not been

conducted as ceritinib elimination via the kidney is low (1.3% of a single oral administered dose). Based on a ~~A~~ population pharmacokinetic analysis of 97 patients with mild renal impairment (CLcr 60 to <90 mL/min), 22 patients with moderate renal impairment (CLcr 30 to <60 mL/min) and 183 patients with normal renal function (≥90 mL/min), ceritinib exposures were similar in patients with mild and moderate renal impairment and normal renal function (b) (4) Patients with severe renal impairment (CLcr <30 mL/min) were not included in the clinical trial.

Pediatrics: No trials have been conducted to evaluate the pharmacokinetics of ceritinib in pediatric patients.

(b) (4)

Drug Interactions

Effect of Strong CYP3A Inhibitors on Ceritinib: In vitro studies show that ceritinib is a substrate of CYP3A. Coadministration of a single 450 mg ZYKADIA dose with ketoconazole (a strong CYP3A inhibitor) 200 mg twice daily for 14 days increased ceritinib AUC (90% CI) by 2.9-fold (2.5, 3.3) and C_{max} (90% CI) by 1.2-fold (1.1, 1.4) in 19 healthy subjects *[see Drug Interactions (7.1)]*. The steady-state AUC of ceritinib at reduced doses after coadministration with ketoconazole 200 mg twice daily for 14 days was predicted by simulations to be similar to the steady-state AUC of ceritinib alone *[see Dose Modification for Concurrent Use with Strong CYP3A4 Inhibitors (2.3)]*.

Effect of Strong CYP3A Inducers on Ceritinib: Coadministration of a single 750 mg ZYKADIA dose with rifampin (a strong CYP3A inducer) 600 mg daily for 14 days decreased ceritinib AUC (90% CI) by 70% (61%, 77%) and C_{max} (90% CI) by 44% (24%, 59%) in 19 healthy subjects *[see Drug Interactions (7.1)]*.

Effect of Ceritinib on CYP Substrates: Based on in vitro data, ceritinib may inhibit CYP3A and CYP2C9 at clinical concentrations *[see Drug Interactions (7.2)]*. Time-dependent inhibition of CYP3A was also observed.

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

Effect of Ceritinib on Transporters: Based on in vitro data, ceritinib does not inhibit apical efflux transporters, P-gp, BCRP, or MRP2, hepatic uptake transporters OATP1B1 and OATP1B3, renal organic anion uptake transporters OAT1 and OAT3, or organic cation uptake transporters OCT1 and OCT2 at clinical concentrations.

Effect of Gastric Acid Reducing Agents on Ceritinib: Gastric acid reducing agents (e.g., proton pump inhibitors, H_2-receptor antagonists, antacids) may alter the solubility of ceritinib and reduce its bioavailability as ceritinib demonstrates pH-dependent solubility and becomes poorly soluble as pH increases in vitro. A dedicated study has not been conducted to evaluate the effect of gastric acid reducing agents on the bioavailability of ceritinib.

4 APPENDICES

4.1 PHARMACOMETRICS REVIEW

OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

PHARMACOMETRIC REVIEW	
NDA	205755
Submission Type	Original
Submission Date	12/24/2013
Generic Name	Ceritinib
Applicant	Novartis
Primary Pharmacometric Reviewer	Pengfei Song, Ph.D.
Secondary Pharmacometric Reviewer	Qi Liu, Ph.D.
Clinical Division	Division of Oncology Products 2 (DOP2)

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1 SUMMARY OF FINDINGS

1.1 BACKGROUND

Ceritinib (also known as LDK378) is an anaplastic lymphoma kinase (ALK) inhibitor. The applicant seeks an accelerated approval of ceritinib for the treatment of patients with NSCLC who have received crizotinib. The efficacy and safety evaluations of ceritinib are based on the registration Phase 1 trial LDK378X2101, in which the proposed dosing regimen of ceritinib [750 mg once daily (QD)] induced a high overall response rate (ORR) [44% (36%, 52%)] of early (median time to first response of approximately 6 weeks) and durable responses (median 7.1 months) in patients with ALK-positive NSCLC who were previously treated with an ALK inhibitor. In the registration trial, Grade 3 or worse adverse events were observed in 73% patients. Dosing interruptions occurred in 69% of patients and dose reductions occurred in 59% of patients for a median dose intensity of 636 mg/day (range: 226.7 mg/day to 750 mg/day). The rate of adverse events resulting in permanent discontinuation was 10%.

The main purpose of this pharmacometric review is to evaluate the appropriateness of the proposed dosing regimen by addressing the following key questions:

1.2 KEY REVIEW QUESTIONS

1.2.1 Are there significant exposure-response relationships for efficacy?

No. No significant exposure-response relationships were identified for the efficacy endpoints per central radiology review including the primary efficacy endpoint ORR and secondary efficacy endpoint progression free survival (PFS). Based on the ORR analysis results, it is unclear whether the plateau of the exposure-efficacy curve has been reached or not, due to the following two possible reasons: (1) the distribution of the available exposure data (primarily driven by the data for patients in the 750 mg dose group) may not be enough to adequately characterize the full exposure-efficacy curve, and (2) the small sample size may limit the robustness for the predicted exposure-efficacy relationship (Figure 1). Furthermore, there is no clear separation of PFS curves stratified by $C_{ss,\ trough}$ quartiles (Figure 2).

Exposure-response analyses were conducted, using the average observed $C_{ss,\ trough}$ of ceritinib at dose levels ranging from 50 mg to 750 mg QD as exposure endpoint, for ORR (N=167) and progression free survival (PFS) (N=167) in patients with ALK-positive NSCLC who were previously treated with an ALK inhibitor in Trial LDK378X2101. The average observed $C_{ss,\ trough}$ used for the efficacy (ORR, PFS) analyses is defined as the geometric mean of all evaluable steady-state trough concentrations (0-6 hours before dose) of each patient between Day15 of Cycle 1 and the minimum of last day of study drug (on or prior to the cut-off date) and date of progression/death (for patients who progressed/died) or date of last adequate tumor assessment (for patients who did not progress/die).

Overall response rate (ORR)

Exposure-response analyses were conducted, using logistic regression model with the average observed $C_{ss,\ trough}$ of ceritinib at dose levels ranging from 50 mg to 750 mg QD as systemic exposure endpoint, for ORR (N=167) in patients with ALK-positive NSCLC who were previously treated with an ALK inhibitor in Trial LDK378X2101.

No significant exposure-response relationships were identified for the primary efficacy endpoint ORR (P = 0.32), after controlling prognostic factors including ECOG status, race, brain metastasis, and baseline sum of longest diameter.

Based on the ORR analysis results, it is unclear whether the plateau of the exposure-response curve has been reached or not, because (1) the distribution of available exposure data (primarily driven by the data for patients in the 750 mg dose group) may not be enough to adequately characterize the full exposure-efficacy curve, and (2) the small sample size limited the robustness for the predicted exposure-efficacy relationship (Figure 1).

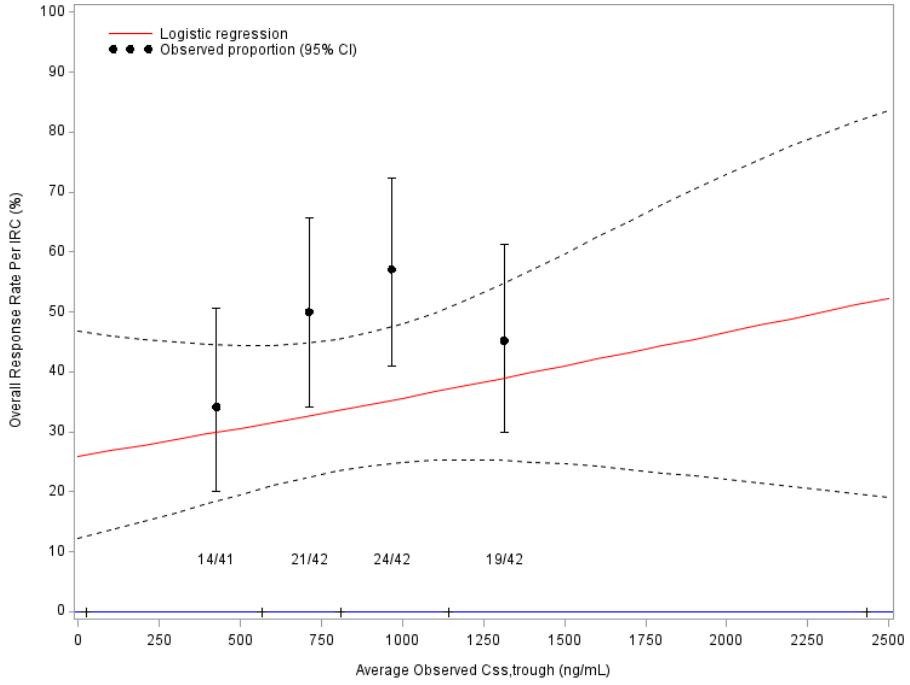

Figure 1. The relationship between the average observed $C_{ss,\ trough}$ of ceritinib at dose levels ranging from 50 mg to 750 mg QD and overall response rate (ORR) per central radiology review in ALK-positive NSCLC patients who were previously treated with an ALK inhibitor in trial LDK378X2101. The solid black symbols represent the observed ORR per central radiology review in each quartile of average observed $C_{ss,\ trough}$ for all subjects. The vertical black bars represent the 95% confidence interval (CI). The solid line and the dashed lines represent the logistic regression model predicted mean and 95% CI of the probability of ORR by average observed $C_{ss,\ trough}$ (P = 0.32) for Caucasian patients with brain metastasis, ECOG status of 1, and a baseline sum of longest diameter of 8.1 cm (Please note that the predictions are not for all patients, therefore do not fit the solid black symbols which represent the observed ORR in each $C_{ss,\ trough}$ quartile for all patients, regardless of the prognostic factors. The logistic regression model prediction is generated as follows: numeric covariates at the median, categorical covariates at the highest frequency level). The exposure range in each quartile of $C_{ss,\ trough}$ is denoted by the horizontal blue line along with the number of responders/total number of patients in each quartile.

* Note: The prognostic factors that were used in the logistic regression model were based on discussion with clinical and clinical pharmacology review team.

Progression free survival (PFS)

Exposure-response analyses were conducted, using the average observed $C_{ss,\ trough}$ of ceritinib at dose levels ranging from 50 mg to 750 mg QD as exposure endpoint, for progression free survival (PFS) (N=167) in patients with ALK-positive NSCLC who were previously treated with an ALK inhibitor in Trial LDK378X2101.

Kaplan-Meier methodology was applied to the PFS using the average observed $C_{ss,trough}$ quartiles as a stratification factor. No clear exposure-PFS relationship was identified.

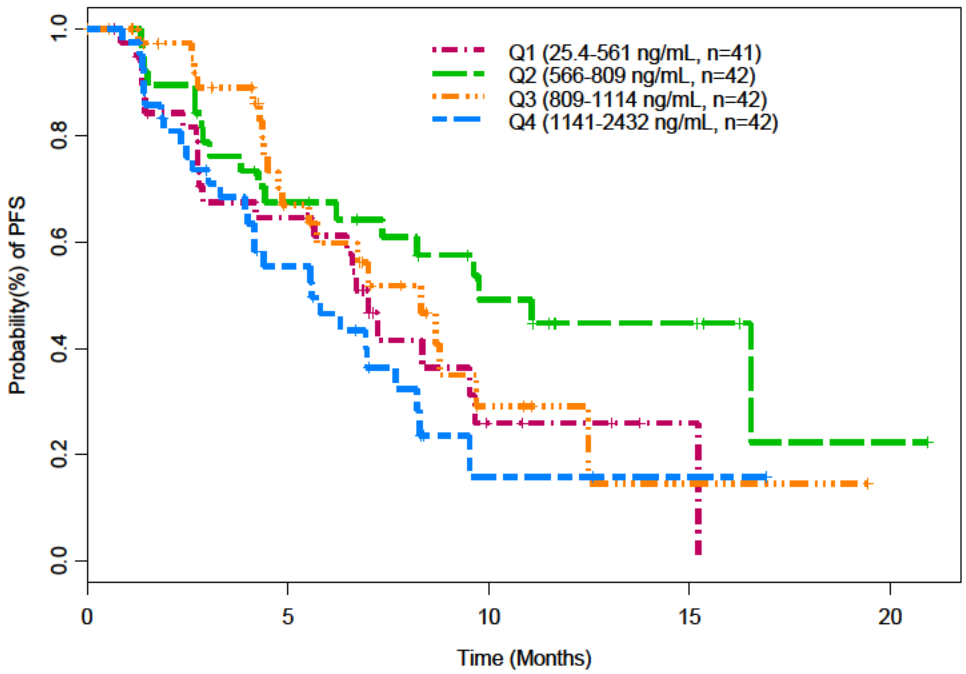

Figure 2. Kaplan-Meier curve of progression free survival (PFS) per central radiology review by $C_{ss,\ trough}$ quartiles at dose levels ranging from 50 mg to 750 mg QD of ceritinib in ALK-positive NSCLC patients who were previously treated with an ALK inhibitor

1.2.2 Are there significant exposure-response relationships for safety?

Yes. Results of exposure-response analyses suggested that higher systemic exposure is associated with more frequent (Figure 3) and earlier (Figure 4) overall Grade 3 or worse (G3+) adverse events (AEs), as well as with higher incidence of individual AEs such as G3+ alanine aminotransferase (ALT) elevation (upper, Figure 6), G3+ aspartate aminotransferase (AST) elevation (lower, Figure 6), and Grade 2 or worse (G2+) hyperglycemia (Figure 7).

No significant relationships were identified between systemic exposure and overall G3+ gastrointestinal tract AEs (Figure 5) or individual AEs such as G2+ diarrhea (upper, Figure 8), possibly because systemic exposure is not a good predictor for GI tract AEs (i.e., the high concentration of drug in the GI tract may lead to GI tract AEs directly).

Similarly to the relationship between the systemic exposure and incidence of G3+ AEs, higher systemic exposure is associated with more frequent and earlier dose reductions (Figure 9) or dose interruptions (Figure 9). Time to first dose change (dose reduction, dose interruption) was also evaluated (Figure 10). Higher systemic exposure is associated with earlier and more frequent dose reductions or dose interruption. Given that the permanent discontinuation due to AEs occurred in only 10% patients, the management of AEs via dose reductions and interruptions is effective in maintaining patients on study drug.

Exposure-response analyses for safety were conducted using the average observed $C_{ss,\ trough}$ of ceritinib as systemic exposure endpoint in patients with ALK-positive tumors who were treated with ceritinib (50-750 mg QD) in Trial LDK378X2101 (N=275). The average observed $C_{ss,\ trough}$ used for the safety analyses is defined as the geometric mean of all evaluable steady-state trough concentrations (0-6 hours before dose) of each patient after Day 15 of Cycle 1 and before the occurrence of the safety events of interest (including AEs, dose reduction, dose interruption, etc). For patients without the safety events of concern, the $C_{ss,\ trough}$ was calculated as the geometric mean of all evaluable steady-state trough concentrations (0-6 hours before dose) up to and on last day of study drug (on or prior to the cut-off date). The sample size may vary for each specific analysis because some patients may experience the safety event of concern before the availability of evaluable steady state trough concentrations.

Exposure-response analyses for overall Grade 3 or worse (G3+) AEs

Exposure-response analyses with $C_{ss,\ trough}$ as the exposure variable were conducted for overall G3+ AEs using logistic regression model. Higher exposures is associated with higher incidence of overall G3+ AEs (P = 0.002), after controlling prognostic factors including prior ALK inhibitor treatment, ECOG status, race, and brain metastasis.

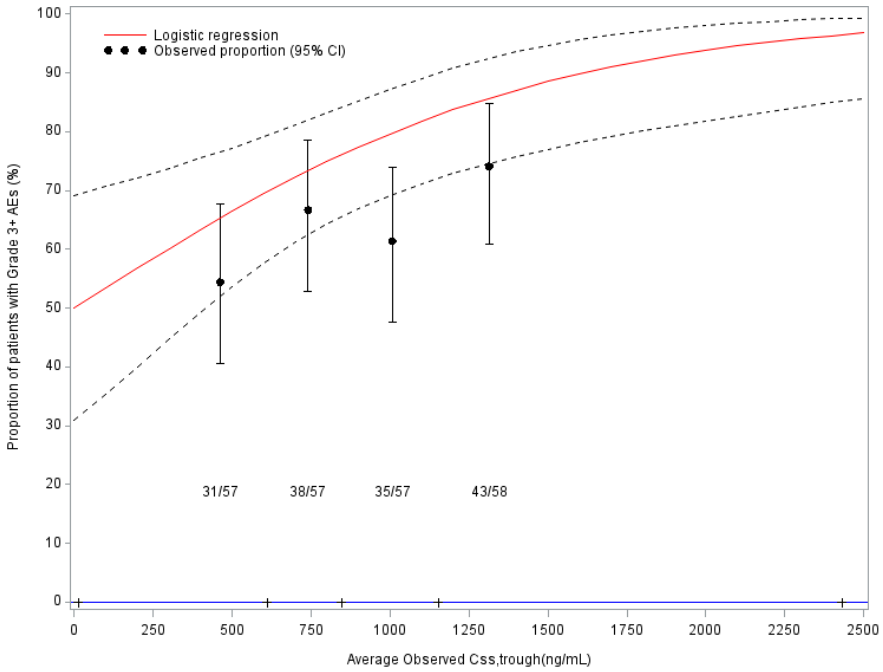

Figure 3. The relationship between average observed $C_{ss,\ trough}$ and Grade 3 or worse (G3+) AEs in patients with ALK-positive tumors who were treated with ceritinib (50-750 mg QD). The solid black symbols represent the observed incidence of G3+ AEs in each quartile of average observed $C_{ss,trough}$ for all subjects, regardless of the prognostic factors. The vertical black bars represent the 95% confidence interval (CI). The solid and dotted lines represent the logistic regression model predicted mean and 95% CI of incidence of G3+ AEs by average observed $C_{ss,\ trough}$ (P = 0.002) for Caucasian patients with brain metastasis, ECOG status of 1, and prior treatment with ALK inhibitors. The exposure range in each quartile of average observed $C_{ss,trough}$ is denoted by the horizontal blue line along with the number of patients who experienced G3+ AEs/total number of patients in each quartile.

* Note: The prognostic factors that were used in the logistic regression model were based on discussion with clinical and clinical pharmacology review team.

Time to first G3+ AEs

Time to first G3+ AE was estimated based on Kaplan-Meier methodology using observed $C_{ss, trough}$ quartiles as a stratification factor in patients with ALK-positive tumors who were treated with ceritinib (50-750 mg QD). The results suggest that higher exposures (Quartile 4) may be associated with earlier and more frequent G3+ AEs than lower exposures (Quartile 1), with no marked differences between the two intermediate concentration quartile ranges (Quartiles 2 and 3). It is noted that the prognostic factors may not be balanced across the quartiles (Table 1).

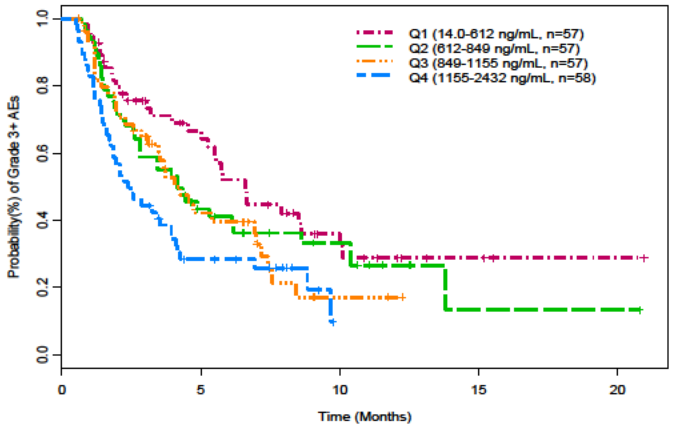

Figure 4. Kaplan-Meier curve of time to first Grade 3 or worse AEs by quartiles of observed average $C_{ss, trough}$ in patients with ALK-positive tumors who were treated with ceritinib (50 - 750 mg QD)

Table 1. Summary of covariates and exposure for patients per quartile of average observed trough concentration at steady-state Css,trough for G3+ AE analyses

Parameters	Quartile 1 (N=57)	Quartile 2 (N=57)	Quartile 3 (n=57)	Quartile 4 (n=58)
$C_{ss,trough}$				
Median [Range] (ng/mL)	[14.0., 607]	[612, 844]	[848, 1146]	[1155, 2432]
Mean ± SD (ng/mL)	399 ± 163	731 ± 66	1006 ± 94	1382 ± 237
Baseline Age (Year)	53 ± 12	53 ± 14	50 ± 12	52 ± 13
Baseline weight (kg)	73.7 ± 15.7	71.4 ± 14.9	67.0 ± 14.5	60.6 ± 10.6
Baseline Body Mass Index (kg/m^2)	25.6 ± 4.8	24.7 ± 3.9	24.0 ± 3.9	22.5 ± 2.9
Patients with prior ALKi	58%	70%	68%	66%
Female	58%	46%	61%	62%
Race				
Asian	7%	16%	41%	36%
Black	0%	0%	0%	5%
Caucacian	89%	79%	44%	47%
Other	0%	0%	2%	2%
ECOG Status				
0	19%	23%	33%	34%
1	81%	77%	67%	66%
Brain Metastasis	37%	51%	45%	55%

Grade 3 or worse (G3+) GI tract AEs

Exposure-response analyses using average observed $C_{ss,trough}$ as the systemic exposure variable were conducted to evaluate whether the high systemic exposure is related to the higher incidence of G3+ GI tract AEs. Results suggested that no apparent trend was identified (P = 0.86), possibly because systemic exposure of ceritinib is not a good predictor for GI tract AEs (i.e., the locally high concentration of drug in the GI tract leads to GI tract AEs directly).

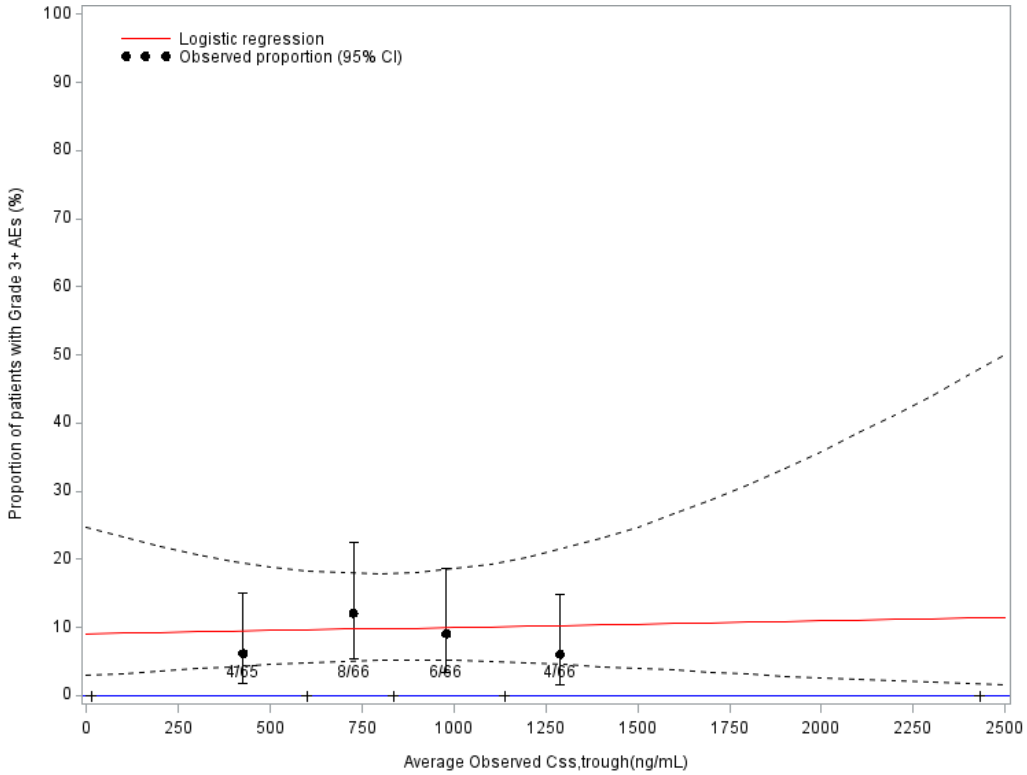

Figure 5. The relationship between average observed $C_{ss,\ trough}$ and Grade 3 or worse (G3+) GI tract AEs in patients with ALK-positive tumors who were treated with ceritinib (50-750 mg QD). The solid black symbols represent the observed incidence of G3+ GI tract AEs in each quartile of $C_{ss,\ trough}$ for all subjects, regardless of the prognostic factors. The vertical black bars represent the 95% confidence interval (CI). The solid line and the area between dotted lines represent the logistic regression model predicted mean and 95% CI for incidence of G3+ AEs by average observed $C_{ss,\ trough}$ (P = 0.86) for Caucasian patients with brain metastasis, ECOG status of 1, and prior treatment with ALK inhibitors. The exposure range in each quartile of $C_{ss,\ trough}$ is denoted by the horizontal blue line along with the number of patients who experienced G3+ GI tract AEs /total number of patients in each quartile.

Individual AEs

The most common individual adverse reactions (incidence of at least 25%) were diarrhea, nausea, vomiting, abdominal pain, fatigue, decreased appetite, and constipation. The most common G3+ adverse reactions (incidence of at least 5%) were diarrhea, fatigue, alanine transaminase (ALT) elevation, aspartate transaminase (AST) elevation, hyperglycemia, and lipase (blood) increase.

Exposure-response analyses were conducted for ALT or AST elevation, GI tract AEs, hyperglycemia, diarrhea, and fatigue using multivariate logistic regression models. Results suggested that increasing systemic exposure is associated with higher incidence of G3+ ALT elevation (P = 0.002) (upper, Figure 6), G3+ AST elevation (P = 0.02) (lower, Figure 6), G2+ hyperglycemia (P = 0.004) (Figure 7) after adjusting with prognostic factors including prior ALK inhibitor treatment, ECOG status, race, and brain metastasis. However, no apparent trends were identified for G2+ diarrhea (P = 0.11) (upper, Figure 8) and G2+ fatigue (P = 0.92) (lower, Figure 8) with $C_{ss,trough}$ of ceritinib.

Grade 3+ ALT or AST elevation

Multivaraite logistic regression model were conducted using average observed $C_{ss,trough}$ as the exposure to evaluate whether the high systemic exposure is related to the higher incidence of G3+ ALT or AST elevation. Results suggested that increasing systemic exposure is associated with higher incidence of G3+ ALT elevation (P = 0.002) (upper, Figure 6), and G3+ AST elevation (P = 0.02) (lower, Figure 6), after controlling race, ECOG status, brain metastasis, and prior ALK inhibitor treatment.

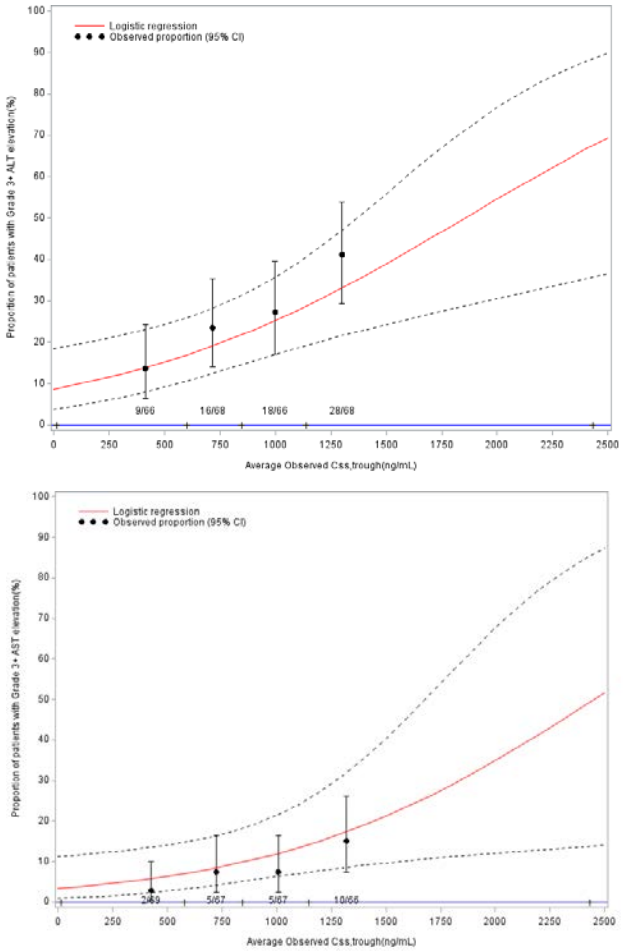

Figure 6. The relationship between average observed $C_{ss,\ trough}$ and Grade 3 or worse (G3+) ALT (upper) or AST (lower) elevation in patients with ALK-positive tumors who were treated with ceritinib (50-750 mg QD). The solid black symbols represent the observed incidence of G3+ ALT or AST elevation in each quartile of $C_{ss,\ trough}$ for all subjects, regardless of the prognostic factors. The vertical black bars represent the 95% confidence interval (CI). The solid line and the area between dotted lines represent the logistic regression model predicted mean and 95% CI for incidence of G3+ ALT elevation (P =0.002) or G3+ AST elevation (P = 0.02) by the average observed $C_{ss,\ trough}$ for Caucasian patients with brain metastasis, ECOG status of 1, and prior treatment with ALK inhibitors. The exposure range in each quartile of $C_{ss,\ trough}$ is denoted by the horizontal blue line along with the number of patients who experienced G3+ ALT or AST elevation /total number of patients in each quartile.

Grade 2 or worse hyperglycemia

Multivariate logistic regression model were conducted using average observed $C_{ss,trough}$ as the exposure to evaluate whether the high systemic exposure is related to the higher incidence of G2+ hyperglycemia. Results suggested that increasing systemic exposure is associated with higher incidence of G2+ hyperglycemia (P = 0.004), after controlling race, ECOG status, brain metastasis, and prior ALK inhibitor treatment.

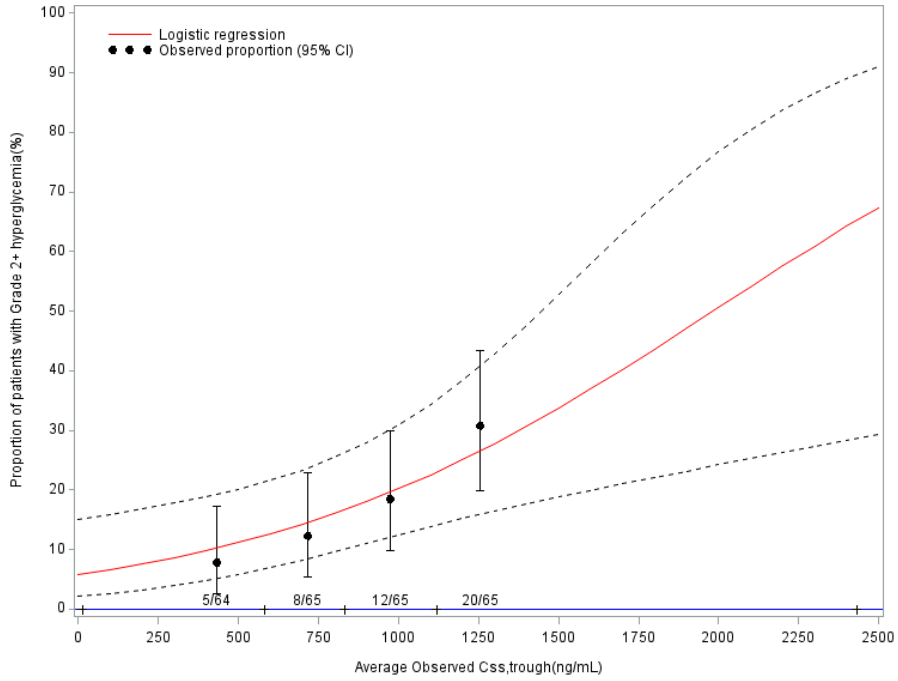

Figure 7. The relationship between observed average $C_{ss,\ trough}$ and Grade 2 or worse (G2+) hyperglycemia in patients with ALK-positive tumors who were treated with ceritinib (50-750 mg QD). The solid black symbols represent the observed incidence of G2+ hyperglycemia in each quartile of $C_{ss,\ trough}$ for all subjects, regardless of the prognostic factors. The vertical black bars represent the 95% confidence interval (CI). The solid line and the area between dotted lines represent the logistic regression model predicted mean and 95% CI for the incidence of G2+ hyperglycemia by the average observed $C_{ss,\ trough}$ (P = 0.004) for Caucasian patients with brain metastasis, ECOG status of 1, and prior treatment with ALK inhibitors. The exposure range in each quartile of the average observed $C_{ss,\ trough}$ is denoted by the horizontal blue line along with the number of patients who experienced G2+ hyperglycemia/total number of patients in each quartile.

Grade 2 or worse diarrhea/fatigue

Multivariate logistic regression model were conducted using average observed $C_{ss,trough}$ as the systemic exposure to evaluate whether the high systemic exposure is related to the higher incidence of G2+ diarrhea or fatigue. Results suggested that increasing systemic exposure is not significantly associated with higher incidence of G2+ diarrhea (P = 0.11) or fatigue (P = 0.92), after controlling race, ECOG status, brain metastasis, and prior ALK inhibitor treatment.

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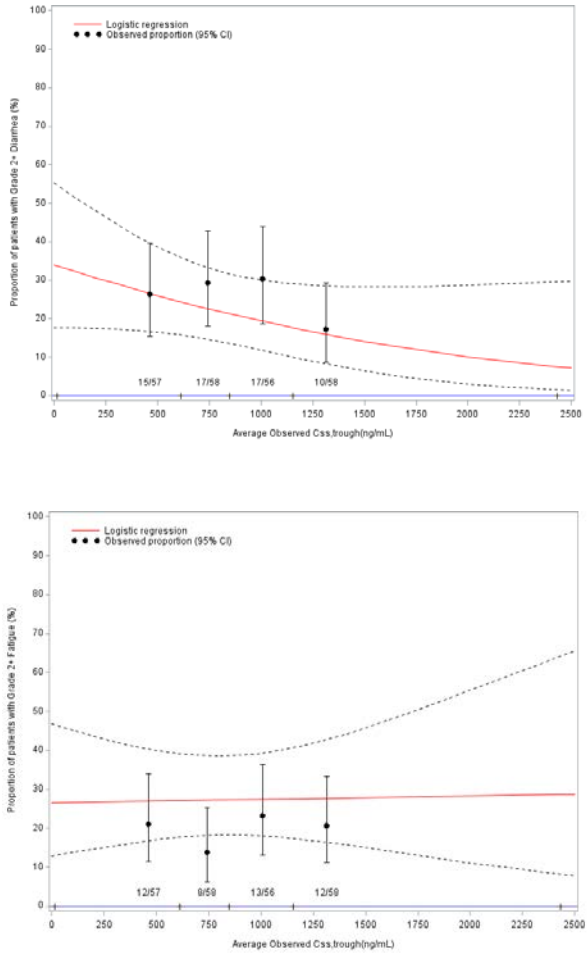

Figure 8. The relationship between average observed $C_{ss,\ trough}$ and Grade 2 or worse (G2+) diarrhea (upper) or fatigue (lower) in patients with ALK-positive tumors who were treated with ceritinib (50-750 mg QD). The solid black symbols represent the observed incidence of G2+ diarrhea/fatigue in each quartile of average observed $C_{ss,\ trough}$ for all subjects, regardless of the prognostic factors. The vertical black bars represent the 95% confidence interval (CI). The solid line and the area between dotted lines represent the logistic regression model predicted mean and 95% CI for the incidence of G2+ diarrhea (P = 0.11) or fatigue (P = 0.92) by the average observed $C_{ss,\ trough}$ for Caucasian patients with brain metastasis, ECOG status of 1, and prior treatment with ALK inhibitors. The exposure range in each quartile of $C_{ss,trough}$ is denoted by the horizontal blue line along with the number of patients who experienced Grade 2+ diarrhea or fatigue /total number of patients in each quartile.

Dose adjustments

Dosing interruptions occurred in 69% of patients and dose reductions occurred in 59% of patients. The rate of adverse events resulting in permanent discontinuation was 10%. Dose reduction or interruption for adverse reactions of diarrhea, nausea, and vomiting was needed in 16%, 20%, and 16% of patients, respectively.

Similarly to the relationship between the systemic exposure and incidence of Grade 3+ AEs, higher systemic exposure is associated with more frequent and earlier dose reductions (upper, Figure 9) ($P < 0.0001$) or dose interruptions (lower, Figure 9) ($P=0.06$).

Time to first dose change (dose reduction, dose delay) was estimated based on Kaplan-Meier methodology using $C_{ss,trough}$ quartile as a stratification factor and including all ALK-positive cancer patients. Results suggested that higher systemic exposure appears to be associated with earlier and more frequent dose reduction (upper, Figure 10) or dose interruption (lower, Figure 10). Given that the permanent discontinuation due to AEs occurred in only 10% patients, the management of AEs via dose reductions and study drug interruptions is effective to maintain patients on study drug.

Exposure-response analyses for dose reduction and dose interruption (delay)

Multvariate logistic regression model were conducted using average observed $C_{ss,trough}$ as the systemic exposure endpoint to evaluate whether the high systemic exposure is related to dose reduction and dose interruption. Results suggested that increasing systemic exposure may be associated with higher incidence of dose reduction (P< 0.0001) and dose interruption (P = 0.06), after controlling race, ECOG status, brain metastasis, and prior ALK inhibitor treatment.

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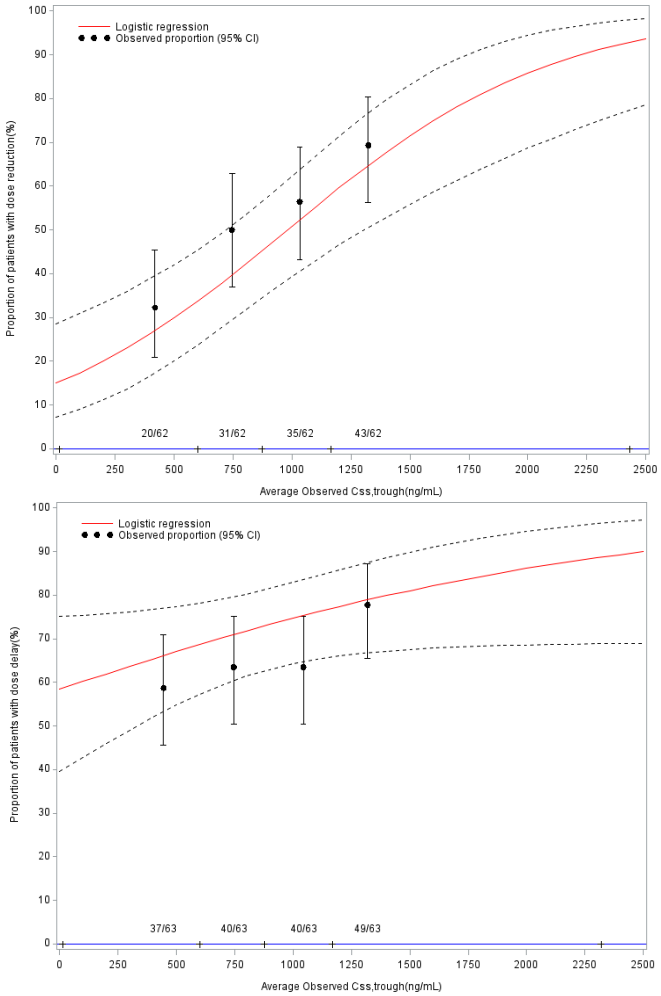
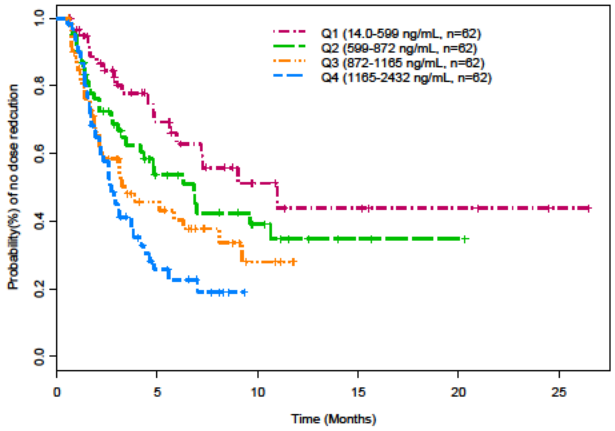


Figure 9. The relationship between observed average $C_{ss,\ trough}$ and the probability of dose reduction (upper) or dose delay (lower) in patients with ALK-positive tumors who were treated with ceritinib (50-750 mg QD). The solid black symbols represent the observed proportion of patients who experienced dose reduction (upper) or delay (lower) in each quartile of $C_{ss,\ trough}$ for all subjects, regardless of the prognostic factors. The vertical black bars represent the 95% confidence interval (CI). The solid line and the area between dotted lines represent the logistic regression model predicted mean and 95% CI for the probability of dose reduction (p < 0.0001) or dose delay (P = 0.06) by the average observed $C_{ss,trough}$ for Caucasian patients with brain metastasis, ECOG status of 1, and prior treatment with an ALK inhibitor. The exposure range in each quartile of $C_{ss,\ trough}$ is denoted by the horizontal blue line along with the number of patients who experienced dose reduction or dose delay /total number of patients in each quartile.

Kaplan-Meier analyses for time to first dose change

Time to first dose change was evaluated separately for dose reduction and dose interruption, based on Kaplan-Meier methodology using the average observed $C_{ss,trough}$ quartiles as a stratification factor in patients with ALK-positive tumors who were treated with ceritinib (50-750 mg QD). Results suggested that higher systemic exposure appear to be associated with earlier and more frequent dose reduction (upper, Figure 10) or dose interruption (lower, Figure 10).



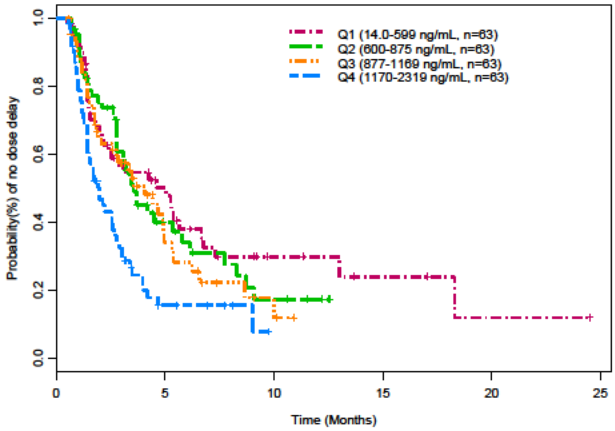


Figure 10. Kaplan-Meier curve of time to first dose reduction (upper), dose interruption (lower) by quartiles of average observed $C_{ss,\ trough}$ in patients with ALK-positive tumors who were treated with ceritinib (50-750 mg QD)

1.2.3 Based on population PK analyses, what covariates affect the systemic exposure of ceritinib?

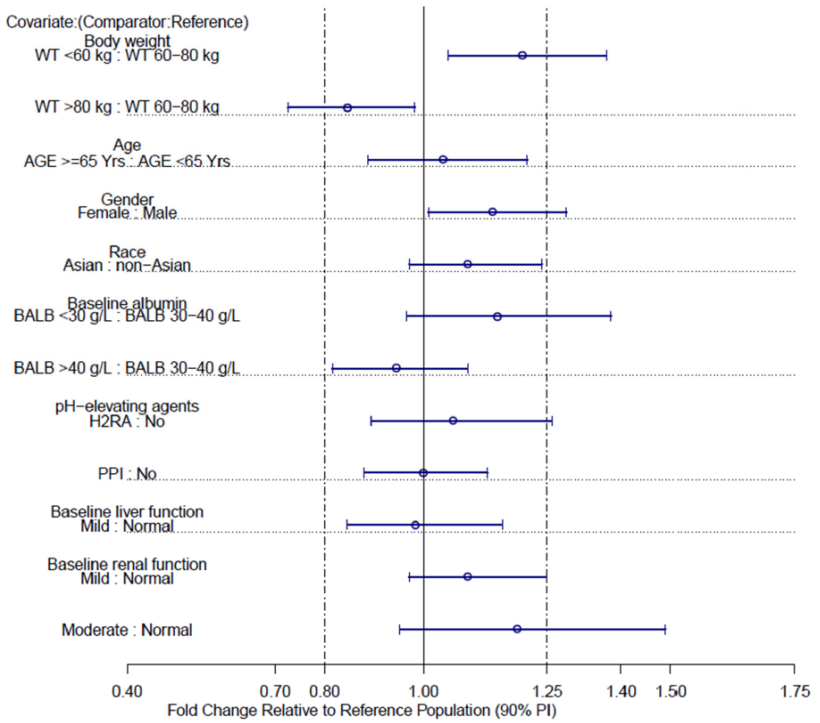
Based on the applicant's population PK analyses, no covariates (including age, gender, race, and body weight, etc) are considered clinically important. Therefore, no dose adjustments are needed for these covariates.

The final population PK model of ceritinib was described by a one-compartment model with delayed first-order absorption and time-dependent elimination by allowing clearance to decrease stepwise over time. The final population PK model contained effect of body weight and baseline albumin on apparent clearance CL/F, body weight on apparent volume of distribution V/F, and concomitant use of H2 receptor antagonists (H2RA) or proton pump inhibitors (PPI) on the absorption rate constant (ka) (Figure 11). Among all the significant covariates included in the final model, body weight had the largest effect on ceritinib PK. The incorporation of these covariates led to the slight decrease in inter-individual variability (IIV) for CL/F (from 36.0% to 33.9%) and ka (from 86.4% to 84.0%) compared to the base model.

The proposed flat dose of 750 mg once daily is acceptable, as the exploratory analyses suggested that body size has no clinically relevant impact on PK. The predicted AUC_{ss} in patients with lower body weight (< 60 kg) was 1.20-fold (90% CI: 1.05-1.37) higher than the reference population (body weight 60-80 kg). The AUC_{ss} in patients with higher body weight (> 80 kg) was 0.85-fold (90% CI: 0.73-0.98) lower.

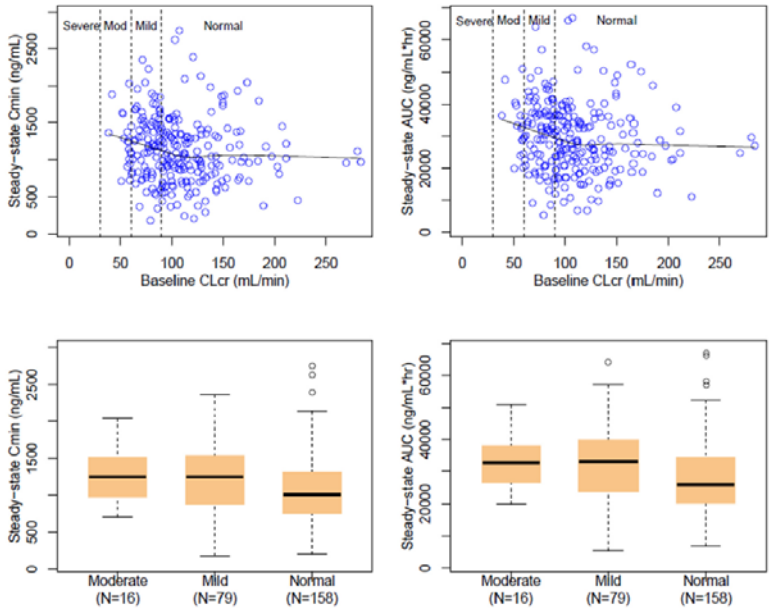
The effect on the systemic exposure of LDK378 of baseline liver function (classified based on the NCI-ODWG criteria) was also evaluated. The AUC_{ss} of LDK378 in patients with mild hepatic impairment (N=48) was similar to the AUC_{ss} in patients with normal hepatic function (N=254).

Renal function was not retained as a covariate in the final population PK model (Figure 12). The AUC_{ss} in patients with mild or moderate renal impairment were predicted to have a 1.09-fold (90% CI: 0.97-1.25) and 1.19-fold (90% CI: 0.95-1.49) increase in AUC_{ss} compared to patients with normal renal function.



Open circle is the fold change of AUC_{ss} for a covariate group compared to AUC_{ss} for its corresponding reference group, and horizontal line represents 90% prediction interval of fold change.

Figure 11. Fold change of LDK378 steady-state exposure (AUC_{ss}) relative to reference group based on the final population pharmacokinetic model



Open circle in the scatter plots represents individual $C_{min,ss}$ and AUC_{ss} predicted by the final population PK model, and solid line represents the local smooth line. The renal function classification (normal, mild, moderate, and severe) is defined in Table 3-5. Boxplots of steady-state $C_{min,ss}$ and AUC_{ss} are presented with median (horizontal bold line) and 5th and 95th percentiles (whiskers).

Figure 12. Effect of renal function on LDK378 steady-state exposure ($C_{min,ss}$ and AUC_{ss}) based on the final population pharmacokinetic model

1.2.4 Is the proposed dosing regimen acceptable for the accelerated approval?

Yes. Based on currently available data, the proposed starting dose of 750 mg QD is acceptable from a clinical pharmacology perspective. At this dose, ceritinib induces a high overall response rate (ORR) [44% (36%, 52%)] of early (median time to first response of approximately 6 weeks) and durable responses [median 7.1 months] in patients with ALK-positive NSCLC who were previously treated with an ALK inhibitor.

The results of exposure-analyses for efficacy did not show a clear relationship between systemic exposure and primary efficacy endpoints ORR or secondary efficacy endpoint PFS. However, the high ORR rate and durable response at the proposed dose suggested that the proposed dose is efficacious.

Higher systemic exposure appears associated with more frequent and earlier overall Grade 3/4 AEs, as well as with higher incidence of individual AEs such as Grade 3/4 alanine aminotransferase (ALT) elevation, Grade 3/4 aspartate aminotransferase (AST) elevation, and Grade 2/3/4 hyperglycemia. Higher systemic exposure also appears to be associated with earlier and more frequent dose reductions or dose interruptions. Given that the permanent discontinuation due to AEs occurred in only 10% patients, the management of AEs via dose reductions and interruptions is effective in maintaining patients on study drug for as long as it is clinically indicated.

1.3 RECOMMENDATIONS

The pharmacometric reviewer finds that the NDA205755 is acceptable from a clinical pharmacology perspective, provided that a satisfactory agreement is reached between the Applicant and the Agency regarding the labeling language.

1.4 POST MARKETING REQUIREMENTS OR COMMITMENTS

None.

1.5 LABEL STATEMENTS

Only relevant clinical pharmacology sections are included.

Applicant's Proposed Language	FDA proposed
8.6 Hepatic Impairment (b) (4) [redacted] *[see Clinical Pharmacology (12.3)]*.	**8.6 Hepatic Impairment** (b) (4) [redacted] As ceritinib is eliminated primarily via the liver, patients with hepatic impairment may have increased exposure. Dose adjustment is not recommended for patients with mild hepatic impairment (total bilirubin ≤ULN and AST >ULN or total bilirubin >1.0 to 1.5 × ULN and any AST) based on results of the population pharmacokinetic analysis *[see Clinical Pharmacology (12.3)]*. A recommended dose has not been established for patients with moderate to severe hepatic impairment. *[see Clinical Pharmacology (12.3)]*.
(b) (4) [redacted]	
12.3 Pharmacokinetics **Specific Populations** (b) (4) [redacted] for patients with moderate or severe hepatic impairment *[see Use in Specific Populations (8.6)]*.	**12.3 Pharmacokinetics** **Specific Populations** *Age, Gender, Race, and Body Weight*: Population pharmacokinetic analyses showed that age, gender, race, and body weight had no clinically important effect on the systemic exposure of ceritinib. *Hepatic Impairment*: As ceritinib is eliminated primarily via the liver, patients with hepatic impairment may have increased exposure. A pharmacokinetic trial in patients with hepatic

(b) (4)	impairment has not been conducted. Based on a population pharmacokinetic analysis of 48 patients with mild hepatic impairment (total bilirubin ≤ULN and AST >ULN or total bilirubin >1.0 to 1.5 × ULN and any AST) and 254 patients with normal hepatic function (total bilirubin ≤ULN and AST ≤ULN), ceritinib exposures were similar in patients with mild hepatic impairment and normal hepatic function. The pharmacokinetics of ceritinib have not been studied in patients with moderate or severe hepatic impairment *[see Use in Specific Populations (8.6)]*. *Renal impairment*: A pharmacokinetic trial in patients with renal impairment has not been conducted as ceritinib elimination via the kidney is low (1.3% of a single oral administered dose). Based on a population pharmacokinetic analysis of 97 patients with mild renal impairment (CLcr 60 to <90 mL/min), 22 patients with moderate renal impairment (CLcr 30 to <60 mL/min) and 183 patients with normal renal function (≥90 mL/min), ceritinib exposures were similar in patients with mild and moderate renal impairment and normal renal function. Patients with severe renal impairment (CLcr <30 mL/min) were not included in the clinical trial.

2 APPLICANT'S ANALYSES

The applicant performed population PK analyses to identify significant factors affecting ceritinib PK in a study report entitled "Population pharmacokinetics of LDK378 in adult patients with tumors characterized by genetic abnormalities in anaplastic lymphoma kinase (ALK)".

The applicant also performed exposure-response analyses for efficacy and safety data submitted in the original NDA submission on December 24, 2013. In response to the FDA clinical pharmacology information requests, the applicant submitted additional exposure-response analyses results on February 14, 19, 20, and 25 in response to the FDA clinical pharmacology information requests.

The key findings from the Applicant's analyses are summarized below:

2.1 POPULATION PHARMACOKINETIC ANALYSIS

The primary objective of the population PK analysis was describe the pharmacokinetics (PK) of ceritinib in adult patients with tumors characterized by genetic abnormalities in ALK using a population PK approach and to investigate the effects of intrinsic and extrinsic factors that may affect the PK of ceritinib in this population.

2.1.1 Datasets

The population PK analysis was performed with 4406 ceritinib concentration values from 302 patients in the registration study LDK378X2101. The study design, study population, and timing of blood samples are summarized in Table 3-1.

Table 3-1 Summary of the clinical study used in the population pharmacokinetic analysis (Study LDK378X2101)

Study	Study population	Study design	Study drug dose regimen	Nominal PK assessment
LDK378X2101	Adult patients with tumors confirmed to have genetic abnormalities in ALK with or without prior ALK inhibitor treatment	Phase I, open label, dose escalation and expansion study	Dose escalation phase: 50, 100, 200, 300, 400, 500, 600, 700, and 750 mg *q.d.* Expansion phase: 750 mg *q.d.*	Dose escalation phase (no. of patients treated: 59) PK run-in[a]: 0.5, 1, 2, 3, 4, 6, 8, 24, 48, 72 hr C1D8: 0, 0.5, 1, 2, 3, 4, 6, 8, 24 hr C2D1[b]: 0, 1, 2, 4, 6, 8, 24 hr C1D15 and C2D15: 0 hr D1 of C3 and subsequent cycles: 0 hr Expansion phase (no. of patients treated: 245) C1D1: 1, 2, 4, 6, 8, 24 hr C2D1[c]: 0, 1, 2, 4, 6, 8, 24 hr C1D15, C2D15, C3D1, and C4D1: 0 hr

[a] A single dose was given in the PK run-in period, the next dose was given on C1D1 (72 hours post 1st dose in the PK run-in period).
[b] Except for pre-dose 0 hour, full PK profiles were planned only for the first three dose cohorts (50, 100, and 200 mg).
[c] PK sample at 24 hr was added in amendment 4 released in early 2013.

2.1.2 Methods

The population PK analysis was performed using the first-order conditional estimation with interaction (FOCEi) as implemented in NONMEM software (Version VII, level 2.0) compiled with Intel Fortran Compiler (Version 11.1) on the MODESIM high performance computing

environment. Diagnostic graphics and post-processing of NONMEM output were performed using the S-Plus software (Version 8.1, TIBCO Software Inc., Palo Alto, CA) and R (Version 2.13.2, http://www.r-project.org/index.html).
The population PK model was developed following 3 steps: base model, full model with covariates, and final model, as briefly described below.

Base model development

The base model for ceritinib consists of the following sub-models:

- Structural model

Three alternative models were evaluated in an attempt to adequately but parsimoniously capture the time- and concentration-dependent auto-inhibition of LDK378:

1) PK-enzyme turnover model
2) first-order inhibition model
3) time-dependent elimination model with ceritinib apparent oral clearance (CL/F) stepwise decreasing after C1D8 and C2D1

Based on the performance of the above three models in regards of successful NONMEM run, Schwartz's Bayesian Criterion (SBC), diagnostic plots, and over-parameterization evaluation, the third model was selected for the full model and final model development.
Given that the steady-state of ceritinib was achieved by approximately C2D1 and full PK concentration-time profiles were collected on C1D8 and C2D1, in the third model, LDK378 CL/F from C1D8 inclusive to C2D1 (CL/F1) was parameterized with CL/F prior to C1D8 (CL/F0), and the fraction coefficient chgA (Equation 8). CL/F from C2D1 inclusive onwards (CL/F2) was parameterized with CL/F0 and the fraction coefficients chgA and chgB (Equation 9). The fraction coefficients were described using a logit model (Equations 10 and 11) to ensure the posterior individual estimates of these coefficients were constrained from 0 to 1.

$$CL/F_{1i} = CL/F_{0i} \cdot chgA_i \quad [8]$$

$$CL/F_{2i} = CL/F_{0i} \cdot chgA_i \cdot chgB_i \quad [9]$$

where

$$chgA_i = \frac{e^{log\frac{TVchgA}{1-TVchgA}+\eta_{chgA,i}}}{1+e^{log\frac{TVchgA}{1-TVchgA}+\eta_{chgA,i}}} \quad [10]$$

$$chgB_i = \frac{e^{log\frac{TVchgB}{1-TVchgB}+\eta_{chgB,i}}}{1+e^{log\frac{TVchgB}{1-TVchgB}+\eta_{chgB,i}}} \quad [11]$$

- Random effects model

Inter-individual variability (IIV) in model parameters was modeled as lognormal distribution:

$$\theta_i = \theta_{TV} \cdot \exp(\eta_i)$$

where θ_i is the value of a compartment model parameter for the i^{th} individual, θ_{TV} is the typical value of the model parameter, η_i denotes the inter-individual random effect accounting for the ith individual's deviation from the typical value, and $\eta i \sim N(0, \omega^2)$ is a realization of a normally

distributed random variable with zero mean and variance ω^2. The IIV is reported as approximate percent coefficient of variation (%CV), calculated as:

$$\%CV = \sqrt{\omega^2} \cdot 100\%$$

- Residual error model

Residual variability was described by a combined proportional and additive error model:

$$w = \sqrt{\left(\theta_{prop} \cdot \hat{Y}_{ij}\right)^2 + \left(\theta_{add}\right)^2}$$

$$Y_{ij} = \hat{Y}_{ij} + w \cdot \varepsilon_{ij}$$

where Y_{ij} denotes the observed ceritinib concentration for the ith individual at time t_j, $\hat{Y}_{ij}$ denotes the corresponding predicted concentration based on the PK model, w is the standard deviation of ceritinib concentration in plasma, and ε_{ij} denotes the intraindividual (residual) random variable, which is assumed to have zero mean and variance 1. *W* is parameterized in terms of proportional (θ_{prop}) and additive (θ_{add}) components.

Full model development

Full model development proceeded by a heuristic, minimal backwards elimination process. First, all PK-covariate relationships listed in Table 4-1 were included in the full model as they were considered to be relevant based on clinical and pharmacological judgment and collinearity of covariates. Then some of these PK-covariate relationships were eliminated if the estimates of covariate parameters appeared to be very weak and/or pharmacological implausible.

Table 4-1 PK parameter-covariate relationships included in full model development

PK Parameters	Continuous Covariates	Categorical Covariates
CL/F	WT0, AGE0	RACE, GENDER, ECOG
	BGFR	ZINH
	BALB, BBILI, and BALT	CIND, CINH, PINH
V/F	WT0	ECOG
		GENDER
k_a		MDPH
F_{rel}		MDPH

CL/F: apparent clearance; V/F: apparent volume of distribution;
k_a: first-order absorption rate; F_{rel}: relative bioavailability and its typical value is fixed to 1

Final model development

The final model was developed from the full model by stepwise backward elimination. Covariate effects were subjected to a backward elimination algorithm using the likelihood ratio test (based on differences in the NONMEM objective function values, ΔOFV) to assess the significance of their effects when excluded one at a time.

2.1.3 Results

The population PK of ceritinib was described by a one-compartment model with delayed first-order absorption and time-dependent elimination that could be described by auto-inhibition or more heuristically but more parsimoniously, by allowing clearance to decrease stepwise over time.

The final model contained effect of body weight and baseline albumin on apparent clearance CL/F, body weight on apparent volume of distribution V/F, and concomitant use of H2 receptor antagonists (H2RA) or proton pump inhibitors (PPI) on the absorption rate constant (ka).

Model-based simulation results showed that body weight has the largest effect on ceritinib exposure. The AUCss in patients with body weight <60 kg was estimated to be 1.20-fold higher than in the reference population with body weight 60-80 kg (90% prediction interval (PI): 1.05-1.37). However, this magnitude of exposure increase was not considered to be clinically relevant.

Although renal function was not retained as a covariate in the final model, model-based simulation identified a mild trend of increase in ceritinib exposure with decrease in baseline creatinine clearance. The AUC_{ss} in patients with mild or moderate renal impairment were predicted to have a 1.09-fold (90%PI: 0.97-1.25) and 1.19-fold (90%PI: 0.95-1.49) increase in AUCss compared to patients with normal renal function.

Table 5-5 Final model parameter estimates and the stability of the parameters using the bootstrap resampling procedure

Parameter	Original data		1000 bootstrap replicates	
	Estimate	RSE [%][a]	Estimate	RSE [%]
Fixed-effect				
CL/F (θ_1) [L/hr]	46.4	7.39	46.3	7.65
WT0 ~ CL/F (θ_{13})	0.661	21.9	0.654	21.5
BALB ~ CL/F (θ_{16})	0.452	38.1	0.442	36.8
chgA (θ_2)	0.750	7.21	0.754	7.43
chgB (θ_3)	0.854	2.11	0.853	2.01
V/F (θ_4) [L]	3270	4.89	3273	4.76
WT0 ~ V/F (θ_{23})	0.468	43.4	0.472	41.4
k_a (θ_5) [hr^{-1}]	0.537	7.56	0.539	6.85
H2RA ~ k_a (θ_{25})	-0.392	23.7	-0.383	26.5
PPI ~ k_a (θ_{26})	-0.292	31.2	-0.286	31.6
t_{lag} (θ_6) [hr]	0.748	1.50	0.750	1.49
F_{rel}	1[c]			
σ_{prop} (θ_7) [%]	22.4	4.35	22.4	3.92
σ_{add} (θ_8) [ng/mL]	12.2	16.4	12.3	11.8
Random-effect[b]				
ωCL/F [%]	33.9	28.4	33.8	26.7
ωchgA [%]	14.6[d]	36.5	15.1[d]	62.8
ωchgB [%]	14.8[d]	17.4	14.9[d]	16.8
ωV/F [%]	62.0	15.9	61.3	16.2
ωk_a [%]	84.0	14.7	84.1	14.5
ωF_{rel} [%]	27.9	37.6	27.9	36.4

[a] RSE% is relative standard error (standard error as a percentage of estimate)

[b] Random-effect is presented as interindividual variability

[c] Fixed

[d] Calculated as $SD = \theta_{TV} \cdot (1 - \theta_{TV}) \cdot \sqrt{\omega_{i,i}^2}$

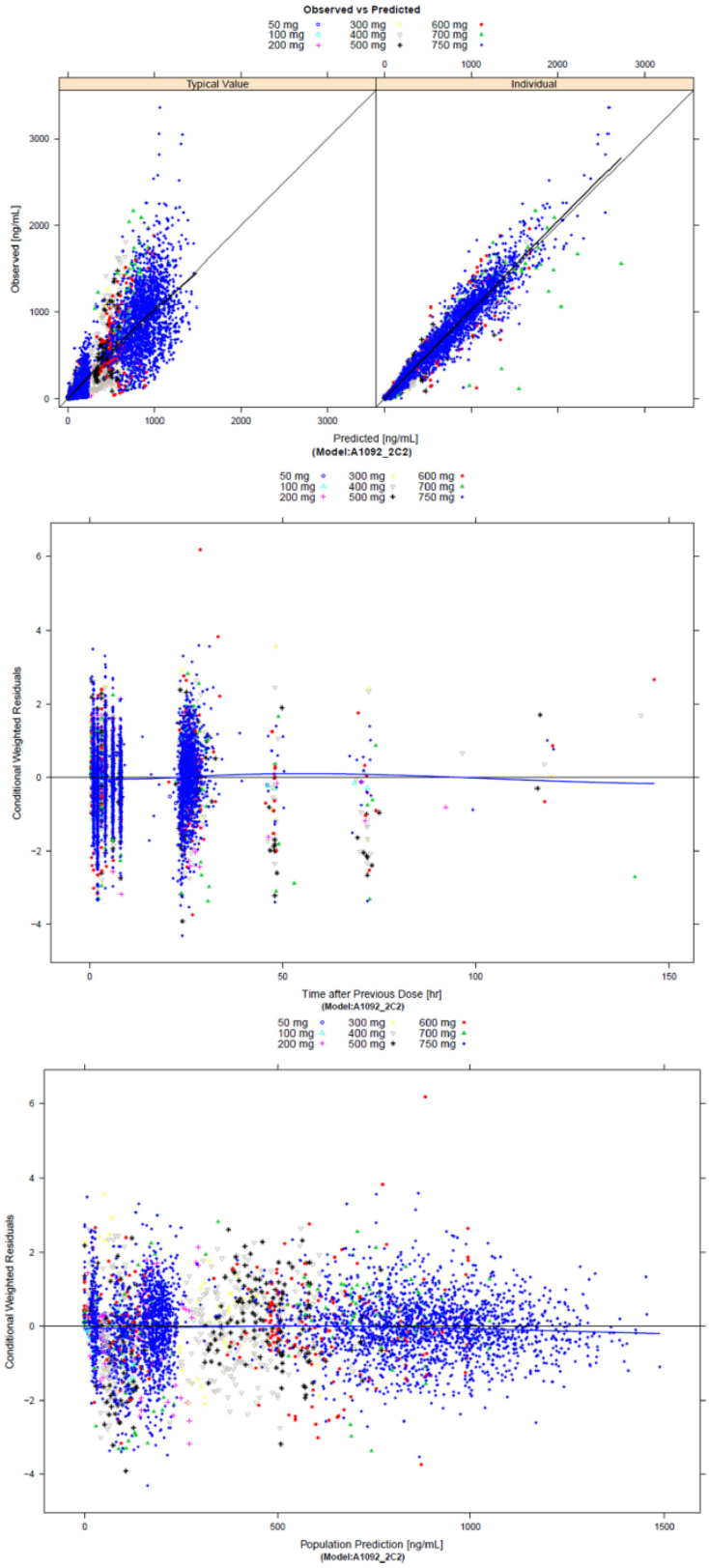


Figure 13: Predicted versus observed goodness-of-fit plots for the final PopPK model

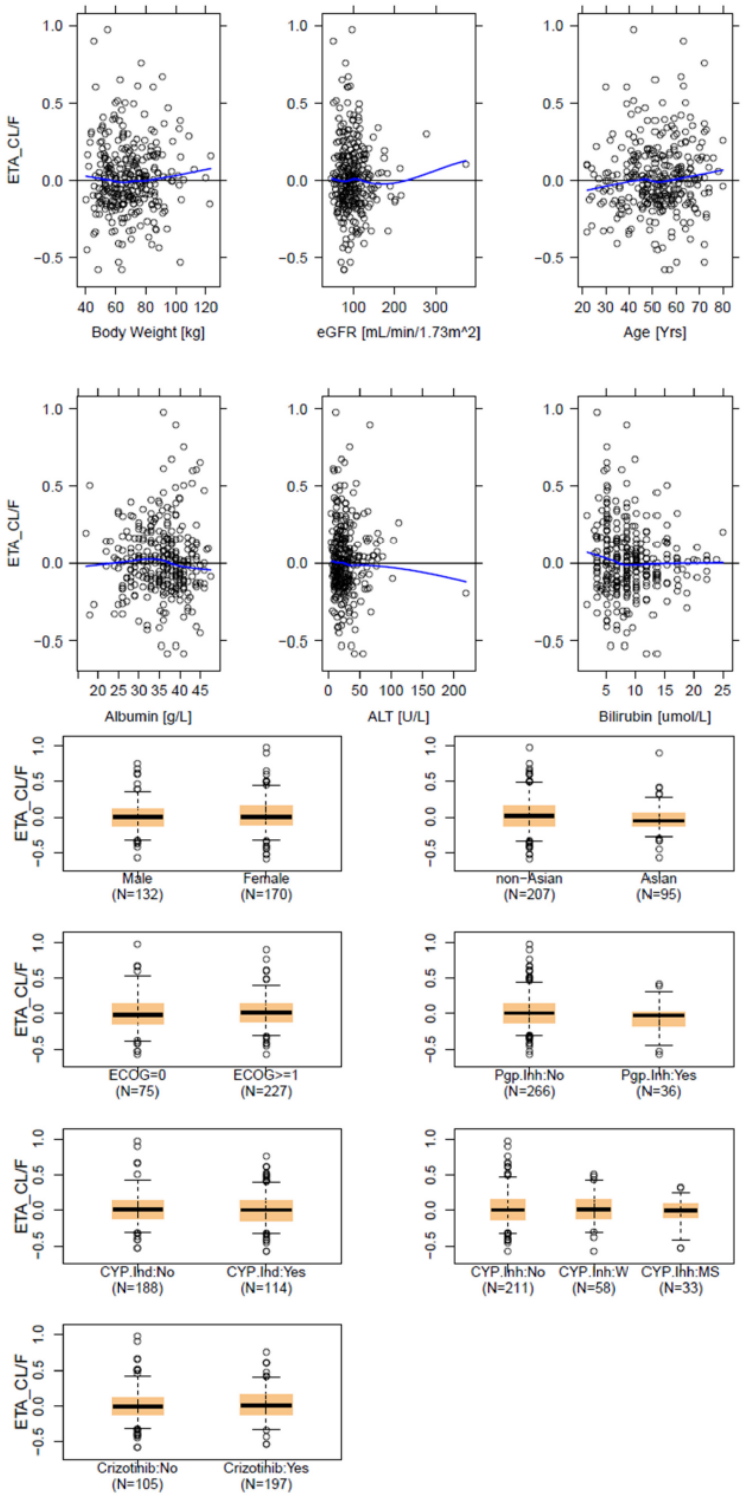


Figure 14: Plot of inter-individual random effects versus covariates on CL/F in the final PK model

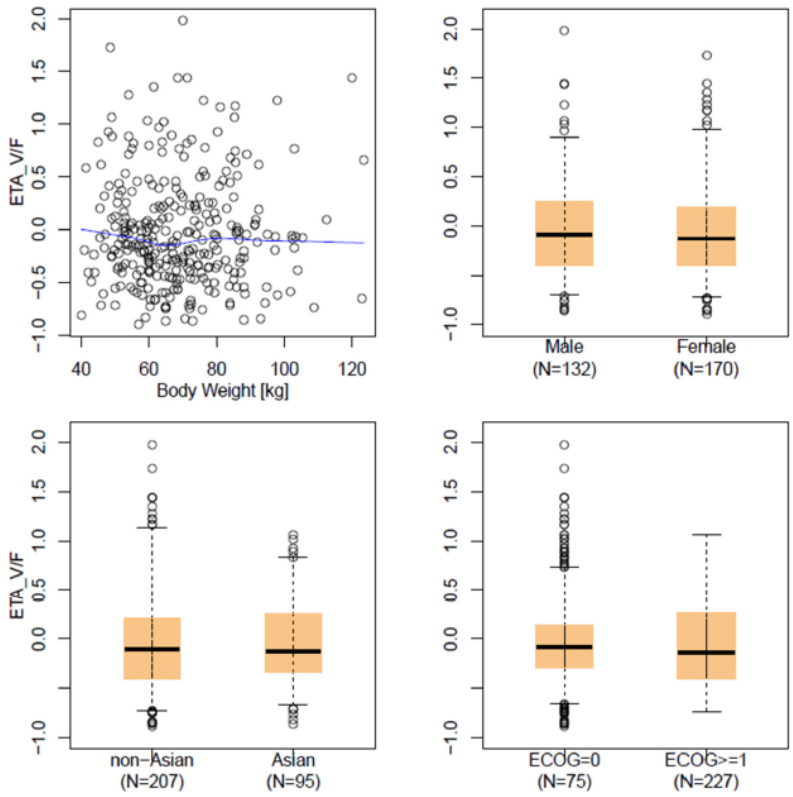


Figure 15: Plot of inter-individual random effects versus covariates on V/F in the final PK model

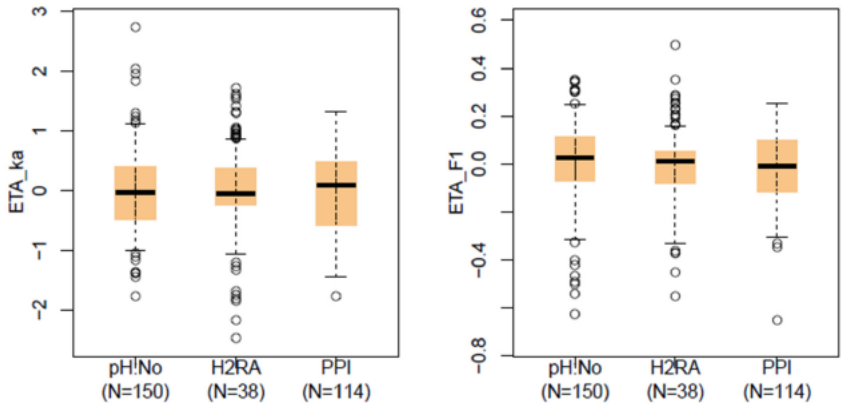
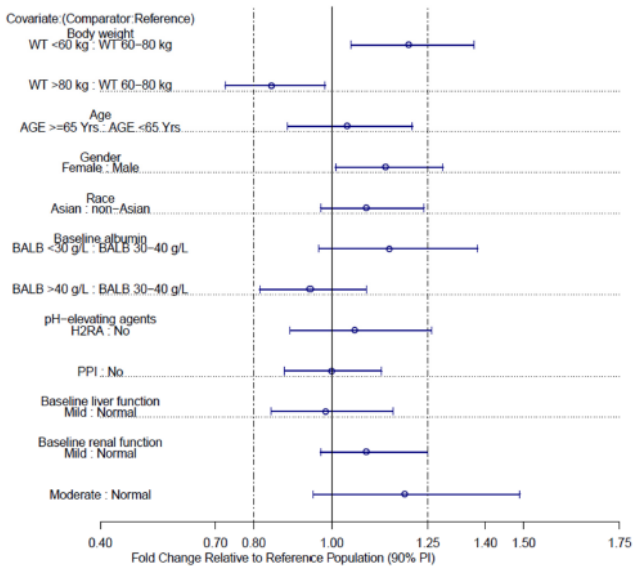


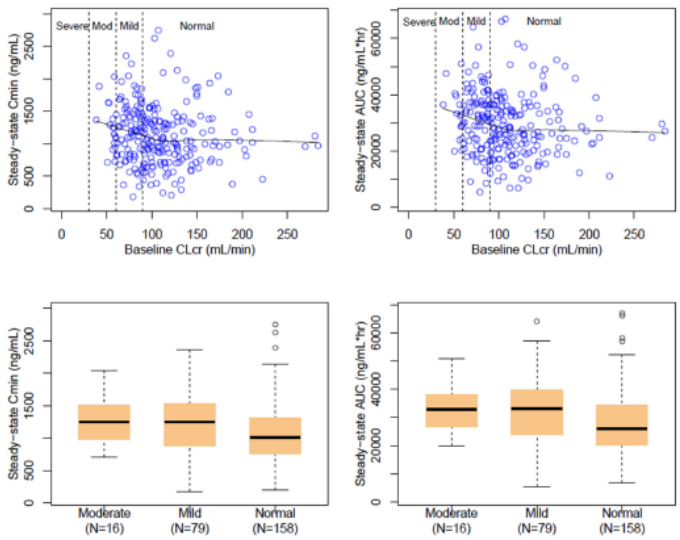
Figure 16: Plot of inter-individual random effects of covariates on Ka in the final PK model

Figure 5-13 Fold change of LDK378 steady-state exposure (AUC_{ss}) relative to reference group



Open circle is the fold change of AUC_{ss} for a covariate group compared to AUC_{ss} for its corresponding reference group, and horizontal line represents 90% prediction interval of fold change.
Source: /vob/CLDK378X/pool/pkpd_001/pgm_02/plot.covEff.popauc.report.R

Figure 5-14 Effect of renal function on LDK378 steady-state exposure ($C_{min,ss}$ and AUC_{ss})



Open circle in the scatter plots represents individual $C_{min,ss}$ and AUC_{ss} predicted by the final population PK model, and solid line represents the local smooth line. The renal function classification (normal, mild, moderate, and severe) is defined in Table 3-5. Boxplots of steady-state $C_{min,ss}$ and AUC_{ss} are presented with median (horizontal bold line) and 5th and 95th percentiles (whiskers).

Reviewer's comment:

The population PK analysis followed a reasonable model selection and optimization process. The applicant's population PK analysis is acceptable.

2.2 EXPOSURE-RESPONSE ANALYSES

Objectives: The objectives of the exposure-response analyses were to explore the exposure-response relationships for safety and efficacy, as well as exposure-dose change relationships.

2.2.1 Methods

Exposure-response analyses based on data from Study LDK378X2101 with a cut-off date of October 31, 2013 were conducted to explore the exposure-efficacy relationship of ceritinib in ALK-positive NSCLC patients, and the exposure-safety and exposure-dose change relationships of ceritinib in ALK-positive malignancies (NSCLC and non-NSCLC) patients using observed and predicted average steady-state trough concentrations.

Efficacy endpoints included overall response rate (ORR) and progression-free survival (PFS) by investigator assessment for NSCLC patients in the efficacy analysis set (EAS), and duration of response (DOR) and time to first response by investigator assessment for NSCLC patients in the EAS with a confirmed response.

Safety endpoints included all grade 3/4 AEs and grade 3/4 gastrointestinal AEs for selected preferred terms in the GI disorders system organ class. For safety endpoints, newly occurring grade 2/3/4 hepatic toxicity (AST, ALT, total bilirubin) and grade 2/3/4 hyperglycemia based on laboratory parameters were also assessed. All analyses were conducted separately for all ceritinib dose groups combined and for the ceritinib 750 mg dose group alone.

Ceritinib dose change assessments included time to the first dose reduction, time to first dose interruption, and time to study drug discontinuation. All analyses were conducted separately for all ceritinib dose groups combined and for the ceritinib 750 mg dose group alone.

The plasma PK exposure measure chosen for the exposure-response analyses was average observed steady-state trough concentration (C_{trough,ss_obs}), The average observed $C_{ss,\ trough}$ used for the efficacy (ORR and PFS) analyses is defined as the geometric mean of all evaluable steady-state trough concentrations (0-6 hours before dose) of each patient between Day15 of Cycle 1 and the minimum of last day of study drug (on or prior to the cut-off date) and date of progression/death (for patients who progressed/died) or date of last adequate tumor assessment (for patients who did not progress/die)..

Exposure-response analyses for safety were conducted using the average observed $C_{ss,\ trough}$ of ceritinib at dose levels ranging from 50 mg to 750 mg QD as exposure endpoint in all ALK-positive patients in Trial LDK378X2101. The average observed $C_{ss,\ trough}$ used for the safety analyses is defined as the geometric mean of all evaluable steady-state trough concentrations (0-6 hours before dose) of each patient after Day 15 of Cycle 1 and before the occurrence of the safety event of interest (including AEs, dose reduction, dose interruption, etc). For patients without the safety events of interest, the $C_{ss,\ trough}$ was calculated as the geometric mean of all evaluable steady-state trough concentrations (0-6 hours before dose) up to and on last day of study drug (on or prior to the cut-off date).

In addition, population PK posthoc estimates of steady-state trough concentration (C_{trough,ss_pred}) was also used as exposure endpoint for analyses. C_{trough,ss_pred} is defined as the geometric mean of trough concentrations predicted from the population PK model at the nominal time of 0 hour on Day 1 of each cycle (starting from Cycle 2) up to eight months after the first dose of study drug.

2.2.2 Results

Note: Only results using C_{trough,ss_obs} as exposure endpoint were summarized below. Results using C_{trough,ss_pred} as exposure endpoint were not shown due to their high similarity to those of

C_{trough,ss_obs}.

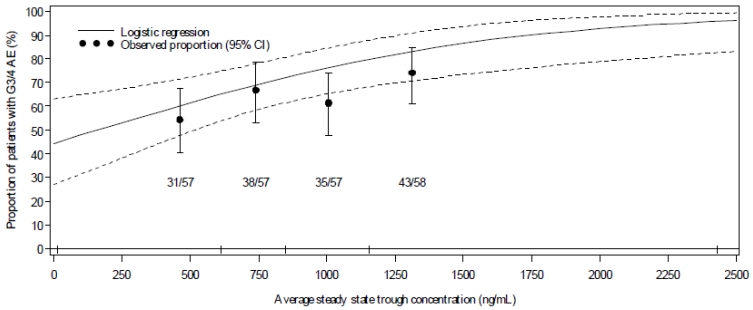
Exposure-safety relationship

Grade 3/4 AEs

When the analysis was conducted with all dose groups combined, the logistic regression analysis revealed a positive association between G3+ AEs and ceritinib $C_{trough,ss}$ (observed), after adjusting for the other covariates (Figure 2-1).

$C_{trough,ss}$ and race were identified as significant predictors of G3+ AEs, indicating that besides exposure, race may potentially have an impact on G3+ AEs. With a 200 ng/ml increase in ceritinib C_{trough,ss_obs} and C_{trough,ss_pred}, the estimated odds ratios of having a grade 3/4 AE is 1.32 (95% CI: 1.11, 1.57) and 1.35 (95% CI: 1.14, 1.60), respectively, in the presence of other covariates.

Figure 2-1 **Logistic regression of grade 3/4 adverse events versus average observed Ctrough,ss of ceritinib, overlaid with observed data**

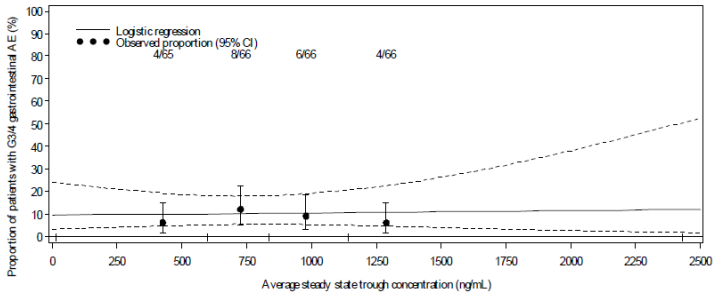


- Covariates include age, gender, race, weight, baseline ECOG status.
- Dashed curves are the 95% CI of the logistic regression model estimation.
- The logistic regression model estimation is generated as follows: numeric covariates at the median, categorical covariates at the highest frequency level.
- Observed proportions are calculated for each quartile range of average SS trough concentration (<25%, 25-<50%, 50-<75%, >=75%).
- n/N is the number of patients with events/total number of patients in the quartile range.

Grade 3/4 gastrointestinal AEs

There was no apparent association between ceritinib $C_{trough,ss}$ (observed and predicted) and grade 3/4 GI events. The number of events was low and similar across exposure quartiles.

Figure 2-3 **Logistic regression of grade 3/4 gastrointestinal adverse events versus average observed Ctrough,ss of ceritinib, overlaid with observed data**



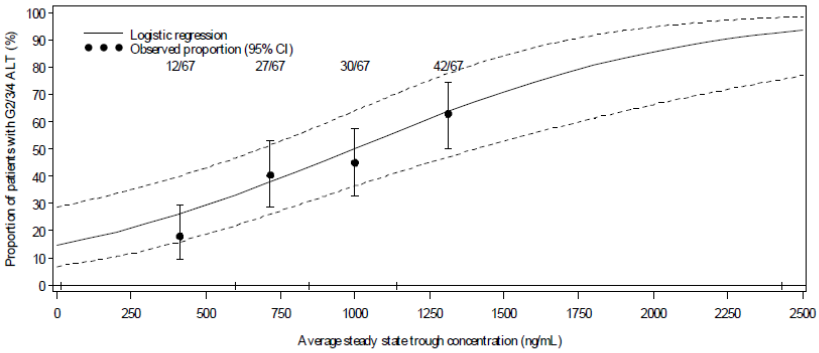
- Covariates include age, gender, race, weight, baseline ECOG status.
- Dashed curves are the 95% CI of the logistic regression model estimation.
- The logistic regression model estimation is generated as follows: numeric covariates at the median, categorical covariates at the highest frequency level.
- Observed proportions are calculated for each quartile range of average SS trough concentration (<25%, 25-<50%, 50-<75%, >=75%).
- n/N is the number of patients with events/total number of patients in the quartile range.

Grade 2/3/4 hepatic elevations

Newly occurring grade 2/3/4 ALT elevations appeared to be more frequent in patients with higher Ctrough,ss (observed and predicted). Similar trends were observed for grade 2/3/4 AST elevations (Figure 2-7 and Figure 2-8).

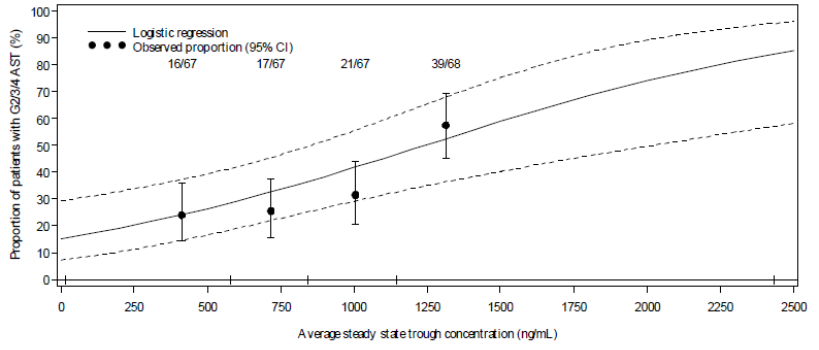
Logistic regression analyses revealed a positive association between newly occurring grade 2/3/4 AST or ALT elevations and $C_{trough,ss}$ (observed and predicted), after adjusting for the other covariates. $C_{trough,ss}$ (observed and predicted) was identified as the only significant predictor of grade 2/3/4 ALT/AST elevations. With a 200 ng/ml increase in ceritinib C_{trough,ss_obs} and C_{trough,ss_pred}, the estimated odds ratio of having ALT elevations are 1.42 (95% CI: 1.21- 1.68) and 1.50 (95% CI: 1.27-1.76), respectively, in the presence of other covariates. The corresponding estimated odds ratio for AST elevations are 1.32 (95% CI: 1.13- 1.54) and 1.38 (95% CI: 1.18-1.60), respectively.

Figure 2-5 **Logistic regression of grade 2/3/4 ALT elevations versus average observed Ctrough,ss of ceritinib, overlaid with observed data**



- Covariates include age, gender, race, weight, baseline ECOG status, normalized baseline lab, prior crizotinib and liver metastasis.
- Dashed curves are the 95% CI of the logistic regression model estimation.
- The logistic regression model estimation is generated as follows: numeric covariates at the median, categorical covariates at the highest frequency level.
- Observed proportions are calculated for each quartile range of average SS trough concentration (<25%, 25-<50%, 50-<75%, >=75%)
- n/N is the number of patients with events/total number of patients in the quartile range.

Figure 2-7 **Logistic regression of grade 2/3/4 AST elevations versus average observed Ctrough,ss of ceritinib, overlaid with observed data**



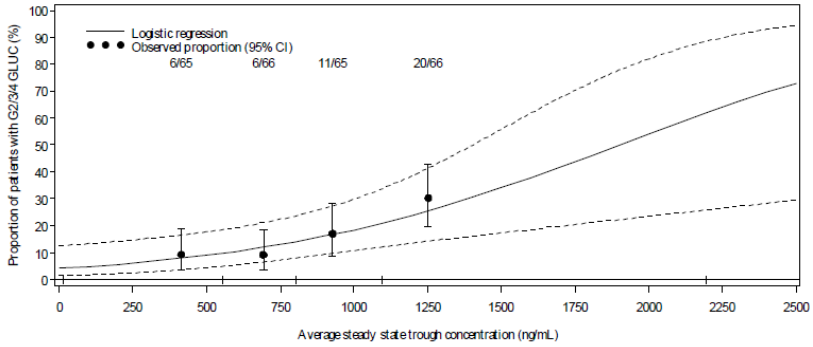
- Covariates include age, gender, race, weight, baseline ECOG status, normalized baseline lab, prior crizotinib and liver metastasis.
- Dashed curves are the 95% CI of the logistic regression model estimation.
- The logistic regression model estimation is generated as follows: numeric covariates at the median, categorical covariates at the highest frequency level.
- Observed proportions are calculated for each quartile range of average SS trough concentration (<25%, 25-<50%, 50-<75%, >=75%).
- n/N is the number of patients with events/total number of patients in the quartile range.

Grade 2/3/4 hyperglycemia

There appeared to be a positive association between newly occurring grade 2/3/4 hyperglycemia based on laboratory parameters and ceritinib average $C_{trough,ss}$ (observed and predicted). With a 200 ng/ml increase in ceritinib Ctrough,ss_obs and Ctrough,ss_pred, the estimated odds ratio of having grade 2/3/4 hyperglycemia is 1.42 (95% CI: 1.13-1.78) and 1.39 (95% CI: 1.11-1.74), respectively.

$C_{trough,ss}$ (observed and predicted) and age were identified as significant predictors of grade 2/3/4 hyperglycemia, indicating that besides exposure, age may potentially have an impact on this safety parameter.

Figure 2-10 Logistic regression of grade 2/3/4 hyperglycemia versus average predicted Ctrough,ss of ceritinib, overlaid with observed data

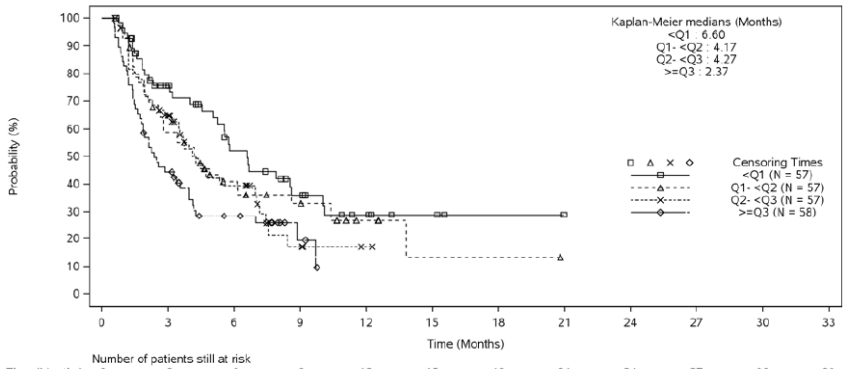


- Covariates include age, gender, race, weight, baseline ECOG status and normalized baseline lab.
- Dashed curves are the 95% CI of the logistic regression model estimation.
- The logistic regression model estimation is generated as follows: numeric covariates at the median, categorical covariates at the highest frequency level.
- Observed proportions are calculated for each quartile range of average SS trough concentration (<25%, 25-<50%, 50-<75%, >=75%).
- n/N is the number of patients with events/total number of patients in the quartile range.

Time to first grade 3/4 AE

The results suggest that higher exposures (≥Q3) are associated with earlier and more frequent grade 3/4 AEs than lower exposures (<Q1) with no marked differences in time to first grade 3/4 AE between the two intermediate concentration quartile ranges (Q1-<Q2 and Q2-<Q3).

Figure 2-11 Kaplan-Meier plot of time to first grade 3/4 adverse events by quartile of average observed Ctrough,ss of ceritinib



Number of patients still at risk

Time (Months)	0	3	6	9	12	15	18	21	24	27	30	33
<Q1	57	35	21	12	6	3	1	0	0	0	0	0
Q1- <Q2	57	32	17	11	4	1	1	0	0	0	0	0
Q2- <Q3	57	32	15	4	1	0	0	0	0	0	0	0
>=Q3	58	25	12	3	0	0	0	0	0	0	0	0

Time to first newly occurring grade 2/3/4 ALT and AST elevations

The time to first newly occurring grade 2/3/4 ALT and AST elevations was estimated based on Kaplan-Meier methodology using $C_{trough,ss}$ (observed and predicted) quartile as a stratification factor and including all ALK-positive cancer patients.

The results suggest that higher exposures (≥Q3) are associated with earlier and more frequent grade 2/3/4 ALT and AST elevations than lower exposures (<Q3) and are consistent with the results of exposure-dose change analyses in which earlier and more frequent dose reductions/interruptions were observed for higher exposures (observed and predicted).

Figure 2-13 Kaplan-Meier plot of time to first newly occurring grade 2/3/4 ALT elevations by quartile of average observed Ctrough,ss of ceritinib

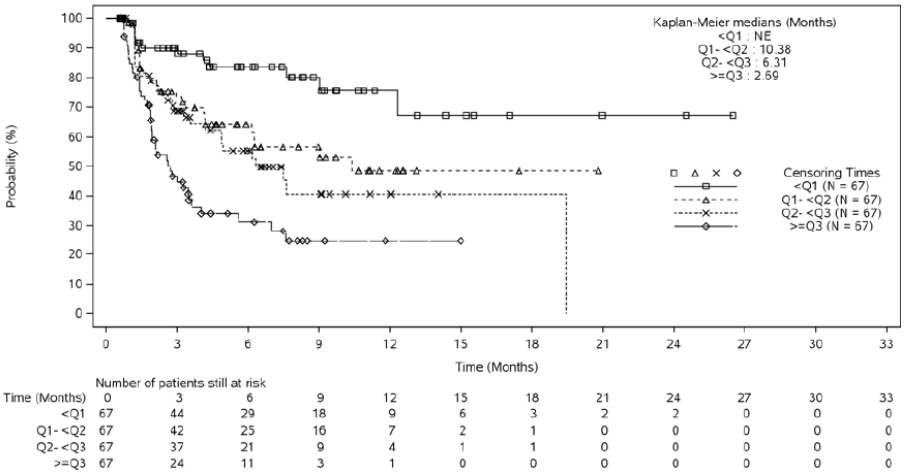
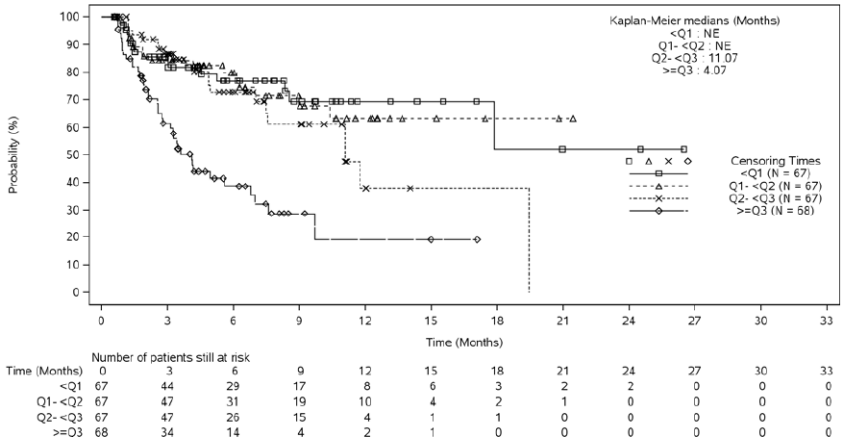


Figure 2-15 Kaplan-Meier plot of time to first newly occurring grade 2/3/4 AST elevations by quartile of average observed Ctrough,ss of ceritinib



Exposure-dosing relationship

Time to dose change

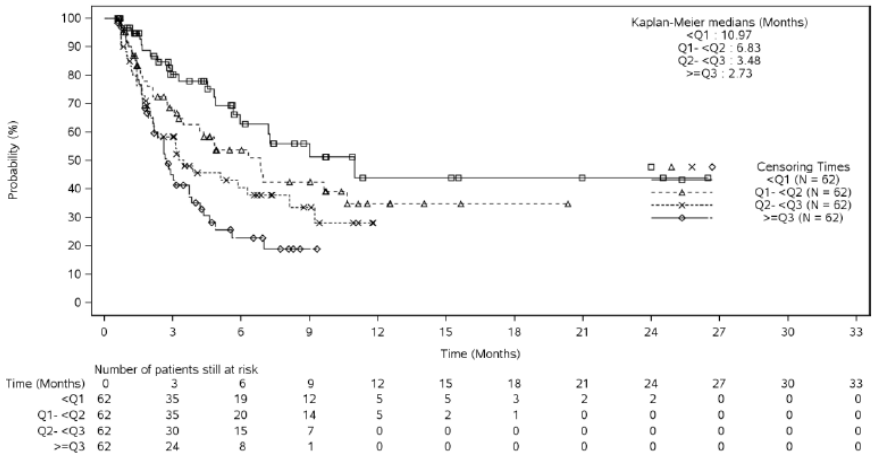
Time to first dose change was estimated based on Kaplan-Meier methodology using C_{trough,ss_obs}

quartile as a stratification factor and including all ALK-positive cancer patients.

Higher C_{trough,ss_obs} appear to be associated with earlier and more frequent dose reductions (Figure 2-17). A similar trend was observed for time to first study drug interruption across quartiles of C_{trough,ss_obs} (Figure 2-19).

The trends observed based on the analyses of C_{trough,ss_obs} coupled with those observed for safety endpoints suggest that dose reductions and study drug interruptions can be used to manage the safety profile of ceritinib. Furthermore, there is no clear association between $C_{trough,ss}$ (observed and predicted) and time to permanent discontinuation of study drug, suggesting that the management of AEs via dose reductions and study drug interruptions is effective to maintain the patients on study drug for as long as clinically indicated.

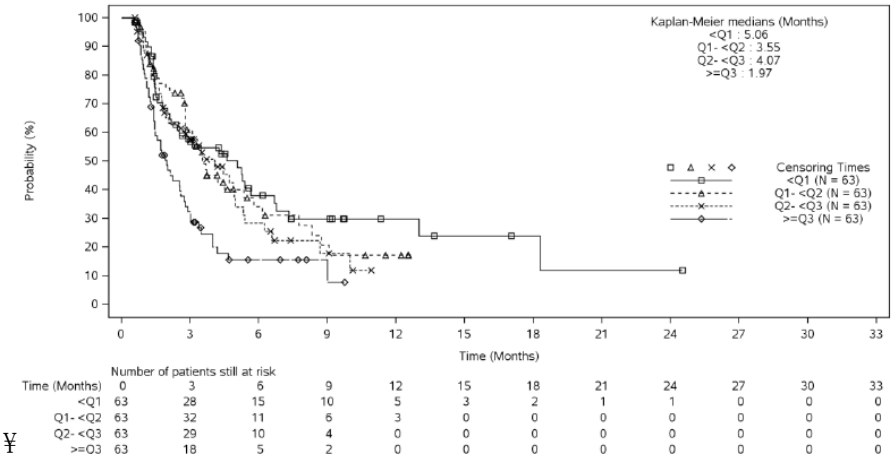
Figure 2-17 Kaplan-Meier plot of time to first dose reduction by quartile of average observed Ctrough,ss of ceritinib



Number of patients still at risk

Time (Months)	0	3	6	9	12	15	18	21	24	27	30	33
<Q1	62	35	19	12	5	5	3	2	2	0	0	0
Q1- <Q2	62	35	20	14	5	2	1	0	0	0	0	0
Q2- <Q3	62	30	15	7	0	0	0	0	0	0	0	0
>=Q3	62	24	8	1	0	0	0	0	0	0	0	0

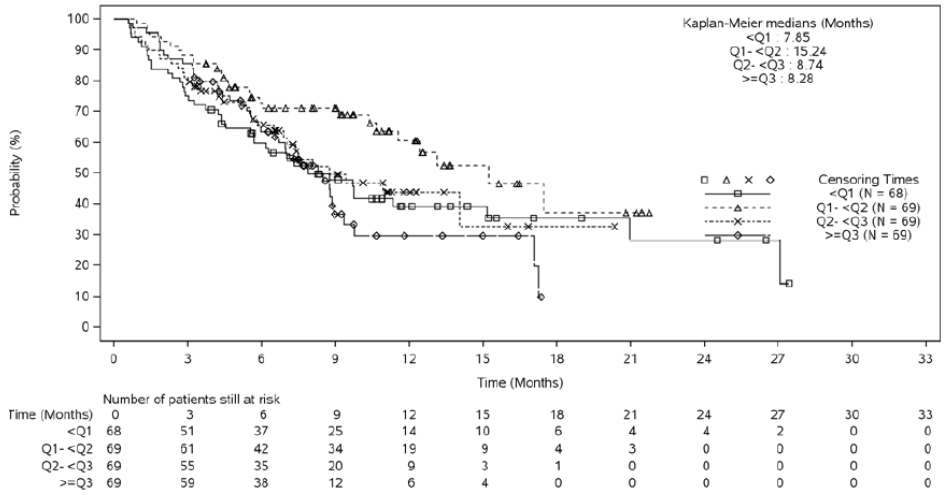
Figure 2-19 Kaplan-Meier plot of time to first dose interruption by quartile of average observed Ctrough,ss of ceritinib



Number of patients still at risk

Time (Months)	0	3	6	9	12	15	18	21	24	27	30	33
<Q1	63	28	15	10	5	3	2	1	1	0	0	0
Q1- <Q2	63	32	11	6	3	0	0	0	0	0	0	0
Q2- <Q3	63	29	10	4	0	0	0	0	0	0	0	0
>=Q3	63	18	5	2	0	0	0	0	0	0	0	0

Figure 2-21 **Kaplan-Meier plot of time to treatment permanent discontinuation by quartile of average observed Ctrough,ss of ceritinib**



Time (Months)	0	3	6	9	12	15	18	21	24	27	30	33
<Q1	68	51	37	25	14	10	6	4	4	2	0	0
Q1- <Q2	69	61	42	34	19	9	4	3	0	0	0	0
Q2- <Q3	69	55	35	20	9	3	1	0	0	0	0	0
>=Q3	69	59	38	12	6	4	0	0	0	0	0	0

Exposure-efficacy relationship

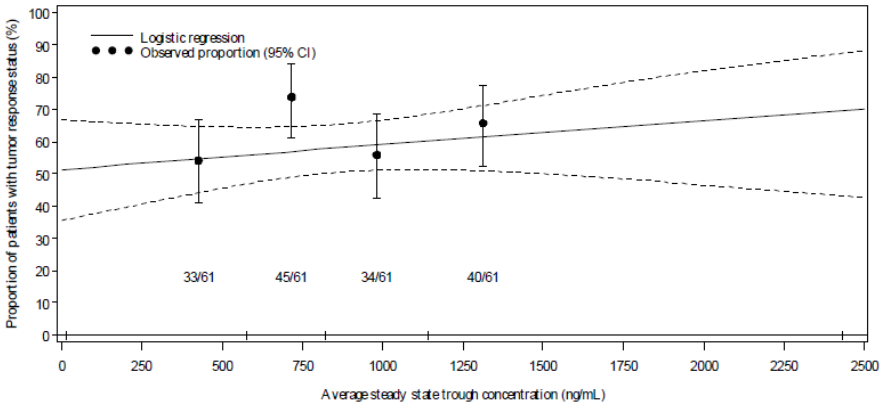
ORR

The relationship between $C_{trough,ss}$ (observed and predicted) and best overall response (BOR) of confirmed PR/CR by Investigator assessment was assessed based on data from all ALK-positive NSCLC patients in the Efficacy Analysis Set (EAS). Patients were grouped by quartiles of $C_{trough,ss}$ and the proportion of patients with response (BOR of confirmed CR/PR by Investigator assessment) was presented separately for each quartile range.

No association between ORR and $C_{trough,ss}$ (observed and predicted) was apparent (Table 2-21 and Table 2-22). Similar results were observed when the analysis was restricted to NSCLC patients in the 750 mg dose group for C_{trough,ss_obs} or for C_{trough,ss_pred}. Prior ALK inhibitor status was identified as a significant predictor of response, indicating that patients who are ALK inhibitor naïve potentially respond better for C_{trough,ss_obs} or for C_{trough,ss_pred}.

The lack of association between increasing exposure and ORR suggests that the range of exposures studied (primarily driven by the data for patients in the 750 mg dose group) did not permit an adequate characterization of the lower part of the dose-response curve yielding an apparently flat exposure-response curve. The applicant stated that an exposure-response relationship may exist for ceritinib and that the flat exposure-response curve observed potentially means that the exposures achieved were in the plateau range of drug effect.

Figure 2-23 Logistic regression of tumor response status versus average observed Ctrough,ss of ceritinib, overlaid with observed data

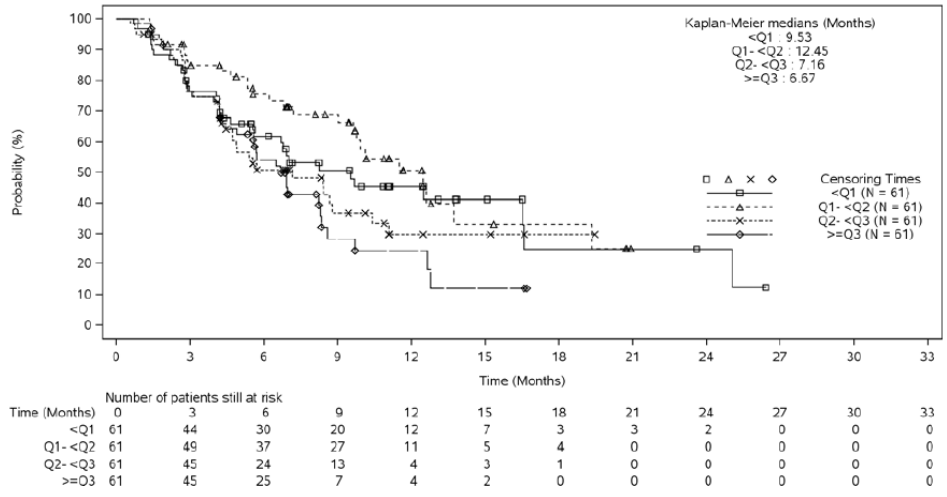


- Prior ALK inhibitor (Y/N) was kept in the final model based on backward covariates selection.
- Dashed curves are the 95% CI of the logistic regression model prediction.
- Observed proportions are calculated for each quartile of average SS trough concentration (<25%, 25-<50%, 50-<75%, >=75%). n/N are shown on the plot.

PFS and DOR

Median PFS and event rates at different time points were estimated based on Kaplan-Meier methodology using $C_{trough,ss}$ (observed and predicted) quartile as a stratification factor and including all ALK-positive NSCLC patients in the EAS. Within the studied exposure range, there is no apparent trend for increasing median PFS with increasing exposure regardless of whether C_{trough,ss_obs} or C_{trough,ss_pred} was used as exposure measure.

Figure 2-25 Kaplan-Meier plot of progression-free survival based on Investigator assessment by quartile of average observed Ctrough,ss of ceritinib



Number of patients still at risk

Time (Months)	0	3	6	9	12	15	18	21	24	27	30	33
<Q1	61	44	30	20	12	7	3	3	2	0	0	0
Q1- <Q2	61	49	37	27	11	5	4	0	0	0	0	0
Q2- <Q3	61	45	24	13	4	3	1	0	0	0	0	0
>=Q3	61	45	25	7	4	2	0	0	0	0	0	0

NSCLC patients in the quartile range with higher systemic exposures (observed or predicted) have shorter estimated median DORs compared to patients in the quartile ranges with lower systemic exposures. As described in the response to FDA IR 10 ([response-fda-ir10]; NDA 205755, Sequence No. 0022, some plausible explanations for such findings are as follows:

- The number of patients with confirmed responses in each of the quartile ranges of average observed $C_{trough,ss}$ is small and interpretation of the results of any such subgroup analysis

needs to be made with extreme caution. Methodological complications related to multiple analyses mean that exploratory investigations into effects in subsets of the trial population must be made with caution taking into consideration all available evidence, not only the point estimates from individual subgroup analyses. It should be noted that the 95% confidence intervals (CIs) for median DOR in each of the three lower quartile ranges overlap with that for the 95% CI for the median DOR in the upper quartile range (the lower bound of the 95% CIs for the 3 lower quartile ranges is within the 95% CI for the upper quartile range).

- The small number of patients across subgroups in any analysis is likely to result in imbalances in baseline characteristics which can have an unexpected impact on the observed results as was observed for this analysis. There is a large imbalance in the number of patients with brain metastases at baseline across the quartile ranges ([Table 2-3] of IR 10), with approximately two-thirds of the patients in the quartile range associated with the highest concentrations having brain metastases at baseline vs approximately one-third in the quartile range associated with the lowest concentrations.
- As noted in the SCE and the SCE-60 day update, although both NSCLC patients with and without brain metastases at baseline have long median DORs, the estimated median DOR for patients with brain metastases at baseline is shorter than that for patients without brain metastases at baseline (median DOR [95% CI]: 7.0 months [5.45, 9.69] vs NE [9.69, NE], [60DU-SCE Appendix 1-Study X2101-Table 14.2-1.4c2]).
- The small number of patients across subgroups determined by quartile ranges of average observed $C_{trough,ss}$ and the resulting imbalance in a baseline characteristic with prognostic value has led to a spurious result that should be interpreted with caution. The high rate of early and durable responses observed in the 750 mg dose group continues to be supportive of the 750 mg dose as the appropriate dose for the proposed indication.

Time to first response

Time to first response based on Investigator assessment for patients with a confirmed PR or CR was summarized by quartile of $C_{trough,ss}$ (observed and predicted). All quartiles have a median time to first response of approximately 6 weeks, irrespective of analyses conducted for all dose groups combined or restricted to the 750 mg dose group. These results indicate that the onset of response is rapid in most patients with response seen around the time of the first tumor assessment (6 week tumor assessment schedule).

FDA request 7 Table 8-12.1 (Page 1 of 2)
Time to first response by quartile of average steady state trough concentration of LDK378
(EAS-NSCLC for patients with confirmed PR or CR and evaluable trough concentrations)

	<Q1 N= 38 n (%)	Q1- <Q2 N= 38 n (%)	Q2- <Q3 N= 38 n (%)	>=Q3 N= 38 n (%)	All patients N= 152 n (%)
Time to tumor response categories (weeks), n (%)					
<=6	12 (31.6)	9 (23.7)	8 (21.1)	10 (26.3)	39 (25.7)
>6-12	17 (44.7)	23 (60.5)	25 (65.8)	23 (60.5)	88 (57.9)
>12-18	8 (21.1)	2 (5.3)	1 (2.6)	4 (10.5)	15 (9.9)
>18-24	1 (2.6)	3 (7.9)	3 (7.9)	1 (2.6)	8 (5.3)
>24	0	1 (2.6)	1 (2.6)	0	2 (1.3)
Time to tumor response (weeks)					
n	38	38	38	38	152
Mean	8.6	8.7	7.9	7.1	8.1
SD	4.45	5.29	4.92	2.95	4.49
Median	6.3	6.1	6.1	6.1	6.1
Min	5.0	4.4	4.7	3.0	3.0
Max	23.6	24.1	24.1	18.1	24.1

2.2.3 The Applicant's Conclusions

In conclusion, the exposure/response analyses suggest that higher steady-state exposure (observed or predicted) appear to be associated with earlier and more frequent grade 3/4 AEs and grade 2/3/4 ALT and AST elevations, consistent with the findings of earlier and more frequent dose reductions/interruptions at higher observed exposures. There is no clear association between increased exposures (observed and predicted) and time to permanent discontinuation of study drug, suggesting that the management of AEs via dose reductions and study drug interruptions is effective in maintaining patients on study drug for as long as it is clinically indicated.

There is no apparent exposure-response relationship for any of the efficacy endpoints (ORR, PFS, DOR) using either observed or predicted average steady-state trough concentrations, suggesting that the range of exposures studied (primarily driven by the data for patients in the 750 mg dose group) did not permit an adequate characterization of the lower part of the dose-response curve. However, the results observed in this trial demonstrate MTD/RD of ceritinib 750 mg once daily induces a high rate of early and durable responses in patients with ALK-positive NSCLC.

Reviewer's Comment: The applicant's analyses and interpretations are acceptable.

3 REVIEWER'S ANALYSES

3.1 EXPOSURE-RESPONSE ANALYSIS

3.1.1 Objectives

The objectives of the reviewer's analyses are:

- To explore the exposure-response relationships for the efficacy endpoints ORR and PFS in the registration trial for the proposed patient population

- To explore exposure-response relationships for overall Grade 3 or worse AEs, overall Grade 3 or worse GI tract AEs, individual AEs such as ALT/AST elevation, hyperglycemia, diarrhea, and fatigue in the safety population

3.1.2 Methods

Exposure-response analyses were conducted, using the average observed $C_{ss,\ trough}$ of ceritinib at 50-750 mg QD as exposure endpoint, for ORR and progression free survival (PFS) in 137 patients with ALK-positive NSCLC who were previously treated with ALK inhibitor(s) in Trial LDK378X2101. The average observed $C_{ss,\ trough}$ used for the efficacy (ORR and PFS) analyses is defined as the geometric mean of all evaluable steady-state trough concentrations (0-6 hours before dose) of each patient between Day15 of Cycle 1 and the minimum of last day of study drug (on or prior to the cut-off date) and date of progression/death (for patients who progressed/died) or date of last adequate tumor assessment (for patients who did not progress/die)..

Logistic regression method was applied to analyze the relationships between $C_{ss,trough}$ and ORR per central radiology review with a cut-off date of October 31, 2013. The probability of ORR was predicted by $C_{ss,\ trough}$ using logistic regression model by adjusting prognostic factors ECOG (0 vs 1), race (Caucasian vs Asian vs African Americans vs others), baseline sum of longest diameter (median 8.2 cm), and brain metastasis (no versus yes).

Exposure-response analyses for safety were conducted using the average observed $C_{ss,\ trough}$ of ceritinib at dose levels ranging from 50 mg to 750 mg QD as exposure endpoint in all ALK-positive patients in Trial LDK378X2101. The average observed $C_{ss,\ trough}$ used for the safety analyses is defined as the geometric mean of all evaluable steady-state trough concentrations (0-6 hours before dose) of each patient after Day 15 of Cycle 1 and before the occurrence of the safety event of interest (including AEs, dose reduction, dose interruption, etc). For patients without the safety events of interest, the $C_{ss,\ trough}$ was calculated as the geometric mean of all evaluable steady-state trough concentrations (0-6 hours before dose) up to and on last day of study drug (on or prior to the cut-off date).

Logistic regression method was also applied to analyze the relationships between $C_{ss,trough}$ and overall Grade 3 or worse AEs, overall Grade 3 or worse GI tract AEs, individual AEs such as ALT/AST elevation, hyperglycemia, diarrhea, and fatigue in the safety population. The probability of the incidence of the safety endpoints was predicted by $C_{ss,\ trough}$ using logistic regression model by adjusting prognostic factors prior ALK inhibitor treatment, ECOG status (0

vs 1), race (Caucasian vs Asian vs African Americans vs others), and brain metastasis (no versus yes).

Kaplan Meier curve analyses were conducted for PFS, time to dose reduction, time to dose interruption, time to Grade 3 or worse AE with $C_{ss,trough}$ stratified by quartiles.

3.1.3 Datasets

Datasets used in the analysis are summarized in Table 2.

Table 2. Analysis datasets

Dataset description	Name	Link to EDR
Population PK analysis	pkall.xpt	\\cdsesub1\evsprod\nda205755\0002\m5\datasets\ldk378a-population-pk\analysis\pkall.xpt
IRC-Efficacy	acenpat.xpt	\\cdsesub1\evsprod\nda205755\0012\m5\datasets\ldk378x2101\analysis\acenpat.xpt
Safety and observed exposure data	apkae2.xpt	\\cdsesub1\evsprod\nda205755\0025\m5\datasets\ldk378x2101\analysis\apkae2.xpt
Safety and predicted exposure data	apkae3.xpt	\\cdsesub1\evsprod\nda205755\0025\m5\datasets\ldk378x2101\analysis\apkae3.xpt
Adverse events data	aaev.xpt	\\cdsesub1\evsprod\nda205755\0012\m5\datasets\ldk378x2101\analysis\aaev.xpt
INV-Efficacy data	atumpat.xpt	\\cdsesub1\evsprod\nda205755\0012\m5\datasets\ldk378x2101\analysis\atumpat.xpt
Dose modification and observed exposure data	apkdose.xpt	\\cdsesub1\evsprod\nda205755\0025\m5\datasets\ldk378x2101\analysis\apkdose.xpt
Efficacy and observed exposure data	apkeff2.xpt	\\cdsesub1\evsprod\nda205755\0025\m5\datasets\ldk378x2101\analysis\apkeff2.xpt
Laboratory data and observed exposure data	apklab2.xpt	\\cdsesub1\evsprod\nda205755\0025\m5\datasets\ldk378x2101\analysis\apklab2.xpt

3.1.3.1 Software

SAS 9.3 and TIBCO Spotfire S-Plus 8.1 were used for the reviewer's analyses.

3.1.4 Results

3.1.4.1 Efficacy

Please refer to Key question 1 for details: Are there significant exposure-response relationships for efficacy?

3.1.4.2 Safety

Please refer to Key question 2 for details: Are there significant exposure-response relationships for safety?

4 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
ORR_Logistic_Adjusting_Plot_PriorALKi_Only_IRC_AllDoses_Final.sas	Logistic regression plot for ORR for the indicated patients population at dose levels ranging from 50 to 750 mg	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Ceritinib_NDA205755_PS\ER Analyses\Final Model
PFS_IRC_alldose_Prior_QuartileCsstroughall_Plot03022014.ssc	S-Plus code for KM Survival curves stratified by exposure quartiles for PFS	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Ceritinib_NDA205755_PS\ER Analyses\Final Model
Gr3AE_Logistic_Adjusting_Plot.sas	SAS code for the logistic regression plot for the Grade 3+ AE in ALK+ NSCLC patients at dose level from 50 mg to 750 mg QD	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Ceritinib_NDA205755_PS\ER Analyses\Final Model
TimetoGr3AE_SurvivalPlot.ssc	Splus code for Time to Grade 3+ AEs logistic regression plot	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Ceritinib_NDA205755_PS\ER Analyses\Final Model
Gr3_GI_AE_Logistic_Adjusting_Plot.sas	SAS code for the Grade 3+ GI tract AE logistic regression plot	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Ceritinib_NDA205755_PS\ER Analyses\Final Model
Gr3_AST_Logistic_Adjusting_Plot.sas	SAS code for the Grade 3+ AST elevation logistic regression plot	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Ceritinib_NDA205755_PS\ER Analyses\Final Model
Gr3_ALT_Logistic_Adjusting_Plot.sas	SAS code for the Grade 3+ ALT elevation logistic regression plot	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Ceritinib_NDA205755_PS\ER Analyses\Final Model
Gr2_Hyperglycemia_Logistic_Adjusting_Plot.sas	SAS code for the Grade 2+ hyperglycemia logistic regression plot	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Ceritinib_NDA205755_PS\ER Analyses\Final Model
Gr2_Fatigue_Logistic_Adjusting_Plot.sas	SAS code for the Grade 2+ fatigue logistic regression plot	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Ceritinib_NDA205755_PS\ER Analyses\Final Model
Gr2_Diarrhea_Logistic_Adjusting_Plot.sas	SAS code for the Grade 2+ diarrhea logistic regression plot	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Ceritinib_NDA205755_PS\ER Analyses\Final Model
DoseReduction_Logistic_Adjusting_Plot.sas	SAS code for the dose reduction logistic regression plot	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Ceritinib_NDA205755_PS\ER Analyses\Final Model
DoseDelay_Logistic_Adjusting_Plot.sas	SAS code for the dose interruption logistic regression plot	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Ceritinib_NDA205755_PS\ER Analyses\Final Model
Time_to_DoseDelay Reduction_SurvivalPlot.ssc	S-Plus code for Time to Dose Delay or Dose reduction plots	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Ceritinib_NDA205755_PS\ER Analyses\Final Model

4.2 PHYSIOLOGICALLY-BASED PHARMACOKINETIC REVIEW

Physiological-based Pharmacokinetic Modeling Review Memo

Division of Pharmacometrics, Office of Clinical Pharmacology

Application Number	NDA 205755
Drug Name	Ceritinib (LDK378)
Proposed Indication	(b) (4) metastatic non-small cell lung cancer (NSCLC) who have (b) (4)
Clinical Division	Division of Oncology Products 2
PBPK Consult request	Ruby Leong, Pharm.D.
Primary PBPK Reviewer	Yuzhuo Pan, Ph.D.
Secondary PBPK Reviewer	Ping Zhao, Ph.D
Sponsor	Novartis

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1. *OBJECTIVES*

The main purposes of this review memo are (a) to review sponsor's physiologically-based pharmacokinetic (PBPK) report entitled "Simulations of the clinical drug interaction potential of ketoconazole or rifampin with LDK378 using the latest version 13 of Simcyp® simulator" [1] and its companion simulation reports [2-4] requested by the FDA during NDA review; and (b) to conduct further simulations to support ceritinib dose regimen in patients taking different CYP3A modulators (inhibitors/inducers).

2. *BACKGROUND*

2.1. Regulatory history on PBPK submission

Ceritinib (LDK378) is an orally-active, small molecule, selective and potent inhibitor of anaplastic lymphoma kinase (ALK). Ceritinib is for the treatment of patients with (b) (4) metastatic non-small cell lung cancer (NSCLC) who have (b) (4) The proposed dosing regimen of ceritinib is 750 mg orally once daily (q.d.) on an empty stomach. A PBPK model was developed by the sponsor during the development to support dose selection of clinical drug-drug interactions studies evaluating the effect of strong CYP3A inhibitor ketoconazole or inducer rifampin on the exposure of ceritinib [5, 6]. After initial review of the findings of these dedicated interaction studies, the reviewers issued an information request to the sponsor on Jan 22, 2014 (01222014IR, Appendix 1). On Jan 24, 2014, sponsor submitted study reports to address issues raised in the IR [1-4].

2.2. Highlight of drug absorption and disposition

Table 1. Summary of ceritinib's absorption, distribution, metabolism and excretion (ADME)[7]

Absorption	After oral administration in humans, ceritinib has a Tmax of approximately 6 hours. The absolute bioavailability of ceritinib was not determined in clinical studies. In mass balance study in humans, 68% of orally administered dose was excreted as unchanged ceritinib and the remainder eliminated as metabolites. Food increased ceritinib AUC by 58%-73%. In vitro ceritinib is a substrate of P-glycoprotein (P-gp)
Distribution	Ceritinib is highly bound to human plasma proteins (97%), with extensive tissue distribution (apparent volume of distribution 4230 L at 750 mg after a single oral dose in patients)
Metabolism	Ceritinib is metabolized mainly by CYP3A. In vitro, ceritinib is a time-dependent inhibitor (TDI) of CYP3A
Excretion	After oral administration, the primary route of excretion 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. Only 1.3% of the single administered oral dose is recovered in the urine

After evaluating the submitted PBPK modeling reports [1-4], the FDA reviewers revised the sponsor's PBPK model (Sponsor's model) of ceritinib and used the updated model (FDA's model) to address key questions on whether PBPK model predicts ceritinib exposure change when the drug is co-administered with CYP3A inhibitors or inducers, and on whether PBPK model predicts the effect of ceritinib on the exposure of a sensitive CYP3A substrate midazolam. Additional simulations were explored using the FDA's model to evaluate the effect of other patient factors on the exposure of ceritinib.

3. METHODS

Simcyp® (V13, release 1, Sheffield, UK) [8, 9] was used by the sponsor and the FDA. Software's "Healthy volunteer" population and cirrhosis populations (Child-Pugh A, B, or C) [10] were tested. Final model parameters and their sources of the sponsor's model are summarized in **Appendix Tables A1 and A2.** Unless otherwise stated, all simulations were conducted according to software "workspace" files submitted by the sponsors. Ten trials with 10 subjects in each trial were run for each simulation. The population contained 50% female, with an age range from 20-50 years. Subjects were under fasted condition. A cross-over design was assumed for the simulation of drug-drug interaction scenarios.

3.1. Sponsor's PBPK model

Sponsor's PBPK modeling of ceritinib can be summarized in three parts.

(A). Model building: Results of in vitro ADME experiments and physicochemical properties, and in vivo PK studies were used. The model incorporated CYP3A time-dependent inhibition (TDI) parameters measured from in vitro experiment.

(B). Model verification: Clinical drug-drug interaction studies with strong CYP3A inhibitor or inducer (ketoconazole 200 mg twice daily, b.i.d. for 8 days, combined with a single dose of 450 mg ceritinib on day 8, and rifampin 600 mg once daily, q.d. for 14 days, combined with single dose of 750 mg ceritinib on day 14 [5-6]) were used to verify ceritinib PBPK model.

(C). Model applications: The sponsor conducted simulations to predict the following:

1. 750 mg q.d. ceritinib at steady state (44 days) in the presence of a strong CYP3A4 inhibitor (ketoconazole 200 mg b.i.d. for 22 days starting on day 22, see 3.2 below).
2. 750 mg q.d. ceritinib at steady state (44 days) in the presence of a strong CYP3A4 inducer (rifampin 600 mg q.d. for 22 days starting on day 22).
3. 750 mg q.d. ceritinib at steady state (44 days) in the presence of a moderate CYP3A4 inhibitor (fluconazole 200 mg q.d. for 23 days starting on day 22).
4. 750 mg q.d. ceritinib at steady state in patients with mild, moderate and severe hepatic impairment.
5. Effect of 750 mg ceritinib at steady state on the PK of midazolam after a single oral dose (5 mg) and the effect of a single dose of 750 mg ceritinib on the PK of midazolam after a single oral dose (5 mg) when midazolam is administered with ceritinib.

3.2. FDA's model: update of Sponsor's model using lower CYP3A inactivation potency

The reviewer updated Sponsor's model (**Appendix Table A2**) by including a 3-fold lower maximal inactivation rate constant (k_{inact} = 1.28/hr, FDA's model). The FDA's model was further verified using observed drug-interaction data and was used to predict the scenarios outlined in Section 3.1. In addition, the reviewer used FDA's model to predict the effect of a moderate CYP3A inducer efavirenz on the exposure of ceritinib, and the effect of ketoconazole on steady state ceritinib PK at lower doses (300 mg, 450 mg, or 600 mg q.d. for 44 days, and ketoconazole 200 mg b.i.d. **was given for 23 days** starting on day 22).

3.3. Additional PBPK modeling and simulations

Both Sponsor's and FDA's models assumed first-order absorption for ceritinib (**Appendix Table A2** and sources for input parameters therein). The reviewer expanded FDA's model by using the software's "Advanced Dissolution, Absorption, and Metabolism (ADAM)" model. Input parameters describing various processes responsible for oral absorption are summarized in **Appendix Table A3**. The following scenarios were explored using the updated FDA's model:

1. Sensitivity of ceritinib exposure to changes in effective permeability (Peff)
2. Food effect
3. Sensitivity of ceritinib exposure to changes in gastric pH

4. RESULTS

4.1. Update of Sponsor's model by incorporating a lower CYP3A inactivation potency

Sponsor's model directly incorporated microsomal time-dependent CYP3A inhibition parameters and predicted geometric mean AUC that was 26% higher than the observed value under the multiple dose condition. The direct use of microsomal TDI parameters in PBPK models may result in over-prediction of the inhibition potential in vivo [11]. Crizotinib, another ALK inhibitor, is a substrate and a TDI of CYP3A. Crizotinib demonstrated nonlinear pharmacokinetics in humans. In addition, exposure of CYP3A substrate midazolam was increased in cancer patients taking crizotinib. PBPK model of crizotinib including microsomal CYP3A TDI parameters significantly over-predicted crizotinib exposure at steady state and the magnitude of interaction with midazolam. In comparison, TDI parameters generated in hepatocytes suggested less potent time-dependent CYP3A inhibition by crizotinib, and simulation using PBPK model including hepatocyte TDI parameters reasonably described in vivo data [11].

The reviewers modified Sponsor's ceritinib model by decreasing the potency of CYP3A TDI. Prediction of the geometric mean AUC of ceritinib after both single dose and multiple dose administration appears to be closer using the FDA's model (**Appendix Table A4**).

4.2. PBPK model prediction of ceritinib exposure change when ceritinib is co-administered with CYP3A inhibitors or inducers

a. Simulation of the effect of strong CYP3A inhibitor and inducer – model verification

Both Sponsor's model and FDA's model were verified using clinical drug-drug interaction data when single oral dose ceritinib was co-administered with a strong CYP3A inhibitor ketoconazole, or a strong CYP3A inducer rifampin. As shown in **Table 2**, the predicted geometric mean AUC ratios of ceritinib (AUCR, with/without an interacting drug) by ketoconazole were 2.23 and 2.44 for Sponsor's model and FDA's model, respectively; the observed AUCR was 2.86. The predicted geometric mean AUCR values of ceritinib by rifampin were 0.33 and 0.33 for Sponsor's model and FDA's model, respectively; the observed AUCR was 0.31. Simulation of the effect on ceritinib AUC by ketoconazole appears to be closer to the observed data using FDA's model (see b below).

Table 2. PBPK model simulated and observed exposure changes of ceritinib (AUC and Cmax) after a single oral dose of 450 mg by ketoconazole (200 mg b.i.d.) or after a single oral dose of 750 mg by rifampin (600 mg q.d.). Values are geometric mean. The observed values and predictions using sponsor's model were obtained from [1].

	Observed	***Prediction using Sponsor's model***	***Prediction using FDA's model***
Exposure ratio with/without ketoconazole			
AUC	2.86	2.23	2.44
Cmax	1.22	1.28	1.31
Exposure ratio with/without rifampin			
AUC	0.31	0.33	0.33
Cmax	0.56	0.62	0.61

Geometric mean and 90% confidence interval can be found in Appendix Table A5.

b. Simulation of the effect of CYP3A inhibitor and inducer under situations that have not been tested in clinical studies

Both Sponsor's and FDA's models were used to predict several untested clinical drug-drug interaction scenarios, and the results are shown in **Table 3** and **Table 4**. Overall, sponsor's model considering stronger TDI of CYP3A appears to predict smaller magnitude of interaction by CYP3A inhibitors or inducers. FDA reviewer also conducted simulation to explore the effect of a moderate CYP3A inducer efavirenz (600 mg q.d.) on the exposure of ceritinib.

Table 3. PBPK model simulated steady state exposure changes of ceritinib (AUC and Cmax) after 750 mg q.d. by various CYP3A modulators. Values are geometric mean

	Sponsor's model		***FDA's model***	
Dosing of modulators	***AUC Ratio***	***Cmax Ratio***	***AUC Ratio***	***Cmax Ratio***
Strong CYP3A inhibitor ketoconazole 200 mg b.i.d. [1]	1.35	1.32	1.51	1.47
Moderate CYP3A inhibitor fluconazole 200 mg q.d. [2]	1.15	1.14	1.37	1.32
Strong CYP3A inducer rifampin 600 mg q.d. [1]	0.51	0.54	0.33	0.37
Moderate CYP3A inducer efavirenz[a] 600 mg q.d.	NA	NA	0.57	0.61

[a]FDA in house database. NA: not applicable

Geometric mean and 90% confidence interval can be found in Appendix Table A6.

Besides the evaluation using recommended dose regimen of 750 mg ceritinib q.d. (Table 3), the FDA's model was used to simulate the effect of strong CYP3A inhibitor ketoconazole on steady state ceritinib exposure when the ceritinib was given once daily at lower doses. The results are shown in **Table 4**. It appears that the steady state ceritinib exposure at 450 mg q.d. coadministered with ketoconazole is similar to the exposure at 750 mg q.d. without ketoconazole; and the steady state ceritinib exposure at 300 mg q.d. coadministered with ketoconazole is similar to the exposure at 450 mg or 600 mg q.d. without ketoconazole. These findings suggested that in order to match steady state ceritinib exposure in subjects who have to

take a strong CYP3A inhibitor concomitantly, subjects on 750 mg q.d. ceritinib regimen may have their doses reduced to 450 mg, and subjects on 450 or 600 mg q.d. ceritinib regimen may have their doses reduced to 300 mg.

Table 4. PBPK model simulated steady state ceritinib exposure (AUC and Cmax) when different doses of ceritinib (q.d.) are coadministered ketoconazole (200 mg b.i.d.). Values are geometric mean.

Steady state ceritinib exposure		***Ceritinib dose (once daily)***			
		300 mg	*450 mg*	*600 mg*	*750 mg*
AUC (ng/mL.h)	Without ketoconazole	4777	8115	11936	16140
	With ketoconazole	9817	14969	20181	25433
Cmax (ng/mL)	Without ketoconazole	209	353	518	699
	With ketoconazole	420	640	862	1086

Note in this simulation ketoconazole was given for 23 days starting day 22. Ceritinib was given 44 days (See Methods 3.2).

4.3. PBPK model prediction of the effect of ceritinib on the exposure of CYP3A substrate midazolam

The effect of ceritinib on midazolam exposure was predicted using PBPK models. As shown in **Table 5**, both sponsor's model and FDA's model predicted much greater magnitudes of interaction when ceritinib was administered to steady state as compared to single dose ceritinib. When a single dose ceritinib was co-administered with a single oral dose of midazolam, the AUC increased by approximately 30%; when ceritinib was dosed to steady state, the exposure increases of a single oral midazolam were approximately 12 and 6-fold, using sponsor's model and FDA's model, respectively.

Table 5. PBPK simulations of exposure changes of midazolam after single oral 5 mg dose by ceritinib (after single and multiple dosing of 750 mg). Values are geometric mean.

Midazolam	**Ceritinib Treatment**	**Sponsor's model**		**FDA's model**	
		AUCR	CmaxR	AUCR	CmaxR
Single dose, 5 mg	750 mg single dose	1.45	1.11	1.34	1.10
Single dose, 5 mg	750 mg q.d. to steady state	11.8	2.90	5.84	2.38

Geometric mean and 90% confidence interval can be found in Appendix Table A7.

4.4. Predicting ceritinib PK in subjects with hepatic impairment

Sponsor's model predicted geometric mean exposure ratio (AUC ratio, hepatic impairment versus healthy subjects) of 1.09, 1.14, and 1.16-fold in mild, moderate, and severe hepatic impaired patients, respectively. Sponsor also assumed that the non-CYP3A4 pathway of

ceritinib was minimally affected by hepatic impairment [4].

4.5. Additional simulations to evaluate the effect on oral absorption of ceritinib

Ceritinib is a substrate of P-glycoprotein (P-gp) and the efflux transport of ceritinib in Caco-2 cells appeared to be dependent on ceritinib concentration [12]. Ceritinib has a low solubility. In humans, low fat and high fat meals increased ceritinib Cmax and AUC by 41-41% and 58-71%, respectively. In order to evaluate the effect of various factors on ceritinib absorption, the reviewer expanded FDA's model, which includes TDI of CYP3A, by considering mechanistic oral drug absorption processes (**Appendix Table 3**). The updated FDA's model was used to simulate the pharmacokinetics of ceritinib after single oral dose of 450 mg and 750 mg. Except for an apparent over prediction (33%) of AUC after single dose 450 mg, the updated FDA's model largely described the observed data, with predicted geometric mean AUC and Cmax within 25% deviation from the observed values. Given the limited pharmacokinetic data and a short review timeline, the reviewer did not further optimize the updated FDA's model. The subsequent analyses of the factors affecting oral absorption of ceritinib should be considered exploratory.

a. Sensitivity analysis of apparent permeability (P_{eff})

A 50% increase in P_{eff} (from default value of $2x10^{-4}$ cm/s, **Appendix Table A3**, to $3x10^{-4}$ cm/s) results in 36 and 34% increase in Cmax and AUC of ceritinib, respectively; a 2-fold increase in P_{eff} (to $4x10^{-4}$ cm/s) results in 66 and 61% increase in Cmax and AUC of ceritinib, respectively The parallel increase in both Cmax and AUC seems to be consistent with the effect of increased fraction absorbed (Fa) when apparent P_{eff} is increased. If intestinal efflux transporter (such as P-gp) significantly contributes to the oral absorption of ceritinib, an inhibition of P-gp will result in an increase in apparent P_{eff} for ceritinib, and one would expect a similar magnitude of increase in AUC and Cmax. These simulations appear to support minimal effect of ketoconazole on intestinal efflux transport of ceritinib, because co-administration with ketoconazole resulted in 28% and 2.8-fold increase in the Cmax and AUC of ceritinib, respectively. Together, the observed effect of ketoconazole on ceritinib exposure can be largely explained by CYP3A inhibition.

b. Sensitivity analysis of gastric pH

When the default value of gastric pH of 1.5 (Appendix Table A3) in the updated FDA's model was increased to 7, Cmax and AUC of ceritinib after a single oral dose of 750 mg decreased by 10%, respectively.

c. Food effect

The updated FDA's model was further used to evaluate the effect of food. First, the default "fed" condition was selected to conduct simulation of ceritinib at single oral dose of 500 mg. The geometric mean Cmax and AUC increased by 38 and 34%, respectively. In comparison in healthy subjects taking the same dose, low fat and high fat meal increased ceritinib Cmax by 43 and 41%, respectively; low fat and high fact meals increased ceritinib AUC by 58 and 73%, respectively [7]. Although food effect on Cmax appears to be reasonably predicted using the updated FDA's model of ceritinib, the effect on AUC appears to be under-predicted, which requires further investigation.

The reviewer also explored the effect of food on the exposure of ceritinib after 600 mg q.d. dosing. The results are shown in **Table 6**. At steady-state, food increased ceritinib Cmax and AUC by 68% and 67%, respectively, after multiple dosing of 600 mg (q.d.) ceritinib. The model predicted Cmax and AUC under fed condition appear comparable to the observed ceritinib exposure after 750 mg (q.d.) without food.

Table 6. Model simulated exposure of ceritinib (AUC and Cmax) after multiple oral doses (q.d.) of 600 mg with/without food using updated FDA's model. Observed exposure data after 750 mg q.d. dosing were included for comparison.

Ceritinib dosing	**Observed geometric mean (CV %)**		**FDA's model simulated geometric mean (90% confidence interval)**		**FDA's model simulated geometric mean (90% confidence interval)**	
Dose	**750 mg of q.d. for 8 days without food**		**600 mg of q.d. for 8 days without food**		**600 mg of q.d. for 8 days with food**	
Exposure	**$AUC_{240-264h}$**	**Cmax**	**$AUC_{240-264h}$**	**Cmax**	**$AUC_{240-264h}$**	**Cmax**
Value	13900 (74.8)	674 (76.2)	9918 (8707 - 11296)	460 (408 - 519)	16671 (15121-18381)	766 (698 – 840)
Ratio of predicted geometric mean/Observed geometric mean			0.71	0.68	1.20	1.14

5. CONCLUSION

The PBPK model of ceritinib considering time-dependent CYP3A mechanism reasonably described ceritinib PK after single oral dose and multiple oral doses. The model predicted the observed effect of strong CYP3A inhibitor and inducer. The simulations of PBPK model can be used to support dosing strategy for the combined use of ceritinib with specific CYP3A inhibitors or inducers.

6. APPENDICES

Abbreviations: ADAM: Advanced dissolution, absorption, and metabolism model; ADME, absorption, distribution, metabolism, and excretion; b.i.d., twice daily dosing; B/P, blood to plasma ratio; AUC, area under the concentration-time profile; AUCR, the ratio of the area under the curve of the substrate drug in the presence and absence of the perpetrator; B/P, blood to plasma ratio; ALK: anaplastic lymphoma kinase; Cmax, maximal concentration in plasma; CmaxR, the ratio of the maximum plasma concentration of the substrate drug in the presence or absence of the perpetrator; CL, clearance; Clint, intrinsic clearance; DDI: drug-drug interaction; F, bioavailability; Fa, fraction absorbed; Fg, fraction that escapes intestinal metabolism; fmj fraction of total clearance mediated by j CYP isoform or renal elimination; fp, fraction unbound in plasma; fu,mic, fraction unbound in microsomes; fu,gut, apparent unbound fraction in enterocytes; GI: gastrointestinal; IR, immediate release formulation; ka, first order absorption rate constant; K_i, reversible inhibition constant; K_I, inactivation constant, inhibitor concentration resulting in half maximal inactivation; k_{inact}, maximal inactivation rate constant; LogP, logarithm of the octanol-water partition coefficient; NA, not applicable; ND, not determined; NDA: new drug application; P_{eff}, passive permeability; PBPK: Physiological-based Pharmacokinetic; P-gp: P-glycoprotein; q.d., once daily dosing; Q_{gut}, a hypothetical flow term for the intestine absorption model; TDI, time-dependent enzyme inhibition; Tmax: time at maximal concentration in plasma; T_{LAG}: lag time; V_{ss}, volume of distribution.

Appendix 1. Information Request-Clinical Pharmacology Jan 17, 2014 (01172014IR)

Please submit a study report for your PBPK simulations using SimCYP software to predict the effect of ketoconazole and rifampin on the pharmacokinetics (PK) of ceritinib after multiple dosing [reference studies LDK378A2104 and LDK378A2106] by January 24, 2014.

The study report should include the purpose of the simulations, assumptions being made, detailed process of PBPK model building and verification, a summary of model input parameters of ceritinib, version of SimCYP being used, simulation results, and conclusions. The parameters can be compiled in the table format with parameter name, parameter values (mean and/or variability), source of the parameter values and assumptions being made. In addition, any modification of the default values of the system and/or drug parameter input of a particular version of the software should be declared and justified.

Specifically for ceritinib, we recommend you construct your PBPK model by considering time-dependent inhibition of CYP3A4. The model should be optimized in order to delineate the nonlinear PK observed in ALK-positive cancer patients ([study LDK378X2101], [study LDK378X1101]) and single dose PK in healthy subjects ([Study LDK378A2101], [Study LDK378A2104], [Study LDK378A2105] and [Study LDK378A2106]). Next, the model should be independently verified by comparing simulated effect of enzyme inhibitor or inducer on ceritinib PK with that observed from drug interaction studies (LDK378A2104 and LDK378A2106 for the effect of ketoconazole and rifampin, respectively). In addition, any modification of the model after verification step should be justified. You should use your final ceritinib model to simulate the scenarios described below:

1. 750 mg once daily (QD) ceritinib at steady state in the presence of a strong CYP3A4 inhibitor (ketoconazole 200 mg twice daily, BID).
2. 750 mg QD ceritinib at steady state in the presence of a strong CYP3A4 inducer (rifampin 600 mg QD).

In addition, please use your final ceritinib model to simulate the following scenarios:

3. 750 mg QD ceritinib at steady state in the presence of a moderate CYP3A4 inhibitor (fluconazole 200 mg QD).
4. 750 mg QD ceritinib at steady state in patients with mild, moderate and severe hepatic

impairment.

5. Effect of 750 mg ceritinib at steady state on the PK of midazolam after a single oral dose (5 mg) and the effect of a single dose of 750 mg ceritinib on the PK of midazolam after a single oral dose (5 mg) when midazolam is administered with ceritinib.

Please provide the model files used to generate the final PBPK simulations (e.g. drug model files, population files, and workspace files, .cmp, .lbr, and .wks). These files should be executable by the FDA reviewers using Simcyp. Software specific excel files such as parameter estimation data files and simulation outputs should be submitted as MS Excel files. Study report(s) should be provided as PDF files (screenshots can be incorporated if required).

Appendix Table A1. Physicochemical parameters of ceritinib for PBPK model [1]

Parameter	Value	Comment
MW (g/mole)	(b) (4)	Experimental data
LogP	6.7	log D (Gastro plus estimated)
pKa	3.28; 9.92	Diprotic base (Gastro plus estimated)
B:P concentration ratio	1.35	Experimental data (DMPK R0900777), similar to the observed value from human ADME study (B/P = 1.56)
*f*u in plasma	0.028	Experimental data (DMPK R0900777)

Appendix Table A2. Input parameters of ceritinib for PBPK model (Simcyp software V13, [1])

Parameter	Value	Comment
Absorption		
*f*a	0.314	(Gastro plus estimated); 750 mg dosage (CLDK378X2101)
*k*a (h^{-1})	0.534	Population PK analysis using Nonmem (CLDK378X2101)
Lag time (h)	0.75	Population PK analysis using Nonmem (CLDK378X2101)
Q_{gut} (L/h)	1.78	SimCYP prediction
*f*u, gut	0.054	See Section 2.7.2
Caco-2 permeability, A to B (10^{-6} cm/s)	0.167	Experimental data (DMPK R1000083); Calibration compound: propranolol (13.2), (passive + active, in the absence of P-gp inhibitor)
Effective human permeability (10^{-4} cm/s)	0.228	SimCYP prediction
Distribution		
Sponsor's and FDA's models		**Minimal PBPK model**
Vss (L/kg)	12	Estimated from preclinical PK data via simple allometry scaling method. See Section 3.2
Elimination		
Sponsor's and FDA's models		
CYP3A4 V_{max} for oxygenation metabolites M35.8 and M27.5 (pmol/min/mg protein)	40.6	Experimental data (DMPK R0900839).
Km (unbound) for M35.8 and M27.5 (µM)	0.279	
Renal clearance (L/h)	0.3	Estimation from human ADME study (CLDK378A2105)
Additional systemic clearance (L/h)	11 (50% of total clearance)	See Section 2.7.4
Interaction (CYP3A4)		
Sponsor's model		
Competitive inhibition Ki, unbound (µM)	0.0469	Experimental data (DMPK R0900796)
Mechanism-based inhibition KI, total (µM) k_{inact} (1/h)	1.47 3.84	Experimental data (DMPK R0900796)
FDA's model		
Competitive inhibition Ki, unbound (µM)	0.0469	Experimental data (DMPK R0900796)

Mechanism-based inhibition KI, total (μM) k_{inact} (1/h)	 1.47 1.28	Kinact optimized as 1/3 that of the Sponsor's model according to prediction of single dose 450 mg and 750 mg ceritinib. See Appendix A3 below

Appendix Table A3. Modification of FDA's model of ceritinib by integrating parameters of Advanced Dissolution, Absorption, Metabolism (ADAM) model

Parameter	Value	Comment
*f*u, gut	0.054	See Section 2.7.2
Input form	Solid formulation	Formulation administered in vivo
Formulation	Immediate release (IR)	Formulation administered in vivo
Solubility type	At given pH	
Solubility (mg/mL)	0.06	Gastro Plus estimated value from sponsor [1]
Precipitation rate (1/h)	(b) (4)	Simcyp V13 default value
Maximal super saturation ratio		Simcyp V13 default value
Radius (micro meters)		Estimated from sponsor's data [1]
Dispersion type		Assumed due to a lack of actual data. Sensitivity analysis revealed that simulations are not sensitive to this parameter (data not shown)
Particle density (g/mL)		Simcyp V13 default value
Diffusion coefficient, ionized (10^{-4} cm^2/min)		Simcyp V13 calculated value from molecular weight
Diffusion coefficient, micelle (10^{-4} cm^2/min) mean		Simcyp V13 default value
Diffusion coefficient, micelle CV (%)		Simcyp V13 default value
Diffusion coefficient. (10^{-4} cm^2/min)		Simcyp V13 calculated value from molecular weight
Effective diffusion layer thickness (μm)		Simcyp V13 calculated value from particle size
Effective human permeability (10^{-4} cm/s)		Optimized using sensitivity analysis by comparing the exposure data after single dose of 450 mg and 750 mg ceritinib
Bile Micelle mediated solubilization	Off	Sponsor's solubility value already takes bile salt mediated solubilization into account

Appendix Table A4. PBPK model simulated and observed exposure of ceritinib (AUC and Cmax) after single oral dose or multiple oral doses (q.d.) of 750 mg

Ceritinib dosing	Observed geometric mean[a] (CV %)		Sponsor's model geometric mean (90% confidence interval)		FDA's model geometric mean (90% confidence interval)	
750 mg of single oral dose	**AUC_{0-24h}**	**Cmax**	**AUC_{0-24h}**	**Cmax**	**AUC_{0-24h}**	**Cmax**
	3390 (121)	186 (127)	3781 (3462 - 4130)	195 (178 - 214)	3596 (3345 – 3865)	188 (175 – 203)
Ratio Pred./Obs.[b]			1.1	1.1	1.1	1.0
750 mg of q.d. for 8 days	**$AUC_{240-264h}$**	**Cmax**	**$AUC_{240-264h}$**	**Cmax**	**$AUC_{240-264h}$**	**Cmax**
	13900 (74.8)	674 (76.2)	17473 (15940 -19154)	803 (735 - 878)	13594 (12500-14784)	642 (594 – 695)
Ratio Pred./Obs.[b]			1.3	1.2	1.0	1.0

[a] Clinical observed values (CLDK378X2101-Table 11-27); [b] Ratio of geometric means

Appendix Table A5. PBPK model simulated and observed exposure changes of ceritinib (AUC and Cmax) after single oral dose of 450 mg by ketoconazole (200 mg b.i.d.) or after single oral dose of 750 mg by rifampin (600 mg q.d.). Values are geometric mean (90% confidence interval). The observed values and predictions using sponsor's model were obtained from [1].

	Observed	***Prediction using Sponsor's model***	***Prediction using FDA's model***
Exposure ratio with/without ketoconazole			
AUC	*2.86 (2.45 - 3.34)*	*2.23 (2.10 - 2.37)*	*2.44 (2.32 - 2.57)*
Cmax	*1.22 (1.07 - 1.39)*	*1.28 (1.26 - 1.30)*	*1.31 (1.29 – 1.33)*
Exposure ratio with/without rifampin			
AUC	0.31 (0.24 - 0.40)	0.33 (0.31 - 0.36)	0.33 (0.31 - 0.36)
Cmax	0.56 (0.41 - 0.76)	0.62 (0.59 - 0.66)	0.61 (0.58 – 0.63)

Appendix Table A6. PBPK model simulated exposure changes of ceritinib (AUC and Cmax) after 750 mg q.d. at steady state by various CYP3A modulators. Values are geometric mean (90% confidence interval)

	Sponsor's model		***FDA's model***	
Dosing of modulators	***AUC Ratio***	***Cmax Ratio***	***AUC Ratio***	***Cmax Ratio***
Strong CYP3A inhibitor ketoconazole 200 mg b.i.d. [1]	*1.35 (1.27,1.42)*	*1.32 (1.26,1.39)*	1.51 (1.43, 1.59)	1.47 (1.40, 1.54)
Moderate CYP3A inhibitor fluconazole 200 mg q.d. [2]	*1.15 (1.12,1.19)*	*1.14 (1.11,1.17)*	1.37 (1.31, 1.42)	1.32 (1.28, 1.37)
Strong CYP3A inducer rifampin 600 mg q.d. [1]	*0.51 (0.45,0.57)*	*0.54 (0.49, 0.60)*	0.33 (0.30, 0.36)	0.37 (0.34, 0.40)
Moderate CYP3A inducer efavirenz[a] 600 mg q.d.	*NA*	*NA*	0.57 (0.52, 0.62)	0.61 (0.56, 0.65)

[a]*FDA in house database.*

Appendix Table A7. PBPK simulations of exposure changes of midazolam after single oral 5 mg dose by ceritinib (after single and multiple dosing of 750 mg). Values are geometric mean (90% confidence interval)

Midazolam	**Ceritinib Treatment**	**Sponsor's model**		**FDA's model**	
		AUCR	CmaxR	AUCR	CmaxR
Single dose, 5 mg	750 mg single dose	1.45 (1.39, 1.51)	1.11 (1.08, 1.13)	1.34 (1.30, 1.37)	1.10 (1.08, 1.12)
Single dose, 5 mg	750 mg q.d. to steady state	11.8 (9.83, 14.2)	2.90 (2.70, 3.11)	5.84 (5.12, 6.66)	2.38 (2.25, 2.51)

7. REFERENCES

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2. NOVARTIS. Drug Metabolism and Pharmacokinetics Study 1400045a: Simulations of the clinical drug interaction potential of fluconazole with LDK378 using the latest version 13 of Simcyp® simulator, 23-Jan-2014.
3. NOVARTIS. Drug Metabolism and Pharmacokinetics Study 1400045b: Simulations of the clinical drug interaction potential of LDK378 with midazolam using the latest version 13 of Simcyp® simulator, 23-Jan-2014.
4. NOVARTIS. Drug Metabolism and Pharmacokinetics Study 1400045c: Simulations of LDK378 in patients with mild, moderate and severe hepatic impairment using the latest version 13 of Simcyp® simulator, 23-Jan-2014.
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/s/

RUBY LEONG
03/25/2014

PENGFEI SONG
03/25/2014

QI LIU
03/25/2014

YUZHUO PAN
03/25/2014

PING ZHAO
03/25/2014

HONG ZHAO
03/25/2014
I concur.

NAM ATIQUR RAHMAN
03/25/2014
I concur.

ONDQA Biopharmaceutics Filing Review

Submission Information

NDA Number	205-755 (4-month Priority Review)
Product name, generic name of the active, and dosage form and strength	Ceritinib Capsules, 150 mg (Immediate-Release)
Submission date	12/2/2013
Applicant	Novartis Pharmaceuticals Corporation
Medical Division	DOP2
Indication	The treatment of patients with [redacted] (b) (4) metastatic non-small cell lung cancer (NSCLC) who have [redacted] (b) (4)
Type of Submission	505(b)(1)
Biopharmaceutics Reviewer	Okpo Eradiri, Ph.D.
Biopharmaceutics Team Leader	Angelica Dorantes, Ph.D.

Biopharmaceutics Assessment

Biopharmaceutics Critical Issues or Complexities

Background: This is a rolling NDA submission; as at December 24, 2013, the Applicant has submitted all technical sections. The drug molecule, an NME, was granted an Orphan designation and the NDA was also granted Priority Review as well as a Breakthrough Therapy designation.

Ceritinib (also referred to as LDK378 by the Applicant) is an ATP-competitive inhibitor of anaplastic lymphoma kinase (ALK) activity. The drug product has been formulated as a single-entity immediate-release 150 mg capsule (hard gelatin capsule, size 00) for oral use. Ceritinib is said to inhibit *in-vitro* and *in-vivo* autophosphorylation of ALK, ALK-mediated phosphorylation of downstream signaling proteins, and proliferation of ALK-dependent cancer cells. The drug substance is achiral.

Submission: The definitive clinical study in the NDA is a Phase 1 open-label, dose-escalation study that investigated the safety, PK, PD and anti-tumor activity of the drug in patients with tumors confirmed to have genetic abnormalities in ALK. The Application also contains a dose-escalation phase of a study in Japanese patients with tumors characterized by genetic alterations in ALK.

The Applicant's proposed dissolution method testing conditions can be summarized as follows:

Apparatus:	*USP 2 (Paddle)*
Medium:	*0.01M HCl (900 mL)*
Rotation speed:	*60 ± 2 rpm*
Sampling Time:	(b) (4) *min*
Analysis:	(b) (4)

Proposed Acceptance Criterion: Q = (b) (4) *% at* (b) (4) *min.*

Review: The NDA contains sufficient biopharmaceutics data/information for review. The Biopharmaceutics review will be focused on the evaluation and acceptability of the following:

- Adequacy of the dissolution method;
- Adequacy of the proposed dissolution acceptance criterion;

Recommendation: This NDA is fileable from the Biopharmaceutics perspective.

Links:

Pharmaceutical Development: \\cdsesub1\evsprod\nda205755\0002\m3\32-body-data\32p-drug-prod\ldk378-hard-gelatin-capsule-01\32p2-pharm-dev\pharmaceutical-development.pdf

Specifications Table: \\cdsesub1\evsprod\nda205755\0002\m3\32-body-data\32p-drug-prod\ldk378-hard-gelatin-capsule-01\32p5-contr-drug-prod\32p52-analyt-proc\specifications-tm-150mg.pdf

Dissolution Method Development: See "Pharmaceutical Development" report.

Biopharmaceutics Filing Conclusions and Recommendations

Is the Product Quality Section of the application fileable from a Biopharmaceutics perspective?
Yes
Biopharmaceutics Filing Issues:
None

Are there potential Biopharmaceutics review issues to be forwarded to the Applicant with the 60-Day-Day letter?
Yes
Biopharmaceutics Comments for 60-Day Letter:

1. The clinical batches of your proposed drug product were manufactured at two manufacturing sites in Switzerland and the United States. Submit to the NDA, comparative dissolution data of representative batches from the two sites demonstrating similarity in dissolution profiles between the two manufacturing sites.
2. The dissolution data from stability samples are reported for only the proposed specification time point of (b) (4) min. Please submit the complete dissolution profile data for the clinical and registration batches, i.e., report the data at all sampling time points. In the event that only the (b) (4) min time point results were recorded, please collect and provide the complete dissolution profile data (n=12) for the clinical and registration batches at the current stability time point and thereafter (submit the data as soon as they become available).
3. We note the investigative experiments that were conducted to select the dissolution equipment, medium, as well as paddle speed (b) (4) well as modifications of the dissolution medium to obtain a profile more representative of the drug product's expected in-vivo release rate.

Biopharmaceutics Filing Review Checklist

The following parameters are usually necessary to initiate a full Biopharmaceutics review (i.e., the NDA is complete enough to review but may have deficiencies). On **initial** overview of the NDA application for filing:

A. BIOPHARMACEUTICS				
	Parameter	**Yes**	**No**	**Comment**
1.	Does the application contain dissolution data?	X		Proposed dissolution method for routine QC release testing: USP 2, 60 rpm, 900 mL of 0.01M HCl, pH (b) (4) Section 3.2.P.2.
2.	Is the dissolution test part of the DP specifications?	X		Q = (b) (4) % at (b) (4) min
3.	Does the application contain the dissolution method development report?	X		Elements of dissolution method development are incorporated in the Pharmaceutical development report (section 3.2.P.2, page 20).
4.	Is there a validation package for the analytical method and dissolution methodology?	X		Section 3.2.P.5.3.
5.	Does the application include a biowaiver request?		X	
6.	Are there adequate data supporting the waiver?			N/A
7.	Does the application include an IVIVC model?		X	
8.	Is information such as BCS classification mentioned, and supportive data provided?	X		Applicant ascribes BCS Class 4 to ceritinib.
9.	Is information on mixing the product with foods or liquids included?		X	
10.	Is there any in *vivo* BA or BE information in the submission?	X		PK data were generated in the definitive Phase 1 study. These PK data will be reviewed by the Clinical Pharmacology Reviewer at OCP.
FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
11.	**ARE THE PRODUCT QUALITY AND BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?**	X		

A. BIOPHARMACEUTICS				
	Parameter	**Yes**	**No**	**Comment**
12.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			N/A
13.	Are there potential Biopharmaceutics review issues to be forwarded to the Applicant with the 60-Day or 74-Day letter?	X		Refer to page 3 of this filing review for the Biopharmaceutics comments to be conveyed to the Applicant in the 60-Day letter.

Okpo Eradiri, Ph. D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

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/s/

OKPONANABOFA ERADIRI
01/24/2014

ANGELICA DORANTES
01/24/2014

CLINICAL PHARMACOLOGY
FILING FORM/CHECKLIST FOR NDA 205755

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	205755	**Brand Name**	To be determined
OCP Division (I, II, III, IV, V)	V	**Generic Name**	Ceritinib
Medical Division	Division of Oncology Products 2	**Drug Class**	Small molecule; Kinase inhibitor
OCP Reviewers	Ruby Leong, Pharm.D. (CP) Pengfei Song, Ph.D. (PM) Yuzhuo Pan, Ph.D. (PBPK)	**Indication(s)**	(b) (4) metastatic non-small cell lung cancer (NSCLC) who have (b) (4)
OCP Team Leaders/Secondary Reviewers	Hong Zhao, Ph.D. (CP) Qi Liu, Ph.D. (PM) Ping Zhao, Ph.D. (PBPK)	**Dosage Form**	150 mg capsule
		Dosing Regimen	750 mg once daily
		Route of Administration	Oral
		Sponsor	Novartis Pharmaceuticals Corporation
Date of Submission	Rolling submission: · Part1 - 11/27/2013 · Part 2 - 12/12/2013 · Part 3 - 12/24/2013		
Estimated Due Date of OCP Review	3/25/2014		
Medical Division (CDTL) Due Date	4/10/2014	**Priority Classification**	Priority, Expedited
PDUFA Due Date **Target Action Date**	8/24/2014 4/17/2014	**eCTD link**	\\CDSESUB1\evsprod\NDA205755\0002

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			Module 5.2
HPK Summary	X			Module 2.7.2
Labeling	X			Module 1.14
Reference Bioanalytical and Analytical Methods	X	2		Report No. R1100240, R1100240-01
I. Clinical Pharmacology				
Mass balance:	X	2		Study CLDK378A2105, Report No. R0900773a
Isozyme characterization:	X	1		Report No. R0900839
Blood/plasma ratio:	X	1		Report No. R0900777
Plasma protein binding:	X			Report No. R0900777
Pharmacokinetics -				
Healthy Volunteers-				

single dose:	X	3		Study CLDK378A2101, CLDK378A2104, CLDK378A2106
multiple dose:				
Patients-				
single dose:				
multiple dose:	X	2		Study CLDK378X2101, CLDK378X1101
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:	X			Study CLDK378X2101
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X			CLDK378A2104, CLDK378A2106
In-vivo effects of primary drug:				
In-vitro:	X	9		Report No. R0900839 / CYP Substrate, R1000083 / BCRP·MRP2·P-gp Substrate, R1000482 / Transporter Substrate Report No. R0900796 / CYP Inhibition, R0900229 / BCRP·MRP2·P-gp Inhibition, R1200913 / OAT Inhibition, R1300023 / OCT Inhibition, R1300170 / OATP Inhibition Report No. R1200856, R0700559 / CYP Induction
Subpopulation studies -				
ethnicity:	X			PopPK
gender:	X			PopPK
pediatrics:				Granted orphan drug designation
geriatrics:	X			PopPK
renal impairment:	X			PopPK
hepatic impairment:	X			PopPK
PD - QT Study:	X			C-QT analysis using QT data from Study CLDK378X2101
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:	X			Study CLDK378X2101
Phase 3 clinical trial:				
Population Analyses -		1		Modeling Report
Data rich:	X			
Data sparse:	X			
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies	X			Study CLDK378A2101
Bio-waiver request based on BCS				
BCS class	X			
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				

Chronopharmacokinetics				
Pediatric development plan				Granted orphan drug designation
Literature References	X			
Total Number of Studies		21		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	No major differences between clinical trial formulation and to-be-marketed formulation
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?		X		ADME data from Study CLDK378A2105 are provided for the labeling
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response	X			

	guidance?				
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	Granted orphan drug designation
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	Granted orphan drug designation
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

Yes, the application is fileable from a clinical pharmacology perspective.

Please identify and list any potential review issues to be forwarded to the Applicant for the 60-day letter.

In the briefing package for the pre-NDA meeting held on November 22, 2013, you agreed to provide the major milestones (e.g., study completion date, submission of final study report) for completion of the hepatic impairment study (CLDK378A2110) in the NDA, but this information is not found in your NDA. Please propose PMR language and provide milestone timelines for completion of the hepatic impairment study.

The following information request was sent to the Applicant on 1/17/2014:

> Please submit a study report for your PBPK simulations using SimCYP software to predict the effect of ketoconazole and rifampin on the pharmacokinetics (PK) of ceritinib after multiple dosing [reference studies LDK378A2104 and LDK378A2106].
>
> The study report should include the purpose of the simulations, assumptions being made, detailed process of PBPK model building and verification, a summary of model input parameters of ceritinib, version of SimCYP being used, simulation results, and conclusions. The parameters can be compiled in the table format with parameter name, parameter values (mean and/or variability), source of the parameter values and assumptions being made. In addition, any modification of the default values of the system and/or drug parameter input of a particular version of the software should be declared and justified.

Specifically for ceritinib, we recommend you construct your PBPK model by considering time-dependent inhibition of CYP3A4. The model should be optimized in order to delineate the nonlinear PK observed in ALK-positive cancer patients ([Study LDK378X2101], [Study LDK378X1101]) and single dose PK in healthy subjects ([Study LDK378A2101], [Study LDK378A2104], [Study LDK378A2105] and [Study LDK378A2106]). Next, the model should be independently verified by comparing simulated effect of enzyme inhibitor or inducer on ceritinib PK with that observed from drug interaction studies (LDK378A2104 and LDK378A2106 for the effect of ketoconazole and rifampin, respectively). In addition, any modification of the model after verification step should be justified. You should use your final ceritinib model to simulate the scenarios described below:

a. 750 mg once daily (QD) ceritinib at steady state in the presence of a strong CYP3A4 inhibitor (ketoconazole 200 mg twice daily, BID).

b. 750 mg QD ceritinib at steady state in the presence of a strong CYP3A4 inducer (rifampin 600 mg QD).

In addition, please use your final ceritinib model to simulate the following scenarios:

c. 750 mg QD ceritinib at steady state in the presence of a moderate CYP3A4 inhibitor (fluconazole 200 mg QD).

d. 750 mg QD ceritinib at steady state in patients with mild, moderate and severe hepatic impairment.

e. Effect of 750 mg ceritinib at steady state on the PK of midazolam after a single oral dose (5 mg) and the effect of a single dose of 750 mg ceritinib on the PK of midazolam after a single oral dose (5 mg) when midazolam is administered with ceritinib.

Please provide the model files used to generate the final PBPK simulations (e.g., drug model files, population files, and workspace files, .cmp, .lbr, and .wks). These files should be executable by the FDA reviewers using Simcyp. Software specific excel files such as parameter estimation data files and simulation outputs should be submitted as MS Excel files. Study report(s) should be provided as PDF files (screenshots can be incorporated if required).

Ruby Leong, Pharm.D.	1-21-2014
Clinical Pharmacology Reviewer	**Date**
Hong Zhao, Ph.D.	1-21-2014
Clinical Pharmacology Team Leader	**Date**

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

/s/

RUBY LEONG
01/21/2014

HONG ZHAO
01/21/2014
I concur.