Report on the Deliberation Results

March 3, 2016
Evaluation and Licensing Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

[Brand name]	Zykadia Capsules 150 mg
[Non-proprietary name]	Ceritinib (JAN*)
[Applicant]	Novartis Pharma K.K.
[Date of application]	June 24, 2015

[Results of deliberation]
In the meeting held on February 26, 2016, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period is 10 years. The drug substance and the drug product are both classified as a powerful drug. The drug product is not classified as a biological product or a specified biological product.

[Conditions for approval]
1. The applicant is required to develop and appropriately implement a risk management plan.
2. The applicant is required to conduct a drug use-results survey covering all patients treated with the product during the early post-marketing phase in order to grasp the characteristics of such patients until data have been accumulated from a specific number of patients, because only a limited number of patients participated in the Japanese clinical studies. At the same time, the applicant should collect data on the safety and efficacy of the product without delay and take necessary measures to ensure the proper use of the product.
3. The applicant is required to take necessary measures to ensure that the product is used only under the supervision of a physician experienced in the diagnosis of lung cancer and chemotherapy in a medical institution capable of managing the risks associated with treatment, and by a supervising pharmacist with knowledge about the use of the product.

**Japanese Accepted Name (modified INN)*

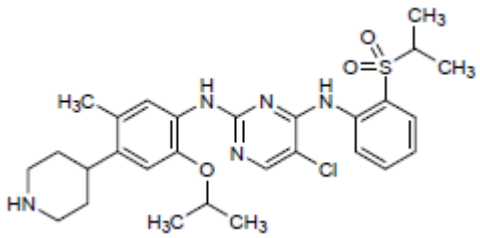
Review Report

February 16, 2016
Pharmaceuticals and Medical Devices Agency

The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following pharmaceutical product submitted for registration are as follows.

[Brand name]	Zykadia Capsules 150 mg
[Non-proprietary name]	Ceritinib
[Applicant]	Novartis Pharma K.K.
[Date of application]	June 24, 2015
[Dosage form/Strength]	Each capsule contains 150 mg of Ceritinib.
[Application classification]	Prescription drugs, (1) Drugs with a new active ingredient

[Chemical structure]



Molecular formula: $C_{28}H_{36}ClN_5O_3S$

Molecular weight: 558.14

Chemical name: 5-Chloro-N^2-{5-methyl-4-(piperidin-4-yl)-2-[(propan-2-yl)oxy]phenyl}-N^4-[2-(propan-2-ylsulfonyl)phenyl]pyrimidine-2,4-diamine

[Items warranting special mention]

Orphan drug (Drug Designation No. 362 of 2015 [*27 yaku*], Notification No. 0615-1 issued by the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW, dated June 15, 2015)

[Reviewing office] Office of New Drug V

Review Results

February 16, 2016

[Brand name]	Zykadia Capsules 150 mg
[Non-proprietary name]	Ceritinib
[Applicant]	Novartis Pharma K.K.
[Date of application]	June 24, 2015

[Results of review]
Based on the submitted data, the Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the product shows a certain level of efficacy in the treatment of patients with anaplastic lymphoma kinase (*ALK*)-positive, unresectable, advanced or recurrent non-small cell lung cancer resistant or intolerant to crizotinib, and that the safety of the product is acceptable in view of its observed benefits. The occurrence of interstitial lung disease, hepatic function disorder, QT interval prolonged, nausea/vomiting/diarrhoea, hyperglycaemia or diabetes mellitus, bradycardia, pericarditis, infections, and pancreatitis need to be further investigated via post-marketing surveillance.

As a result of its regulatory review, PMDA has concluded that the product may be approved for the indication and the dosage and administration as shown below, with the following conditions.

[Indication] *ALK*-positive, unresectable, advanced or recurrent non-small cell lung cancer resistant or intolerant to crizotinib

[Dosage and administration] The usual adult dosage is 750 mg of ceritinib administered orally once daily in the fasted state. The dose may be reduced according to the patient's condition.

[Conditions for approval]

1. The applicant is required to develop and appropriately implement a risk management plan.
2. The applicant is required to conduct a drug use-results survey covering all patients treated with the product during the early post-marketing phase in order to grasp the characteristics of such patients until data have been accumulated from a specific number of patients, because only a limited number of patients participated in the Japanese clinical studies. At the same time, The applicant should collect data on the safety and efficacy of the product without delay and take necessary measures to ensure the proper use of the product.
3. The applicant is required to take necessary measures to ensure that the product is used only under the supervision of a physician experienced in the diagnosis of lung cancer and chemotherapy in a medical institution capable of managing the risks associated with treatment, and by a supervising pharmacist with knowledge about the use of the product.

Review Report (1)

January 15, 2016

I. Product Submitted for Registration

[Brand name]	Zykadia Capsules 150 mg
[Non-proprietary name]	Ceritinib
[Name of applicant]	Novartis Pharma K.K.
[Date of application]	June 24, 2015
[Dosage form/Strength]	Each capsule contains 150 mg of Ceritinib.
[Proposed indication]	Anaplastic lymphoma kinase (ALK)-positive, unresectable, advanced or recurrent non-small cell lung cancer resistant or intolerant to other ALK inhibitors
[Proposed dosage and administration]	The usual adult dosage is 750 mg of ceritinib administered orally once daily in the fasted state. The dose may be reduced according to the patient's condition.

II. Summary of the Submitted Data and the Outline of Review by the Pharmaceuticals and Medical Devices Agency

The submitted data and the review thereof by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below.

1. Origin or history of discovery, use in foreign countries, and other information

1.(1) Drug overview

The literature has reported that anaplastic lymphoma kinase (ALK) gene rearrangement in non-small cell lung cancer (NSCLC) generates ALK fusion proteins such as an echinoderm microtubule-associated protein-like 4 (EML4)-ALK fusion gene (EML4-ALK), which contributes to the growth and survival of tumor cells as well as tumorigenesis in normal cells (*Nature.* 2007;448:561-6, and others). *ALK*-positive NSCLC patients account for 2% to 5% of all patients with NSCLC (Guidance for ALK Gene Testing in Lung Cancer Patients. Version 1.2, edited by the Biomarker Committee of the Japan Lung Cancer Society).

Ceritinib is a tyrosine kinase inhibitor developed by Novartis International AG (Switzerland) and is thought to suppress tumor growth by inhibiting the phosphorylation of ALK.

In Japan, crizotinib and alectinib hydrochloride, both of which are drugs that inhibit the phosphorylation of ALK similarly to ceritinib, have been approved for the treatment of *ALK*-positive, unresectable, advanced or recurrent NSCLC.

1.(2) Development history etc.

Outside Japan, a foreign phase I study in patients with *ALK*-positive advanced malignant tumor (Study X2101) was initiated by Novartis International AG (Switzerland) in January 2011. A global phase II study in patients with *ALK*-positive advanced or recurrent NSCLC previously treated with platinum-based chemotherapy and crizotinib (Study A2201) was initiated in November 2012, and a global phase II study in patients with *ALK*-positive advanced or recurrent NSCLC who were treatment-naïve or had received ≤3 chemotherapy regimens (except for crizotinib) (Study A2203) in December 2012.

In the US, a new drug application for ceritinib was submitted in December 2013 on the basis of the results of Study X2101 as a pivotal study. In April 2014, ceritinib (Zykadia) was approved under the expedited review procedure for the following indication: "Zykadia is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib." In the EU, a marketing authorization application was submitted in March 2014 on the basis of the results of Study X2101 as a pivotal study,

on condition that the results of Studies A2201 and A2203 would be submitted during the review. In May 2015, ceritinib was approved for the following indication: "Zykadia is indicated for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously treated with crizotinib."

As of November 2015, Zykadia is approved in 45 countries and regions.

In Japan, the applicant initiated a Japanese phase I study in patients with *ALK*-positive advanced malignant tumor (Study X1101) in June 2012. Patient enrollment in Studies A2201 and A2203 was started in [redacted] 20[redacted].

The new drug application for ceritinib was submitted on the basis of the results of Studies A2201 and X2101 as pivotal studies.

Ceritinib was designated as an orphan drug in June 2015 with the intended indication of "*ALK*-positive, unresectable, advanced or recurrent NSCLC resistant or intolerant to crizotinib" (Drug Designation No. 362 of 2015 [*27 yaku*]).

2. Data relating to quality

2.A Summary of the submitted data

2.A.(1) Drug substance

2.A.(1).1) Characterization

The drug substance is a white to light yellow or light brown powder, and its description, solubility, pH, melting point, dissociation constant, partition coefficient, and hygroscopicity have been determined. The drug substance exists in 3 crystalline forms (Forms A, B, and C). [redacted] Form A is produced by the commercial manufacturing process, and stability studies have demonstrated that the generated Form A remains unchanged.

The chemical structure of the drug substance has been elucidated by elementary analysis, ultraviolet-visible spectroscopy (UV/VIS), infrared spectrophotometry (IR), nuclear magnetic resonance spectrometry (^{1}H-NMR and ^{13}C-NMR), mass spectrometry, X-ray powder diffraction, and single crystal X-ray crystallography.

2.A.(1).2) Manufacturing process

The drug substance is synthesized using C1-1,[*1] C1-2,[*2] C3-2,[*3] and C3-3[*4] as starting materials. [redacted] of C1[*5] as well as [redacted] and [redacted] are identified as critical steps. Process control parameters and process control values are specified for [redacted] of C3-3, [redacted] of C3-1,[*6] [redacted] of C1-1 and C1-2, [redacted] of C1, [redacted] of C3,[*7] and [redacted].

*1 [redacted]
*2 [redacted]
*3 [redacted]
*4 [redacted]
*5 [redacted]
*6 [redacted]
*7 [redacted]

2.A.(1).3) Control of drug substance

The proposed specifications for the drug substance consist of strength, description, identification (IR and X-ray powder diffraction), purity (heavy metals [inductively coupled plasma-atomic emission spectroscopy], related substances [high performance liquid chromatography (HPLC)], and residual solvents [gas chromatography]), loss on drying, residue on ignition, microbial limits, [redacted] ([redacted]), and assay (HPLC).

2.A.(1).4) Stability of drug substance

The stability studies of the drug substance are shown in the table below. In addition, a photostability study has shown that the drug substance is photostable.

Stability studies of the drug substance

Study	Batches used in the study	Temperature	Humidity	Storage form	Storage period
Long-term testing	[redacted] / 3 pilot scale batches	25°C	60%RH	Polyethylene bag + aluminum foil laminated bag	24 months
	[redacted] / 3 pilot scale batches				18 months
Accelerated testing	[redacted] / 3 pilot scale batches	40°C	75%RH	Polyethylene bag + aluminum foil laminated bag	6 months
	[redacted] / 3 pilot scale batches				

* The drug substance batches manufactured by [redacted] and [redacted] were confirmed to be [redacted] by batch analysis data and obtained stability study data.

Based on the above, the retest period of [redacted] months has been proposed for the drug substance when stored in a polyethylene bag inside an aluminum foil laminated bag (light-protected condition) at room temperature. The long-term testing will be continued for up to [redacted] months.

2.A.(2) Drug product

2.A.(2).1) Description, composition, and formulation development of the drug product

The drug product is an immediate-release hard capsule containing 150 mg of the drug substance. Excipients contained in the drug product are [redacted], [redacted], sodium starch glycolate, magnesium stearate, and light anhydrous silicic acid.

2.A.(2).2) Manufacturing process

The drug product is manufactured by the process consisting of the following steps: mixing, sieving, mixing, [redacted], mixing, [redacted], primary packaging, and final packaging.

The critical steps is [redacted], for which process control parameters and process control values are specified.

2.A.(2).3) Control of drug product

The proposed specifications for the drug product consist of strength, description, identification (UV/VIS), purity (related substances [HPLC]), uniformity of dosage units (mass variation test), dissolution (ultraviolet-visible spectrophotometry), and assay (HPLC).

2.A.(2).4) Stability of drug product

The stability studies of the drug product are shown in the table below. In addition, a photostability study has demonstrated that the drug product is photostable.

Stability studies of the drug product

Study	Batches used in the study	Temperature	Humidity	Storage form	Storage period
Long-term testing	3 commercial scale batches	25°C	60%RH	Blister pack	12 months
Accelerated testing	3 commercial scale batches	40°C	75%RH		6 months

Based on the above results, a shelf life of 24 months has been proposed for the drug product when packaged in a blister pack (made of polychlorotrifluoroethylene, polyvinyl chloride film, and aluminum foil) and stored at room temperature, in accordance with the "Guideline for the Evaluation of Stability Data" (PFSB/ELD Notification No. 0603004 dated June 3, 2003). The long-term testing will be continued for up to [redacted] months.

2.B Outline of the review conducted by PMDA

Based on the submitted data, PMDA concluded that the quality of the drug substance and drug product is adequately controlled.

3. Non-clinical data

3.(i) Summary of pharmacology studies

3.(i).A Summary of the submitted data

3.(i).A.(1) Primary pharmacodynamics

3.(i).A.(1).1) Inhibitory activity against phosphorylation of various kinases (Report Nos. RD-2010-00649 and RD-2010-00651)

Inhibitory effects of ceritinib and crizotinib on phosphorylation of 36 kinases (recombinant proteins) including anaplastic lymphoma kinase (ALK) were investigated by assessing phosphorylation of the corresponding substrate. The IC_{50} values of ceritinib or crizotinib against the kinases (for those with IC_{50} <100 nmol/L).

Inhibitory effects of ceritinib and crizotinib on phosphorylation of various kinases

Kinase	IC_{50} (nmol/L)	
	Ceritinib	Crizotinib
ALK	0.14, 0.15*	3 ± 1.7
INSR	7 ± 1.3	290 ± 71
IGF-1R	8 ± 3.5	400 ± 240
AURORA-A	110 ± 15	60 ± 52
cABL-T315I	130 ± 12	6 ± 2.1
AXL	180 ± 26	13 ± 7.8
JAK2	600 ± 170	60 ± 31
LCK	600 ± 180	80 ± 40
MET	3200 ± 640	8 ± 3.6

Mean ± standard deviation (SD), n = 3

* All samples were tested 3 times. One IC_{50} value against ALK was below the lower limit of quantitation (0.128 nmol/L), and thus the remaining 2 values are shown.

3.(i).A.(1).2) Anti-proliferative activity against cells transduced with *ALK* fusion gene (Report Nos. RD-2009-50672 and RD-2013-50375)

A mouse pro-B cell-derived cell line (Ba/F3) was transduced with *ALK* fusion gene (echinoderm microtubule-associated protein-like 4 [EML4]-*ALK* or nucleophosmin [NPM]-*ALK*) and luciferase gene to generate Ba/F3 cells that proliferate in an ALK-dependent manner. The anti-proliferative activity of ceritinib was investigated using luciferase activity assay. The IC_{50} values (mean ± standard deviation [SD]) of ceritinib against *EML4-ALK* gene- and *NPM-ALK* gene-transduced Ba/F3 cells were 27 ± 9 and 35 ± 15 nmol/L, respectively. In addition, Ba/F3 cells were transduced with *EML4-ALK* gene which harbored no secondary mutations rendering the cells resistant to existing ALK inhibitors ("resistant mutation") or *EML4-ALK* gene which harbored crizotinib-resistant mutation* (C1156Y, I1171T, L1196M, or G1202R) to investigate the anti-proliferative effects of ceritinib and crizotinib on Ba/F3 cells expressing these genes. The IC_{50} values are shown in the table below.

* The following resistant mutations in ALK gene are known: C1156Y mutation involving substitution of cysteine (C) by tyrosine (Y) at position 1156, I1171T mutation involving substitution of isoleucine (I) by threonine (T) at position 1171, L1196M mutation involving substitution of leucine (L) by methionine (M) at position 1196, and G1202R mutation involving substitution of glycine (G) by arginine (R) at position 1202 (*New Engl J Med.* 2010;363:1734-9, and others).

Anti-proliferative effects of ceritinib and crizotinib on *EML4-ALK* gene-transduced Ba/F3 cells

Resistant mutation	IC_{50} (nmol/L)	
	Ceritinib	Crizotinib
None	31 ± 2	160 ± 20
C1156Y	160 ± 10	440 ± 80
I1171T	38 ± 1	340 ± 80
L1196M	69 ± 7	1460 ± 230
G1202R	940 ± 270	1370 ± 100

Mean ± SD, n = 4

3.(i).A.(1).3) Anti-proliferative activity against cells transduced with various kinase fusion genes (Report Nos. RD-2009-50670 and RD-2009-50673)

Ba/F3 cells transduced with fusion gene consisting of *Translocation Ets Leukemia* gene and an enzyme domain gene of 39 kinases and Ba/F3 cells transduced with luciferase gene were used in a study. The anti-proliferative effect of ceritinib on Ba/F3 cells expressing various kinase fusion genes was investigated using luciferase activity assay. The table below shows the IC_{50} values of ceritinib against Ba/F3 cells expressing various kinase fusion genes (for kinases with IC_{50} <1 μmol/L).

Anti-proliferative effect of ceritinib on Ba/F3 cells expressing various kinase fusion genes

Kinase	IC_{50} (μmol/L)
ALK	0.055, 0.058
ROS1	0.170, 0.182
IGF-1R	0.205, 0.243
INSR	0.378, 0.419

Individual value

3.(i).A.(1).4) Effect on ALK signal transduction pathway

i) *In vitro* (Report No. RD-2008-50914, *Cancer Discov*. 2014;4:662-73 [Reference data])

The inhibitory effect of ceritinib on phosphorylation of ALK and the signal transducer and activator of transcription (STAT) 3, a downstream signaling molecule of ALK, was investigated in a human anaplastic large cell lymphoma-derived Karpas 299 cells expressing NPM-ALK by Western blotting. Ceritinib inhibited phosphorylation of ALK and STAT3 in a concentration-dependent manner.

The inhibitory effect of ceritinib on phosphorylation of ALK and its downstream signaling molecules (AKT, extracellular signal-regulated kinase [ERK], and S6) was investigated using NSCLC cell line (NCI-H2228) expressing EML4-ALK by Western blotting. Ceritinib inhibited phosphorylation of ALK, AKT, ERK, and S6 in a concentration-dependent manner.

ii) *In vivo* (Report No. RD-2008-50976)

Karpas 299 cells were implanted intravenously into severe combined immunodeficiency (SCID) mice, which then developed a tumor at the cervical lymphatic area. A single dose of ceritinib was orally administered to these SCID mice bearing Karpas 299 cell-derived tumor at 5, 12.5, 25, 50, and 100 mg/kg to investigate the inhibitory effect of ceritinib against phosphorylation of STAT3 in the tumor by Western blotting. Phosphorylation of STAT3 was inhibited by ceritinib at doses of ≥12.5 mg/kg.

3.(i).A.(1).5) Anti-tumor activity against malignant tumor cells

i) *In vitro*

(a) Effect on NSCLC cells (Report Nos. RD-2008-50914 and RD-2013-50316, *Cancer Discov*. 2014;4:662-73 [Reference data], *Clin Cancer Res*. 2014;20:1-11 [Reference data])

The anti-tumor effect of ceritinib on NCI-H2228 cells transduced with luciferase gene was investigated using luciferase activity assay. Ceritinib inhibited proliferation of NCI-H2228 cells in a concentration-dependent manner with the IC_{50} (mean ± SD) of 11 ± 1 nmol/L.

The anti-tumor effect of ceritinib was investigated in a panel of 95 human NSCLC cell lines, using intracellular ATP as a measure of cell viability. The relative IC_{50} values* of ceritinib against NCI-2228 cells and 94 NSCLC cells expressing wild-type ALK were 0.8 μmol/L and >5 μmol/L, respectively.

* Concentration at which proliferation is inhibited by ceritinib by 50% in assay where the negative control (vehicle) and positive control (MG132) exhibit 0% and 100% inhibition, respectively.

The anti-tumor effects of ceritinib and crizotinib on human NSCLC-derived NCI-H2228 and H3122 cells expressing EML4-ALK were investigated using intracellular ATP as a measure of cell viability. The IC_{50} values of ceritinib and crizotinib against the cell lines tested are shown in the table below.

Anti-tumor effects of ceritinib and crizotinib on human NSCLC cell lines

Cell line	IC_{50} (nmol/L)	
	Ceritinib	Crizotinib
NCI-H2228	3.8	107
H3122	6.3	245

n = 1

The anti-tumor effects of ceritinib and crizotinib on crizotinib-resistant human NSCLC-derived H3122 CR1, MGH045, and MGH021-4 cells with L1196M or G1269A mutation as well as a crizotinib-resistant human NSCLC-derived MGH051 cells without resistant mutation were investigated using intracellular ATP as a measure of cell viability. The IC_{50} values of ceritinib and crizotinib against the cell lines tested are shown in the table below.

Anti-tumor effects of ceritinib and crizotinib on crizotinib-resistant cells

Cell line	Resistant mutation	IC_{50} (nmol/L)	
		Ceritinib	Crizotinib
H3122 CR1	L1196M	230	2884
MGH045	L1196M	25	891
MGH021-4	G1269A	80	500
MGH051	None	2.6	62

n = 1

The anti-tumor effects of ceritinib, crizotinib, and alectinib on alectinib hydrochloride (alectinib)-resistant human NSCLC-derived MGH056-1 cells with I1171T mutation were investigated using intracellular ATP as a measure of cell viability. The IC_{50} values of ceritinib, crizotinib, and alectinib (n = 1) were 4.3, 236, and 80 nmol/L, respectively.

(b) Effect on cells derived from non-NSCLC malignant tumors (Report Nos. RD-2008-50914 and RD-2010-50442)

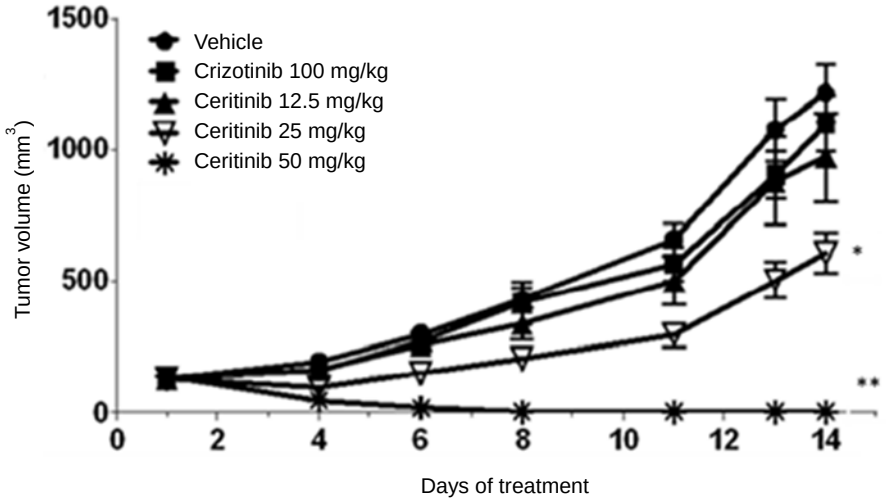
The anti-tumor effect of ceritinib on Karpas 299 cells and ALK-amplified human neuroblastoma cell line (NB-1), both transduced with luciferase gene, was investigated using luciferase activity assay. Ceritinib inhibited proliferation of Karpas 299 and NB-1 cells in a concentration-dependent manner, and the IC_{50} values (mean ± SD) were 45 ± 25 and 24 ± 4 nmol/L, respectively.

ii) *In vivo*

(a) Effect on NSCLC cell lines (Report Nos. RD-2008-50926, RD-2008-50933, RD-2013-50301, RD-2013-50300, RD-2013-50302, and RD-2013-50303, *Cancer Discov*. 2014;4:662-73 [Reference data])

The anti-tumor activity of ceritinib was investigated in SCID mice bearing subcutaneously-implanted NCI-H2228 cells. Starting at 18 days post-implantation (mean tumor volume, 85 ± 35 mm^3), ceritinib was orally administered at a dose of 3.125, 6.25, 12.5, or 25 mg/kg once daily (QD) for 14 days. Tumor volume was determined on Day 15. Compared with vehicle (0.5% methylcellulose, 0.5% polysorbate [Tween] 80), ceritinib showed statistically significant inhibition of tumor growth[*1] at a dose of 6.25 mg/kg ($P < 0.05$, Tukey's test) and statistically significant tumor regression[*2] at doses of 12.5 and 25 mg/kg ($P \leq 0.001$, Tukey's test). Similarly, the anti-tumor activity of ceritinib was investigated in athymic rats (nude rats) bearing subcutaneously-implanted NCI-H2228 cells. Ceritinib showed statistically significant inhibition of tumor growth or statistically significant tumor regression ($P < 0.05$, Tukey's test), compared with vehicle (0.5% methylcellulose, 0.5% Tween 80).

The anti-tumor activity of ceritinib was investigated in SCID mice bearing subcutaneously-implanted NCI-H2228 cells. Starting at 9 days post-implantation (mean tumor volume, 150 mm^3), ceritinib (25 or 50 mg/kg) or crizotinib (100 mg/kg) was orally administered QD for 14 days. Tumor volume was determined on Day 15. All the treated animals showed tumor regression in both the ceritinib and crizotinib groups (n = 8/group). Ceritinib or crizotinib was discontinued on Day 15 to observe the tumor for re-growth until Day 198. As a result, re-growth of the tumor was seen in all the animals treated with crizotinib (n = 8), while 100% tumor regression was noted in 4 of 8 animals treated with ceritinib 25 mg/kg and in 7 of 8 animals treated with ceritinib 50 mg/kg and it remained unchanged until the end of the study.



Anti-tumor activity of ceritinib in mice bearing subcutaneously-implanted crizotinib-resistant tumor derived from NCI-H2228 cells with I1171T mutation

n = 6; mean ± standard error; *, $P < 0.05$ vs. vehicle; **, $P < 0.0001$ vs. vehicle (Tukey's test)

The anti-tumor activity of ceritinib was investigated in SCID mice bearing subcutaneously-implanted crizotinib-resistant tumor derived from an NCI-H2228 cells with I1171T mutation.[*3] Starting at 9 days post-implantation (mean tumor volume, 130 mm^3), ceritinib (12.5, 25, or 50 mg/kg) or crizotinib (100 mg/kg) was orally administered QD for 14 days. Tumor volume was determined on Day 14. Compared with vehicle (0.5% methylcellulose, 0.5% Tween 80), crizotinib did not inhibit tumor growth, while ceritinib showed statistically significant inhibition of tumor growth at a dose of 25 mg/kg ($P < 0.05$, Tukey's test) and statistically significant tumor regression at a dose of 50 mg/kg ($P < 0.0001$, Tukey's test). Similarly, the anti-tumor activity of ceritinib was investigated in SCID mice bearing subcutaneously-implanted crizotinib-resistant tumor derived from NCI-H2228 cells with C1156Y mutation or without resistant mutations.[*3] Compared with vehicle (0.5% methylcellulose, 0.5% Tween 80), crizotinib did not inhibit tumor growth, while ceritinib showed statistically significant tumor growth inhibition or tumor regression ($P < 0.05$, Tukey's test).

The anti-tumor activity of ceritinib was investigated in athymic mice (nude mice) bearing subcutaneously-implanted crizotinib-resistant MGH045 cells with L1196M mutation. Starting on the day when the mean tumor volume reached approximately 150 mm^3, ceritinib (25 mg/kg) or crizotinib (100 mg/kg) was orally administered QD for 28 days or 14 days. The tumor volume was determined on Day 14. Ceritinib reduced tumor volume compared with crizotinib.

*1 Anti-tumor rate = (increase in tumor volume in the ceritinib group)/(increase in tumor volume in the vehicle group) × 100

*2 Tumor regression rate = (decrease in tumor volume in the ceritinib group)/(median tumor volume at baseline) × 100

*3 Crizotinib was orally administered at a dose of 50 mg/kg QD for 9 days to SCID mice bearing subcutaneously-implanted NCI-H2228 cells, followed by 75 mg/kg QD for 9 days, and then 100 mg/kg QD, so as to obtain crizotinib-resistant tumor with I1171T or C1156Y mutation and crizotinib-resistant tumor without resistant mutation.

(b) Effect on cells derived from non-NSCLC malignant tumor (Report Nos. RD-2008-50927 and RD-2008-50942)

The anti-tumor activity of ceritinib was investigated in SCID mice bearing subcutaneously-implanted Karpas 299 cells. Starting at 9 days post-implantation (mean tumor volume, 74 ± 11 mm^3), ceritinib was orally administered at a dose of 6.25, 12.5, or 25 mg/kg QD for 13 days, and the tumor volume was determined. Ceritinib inhibited tumor growth at a dose of 12.5 mg/kg and induced tumor regression at a dose of 25 mg/kg, compared with vehicle (0.5% methylcellulose, 0.5% Tween 80). The anti-tumor activity of ceritinib was investigated in nude rats bearing subcutaneously-implanted Karpas 299 cells.

Ceritinib inhibited tumor growth or induced tumor regression, compared with vehicle (0.5% methylcellulose, 0.5% Tween 80).

3.(i).A.(2) Secondary pharmacodynamics

3.(i).A.(2).1) *In vitro* (Report Nos. RD-2008-50904, RD-2010-50499, RD-2008-50906, and RD-2010-50501)

The binding profile of ceritinib for 84 receptor proteins, including G-protein-coupled receptors (GPCRs), transporters, ion channels, nuclear receptors, and enzymes, was investigated based on the inhibition of binding of radiolabeled ligands to those receptors. Ceritinib at 10 μmol/L showed >50% inhibition of ligand binding to 15 target receptors. Of the 15 receptors, 9 (monoamine transporter, potassium channel, serotonin 5A receptor, and somatostatin receptors [SST] 1, 2, 3, and 4 as well as benzodiazepine binding site and phenylalkylamine binding site of L-type calcium channel) were subjected to a dose response study, and the IC_{50} was found to be 0.33, 0.68, 5.0, 2.4, 2.3, 5.1, 1.9, 1.8, and 2.4 μmol/L, respectively.

The binding profile of ceritinib for 73 receptor proteins, including GPCRs, transporters, ion channels, nuclear receptors, and enzymes, was investigated based on the inhibition of binding of radiolabeled ligands to those receptors. A total of 19 target receptors showed IC_{50} values <5 μmol/L. Among the 19 receptors, adenosine 3 receptor, adrenaline α1A receptor, melanocortin-4 receptor, histamine H2 and H3 receptors, neurokinin-1 receptor, opioid κ receptor, and dopamine D2 receptor were subjected to a cellular function study on calcium influx for assessment of ceritinib-mediated activation and inhibition of these receptors. The EC_{50} of ceritinib for dopamine D2 receptor was 6.0 μmol/L. Ceritinib did not induce activation or inhibition of other receptors at concentrations of ≤10 μmol/L.

In the above-mentioned study on binding of ceritinib to 73 target receptors, the IC_{50} of ceritinib against pregnane X receptor (PXR) was 4.4 μmol/L. In response to this finding, cytochrome P450 (CYP) 3A4 expression induced through ceritinib-mediated activation of PXR was investigated in human hepatocellular carcinoma-derived HepG2 cells expressing human PXR (DPX-2 cell line), using luciferase activity assay. Ceritinib at 3 μmol/L weakly induced CYP3A4 expression (up to 9.8%).

The applicant's explanation:
The effect of ceritinib on non-ALK targets is considered to be minimal because (1) all the IC_{50} and EC_{50} values of ceritinib for non-ALK targets were higher than those for ALK and (2) the effect of ceritinib on PXR-dependent CYP3A4 expression was weak.

3.(i).A.(2).2) *In vivo* (Report Nos. RD-2013-00413 and RD-2010-50507)

Murine fibroblast-derived NIH3T3 cells stably expressing insulin-like growth factor-1 receptor (IGF-1R) were subcutaneously implanted to nude mice. When the tumor volume reached approximately 200 mm^3, a single dose of ceritinib (25, 50, or 100 mg/kg) was orally administered to the nude mice. The inhibitory effect of ceritinib on phosphorylation of IGF-1R and AKT (a downstream signaling molecule of IGF-1R) in the tumor was investigated by Western blotting. Ceritinib did not inhibit phosphorylation of IGF-1R or AKT.

Ceritinib was orally administered at a dose of 25, 50, or 100 mg/kg QD for 7 days to mice, and then glucose (3 g/kg) was orally administered at 3 hours after the last dose. Blood glucose levels were determined before administration of glucose and at 20, 40, 60, and 120 minutes after administration of glucose, and plasma insulin levels were determined before administration of glucose. Ceritinib did not have a significant effect on blood glucose or fasting plasma insulin levels.

The applicant's explanation:
The above findings suggests that ceritinib is unlikely to affect IGF-1R signal transduction pathway or glucose metabolism, but hyperglycaemia and diabetes mellitus occurred in patients treated with ceritinib in clinical studies [see "4.(iii).B.(3).6) Hyperglycaemia/diabetes mellitus"]. Therefore, precautionary advice on the occurrence of hyperglycaemia and diabetes mellitus will be included in the package insert.

3.(i).A.(3) Safety pharmacology

3.(i).A.(3).1) Effects on the central nervous system (Report No. 0970415)

A single dose of ceritinib was orally administered at 100 mg/kg to rats (n = 10) to investigate effects on functional observational battery results as well as clinical signs and body weight. No effects of ceritinib were observed.

3.(i).A.(3).2) Effects on the cardiovascular system

i) Effects on human *ether-a-go-go*-related gene potassium current (Report No. 0970418)

The effects of ceritinib on *ether-a-go-go*-related gene (hERG) potassium current were investigated in human embryonic kidney-derived HEK293 cells transfected with human hERG. The IC_{50} of ceritinib was 0.4 μmol/L.

ii) Effects on blood pressure and electrocardiogram (Report No. 0770889 [Reference data] and 0970420)

Cynomolgus monkeys (n = 2) were orally given vehicle on Day 1 and ceritinib 250 mg/kg on Day 2. The effects on blood pressure (systolic, diastolic, and mean), heart rate, body temperature, electrocardiogram (ECG), clinical signs, body weight, and food consumption were investigated in animals. Emesis with feed, loose stool, and decreased food consumption occurred following administration of ceritinib.

Cynomolgus monkeys (n = 4) were orally given vehicle on Day 1, ceritinib 10 mg/kg on Day 8, ceritinib 30 mg/kg on Day 15, and ceritinib 100 mg/kg on Day 22. The effects on blood pressure (systolic, diastolic, and mean), heart rate, body temperature, ECG, clinical signs, body weight, and food consumption were investigated in animals. The findings included loose stool at doses of ≥10 mg/kg, vomiting at doses of ≥30 mg/kg, and diarrhoea and QT interval prolonged at a dose of 100 mg/kg.

The applicant's explanation:
In addition to the above results, QT interval prolongation occurred in patients treated with ceritinib in the clinical studies [see "4.(iii).B.(3).4) QT interval prolonged"], and a correlation between ceritinib exposure and QT interval prolonged was demonstrated [see "4.(ii).A.(4) Relationship between exposure and changes in QT/QTc interval"]. Thus, precautionary advice on the occurrence of QT interval prolonged will be included in the package insert. Because gastrointestinal toxicity (e.g., vomiting, diarrhoea) occurred following administration of ceritinib in the single-dose and repeat-dose toxicity studies in monkeys as well as in the clinical studies [see "3.(iii).A.(1) Single-dose toxicity," "3.(iii).A.(2) Repeat-dose toxicity," and "4.(iii).B.(3).5) Nausea, vomiting, and diarrhoea"], precautionary advice on the occurrence of gastrointestinal toxicity will also be included in the package insert.

3.(i).A.(3).3) Effects on respiratory system (Report 0970415)

A single dose of ceritinib 100 mg/kg was orally administered to rats (n = 10) to investigate the effects on tidal volume, respiratory rate, and respiratory minute volume. No effects of ceritinib were observed.

3.(i).B Outline of the review conducted by PMDA

On the basis of the submitted non-clinical data and the following review, PMDA has concluded that ceritinib is expected to be effective in patients with *ALK*-positive NSCLC resistant to existing ALK inhibitors (crizotinib and alectinib).

Mechanism of action and efficacy of ceritinib

The applicant's explanation of the mechanism of action of ceritinib and the efficacy in patients with NSCLC resistant to existing ALK inhibitors:
Many patients with *ALK*-positive NSCLC become resistant to existing ALK inhibitors (*N Engl J Med.* 2010;363:1734-9, and others). Reported mechanisms of development of resistance to two ALK inhibitors (crizotinib and alectinib) are as follows: (a) crizotinib involves resistant mutations in *ALK* fusion gene (L1196M, G1269A, C1156Y, S1206Y, 1151Tins, G1202R, I1171T, F1174V, and L1152R) and epidermal growth factor receptor (*EGFR*) gene mutations (*New Engl J Med.* 2010;363:1734-9, and others), and (b) alectinib involves resistant mutations in *ALK* fusion gene (I1171T/S/N and G1202R) and *MET* gene amplification (*Cancer Res.* 2014;20:1-11, and others).

Ceritinib inhibits phosphorylation of ALK by binding to the ATP-binding site in the ALK kinase domain (*J Med Chem.* 2013;56:5675-90) as with existing ALK inhibitors. It also binds to ALK fusion proteins harboring the above resistant mutations (*J Mol Model.* 2015;21:175). In addition, ceritinib inhibited proliferation of NSCLC-derived cell lines with resistant mutations (L1196M, G1269A, C1156Y, and I1171T) [see "3.(i).A.(1).5) Anti-tumor activity against malignant tumor cells"]. Furthermore, ceritinib inhibits EML4-ALK with S1206Y or I1171T/N mutation (*Cancer Discov.* 2014;4:662-73, and others). These findings are considered to support the efficacy of ceritinib in patients with NSCLC resistant to the existing ALK inhibitors.

PMDA's view:
The applicant's explanation is generally acceptable. However, the efficacy of ceritinib remains unknown in patients with NSCLC that has developed resistance to existing ALK inhibitors due to expression of resistant *non-ALK* mutations such as *EGFR* gene mutation and *MET* gene amplification. Only limited information on the relationship between the mechanisms involved in development of resistance to existing ALK inhibitors and the efficacy of ceritinib is available, but it may be beneficial from the viewpoint of predicting the efficacy of ceritinib in clinical settings. The relevant information therefore should continue to be collected. New information should be communicated to healthcare professionals appropriately when it becomes available.

3.(ii) Summary of pharmacokinetic studies

3.(ii).A Summary of the submitted data

Nonclinical pharmacokinetics (PK) studies of ceritinib was conducted in mice, rats, dogs, and monkeys. Biological samples from humans and animals were used to investigate plasma protein binding, drug-metabolizing enzymes, and transporters of ceritinib.

3.(ii).A.(1) Absorption

3.(ii).A.(1).1) Single-dose administration

Following a single intravenous dose of ceritinib 5 mg/kg or a single oral dose of ceritinib 20 mg/kg to male mice, plasma ceritinib concentrations were determined (the table below). Bioavailability (BA) of ceritinib orally administered at 20 mg/kg was 54.6%.

Following a single intravenous dose of ^{14}C-labeled ceritinib ([^{14}C]ceritinib) 10 mg/kg or a single oral dose of [^{14}C]ceritinib 25 mg/kg to male rats, plasma ceritinib concentrations or blood and plasma radioactivity concentrations were determined (the table below). The BA of ceritinib after oral administration of [^{14}C]ceritinib 25 mg/kg was 46.4% and 50.1% (individual values).

Following a single intravenous dose of ceritinib 5 mg/kg or a single oral dose of ceritinib 20 mg/kg to male dogs, plasma ceritinib concentrations were determined (the table below). The BA of ceritinib orally administered at 20 mg/kg was 119%.

Following a single intravenous dose of ceritinib 5 mg/kg or a single oral dose of ceritinib 60 mg/kg, or following a single intravenous dose of [^{14}C]ceritinib 10 mg/kg or a single oral dose of [^{14}C]ceritinib 30 mg/kg to male monkeys, plasma ceritinib concentrations or blood and plasma radioactivity concentrations were determined (the table below). The BA of [^{14}C]ceritinib administered at 30 mg/kg orally relative to that of [^{14}C]ceritinib administered at 10 mg/kg intravenously was 43%. The BA of ceritinib administered at 60 mg/kg orally relative to that of ceritinib administered at 5 mg/kg intravenously was 58%.

The BA of ceritinib in dogs was higher than that in mice, rats, and monkeys. The applicant explained the following reasons for this result: dogs orally received ceritinib in the fed state, but mice, rats, and monkeys did not receive it in the fed state; and thus food might have increased absorption of ceritinib in dogs.

PK parameters of ceritinib in tested species

Species	Route of administration	Dose (mg/kg)	Feeding	Sex	n	C_{max} (ng/mL)	t_{max} (h)	AUC_{inf} (ng·h/mL)	$t_{1/2}$ (h)
Mouse	Intravenous	5	Non-fasted	Male	3	977 ± 284	0.03*1	3140 ± 246	6.2 ± 0.5
	Oral	20	Non-fasted	Male	3	388 ± 17	7.0 ± 0	6870 ± 548	-
Rat	Intravenous	10	Non-fasted	Male	3	975 ± 139	0.083*1	6950 ± 1470	9.7 ± 1.2
	Oral	25	Non-fasted	Male	2	312, 414*2	12.0, 12.0*2	8063, 8707*2	9.64, 16.7*2
Dog	Intravenous	5	Fasted	Male	2	1080, 1530*2	0.083*1	7150, 13,100*2	17, 25*2
	Oral	20	Fed	Male	2	1010, 1100*2	8, 8*2	67,600, 94,500*2	44, 55*2
Monkey	Intravenous	5	Fasted	Male	2	1260, 1560*2	0.083*1	5660, 7400*2	26, 32*2
		10	Fasted	Male	2	2820, 3550*2	0.083*1	24,200, 31,400*2	14.0, 15.0*2
	Oral	30	Fasted	Male	3	881 ± 12.5	18.3 ± 9.81	35,800 ± 3460	12.1 ± 2.05
		60	Fasted	Male	3	947 ± 140	13 ± 9.2	45,300 ± 8860	16 ± 0.61

Arithmetic mean ± SD; -, Not calculated; *1, First measurement time point; *2, Individual values

PK parameters of radioactivity in tested species (single intravenous or oral administration)

Species	Route of administration	Dose (mg/kg)	Feeding	Sex	n	Measured sample	C_{max} (ngEq./mL)	t_{max} (h)	AUC_{inf} (ngEq.·h/mL)	$t_{1/2}$ (h)
Rat	Intravenous	10	Non-fasted	Male	3	Blood	2800 ± 153	0.083*1	20,600 ± 3350	20.7 ± 4.3
						Plasma	2030 ± 242	0.083*1	10,200 ± 2150	15.4 ± 4.0
	Oral	25	Non-fasted	Male	2	Blood	779, 860*2	8.0, 12.0*2	19,400, 21,300*2	11.6, 13.8*2
						Plasma	317, 417*2	12.0, 12.0*2	8630, 10,300*2	13.2, 14.3*2
Monkey	Intravenous	10	Fasted	Male	2	Blood	4640, 6390*2	0.083*1	51,000, 61,900*2	53.0, 70.5*2
						Plasma	3660, 4510*2	0.083*1	42,600, 53,100*2	70.3, 74.0*2
	Oral	30	Fasted	Male	3	Blood	1020 ± 127	13.7 ± 9.1	43,000 ± 10,400	15.7 ± 1.7
						Plasma	499 ± 19.1	18.3 ± 9.81	22,600 ± 2460	19.2 ± 4.08

Arithmetic mean ± SD; *1, First measurement time point; *2, Individual values

3.(ii).A.(1).2) Repeat-dose administration

Ceritinib was orally administered at doses ranging from 3 to 20 mg/kg QD for 26 weeks to female and male rats in the non-fasted state to determine plasma ceritinib concentrations (the table below). Within the dose range studied, the C_{max} and $AUC_{0\text{-}24h}$ of ceritinib increased more than dose-proportionally on any day of measurement. No consistent sex differences were observed in the C_{max} and $AUC_{0\text{-}24h}$ values of ceritinib.

The applicant's interpretation of the above results, namely, the more than dose-proportional increase in exposure to ceritinib:
Since ceritinib is a substrate of P-glycoprotein (P-gp) [see "3.(ii).A.(5).3) Transporters"], saturation of P-gp-mediated transportation of ceritinib may have resulted in increased absorption of ceritinib. In addition, the ratio of C_{max} on Day 154 to that on Day 1 in the 20 mg/kg group was 1.7 and 1.4 for females and males, respectively, and the ratio of $AUC_{0\text{-}24h}$ on Day 154 to that on Day 1 was 1.7 and 1.3 for females and males, respectively. No clear increases in the C_{max} or $AUC_{0\text{-}24h}$ of ceritinib were observed following repeated administration.

PK parameters of ceritinib (female and male rats, 26-week oral administration)

Dose (mg/kg)	Time point (Day)	C_{max} (ng/mL)		t_{max} (h)		$AUC_{0\text{-}24h}$ (ng·h/mL)	
		Male	Female	Male	Female	Male	Female
3	1	73.3	59.6	5	5	1150	759
	28	104	68.7	7	5	1790	722
	154	205	102	7	7	2090	1430
10	1	381	303	10	10	6280	4770
	28	443	606	7	7	6930	10,200
	154	787	707	3	7	10,200	7940
20	1	947	739	5	10	16,600	13,100
	28	1440	1070	5	3	24,000	18,500
	154	1290	1260	5	10	22,400	21,800

n = 4 per time point (PK parameters were calculated from mean plasma ceritinib concentration at each time point)

Ceritinib was orally administered at doses ranging from 3 to 30 mg/kg QD for 39 weeks to female and male monkeys in the non-fasted state to determine plasma ceritinib concentrations (the table below). Within the dose range studied, the C_{max} and $AUC_{0\text{-}24h}$ of ceritinib increased more than dose-

proportionally. No clear sex differences were observed in the C_{max} and $AUC_{0\text{-}24h}$ values of ceritinib. The ratios of $AUC_{0\text{-}24h}$ on Day 28 and Day 273 to that on Day 1 in the 30 mg/kg group were 2.3 and 2.3, respectively, for males and 1.8 and 2.2, respectively, for females.

The applicant's interpretation of the above results, namely, the increased exposure to ceritinib following repeated administration:
Although metabolizing enzymes of ceritinib in monkeys remain unknown, ceritinib is reported to inhibit CYP3A [see "3.(ii).A.(5).1) Enzyme inhibition"], a metabolizing enzyme of ceritinib in humans [see "3.(ii).A.(3).1) *In vitro* metabolism"], and thus ceritinib may have induced autoinhibition of its own metabolism in monkeys as well. The inter-species difference in increases in exposure to ceritinib following repeated administration is attributable to a greater contribution of metabolism to the elimination of ceritinib in monkeys than in rats, because the rate of ceritinib metabolism was higher in monkeys than in rats [see "3.(ii).A.(3) Metabolism"].

PK parameters of ceritinib (female and male monkeys, 39-week oral administration)

Dose (mg/kg)	Time point (Day)	n	C_{max} (ng/mL)		t_{max} (h)		$AUC_{0\text{-}24h}$ (ng·h/mL)	
			Male	Female	Male	Female	Male	Female
3	1	4	39.2 ± 16.1	36.0 ± 4.86	5.0 ± 0	4.0 ± 1.2	486 ± 224	437 ± 100
	28	4	44.0 ± 19.6	59.4 ± 5.49	5.0 ± 0	5.5 ± 1.0	539 ± 194	865 ± 113
	273	4	28.8 ± 17.5	56.4 ± 18.7	4.5 ± 1.9	6.5 ± 1.0	422 ± 290	861 ± 266
10	1	4	154 ± 65.7	172 ± 45.6	6.8 ± 2.4	5.0 ± 0	2540 ± 1260	2310 ± 677
	28	4	300 ± 123	267 ± 126	5.0 ± 0	4.5 ± 1.0	4410 ± 2110	4000 ± 2000
	273	4	213 ± 87.1*	325 ± 230	6.7 ± 3.5*	6.0 ± 2.0	3530 ± 1450*	5430 ± 3910
30	1	6	597 ± 135	670 ± 198	7.2 ± 1.6	5.5 ± 2.4	10,200 ± 2560	11,300 ± 3990
	28	6	1280 ± 473	1230 ± 416	5.7 ± 1.0	5.2 ± 2.6	23,300 ± 9480	20,900 ± 7860
	273	6	1350 ± 590	1340 ± 474	7.5 ± 1.2	7.8 ± 2.8	23,100 ± 9710	25,100 ± 9640

Arithmetic mean ± SD, * n = 3

3.(ii).A.(1).3) *In vitro* membrane permeability

A human colon carcinoma-derived cell line (Caco-2) was used to investigate the membrane permeability of ceritinib. The apparent permeability coefficient of [^{14}C]ceritinib at 3 and 14 μmol/L was determined in both the basolateral to apical direction ($P_{app\ B\rightarrow A}$) and the apical to basolateral direction ($P_{app\ A\rightarrow B}$), and the $P_{app\ B\rightarrow A}/P_{app\ A\rightarrow B}$ ratio (efflux ratio) was 182 and 19.5, respectively. In the presence of LY335979 (1 μmol/L), a P-gp inhibitor, the $P_{app\ A\rightarrow B}$ of [^{14}C]ceritinib at 3 and 14 μmol/L was 1.03×10^{-5} and 1.57×10^{-5} cm/min, respectively. The $P_{app\ A\rightarrow B}$ values of [^{14}C]mannitol (3.9 μmol/L), a negative control, and [^{3}H]propranolol (4.5 μmol/L), a positive control, were 4.0×10^{-5} and 79.2×10^{-5} cm/min, respectively. In light of the above findings, the applicant considers that the passive membrane permeability of ceritinib is low.

3.(ii).A.(2) Distribution

3.(ii).A.(2).1) Tissue distribution

A single dose of [^{14}C]ceritinib was orally administered at 25 mg/kg to pigmented or albino male rats to investigate tissue distribution of radioactivity using quantitative whole-body autoradiography. Tissue radioactivity concentrations were determined in pigmented rats from 1 to 168 hours post-dose and in albino rats at 168 hours post-dose. In pigmented rats, radioactivity levels peaked at 4 hours post-dose in most tissues. The AUC_{inf} of radioactivity was higher in most tissues than in blood, especially in the intestinal wall, pituitary gland, uvea, bile, adrenal cortex, Harderian gland, liver, spleen, lymph node, and lung (the ratios of AUC_{inf} of radioactivity in these tissues to that in blood were 413, 211, 176, 155, 72.4, 62.8, 52.6, 47.6, 45.1, and 37.2, respectively). At 168 hours post-dose, radioactivity remained measurable in the uvea, Harderian gland, pituitary gland, liver, testis, epididymis, kidneys, skin, and spleen (21.2-8160 ngEq./g). The radioactivity tissue-to-blood ratio based on AUC_{inf} in the brain was 0.148, suggesting that ceritinib or its metabolites cross the blood brain barrier. While the radioactivity in the uvea was not measurable in albino rats at 168 hours post-dose, it was 8160 ngEq./g in pigmented rats. The above findings, according to the applicant, suggest that ceritinib or its metabolites bind to uveal melanin.

Ceritinib was administered to male albino rats at 25 or 50 mg/kg QD, or at 100 mg/kg 3 times a week, for 4 weeks to investigate tissue distribution. The $AUC_{0\text{-}96h}$ values of ceritinib in the lungs, spleen, liver,

bone marrow, and heart after the first dose were 34.4, 9.53, 8.53, 6.51, and 2.86 mg·h/mL, respectively, in the 100 mg/kg group. At all dose levels tested, the $AUC_{0\text{-}96h}$ was higher in those tissues than in plasma (0.0757 mg·h/mL in the 100 mg/kg group).

3.(ii).A.(2).2) Plasma protein binding

Plasma samples from rats, dogs, monkeys, and humans were incubated with [^{14}C]ceritinib at concentrations ranging from 50 to 10,000 ng/mL at 37°C for 3 hours, and then the samples were subjected to ultracentrifugation for determination of plasma protein binding of ceritinib. The plasma protein binding of ceritinib was generally consistent across the tested species, irrespective of ceritinib concentration. The mean percentage of ceritinib bound to proteins at all concentrations investigated was 98.3%, 98.5%, 94.6%, and 97.2% in rat, dog, monkey, and human samples, respectively. Human serum samples were incubated with [^{14}C]ceritinib at concentrations of 100 and 10,000 ng/mL, and the serum protein binding of ceritinib was evaluated. The serum protein binding rate of ceritinib was 97.6% and 98.6%, respectively, and both were comparable to the plasma protein binding rate.

3.(ii).A.(2).3) Distribution in blood cells

Blood samples from rats, dogs, monkeys, and humans were incubated with [^{14}C]ceritinib at concentrations ranging from 50 to 10,000 ng/mL at 37°C for 30 minutes, and distribution of ceritinib into blood cells was determined. The blood-to-plasma ratio of radioactivity was generally consistent across the species tested, irrespective of ceritinib concentration. The mean of blood-to-plasma ratios at all concentrations investigated was 1.72, 1.38, 2.59, and 1.35 in rat, dog, monkey, and human samples, respectively. The mean distribution rates within blood cells at all concentrations investigated were 67.1%, 67.6%, 77.7%, and 58.2% in rat, dog, monkey, and human samples, respectively. These findings, according to the applicant, suggest that ceritinib is distributed into blood cells.

3.(ii).A.(2).4) Placental permeability and placental to fetal transfer

A single dose of ceritinib (10 or 50 mg/kg) was orally administered to pregnant rats (gestation days 16 and 17) to investigate placental transfer and maternal-fetal transfer of ceritinib. Plasma ceritinib concentrations in dams were 137 and 648 ng/mL (individual values) at 3 hours post-dose on gestation day 16, and plasma ceritinib concentrations in fetuses were 9.23 and 61.2 ng/mL (individual values) at 3 hours post-dose on gestation day 17.

A single dose of ceritinib (2, 10, or 25 mg/kg) was orally administered to pregnant rabbits (gestation days 19 and 20) to investigate placental transfer and maternal-fetal transfer of ceritinib. Following administration of ceritinib at 2, 10, and 25 mg/kg, plasma ceritinib concentrations in dams were 23.7, 123, and 528 ng/mL, respectively, at 3 hours post-dose on gestation day 19, and plasma ceritinib concentrations in fetuses were 1.58, 6.50, and 41.2 ng/mL, respectively, at 3 hours post-dose on gestation day 20.

The above findings, according to the applicant, suggest that ceritinib crosses the placenta.

3.(ii).A.(3) Metabolism

3.(ii).A.(3).1) *In vitro* metabolism

Rat, monkey, and human hepatocytes were incubated with [^{14}C]ceritinib at concentrations of 2.5 and 12.5 µmol/L at 37°C for 24 hours to investigate metabolites of ceritinib. Unchanged ceritinib was mainly detected in the samples from all tested species. The major metabolites detected in human hepatocytes were M27.5 (mono-oxygenated metabolite), M27.6 (glucuronide conjugate of mono-oxygenated metabolite), M32.9 (*O*-dealkylated metabolite), M33.4 (mono-oxygenated metabolite), and M37.3 (metabolite with loss of the sulfonylpropyl group).

The studies presented below were conducted to investigate human CYP isozymes involved in the metabolism of ceritinib. The applicant considers that CYP3A is mainly responsible for the metabolism of ceritinib in humans, based on the investigation results and in light of no expression of CYP1B1 in normal liver (*Toxicol Sci*. 2003;71:11-9).

- Human liver microsome was incubated with [^{14}C]ceritinib at 37°C for 30 minutes in the presence of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A inhibitor. In the presence of ketoconazole and azamulin (CYP3A inhibitors), metabolism of ceritinib was inhibited by 90.5% and 100%, respectively. Inhibitors against the other CYP isozymes did not clearly inhibit metabolism of ceritinib.

- Recombinant human CYP isozymes (CYP1A1, CYP1A2, CYP1B1, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2J2, CYP3A4, CYP3A5, CYP4A11, CYP4F2, CYP4F3A, CYP4F3B, and CYP4F12) were incubated with [^{14}C]ceritinib at 37 μmol/L at 37°C for 30 minutes. Ceritinib was metabolized in CYP1B1 and CYP3A4 expression systems; M35.8 (mono-oxygenated metabolite) was detected in the CYP1B1 expression system, and M27.5 and M35.8 in the CYP3A4 expression system.

3.(ii).A.(3).2) *In vivo* metabolism

A single dose of [^{14}C]ceritinib was administered at 10 mg/kg intravenously or at 25 mg/kg orally to intact or bile duct-cannulated male rats to investigate metabolites of ceritinib in plasma, urine, feces, and bile. The results are shown below.

- In both intact and bile duct-cannulated male rats, only unchanged ceritinib was detected in plasma by 168 hours post-dose. No metabolites were detected.

- In both intact and bile duct-cannulated male rats, radioactivity detected in urine by 72 or 168 hours post-dose accounted for <2% of the administered radioactivity, and thus identification of the metabolites in urine was not performed.

- In intact male rats, unchanged ceritinib was mainly detected in feces by 72 hours post-dose (82.65% and 80.40% of the intravenously and orally administered radioactive doses, respectively), and the major metabolite was M33.4 (mono-oxygenated metabolite) (7.20% and 6.13% of the intravenously and orally administered radioactive doses, respectively). Unchanged ceritinib was mainly detected in feces by 72 hours post-dose in bile duct-cannulated male rats (12.05% and 51.77% of the intravenously and orally administered radioactive doses, respectively). The major metabolite was M23.6 (mono-oxygenated metabolite of M32.9) (4.56% and 5.88% of the intravenously and orally administered radioactive doses, respectively).

- Unchanged ceritinib was mainly detected in bile by 72 hours post-dose in bile duct-cannulated rats (34.89% and 9.19% of the intravenously and orally administered radioactive doses, respectively), and each of the recovered metabolites accounted for <5% of the administered radioactive dose.

A single dose of ^{14}C-ceritinib was administered intravenously at 10 mg/kg or orally at 30 mg/kg to male monkeys to investigate metabolites of ceritinib in plasma and feces. The results are shown below.

- Unchanged ceritinib was mainly detected in plasma (89.9% and 84.4% of total plasma radioactivity $AUC_{0\text{-}24h}$ following intravenous and oral administration, respectively). The major metabolites were M46.1 (mono-oxygenated and dehydrogenized metabolites) (3.0% and 3.1% of total plasma radioactivity $AUC_{0\text{-}24h}$ following intravenous and oral administration, respectively), M21.6 (*S*-dealkylated metabolite) (1.4% and 3.6%, respectively), and M27.6 (1.8% and 2.5%, respectively).

- Unchanged ceritinib was mainly detected in feces (55.1% and 60.2% of the intravenously and orally administered radioactive doses, respectively). The major metabolite was M35.8 (17.9% and 8.7% of the intravenous and orally administered radioactive doses, respectively).

3.(ii).A.(4) Excretion

3.(ii).A.(4).1) Biliary, urinary, and fecal excretion

The following study results, according to the applicant, suggest that ceritinib is mainly excreted in feces through bile.

- A single dose of [^{14}C]ceritinib was administered to male rats at 10 mg/kg intravenously or at 25 mg/kg orally to investigate the cumulative excretion of radioactivity in urine and feces. The radioactivity recovered in urine and feces up to 168 hours post-dose accounted for 0.24% and 107%, respectively, of the intravenous dose, and 0.18% and 101%, respectively, of the oral dose.

- A single dose of [^{14}C]ceritinib was administered to bile duct-cannulated male rats at 10 mg/kg intravenously or at 25 mg/kg orally to investigate the cumulative excretion of radioactivity in bile, urine, and feces. The radioactivity recovered in bile, urine, and feces up to 72 hours post-dose accounted for 65.4%, 0.62%, and 29.8%, respectively, of the intravenous dose and 24.3%, 1.05%, and 65.0%, respectively, of the oral dose.

- A single dose of [^{14}C]ceritinib was administered to male monkeys at 10 mg/kg intravenously or at 30 mg/kg orally to investigate the cumulative excretion of radioactivity in urine and feces. The radioactivity recovered in urine and feces up to 168 hours post-dose accounted for 0.59% and 105%, respectively, of the intravenous dose and 0.71% and 92.3%, respectively, of the oral dose.

3.(ii).A.(4).2) Excretion in milk

Excretion of ceritinib in milk has not been investigated. According to the applicant, the possibility that ceritinib is excreted in milk could not be ruled out, because ceritinib is a low molecular weight compound with high lipophilicity (logP value = 4.6).

3.(ii).A.(5) Pharmacokinetic interactions

3.(ii).A.(5).1) Enzyme inhibition

In the presence of ceritinib at concentrations ranging from 0.5 to 100 μmol/L, substrates of CYP isozymes (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A) were incubated with liver microsome to investigate the inhibitory effect of ceritinib on CYP isozymes. Ceritinib inhibited metabolism of CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A substrates with the IC_{50} values of 5, 2, 25, 2, 2, 70, 20, 30, and 0.2 μmol/L, respectively. The Ki values of ceritinib against CYP2A6, CYP2B6, CYP2C8, CYP2C9, and CYP3A were 0.0316, 5.34, 16.7, 0.241, and 0.161, respectively. Ceritinib inhibited CYP3A in a time-dependent manner (K_i = 1.47 μmol/L, K_{inact} = 0.0642 min^{-1}).

The applicant's explanation:

The C_{max} of ceritinib in patients with *ALK*-positive NSCLC receiving multiple oral doses of ceritinib 750 mg was 1440 ng/mL (approximately 2.58 μmol/L) [see "4.(ii).A.(2).1) Japanese phase I study"]. Ceritinib is unlikely to be concomitantly used with substrates of CYP2A6 (letrozole, tegafur, etc.) in clinical practice. These findings and the results presented in the above paragraph suggest the possibility that pharmacokinetic interaction is mediated by ceritinib-induced inhibition of CYP2C9 and CYP3A in clinical settings.

3.(ii).A.(5).2) Enzyme induction

Human hepatocytes were treated with ceritinib (at 0.25-2.5 μmol/L) for 48 hours to investigate mRNA expression and enzyme activities of CYP isozymes (CYP1A2, CYP2B6, CYP2C9, and CYP3A4). In hepatocytes treated with ceritinib at 2.5 μmol/L, mRNA levels of CYP3A4 increased to 3.24- to 8.74-fold that in hepatocytes treated with vehicle (0.1% DMSO solution), but ceritinib did not clearly increase CYP3A enzyme activity. The applicant considers that the inhibitory effect of ceritinib on CYP3A [see "3.(ii).A.(5).1) Enzyme inhibition"] may have hampered the increase of enzyme activity induced by ceritinib. In addition, ceritinib showed no clear increase in mRNA levels or enzyme activity of other CYP isozymes investigated.

Human hepatocytes were treated with ceritinib (0.25-2.5 μmol/L) for 48 hours to investigate mRNA expression of UDP-glucuronosyltransferase (UGT) isozymes (UGT1A1, UGT1A3, UGT1A4, and UGT1A8). Ceritinib showed no increase in mRNA expression of UGT isozymes investigated.

The applicant's explanation:

The ability of ceritinib to induce CYP and UGT isozymes in human hepatocytes could not be investigated at concentrations >2.5 μmol/L, because cytotoxicity was observed at >2.5 μmol/L. Pharmacokinetic interaction mediated by CYP and UGT isozyme induction by ceritinib is unlikely to occur in clinical settings, based on the results presented in the above paragraph and in consideration that C_{max} of ceritinib in patients with *ALK*-positive NSCLC treated with multiple oral doses of ceritinib 750 mg was 1440 ng/mL (approximately 2.58 μmol/L).

3.(ii).A.(5).3) Transporters

The following study results, according to the applicant, suggest that ceritinib is a substrate of P-gp.

- Transport of [^{14}C]ceritinib (at concentrations of 3 and 14 μmol/L) via P-gp, multidrug resistance-associated protein (MRP) 2, or breast cancer resistance protein (BCRP) was investigated in Caco-2 cells. The efflux ratio of [^{14}C]ceritinib at 3 and 14 μmol/L was 182 and 19.5, respectively, in the absence of P-gp, MRP2, and BCRP inhibitors, and 5.77 and 6.46, respectively, in the presence of a P-gp inhibitor (LY335979, 1 μmol/L). The efflux ratio of [^{14}C]ceritinib at 3 μmol/L, in the presence of MRP2 inhibitor (MK571, 10 μmol/L) and BCRP inhibitor (Ko143, 1 μmol/L), was 41.5 and 121, respectively.

- P-gp-mediated transport of [^{14}C]ceritinib (2 and 11 μmol/L) was investigated in porcine kidney cells (LLC-PK1) expressing human P-gp. The efflux ratio of [^{14}C]ceritinib at 2 and 11 μmol/L was 1.22 and 0.62, respectively, in the presence of a P-gp inhibitor (GF120918, 4 μmol/L), and 45.8 and 4.14, respectively, in the absence of the inhibitor.

- Human organic anion transporter (OAT) 2-, human organic anion transport polypeptide (OATP) 1B1 or OATP2B1-, or human organic cation transporter (OCT) 1-mediated transport of [^{14}C]ceritinib (5.0-6.3 μmol/L) was investigated in human embryonic kidney cells (HEK293) expressing these transporters. No clear difference in the cellular uptake of [^{14}C]ceritinib was observed between transporter-expressing cells and non-expressing cells.

The applicant's explanation:
Although the following findings show that ceritinib inhibits P-gp, BCRP, OAT1, OATP1B1, OATP1B3, and OCT2, pharmacokinetic interaction mediated by ceritinib-induced inhibition of OAT1, OAT13, OATP1B1, OATP1B3, and OCT2 is unlikely to occur in clinical settings because (1) the C_{max} of ceritinib in patients with *ALK*-positive NSCLC receiving multiple oral doses of ceritinib 750 mg QD was 1440 ng/mL (approximately 2.58 μmol/L) [see "4.(ii).A.(2).1) Japanese phase I study"] and (2) the plasma protein binding of ceritinib was 97.2% [see "3.(ii).A.(2).2) Plasma protein binding"].

- The inhibitory effect of ceritinib (0.63-20 or 1.0-25 μmol/L) on P-gp-mediated transport of Rhodamine123 (0.1 μmol/L) and digoxin (0.054 μmol/L) was investigated in human breast cancer cells (MDA435T0.3) expressing human P-gp or Caco-2 cells. Ceritinib inhibited transport of Rhodamine123 and digoxin with the IC_{50} of 4.5 and 8.6 μmol/L, respectively.

- The inhibitory effect of ceritinib (1.3-20 or 1.0-25 μmol/L) on BCRP-mediated transport of Bodipy FL prazosin (BDP, 0.05 μmol/L) and estrone-3-sulfate was investigated in human ovarian cancer cells (IGROV1) expressing human BCRP or Caco-2 cells. Ceritinib inhibited transport of BDP and estrone-3-sulfate with the IC_{50} of 7.5 and 8.9 μmol/L, respectively.

- The inhibitory effect of ceritinib (1.0-25 μmol/L) on MRP2-mediated transport of CDCFDA (1.0 μmol/L) was investigated in Caco-2 cells. The inhibitory effect of ceritinib on MRP2 was not evident even at the highest concentration investigated.

- The inhibitory effect of ceritinib (0.05-5 μmol/L) on OAT1- or OAT3-mediated transport of the substrates* of the transporters was investigated in HEK293 cells expressing human OAT1 or OAT3. Ceritinib at 5 μmol/L inhibited transport of the OAT1 substrate by 16.3%. In contrast, the inhibitory effect of ceritinib on OAT3 was not evident even at the highest concentration investigated.

- The inhibitory effect of ceritinib (0.01-5 μmol/L) on OATP1B1- or OATP1B3-mediated transport of the substrates* of the transporters was investigated in HEK293 cells expressing human OATP1B1 or OATP1B3. Ceritinib at 5 μmol/L inhibited transport of the substrates of OATP1B1 and OATP1B3 by 31.8% and 24.1%, respectively.

- The inhibitory effect of ceritinib (0.05-5 μmol/L) on OCT1- or OCT2-mediated transport of the substrates* of the transporters was investigated in HEK293 cells expressing human OCT1 or OCT2. Ceritinib at 5 μmol/L inhibited transport of the OCT2 substrate by 35.4%. In contrast, the inhibitory effect of ceritinib on OCT1 was not evident even at the highest concentration investigated.

  * Transporter substrates used in the studies include ^{3}H-labeled cidofovir (1.4 μmol/L) for OAT1, ^{3}H-labeled estrone-3-sulfate (0.73 μmol/L) for OAT3, ^{3}H-labeled estradiol-17β-D-glucuronide (1.6 μmol/L) for OATP1B1 and OATP1B3, ^{3}H-labeled *N*-methyl-4-phenylpyridinium (7.3 nmol/L) for OCT1, and ^{14}C-labeled metformin (11.3 nmol/L) for OCT2.

3.(ii).B Outline of the review conducted by PMDA

Based on the submitted data and the following review, PMDA concluded that the applicant's discussions on absorption, distribution, metabolism, excretion, and pharmacokinetic interactions of ceritinib are acceptable.

3.(ii).B.(1) Tissue distribution

In consideration of the findings suggestive of melanin binding of ceritinib or its metabolites, PMDA asked the applicant to explain whether distribution of ceritinib and its metabolites in melanin-containing tissues may raise safety concerns in clinical settings.

The applicant's response:
The results of the tissue distribution study in pigmented rats suggest that ceritinib potentially accumulate in melanin-containing tissues when used in accordance with the proposed dosage and administration. However, distribution of ceritinib or its metabolites in melanin-containing tissues is unlikely to cause safety issues in clinical settings, in light of the following points:

- No ceritinib-related toxicity findings were observed in melanin-containing tissues including the eyes and skin in a 39-week repeat-dose toxicity study in monkeys [see "3.(iii).A.(2).6) Thirty-nine-week oral dose toxicity study in monkeys"].
- In 2 global phase II studies in patients with *ALK*-positive NSCLC (Studies A2201 and A2203), eye disorders occurred in 8.6% (12 of 140) of patients and 8.1% (10 of 124) of patients, respectively, and skin and subcutaneous tissue disorders occurred in 35.7% (50 of 140) of patients and 29.8% (37 of 124) of patients, respectively. Of these, eye disorder (1 subject) in Study A2201 as well as rash, rash maculo-papular, and photosensitivity reaction (1 subject each) in Study A2203 were Grade ≥3 events. None of them resulted in treatment discontinuation, and all were controllable with treatment interruption. Grade ≥3 adverse events which were more common in Japanese patients than in Caucasian patients were only rash maculo-papular and photosensitivity reaction (1 subject each) in Study A2203.

PMDA accepted the applicant's explanation.

3.(ii).B.(2) Pharmacokinetic interactions

An *in vitro* study has demonstrated that ceritinib is mainly metabolized by CYP3A [see "3.(ii).A.(3).1) *In vitro* metabolism"]. In response to the finding, clinical studies were conducted to investigate pharmacokinetic interactions between ceritinib and CYP3A inhibitors or inducers [see "4.(ii).A.(3) Drug interaction studies"]. In addition, *in vitro* studies have suggested that ceritinib inhibits CYP2C9, CYP3A, P-gp, and BCRP and serves as a substrate of P-gp [see "3.(ii).A.(5).1) Enzyme inhibition" and "3.(ii).A.(5).3) Transporters"].

The applicant's explanation of clinical studies on pharmacokinetic interactions between ceritinib and substrates of CYP2C9, CYP3A, P-gp, and BCRP or P-gp inhibitors:
The applicant will conduct a clinical study (Study CLDK378A2103) overseas to investigate pharmacokinetic interactions between ceritinib and a CYP2C9 substrate (warfarin) or a CYP3A

substrate (midazolam). On the other hand, no clinical studies on pharmacokinetic interactions between ceritinib and substrates of P-gp or BCRP or P-gp inhibitors are planned for the following reasons:

- No safety concerns attributable to pharmacokinetic interactions between ceritinib and substrates of P-gp or BCRP have been suggested at present.
- In Studies A2201 and A2203 in patients with *ALK*-positive NSCLC, the overall incidence of adverse events in the patients receiving ceritinib concomitantly with a P-gp inhibitor was 100% (6 of 6 patients) and 100% (2 of 2 patients), respectively, while that in the patients not on concomitant P-gp inhibitors was 100% (134 of 134 patients) and 99.2% (120 of 121 patients), respectively. The incidence of Grade ≥3 adverse events in the patients receiving ceritinib concomitantly with a P-gp inhibitor was 33.3% (2 of 6 patients) and 50% (1 of 2 patients), respectively, while that in the patients not on concomitant P-gp inhibitors was 70.1% (94 of 134 patients) and 65.3% (79 of 121 patients), respectively. Based on the above findings, at present no safety concerns attributable to pharmacokinetic interactions have been identified in patients receiving ceritinib concomitantly with a P-gp inhibitor, although the number of patients treated with ceritinib in combination with a P-gp inhibitor was limited.

PMDA's view:
Because information on CYP2C9- and CYP3A-mediated pharmacokinetic interactions of ceritinib is important for ensuring the proper use of ceritinib, data from Study CLDK378A2103 should be appropriately communicated to healthcare professionals when they become available.

In the clinical studies conducted so far, no serious safety concerns attributable to pharmacokinetic interactions between ceritinib and substrates of P-gp and BCRP or P-gp inhibitors have been identified. However, information on P-gp- and BCRP-mediated pharmacokinetic interactions of ceritinib is still important for ensuring the proper use of ceritinib. The relevant information should continue to be collected. Any useful information should be communicated to healthcare professionals when it becomes available.

3.(iii) Summary of toxicology studies

3.(iii).A Summary of the submitted data

In *in vivo* studies, 0.5% (w/v) methylcellulose solution was used as vehicle unless otherwise specified.

3.(iii).A.(1) Single-dose toxicity

Escalating single oral dose toxicity study in monkeys (Reference data)

Two male cynomolgus monkeys were orally given a single rising dose of ceritinib 20, 60, 120, and 250 mg/kg/day on Day 1, Day 6, Day 12, and Day 19, respectively.

No deaths occurred during the study period. Diarrhea, loose stool, and increases in aspartate aminotransferase (AST), alanine aminotransferase (ALT), and creatine kinase as well as decreased cholesterol were observed at doses of ≥120 mg/kg. Emesis with feed was observed after administration of the 250 mg/kg dose.

Based on the above, the approximate lethal dose was determined to be >250 mg/kg.

3.(iii).A.(2) Repeat-dose toxicity

3.(iii).A.(2).1 Four-week repeated oral dose toxicity study in rats

Ceritinib was orally administered at a dose of 0 (vehicle), 7.5, 25, or 75 mg/kg/day for 4 weeks to rats (Wistar Hannover, n = 10-16/sex/group). Six females and 6 males in each of the 0 and 75 mg/kg/day groups had a 4-week recovery period after the end of treatment, and then the reversibility of toxicity was assessed.

As decreases in body weight and food consumption occurred in the 75 mg/kg/day group, the treatment was interrupted for 4 days starting on Day 9 and then resumed at a reduced dose of 50 mg/kg/day.

No deaths occurred during the study period. Findings at doses of ≥25 mg/kg/day included reduced body weight gain; increased neutrophil count; increases in fibrinogen, globulin, and insulin levels; decreased

albumin/globulin ratio; erosion and hyperplasia of the extra-hepatic bile duct; epithelial mixed cell inflammation, necrosis, and vacuolation of the extra-hepatic bile duct; epithelial vacuolation of the intra-hepatic bile duct; foamy alveolar macrophage aggregates in the lung; macrophage aggregates in the mesenteric lymph node; and inflammatory cell infiltration in the pancreatic stroma. Findings at 75 mg/kg/day included increases in monocyte count and platelet count; increases in AST, ALT, and potassium levels; decreased albumin level; dilation of the extra-hepatic bile duct and increased mitotic figures in the extra-hepatic bile duct; decreased weights of the spleen, thymus, prostate, and pituitary gland; sinus histiocytosis in the mesenteric lymph node; pancreatic acinar atrophy; and alveolar macrophages and laminar structures in the intra-hepatic bile duct epithelium. In addition, findings included increases in lymphocyte count and calcium and glucose levels as well as decreases in reticulocyte count and urea, magnesium, and inorganic phosphate levels. These findings resolved after dose reduction to ceritinib 50 mg/kg/day.

At the end of the recovery period, all of these findings were reversible or tended to be reversible.

Based on the above, the no observed adverse effect level (NOAEL) in this study was determined to be 7.5 mg/kg/day.

3.(iii).A.(2).2) Thirteen-week repeated oral dose toxicity study in rats

Ceritinib was orally administered at a dose of 0 (vehicle), 3, 10, or 30 mg/kg/day for 13 weeks to rats (Wistar Hannover, n = 10-16/sex/group). Six females and 6 males in each of the 0 and 30 mg/kg/day groups had an 8-week recovery period after the end of treatment and then the reversibility of toxicity was assessed.

No deaths occurred during the study period. Findings at doses of ≥3 mg/kg/day included degeneration/necrosis, dilation, erosion/ulcer, hyperplasia, chronic inflammation, and epithelial vacuolation of the extra-hepatic bile duct, and degeneration/necrosis and epithelial vacuolation of the major duodenal papillae. Findings at doses of ≥10 mg/kg/day included increased thyroid-stimulating hormone level and epithelial vacuolation of the intrahepatic bile duct. Findings at 30 mg/kg/day included reduced body weight gain; decreased food consumption; increased platelet count; increases in fibrinogen, total protein, calcium, triiodothyronine, thyroxine, cholesterol, and globulin levels; decreased albumin level; decreased albumin/globulin ratio; and decreased triglyceride level; swelling of the extra-hepatic bile duct; chronic inflammation, hyperplasia, and lumenal dilation in the major duodenal papilla; foamy alveolar macrophage aggregates in the lung; and macrophage aggregates in the mesenteric lymph node. Increases in platelet count and fibrinogen and total protein levels were considered related to inflammatory changes as pathological findings. Increases in thyroid-stimulating hormone, triiodothyronine and thyroxine levels were considered to be of little toxicological significance, because neither weight change nor pathological findings were observed in the thyroid or the pituitary gland.

At the end of the recovery period, all of these findings were reversible or tended to be reversible.

Based on the above, the NOAEL in this study was determined to be <3 mg/kg/day.

3.(iii).A.(2).3) Twenty-six-week oral dose toxicity study in rats

Ceritinib was orally administered at a dose of 0 (vehicle), 3, 10, or 20 mg/kg/day for 26 weeks to rats (Wistar Hannover, n = 20-30/sex/group). Ten females and 10 males in each of the 0 and 20 mg/kg/day groups had an 8-week recovery period after the end of treatment, and then the reversibility of toxicity was assessed.

No treatment-related deaths occurred during the study period. Findings at doses ≥3 mg/kg/day included decreases in magnesium and inorganic phosphate levels; degeneration/necrosis, erosion/ulcer, hyperplasia, chronic inflammation, and epithelial vacuolation of the extra-hepatic bile duct; chronic inflammation of the hepatic portal connective tissue; and macrophage aggregates in the mesenteric lymph node. Findings at doses ≥10 mg/kg/day included increased globulin level; decreased albumin level; decreased albumin/globulin ratio; degeneration/necrosis, epithelial vacuolation, and chronic inflammation of the major duodenal papilla; epithelial vacuolation of the intra-hepatic bile duct; and

foamy alveolar macrophage aggregates in the lung. Findings at 20 mg/kg/day included reduced body weight gain, decreases in hemoglobin and hematocrit levels, decreased mean corpuscular volume, decreases in mean corpuscular haemoglobin and triglyceride levels, discoloration in the lung, dilation/swelling of the extra-hepatic bile duct, and epithelial hyperplasia of the major duodenal papilla.

At the end of the recovery period, all of these findings were reversible or tended to be reversible.

Based on the above, the NOAEL in this study was determined to be <3 mg/kg/day. The $AUC_{0\text{-}24h}$ value (1760 ng·h/mL) of ceritinib at 3 mg/kg/day was approximately 0.07-fold the human exposure at the clinical dose.*

* In Japanese phase I study (Study X1101), the $AUC_{0\text{-}24h}$ in Japanese patients with solid cancer receiving oral ceritinib 750 mg QD was 26,400 ng·h/mL.

3.(iii).A.(2).4) Four-week oral dose toxicity study in monkeys

Ceritinib was orally administered at a dose of 0 (vehicle), 3, 10, or 30 mg/kg/day for 4 weeks to cynomolgus monkeys (n = 3-5/sex/group). Two females and 2 males in each of the 0 and 30 mg/kg/day groups had a 4-week recovery period after the end of treatment, and then the reversibility of toxicity was assessed.

No deaths occurred during the study period. Findings included small thyroid gland in males at a dose of 10 mg/kg/day, and decreased thyroid gland weight and small follicles with decreased amount of colloids in the thyroid gland in males at doses of ≥10 mg/kg/day. Because (1) the changes in the thyroid gland was observed only in males and (2) the weight and morphology of the thyroid gland are highly variable among individual monkeys in general, the relationship between the changes and ceritinib was considered to be unknown. Animals with changes in the thyroid gland did not show any changes in body weight or clinical signs suggestive of decreased thyroid function. Thus these changes were considered to be of little toxicological significance. Findings in females at doses ≥10 mg/kg/day and males at 30 mg/kg/day included sinus histiocytosis in the mesenteric lymph node. Findings at 30 mg/kg/day included increased ALT; epithelial erosion, hyperplasia, and vacuolation of the hepatopancreatic ampulla; foamy macrophage infiltration in the submucosa of the hepatopancreatic ampulla; neutrophilic infiltration of the hepatopancreatic ampulla and adjacent duodenal mucosa; decreased zymogen granules in the pancreas; and lymphoid depletion of the thymus. Sinus histiocytosis in the mesenteric lymph nodes in females in the 10 mg/kg/day group was considered to be of little toxicological significance, because the change was mild in severity.

At the end of the recovery period, small follicle with decreased amount of colloids in the thyroid gland was observed in 1 male at a dose of 30 mg/kg/day, but other findings were reversible or tended to be reversible.

Based on the above, the NOAEL in this study was determined to be 10 mg/kg/day.

3.(iii).A.(2).5) Thirteen-week oral dose toxicity study in monkeys

Ceritinib was orally administered at a dose of 0 (vehicle), 3, 10, or 30 mg/kg/day for 13 weeks to cynomolgus monkeys (n = 4-6/sex/group). Two females and 2 males in each of the 0 and 30 mg/kg/day groups had an 8-week recovery period after the end of treatment, and then the reversibility of toxicity was assessed.

No deaths occurred during the study period. Vomiting occurred in males at doses ≥3mg/kg/day. Findings at 30 mg/kg/day included liquid feces, increased ALT, and mixed cell inflammation around the intra-hepatic bile duct, including mixed cell inflammation and epithelial vacuolation of the hepatic duct, cystic duct, common bile duct, and major duodenal papilla. Vomiting and liquid feces were considered to be of little toxicological significance, because they occurred sporadically and did not affect body weight or food consumption. Increased ALT was not accompanied by histopathological changes related to the liver and considered to be of little toxicological significance. Histopathological changes in the hepatic duct, cystic duct, common bile duct, and major duodenal papilla and around the intrahepatic bile duct were mild in severity and considered to be of little toxicological significance. Increased thyroid-stimulating hormone level and diffuse hyperplasia of thyroid follicular cells were observed in males at 30 mg/kg/day,

but these findings in the thyroid gland were considered to be changes unrelated to ceritinib, because they occurred in only 1 of 4 males and no changes in the thyroid gland were identified in the 30 mg/kg/day group in the 39-week oral dose toxicity study in monkeys [see "3.(iii).A.(2).6) Thirty-nine-week oral dose toxicity study in monkeys"].

At the end of the recovery period, all of these findings were reversible.

Based on the above, the NOAEL in this study was determined to be 30 mg/kg/day.

3.(iii).A.(2).6) Thirty-nine-week oral dose toxicity study in monkeys

Ceritinib was orally administered at a dose of 0 (vehicle), 3, 10, or 30 mg/kg/day for 39 weeks to cynomolgus monkeys (n = 4-6/sex/group). Two females and 2 males in each of the 0 and 30 mg/kg/day groups had an 8-week recovery period after the end of treatment and then the reversibility of toxicity was assessed.

One of 4 males in the 10 mg/kg/day group was sacrificed moribund during the study period because of repeated watery stool. No other animals died during the study period. The sacrificed animal was found to have infiltration of mononuclear cells and eosinophils in the gastrointestinal tract, but no dose-response relationship was identified. Thus, this finding was considered to be unrelated to ceritinib. Findings at doses of ≥10 mg/kg/day included increased frequency of mixed cell inflammation in the major duodenal papilla, macrophage infiltration in the lamina propria mucosae, and sinus histiocytosis in the mesenteric lymph node. Findings at 30 mg/kg/day included salivation, reduced body weight gain, increased ALT, and mixed cell inflammation in the common bile duct and cystic duct. All of these findings were mild in severity and considered to be of little toxicological significance.

At the end of the recovery period, all of these findings were reversible or tend to resolve.

Based on the above, the NOAEL in this study was determined to be 30 mg/kg/day. The $AUC_{0\text{-}24h}$ value (24,100 ng·h/mL) of ceritinib at 30 mg/kg/day was approximately 0.9-fold the human exposure at the clinical dose.*

* In Japanese phase I study (Study X1101), the $AUC_{0\text{-}24h}$ of ceritinib in Japanese patients with solid cancer receiving oral ceritinib 750 mg QD was 26,400 ng·h/mL.

3.(iii).A.(3) Genotoxicity

3.(iii).A.(3).1) Bacterial reverse mutation assay

The reverse mutation assays using *Salmonella typhimurium* (TA98, TA100, TA1535, TA102, and TA97a) demonstrated that ceritinib was not mutagenic.

3.(iii).A.(3).2) Test for induction of chromosomal aberrations in human peripheral blood lymphocytes

In the tests for induction of chromosomal aberrations in human peripheral blood lymphocytes, ceritinib at concentrations ≥2.0 μg/mL induced chromosomal numerical aberrations (aneuploidy) both with and without metabolic activation, but did not increase chromosomal structural aberrations.

3.(iii).A.(3).3) Micronucleus test

In the micronucleus tests using human lymphoblastoid TK6 cells (reference data), ceritinib at concentrations ≥2.6 μg/mL weakly induced micronuclei. In a micronucleus test in rats (evaluation data), no micronuclei were induced at a dose*2 which is inferred to provide exposure equivalent to the human exposure at the recommended clinical dose.*1 Ceritinib was considered unlikely to induce micronuclei in clinical settings.

*1 In Japanese phase I study (Study X1101), the $AUC_{0\text{-}24h}$ of ceritinib in Japanese patients with solid cancer receiving oral ceritinib 750 mg QD was 26,400 ng·h/mL.

*2 The $AUC_{0\text{-}24h}$ of ceritinib at a dose of 75 mg/kg/day on Day 1 in the 4-week oral dose toxicity study in rats was 41,200 ng·h/mL, and the $AUC_{0\text{-}24h}$ of ceritinib at a dose of 2000 mg/kg in the micronucleus test in rats was estimated to exceed 41,200 ng·h/mL.

3.(iii).A.(4) Carcinogenicity

No carcinogenicity studies have been conducted with ceritinib because the drug product is being developed as a therapy for advanced or recurrent NSCLC.

3.(iii).A.(5) Reproductive and developmental toxicity

3.(iii).A.(5).1) Study of fertility and early embryonic development to implantation

No studies of fertility and early embryonic development to implantation have been conducted with ceritinib because ceritinib is being developed as a therapy for patients with advanced or recurrent NSCLC.

The applicant considers that ceritinib is unlikely to affect female or male fertility, because no histopathological changes related to ceritinib were observed in the female and male reproductive organs in repeat-dose toxicity studies in rats for up to 26 weeks and repeat-dose toxicity studies in monkeys for up to 39 weeks [see "3.(iii).A.(2) Repeat-dose toxicity"].

3.(iii).A.(5).2) Embryo-fetal development study

i) Embryo-fetal development study in rats

Ceritinib was orally administered at a dose of 0 (vehicle), 1, 10, or 50 mg/kg/day to pregnant rats (Wistar Hannover, n = 27-29/group) from gestation day 6 to gestation day 17. Three to 5 animals per group were subjected to toxicokinetic (TK) evaluation.

No deaths occurred during the study period. In dams, reduced body weight gain and decreased food consumption occurred at 50 mg/kg/day. In embryos and fetuses, the overall incidence of skeletal abnormalities (77.0%) at 50 mg/kg/day was higher than the historical control range (47.9%-70.6%), but the finding was unlikely to be related to ceritinib, because the incidence of individual skeletal abnormalities was comparable to that in the control group.

Based on the above, the NOAELs for maternal and fetal toxicity in this study were determined to be 10 and 50 mg/kg/day, respectively.

Exposure to ceritinib increased with increasing dose in dams, and the maternal plasma concentrations were 7- to 20-fold the fetal plasma concentrations. The $AUC_{0\text{-}24h}$ values (2940 and 14,900 ng·h/mL) at the NOAEL for maternal and fetal toxicity (10 and 50 mg/kg/day) were approximately 0.1- and 0.6-fold the human exposure at the clinical dose.*

* In Japanese phase I study (Study X1101), the $AUC_{0\text{-}24h}$ of ceritinib in Japanese patients with solid cancer receiving oral ceritinib 750 mg QD was 26,400 ng·h/mL.

ii) Embryo-fetal development study in rabbits

Ceritinib was orally administered at a dose of 0 (vehicle), 2, 10, or 25 mg/kg/day to pregnant rabbits (New Zealand White, n = 23-25/group) from gestation day 7 to gestation day 20. Three to 5 animals per group were subjected to TK evaluation.

One of 20 animals in the 25 mg/kg/day group was sacrificed moribund on gestation day 18 because of poor clinical condition possibly caused by medication error. No other treatment-related deaths occurred during the study period.

In dams in the 25 mg/kg/day group, reduced body weight gain and decreased food consumption occurred. In embryos and fetuses, the incidence of skeletal abnormalities in the sternebra (42.9%-51.4%) was high at doses ≥2 mg/kg/day, but the finding was unlikely to be related to ceritinib, because the incidence was not dose-dependent and was within the historical control range (22.8%-74.0%).

Based on the above, the NOAELs for maternal and fetal toxicity in this study were determined to be 10 and 25 mg/kg/day, respectively.

Exposure to ceritinib increased with increasing dose in dams, and the maternal plasma concentrations were 12.8- to 18.9-fold the fetal plasma concentrations. The $AUC_{0\text{-}24h}$ values at the NOAELs for

maternal and fetal toxicity (10 and 25 mg/kg/day) were 2340 and 11,200 ng·h/mL, respectively, being approximately 0.1- and 0.4-fold the human exposure at the clinical dose,* respectively.

* In Japanese phase I study (Study X1101), the $AUC_{0\text{-}24h}$ of ceritinib in Japanese patients with solid cancer receiving oral ceritinib 750 mg QD was 26,400 ng·h/mL.

The exposure in dams at the high dose in the embryo-fetal development studies in rats and rabbits was lower than the human exposure at the recommended clinical dose (i.e., the $AUC_{0\text{-}24h}$ values in rats and rabbits were approximately 0.6-fold and 0.4-fold the human exposure, respectively), and thus the possibility of fetal skeletal abnormalities caused by ceritinib in clinical use cannot be ruled out. The applicant therefore explained that the following precautionary statement will be included in the package insert: Ceritinib should not be used in pregnant women or possibly pregnant women unless the expected therapeutic benefits outweigh the possible risks associated with the treatment; and women of childbearing potential should be advised to use appropriate contraception measures.

3.(iii).A.(6) Other toxicity studies

3.(iii).A.(6).1) Safety evaluation of impurities

The acceptance criteria for Impurity A and Impurity B in the drug substance (≤[redacted]% for both) exceeded the safety threshold defined in "Guideline for Impurities in New Drug Substances" (PFSB/ELD Notification No. 1216001 dated December 16, 2002, issued by the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau). The safety of these impurities was evaluated.

The applicant's explanation:

Impurity A and Impurity B were evaluated for general toxicity. In the 4-week oral dose toxicity studies in rats and monkeys, the estimated amount of these impurities administered to animals in the high dose groups exceeded the maximum daily intake* of these impurities at the clinical dose [see "3.(iii).A.(2).1) Four-week oral dose toxicity study in rats" and "3.(iii).A.(2).4) Four-week oral dose toxicity study in monkeys"]. Therefore, the safety of these impurities at the upper limit of acceptance criteria has been confirmed.

Genotoxicity attributable to Impurity A or Impurity B is unlikely to develop in patients treated with ceritinib for the following reasons: (a) ceritinib was not mutagenic in the bacterial reverse mutation assays; (b) ceritinib induced chromosomal numerical aberrations were in the chromosomal aberration tests, but the concentrations of these impurities in ceritinib at the relevant concentration were higher than the estimated maximum exposure to these impurities at the clinical dose [see "3.(iii).A.(3) Genotoxicity"]; and (c) *in silico* analyses using DEREK (v.4.0.5), Case Ultra (v.1.5.0.1), and Sarah (v.1.1.2) did not suggest genotoxicity of either impurity.

* The maximum amounts of Impurity A and Impurity B potentially present in ceritinib at a dose of 750 mg/day were calculated based on the (upper limit of) acceptance criteria for Impurity A and Impurity B.

3.(iii).A.(6).2) Phototoxicity

The phototoxic potential of ceritinib was investigated because [redacted].

i) *In vitro* phototoxicity (Reference data)

To assess cytotoxicity of ceritinib with and without UV-A irradiation, *in vitro* phototoxicity test using mouse 3T3 fibroblasts was conducted twice. The resulting photo irritation factor values were 5.1 and 8.1, suggesting that ceritinib has phototoxic potential.

ii) *In vivo* phototoxicity study in mice

Albino mice (n = 6 females/group) orally received ceritinib at a dose of 0, 10, 30, or 100 mg/kg/day and then underwent ultraviolet irradiation. No findings suggesting phototoxicity were observed. Findings were incomplete eyelid opening in the ≥30 mg/kg/day groups and decreased locomotor activity in the 100 mg/kg/day group, but all were transient. These findings were therefore considered to be of little toxicological significance.

Based on the above, ceritinib was unlikely to have phototoxic potential.

3.(iii).B Outline of the review conducted by PMDA

Based on the submitted data and the following review, PMDA has concluded that no concerns over the clinical use of ceritinib were identified in the non-clinical toxicity evaluation.

Effect on the thyroid

In the 4-week and 13-week oral dose toxicity studies in monkeys, increased thyroid hormone levels or histopathological changes in the thyroid were observed. PMDA asked the applicant to explain the relationship of these findings with ceritinib and the potential effects of ceritinib on the thyroid in patients in clinical use.

The applicant's response:

The relationship of ceritinib and the small follicles with decreased amount of colloids in the thyroid observed in the 4-week oral dose toxicity study in monkeys cannot be ruled out. However, the morphology of the thyroid is greatly variable among individual monkeys, even untreated ones. The animals with changes in the thyroid did not show any changes in body weight or clinical signs which were suggestive of decreased thyroid function. These changes were therefore considered to be of little toxicological significance. Increased thyroid-stimulating hormone level and hyperplasia of thyroid follicular cells in the 13-week oral dose toxicity study in monkeys were considered to be unrelated to ceritinib, because (1) the changes occurred in only 1 of the 4 males in the 30 mg/kg/day group, and (2) no changes were observed in the thyroid at 30 mg/kg/day in the 39-week oral dose toxicity study in monkeys. In the clinical studies of ceritinib, no treatment-related effects on the thyroid were observed.

As described above, changes in the thyroid are unlikely to be related to ceritinib. There is little need to provide information on the changes in the thyroid observed in the 4-week and 13-week oral dose toxicity studies in monkeys.

PMDA accepted the applicant's explanation.

4. Clinical data

4.(i) Summary of biopharmaceutic studies and associated analytical methods

4.(i).A Summary of the submitted data

Formulations used in the clinical studies of ceritinib are capsules ([redacted], [redacted], and 150 mg) and [redacted] ([redacted]) (the table below). The commercial formulation is the same as the 150 mg capsule formulation used in the clinical studies.

Formulations used in clinical studies

Formulation	Strength	Study
Capsule	[redacted], [redacted], and 150 mg	Foreign phase I study (Study CLDK378X2101)
	[redacted] and 150 mg	Japanese phase I study (Study CLDK378X1101), foreign phase I study (Study CLDK378A2101)
	150 mg	Foreign phase I studies (Studies CLDK378A2104, CLDK378A2105, CLDK378A2106, and CLDK378A2108), global phase II studies (Studies CLDK378A2201 and CLDK378A2203)
[redacted]	[redacted]	Foreign phase I study (Study CLDK378A2108)

4.(i).A.(1) Assay

In the foreign phase I study (Study CLDK378A2108), the quantitative analysis of ceritinib in human plasma samples was performed by laser diode thermal desorption-atmospheric pressure chemical ionization coupled to tandem mass spectrometry (LDTD-APCI-MS/MS) (lower limit of quantitation [LLOQ], 5 ng/mL), and liquid chromatography-tandem mass spectrometry (LC-MS/MS) was used in other clinical studies (LLOQ, 1 ng/mL).

4.(i).A.(2) Foreign phase I study (5.3.1.1-1, Study CLDK378A2101 [[redacted] to [redacted] 20[redacted]])

A crossover study was conducted in 28 healthy adult subjects to investigate the effect of food on the PK of ceritinib.

A single dose of ceritinib 500 mg was orally administered (a) under fasted conditions (fasting for ≥10 hours pre-dose and for ≥4 hours post-dose) or after a low-fat meal (approximately 330 total calories, with 20% of the calories from fat), or (b) under fasted conditions or after a high-fat meal (approximately 1000 total calories, with 50% of the calories from fat). A washout period of 14 days was included between Period 1 and Period 2.

PK parameters of ceritinib administered under fasted conditions, after a low-fat meal, or after a high-fat meal are shown in the table below. The ratios [90% confidence interval (CI)]* of geometric mean C_{max} and AUC_{inf} of ceritinib administered after a low-fat meal to those under fasted conditions were 1.43 [1.21, 1.71] and 1.58 [1.34, 1.86], respectively, while the ratios [90% CI]* of geometric mean C_{max} and AUC_{inf} of ceritinib administered after a high-fat meal to those under fasted conditions were 1.41 [1.18, 1.68] and 1.73 [1.46, 2.05], respectively, indicating that exposure to ceritinib after a low-fat meal or a high-fat meal is higher than that under fasted conditions. The applicant considers that food consumption may have stimulated secretion of digestive juice such as bile acid, resulting in increased solubility of ceritinib, thereby enhancing the absorption of ceritinib in the gastrointestinal tract.

* Analysis was performed in a linear mixed-effects model using administration condition, treatment duration, and treatment order as fixed effects and subjects as a random effect.

PK parameters of ceritinib administered under fasted or fed conditions

Administration condition	n	C_{max} (ng/mL)	t_{max}* (h)	$t_{1/2}$ (h)	AUC_{inf} (ng·h/mL)
Fasted condition	27	159 (43.5)	8.0 (6.0, 12.0)	36.2 (23.9)	6910 (41.8)
After a low-fat meal	14	220 (19.7)	7.0 (3.0, 12.1)	34.6 (11.9)	10,300 (22.6)
After a high-fat meal	14	235 (29.4)	10.0 (6.0, 12.0)	34.2 (15.2)	12,700 (31.7)

Geometric mean (geometric coefficient of variation [CV] %); *, Median (range)

4.(i).A.(3) Foreign phase I study (5.3.1.1-2, Study CLDK378A2108 [[redacted] to [redacted] 20[redacted]])

A crossover study was conducted in 12 healthy adult subjects to investigate the effect of food on the PK of ceritinib.

A single dose of ceritinib 750 mg (five 150 mg capsules) was orally administered under fasted conditions (fasting for ≥10 hours pre-dose and for ≥4 hours post-dose) or after a light snack (approximately 118 total calories, with approximately 11% of the calories from fat; or 275 total calories, with approximately 4.6% of the calories from fat). A washout period of 16 days was included between Period 1 and Period 2.

PK parameters of ceritinib administered under fasted conditions or after a light snack are shown in the table below. The ratios [90% CI]* of geometric mean C_{max} and AUC_{inf} of ceritinib after a light snack to those under fasted conditions were 1.45 [1.15, 1.82] and 1.54 [1.19, 1.99], respectively, indicating that exposure to ceritinib after a light snack is higher than that under fasted conditions.

* Analysis was performed in a linear mixed-effects model using administration condition, treatment duration, and treatment order as fixed effects and subjects as a random effect.

PK parameters of ceritinib administered under fasted or fed conditions

Administration condition	C_{max} (ng/mL)	t_{max}* (h)	$t_{1/2}$ (h)	AUC_{inf} (ng·h/mL)
Fasted conditions	213 (71.7)	6.0 (6.0, 10.0)	35.6 (13.0)	9390 (82.2)
After a light meal	308 (39.9)	8.0 (6.0, 10.1)	40.2 (25.2)	14,500 (41.7)

Geometric mean (geometric CV%); n = 12; *, Median (range)

A single dose of ceritinib 750 mg (five 150 mg tablets or five 150 mg capsules) was orally administered to 12 healthy adult subjects under fasted conditions to investigate the bioavailability of the ceritinib 150 mg tablets relative to the ceritinib 150 mg capsules. The ratios of geometric mean C_{max} and AUC_{inf} of the ceritinib 150 mg tablets to the ceritinib 150 mg capsules were 1.03 [0.86, 1.24] and 1.04 [0.82, 1.32], respectively.

4.(i).B Outline of the review conducted by PMDA

4.(i).B.(1) Food effect

The applicant's explanation of the timing of administration of ceritinib:
The results of the foreign phase I studies (Studies CLDK378A2101 and CLDK378A2108) suggested that food increase exposure to ceritinib [see "4.(i).A.(2) Foreign phase I study" and "4.(i).A.(3) Foreign phase I study"]. In a global phase II study (Study CLDK378A2201 [Study A2201]), the protocol initially required that ceritinib should be administered at "≥2 hours before or after a meal." Consequently, the study demonstrated the efficacy and safety of ceritinib. The rule was later changed to "≥1 hour before or ≥2 hours after a meal" in consideration of convenience of patients, but in Study A2201, ceritinib was administered to all the patients in the ceritinib group ≥2 hours before or after a meal, because (1) the amendment was made after completion of enrollment of all the patients, and (2) the study protocol specified that ceritinib should be administered at the same time every day.

Based on the above, the "Precautions for Dosage and Ddministration" section will include a precautionary statement that ceritinib should not be administered within 2 hours before or after a meal. Also, the dosage and administration will specify that ceritinib should be administered in the fasted state.

PMDA accepted the applicant's explanation.

4.(i).B.(2) Effect of gastric pH on PK of ceritinib

The applicant's explanation of the effect of increased gastric pH associated with low gastric acid levels and coadministration of proton-pump inhibitors (PPIs) on the PK of ceritinib:
Since the solubility of ceritinib is lower at pH 6.8 (0.01 mg/mL) than at pH 1.0 (11.9 mg/mL), increased gastric pH associated with low gastric acid levels and coadministration of PPIs possibly reduces absorption of ceritinib, resulting in decreased exposure. A clinical study (Study CLDK378A2113) is planned to investigate the effect of a PPI (esomeprazole) on the PK of ceritinib, and its data are expected to be available by [redacted], 20[redacted]. In Study A2201, the efficacy and safety of ceritinib did not clearly differ between patients receiving concomitant gastric pH-elevating agents such as PPIs (64 of 140 patients)* and those not receiving such agents (73 of 140 patients). At present, no clinical issues associated with changes in gastric pH have been identified.

* Patients receiving ceritinib concomitantly with a gastric pH-elevating agent for ≥50% of the duration of treatment with ceritinib. Three patients were excluded from the analysis because the date of the first dose or last dose of the concomitant drug was unknown for them.

PMDA's view:
Increased gastric pH may decrease exposure to ceritinib. This information should be communicated to healthcare professionals appropriately through information materials, etc. Data from the planned Study CLDK378A2113 should be communicated to healthcare professionals appropriately when the data become available.

4.(ii) Summary of clinical pharmacology studies

4.(ii).A Summary of the submitted data

The PK of ceritinib was evaluated in healthy adult subjects and patients with malignant tumor following administration of ceritinib alone and in combination with ketoconazole (KCZ) or rifampicin (RFP).

4.(ii).A.(1) Healthy adult subjects

Foreign phase I study (5.3.3.1-1, Study CLDK378A2105 [[redacted] to [redacted] 20[redacted]])

An open-label study was conducted in 6 healthy adult subjects (6 subjects included in PK analysis) to investigate metabolites and mass balance of ceritinib. Subjects received a single dose of [^{14}C]ceritinib 750 mg orally under fasted conditions. Radioactivity levels were measured in blood, plasma, urine, and feces and plasma ceritinib and metabolite concentrations were measured.

PK parameters of ceritinib and radioactivity in plasma and blood are shown in the table below. Unchanged ceritinib was mainly detected in plasma by 144 hours post-dose (accounting for 81.9% of total radioactivity in plasma). Metabolites detected in plasma accounted for ≤2.3% of the total radioactivity in plasma. The blood/plasma ratio of radioactivity detected by 24 hours post-dose was 1.65.

Radioactivity excreted in urine and feces by 15 days post-dose accounted for 1.3% and 91.0%, respectively, of the administered radioactive dose. Unchanged ceritinib was mainly detected in feces (accounting for 68.0% of the administered radioactive dose), and the major metabolites detected in feces were M35.8 (mono-oxygenated metabolite) and M23.6 (dealkylated metabolite) (accounting for 6.5% and 3.9%, respectively, of the administered radioactive dose).

PK parameters of ceritinib and radioactivity

Analyte	Measured sample	C_{max} (ngEq./mL)	t_{max}* (h)	$t_{1/2}$ (h)	$AUC_{0\text{-}24h}$ (ngEq.·h/mL)	AUC_{inf} (ngEq.·h/mL)	CL/F (L/h)
Radioactivity	Blood	373 (48.7)	6 (6, 10)	-	6620 (49.0)	-	-
	Plasma	244 (57.3)	6 (6, 10)	47.3 (14.4)	-	12,560 (67.7)	-
Ceritinib	Plasma	200 (61.2)	8 (6, 12)	40.8 (15.5)	-	9509 (75.1)	79.0 (75.0)

Geometric mean (geometric CV%); n = 6; -, Not applicable; *, Median (range)

4.(ii).A.(2) Patients with malignant tumor

4.(ii).A.(2).1) Japanese phase I study (5.3.5.2-4, Study CLDK378X1101 [ongoing since June 2012(data cut-off on August 2, 2013)])

An open-label, uncontrolled study was conducted to investigate the safety and PK of ceritinib in 19 patients with anaplastic lymphoma kinase (ALK)-positive advanced malignant tumor (18 patients evaluable for PK analysis). This study consisted of a dose-escalation phase and an expansion phase: (a) in the dose-escalation phase, a single dose of ceritinib at 300, 450, 600, or 750 mg was orally administered 2 hours after a meal, followed by a washout period of 2 days, and then multiple doses of ceritinib were orally administered once daily (QD) 2 hours after a meal; and (b) in the expansion phase, a single dose of ceritinib at 750 mg was orally administered 2 hours after a meal, followed by a washout period of 2 days, and then multiple doses of ceritinib were orally administered QD 2 hours after a meal. No meals were allowed until 2 hours after administration of ceritinib.

PK parameters of ceritinib in the dose-escalation phase are shown in the table below. The ratios of $AUC_{0\text{-}24h}$ following multiple doses of ceritinib 750 mg on Day 8 and Day 22 to that following a single dose of ceritinib 750 mg were 8.3 and 7.3, respectively, which were higher than the accumulation ratio predicted from the exposure after a single dose of ceritinib. This suggested that multiple-dose administration resulted in a more than dose-proportional increase in exposure to ceritinib. Given that ceritinib induces time-dependent inhibition of cytochrome P450 (CYP) 3A [see "3.(ii).A.(5).1) Enzyme inhibition"], the applicant considers that CYP3A inhibition mediated by multiple doses of ceritinib (the metabolizing enzyme of ceritinib) contributed to the more than dose-proportional increase in exposure.

PK parameters following single dose of ceritinib (dose-escalation phase)

Dose (mg)	n	C_{max} (ng/mL)	t_{max}*1 (h)	$t_{1/2}$ (h)	$AUC_{0\text{-}24h}$ (ng·h/mL)	CL/F (L/h)
300	2*2	166, 170	4.2, 6.0	19.7, 24.5	2730, 2780	42.6, 59.2
450	5	48.1 (176)	5.9 (3.0, 24.1)	21.6, 30.5*2*3	648 (169)	94.0, 829*2*3
600	4	126 (245)	6.0 (4.0, 6.0)	30.5 (11.6)	2080 (270)	26.4, 893*2*3
750	6	192 (46.0)	6.0 (2.9, 72.0)	33.2 (12.9)	3160 (66.9)	123*4

Geometric mean (geometric CV%); *1, Median (range); *2, Individual values; *3, n = 2; *4, n = 1

PK parameters following multiple doses of ceritinib (dose-escalation phase)

Dose (mg)	Day of measurement (Day)	n	C_{max} (ng/mL)	t_{max}*1 (h)	$AUC_{0\text{-}24h}$ (ng·h/mL)	CL_{ss}/F (L/h)
300	8	3	510 (41.3)	3.0 (3.0, 8.0)	10,000 (47.6)	29.9 (47.6)
	22	2*2	825, 908	6.0, 6.0	-	-
450	8	5	837 (25.1)	4.0 (0, 7.9)	18,100 (22.7)*3	24.9 (22.7)*3
	22	5	977 (11.1)	6.0 (4.0, 8.1)	20,600 (20.5)*4	21.8 (20.5)*4
600	8	4	880 (87.1)	3.4 (1.0, 4.0)	14,100 (83.7)*4	42.5 (83.7)*4
	22	4	1020 (64.6)	4.9 (3.9, 8.0)	10,600, 32,200*2*5	18.6, 56.6*2*5
750	8	6	1210 (17.3)	7.0 (3.0, 23.8)	25,400 (17.3)*6	29.6 (17.3)*6
	22	3	1440 (25.5)	1.9 (0, 6.0)	22,300, 30,500*2*5	24.6, 33.6*2*5

Geometric mean (geometric CV%); -, Not applicable; *1, Median (range); *2, Individual values; *3, n = 4; *4, n = 3; *5, n = 2; *6, n = 5

4.(ii).A.(2).2) Foreign phase I study (5.3.5.2-3, Study CLDK378X2101 [ongoing since January 2011 (data cut-off on August 2, 2013)])

An open-label, uncontrolled study was conducted to investigate the safety and PK of ceritinib in 304 patients with *ALK*-positive advanced malignant tumor (59 patients included in [a] dose-escalation phase and 245 patients included in [b] expansion phase) (59 patients from [a] and 242 patients from [b] were evaluable for PK analysis). This study consisted of a dose-escalation phase and an expansion phase: (a) in the dose-escalation phase, a single dose of ceritinib at a dose ranging from 50 to 750 mg was orally administered under fasted conditions (≥2 hours before and after a meal) followed by a washout period of 2 days, and then multiple doses of ceritinib were orally administered QD under fasted conditions; and (b) in the expansion phase, multiple doses of ceritinib 750 mg were orally administered QD under fasted conditions.

PK parameters following a single dose of and 8-day multiple doses of ceritinib in the dose-escalation phase are shown in the table below. According to the applicant, a linear regression analysis using a power model revealed almost dose-proportional increases in the C_{max} and $AUC_{0\text{-}24h}$ of ceritinib following a single dose across the studied dose range (50-750 mg).

PK parameters following single dose of ceritinib

Dose (mg)	n	C_{max} (ng/mL)	t_{max}[*1] (h)	$t_{1/2}$ (h)	$AUC_{0\text{-}24h}$ (ng·h/mL)	CL/F (L/h)	Vz/F (L)
50	1	13.1	6.0	19.5	226	126	3540
100	2[*2]	27.3, 31.5	6.0, 24.0	19.4[*3]	433, 504	116[*3]	3250[*3]
200	2[*2]	23.5, 68.9	4.2, 6.0	33.2[*3]	487, 1010	77.5[*3]	3720[*3]
300	3	198 (41.5)	4.0 (4.0, 6.0)	30.1 (10.0)	3440 (44.7)	34.6, 57.2[*2*4]	1340, 2630[*2*4]
400	12	120 (80.9)	5.0 (3.0, 6.7)	30.7 (39.1)[*5]	1920 (78.0)	95.9 (58.6)[*6]	3470 (74.4)[*6]
500	8	153 (86.5)	4.0 (3.0, 23.5)	31.1 (11.1)[*7]	2350 (87.9)	147 (170)[*8]	6230 (218.9)[*8]
600	9	212 (59.7)	6.0 (3.0, 24.1)	37.6 (24.6)[*9]	3590 (53.4)	43.2, 49.5[*2*4]	1930, 2050[*2*4]
700	4	206 (146)	6.0 (4.0, 25.0)	38.9 (98.4)[*8]	3450 (138)	52.1, 85.2[*2*4]	1610, 3400[*2*4]
750	10	186 (127)	6.0 (4.0, 23.8)	40.6 (34.7)[*10]	3390 (121)	88.5 (163)[*8]	4230 (164.4)[*8]

Geometric mean (geometric CV%); *1, Median (range); *2, Individual values; *3, n = 1; *4, n = 2; *5, n = 10; *6, n = 5; *7, n = 7; *8, n = 3; *9, n = 6; *10, n = 9

PK parameters following multiple doses of ceritinib (Day 8)

Dose (mg)	n	C_{max} (ng/mL)	t_{max}[*1] (h)	$AUC_{0\text{-}24h}$ (ng·h/mL)	CL_{ss}/F (L/h)
50	2[*2]	19.4, 32.4	2.0, 2.9	327, 578	86.5, 153
100	2[*2]	66.3, 88.8	3.0, 4.0	1150, 2010	49.7, 87.0
200	3	212 (18.0)	3.0 (3.0, 8.0)	4150 (32.2)	48.2 (32.2)
300	3	381 (168)	4.0 (3.0, 7.2)	2320, 25,300[*2*3]	11.9, 129[*2*3]
400	13	419 (69.7)	6.1 (3.0, 24.0)	7680 (77.4)[*4]	52.1 (77.4)[*4]
500	9	641 (40.0)	4.0 (1.9, 6.0)	12,300 (37.4)	40.7 (37.4)
600	9	688 (68.3)	4.0 (0, 23.6)	14,700 (71.7)[*5]	40.8 (71.7)[*5]
700	5	1140 (37.7)	6.0 (2.0, 24.0)	35,000, 35,400[*2*3]	19.8, 20.0[*2*3]
750	8	674 (76.2)	5.0 (3.0, 8.0)	13,900 (74.8)	53.9 (74.8)

Geometric mean (geometric CV%); *1, Median (range); *2, Individual values; *3, n = 2; *4, n = 9; *5, n = 7

In the expansion phase, the C_{max} and $AUC_{0\text{-}24h}$ of ceritinib were 203 ng/mL and 3340 ng·h/mL, respectively, on Day 1, and 1010 ng/mL and 22,600 ng·h/mL, respectively, on Day 22. The ratio of the $AUC_{0\text{-}24h}$ on Day 22 to that on Day 1 was 6.2.

4.(ii).A.(3) Drug interaction studies

4.(ii).A.(3).1) Study on drug interaction of ceritinib with KCZ (5.3.3.4-1, Study CLDK378A2104 [[redacted] to [redacted] 20[redacted]])

An open-label, uncontrolled study was conducted in 19 healthy adult subjects to investigate the effect of KCZ (CYP3A inhibitor) on the PK of ceritinib (the table below). Ceritinib 450 mg was orally administered on Day 1 and Day 18, while KCZ 200 mg was orally administered twice daily from Day 15 to Day 28.

The ratios [90% CI][*] of geometric mean C_{max} and AUC_{inf} of ceritinib in combination with KCZ to those of ceritinib alone were 1.22 [1.07, 1.39] and 2.86 [2.46, 3.33], respectively. The results suggest that

coadministration of a CYP3A inhibitor increased exposure to ceritinib. The applicant thus considers that precautions should be taken for coadministration of CYP3A inhibitors.

* Analysis was performed in a linear mixed-effects model using presence or absence of concomitant KCZ as a fixed effect and subjects as a random effect.

PK parameters of ceritinib alone or in combination with KCZ

	n	C_{max} (ng/mL)	t_{max}* (h)	$t_{1/2}$ (h)	AUC_{inf} (ng·h/mL)
Ceritinib alone	18	133 (34.9)	6.0 (6.0, 12.0)	47.7 (32.9)	5760 (43.4)
Ceritinib + KCZ	19	164 (40.3)	10.0 (6.0, 11.9)	52.0 (30.1)	16,600 (47.2)

Geometric mean (geometric CV%); *, Median (range)

4.(ii).A.(3).2) Study on drug interaction of ceritinib with RFP (5.3.3.4-2, Study CLDK378A2106 [[redacted] to [redacted] 20[redacted]])

An open-label, uncontrolled study was conducted in 19 healthy adult subjects (17 subjects evaluable for PK analysis) to investigate the effect of RFP (CYP3A inducer) on the PK of ceritinib (the table below). Ceritinib 750 mg was orally administered on Day 1 and Day 21, while RFP 600 mg was orally administered QD from Day 15 to Day 28.

The ratios [90% CI]* of geometric mean C_{max} and AUC_{inf} of ceritinib in combination with RFP to those of ceritinib alone were 0.56 [0.41, 0.76] and 0.30 [0.23, 0.39], respectively. The results suggest that coadministration of a CYP3A inducer decreased exposure to ceritinib. The applicant thus considers that precautions should be taken for coadminsitration of CYP3A inducers.

* Analysis was performed in a linear mixed-effects model using presence or absence of concomitant RFP as a fixed effect and subjects as a random effect.

PK parameters of ceritinib alone or in combination with RFP

	C_{max} (ng/mL)	t_{max}* (h)	$t_{1/2}$ (h)	AUC_{inf} (ng·h/mL)
Ceritinib alone	219 (93.6)	8.0 (6.0, 24.0)	38.9 (18.5)	10,600 (72.1)
Ceritinib + RFP	122 (85.1)	6.0 (4.0, 10.0)	30.3 (23.0)	3210 (85.4)

Geometric mean (geometric CV%); n = 17; *, Median (range)

4.(ii).A.(4) Relationship between exposure and changes in QT/QTc interval

Based on the data from the foreign phase I study (Study CLDK378X2101), an analysis using a linear mixed-effects model was performed for the relationship of plasma ceritinib concentrations and changes in QT interval from baseline corrected by population-based linear regression method (QTcP). The analysis revealed that QTcP prolonged with an increase in plasma ceritinib concentrations. When the plasma ceritinib concentration reached 1080 ng/mL, which was equivalent to C_{max} following multiple doses of ceritinib 750 mg, the change in QTcP from baseline [90% CI] (msec) was estimated to be 13.6 [11.7, 15.5].

Based on the above, the applicant considers that ceritinib prolongs QT interval.

4.(ii).A.(5) Population pharmacokinetic (PPK) analysis

A population pharmacokinetic (PPK) analysis using a non-linear mixed-effects model was performed on the pharmacokinetic data of ceritinib collected in the foreign phase I study (Study CLDK378X2101) (data from 302 subjects at 4406 time points) (software, NONMEM ver. 7.2.0). The PK of ceritinib was described by a one-compartment model with a time-lagged first-order absorption process. This model included the effect of ceritinib-induced time-dependent inhibition of the metabolizing enzyme of ceritinib.

To identify covariates for (a) CL/F, (b) V/F, and (c) absorption rate constant (ka), and relative bioavailability (F_{rel}), the following factors were examined in this analysis: (a) body weight, age, race, sex, Eastern Cooperative Oncology Group performance status (ECOG PS), estimated glomerular filtration rate (eGFR), albumin concentration, alanine aminotransferase (ALT), total bilirubin, coadministration of CYP3A inhibitors, CYP3A inducers, or P-glycoprotein inhibitors, and history of crizotinib therapy; (b) sex, body weight, and ECOG PS; and (c) coadministration of histamine H2 receptor inhibitors or PPIs.

As a result, the factors selected as significant covariates were body weight and albumin concentration for CL/F, body weight for V/F, and coadministration of histamine H2 receptor inhibitors or PPIs for ka. The applicant's explanation is as follows: the results of this analysis suggested that coadministration of histamine H2 receptor inhibitors or PPIs decreases ka of ceritinib, but no clear differences were presumed to be found in the steady-state AUC (AUC_{ss}) or C_{max} of ceritinib between with and without coadministration of histamine H2 receptor inhibitors or PPIs.

In addition, a PPK analysis in a non-linear mixed-effects model was performed on the PK data of ceritinib obtained from the Japanese phase I study (Study CLDK378X1101), foreign phase I study (Study CLDK378X2101), and global phase II studies (Study CLDK378A2201 and Study CLDK378A2203) (581 subjects, 6671 measurement timepoints) (software, NONMEM ver. 7.2.0). The PK of ceritinib was described by a one-compartment model with a time-lagged first-order absorption process. This model included the effect of ceritinib-induced time-dependent inhibition of the metabolizing enzyme of ceritinib.

To identify covariates for CL/F, V/F, metabolic turnover rate (k_{out}), and ka and F_{rel}, the following factors were examined in this analysis: body weight, sex, race, albumin concentration, ALT, total bilirubin, eGFR, and presence or absence of history of crizotinib therapy for CL/F; body weight, ECOG PS, race, and sex for V/F; race for k_{out}; and coadministration of PPIs for ka and F_{rel}.

As a result, the factors selected as significant covariates were body weight, albumin concentration, and ALT for CL/F; and Japanese for k_{out}. The applicant's explanation of the results of this analysis is as follows:

- Although the results suggested an increase in CL/F with increasing body weight, a simulation in the above PPK model revealed that the ratios [90% CI] of geometric mean AUC_{ss} in patients weighing <60 kg and those weighing >80 kg to that in typical patients in this analysis (weighing 60-80 kg) were estimated to be 1.15 [1.07, 1.24] and 0.86 [0.79, 0.94], respectively. The effect of body weight on the PK of ceritinib is therefore considered of no clinical significance.
- Because no clear differences were presumed to be found in the C_{max} or AUC_{ss} of ceritinib between patients with normal hepatic function (493 patients) and patients with mild hepatic impairment classified according to National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG) criteria (88 patients) (1129 ng/mL and 25,288 ng·h/mL, respectively, in patients with normal hepatic function; 1156 ng/mL and 25,913 ng·h/mL, respectively, in patients with mild hepatic impairment), the effects of albumin concentration and ALT on the PK of ceritinib are considered of no clinical significance.
- A simulation in the above PPK model revealed that the AUC_{ss} of ceritinib was 31% higher in Japanese patients than in Caucasian patients. This is considered attributable to lower mean body weight in Japanese patients than in Caucasian patients (58.5 kg vs. 71.6 kg).

4.(ii).A.(6) Effect of renal impairment on PK of ceritinib

The applicant considers that renal impairment is unlikely to affect the PK of ceritinib, taking the following points into account.

- In a foreign phase I study (Study CLDK378A2105), the urinary excretion rates of ceritinib and its metabolites (% of the administered radioactive dose) was 1.3% [see "4.(ii).A.(1).1) Foreign phase I study"], suggesting that the contribution of renal excretion to the elimination of orally administered ceritinib is small.
- Although the PPK analysis included 208 patients with mild renal impairment (creatinine clearance [CLcr], ≥60 mL/min and <90 mL/min) and 49 patients with moderate renal impairment (CLcr, ≥30 mL/min and <60 mL/min), renal function was not selected as a significant covariate for the PK of ceritinib [see "4.(ii).A.(5) Population pharmacokinetic (PPK) analysis"].

4.(ii).A.(7) Relationship between exposure and efficacy or safety

4.(ii).A.(7).1) Relationship between exposure and efficacy

The data from a global phase II study (Study CLDK378A2201) in patients with *ALK*-positive non-small-cell lung cancer (NSCLC) previously treated with platinum-based chemotherapy and crizotinib were used to investigate the relationship of the trough plasma ceritinib concentration and response rate. Based on the data, patients were divided by quartiles of trough plasma ceritinib concentrations. The response rates in the groups with trough plasma ceritinib concentrations ranging from 120 to 876 ng/mL, from 876 to 1120 ng/mL, from 1120 to 1428 ng/mL, and from 1428 to 2435 ng/mL were 37.0%, 29.6%, 44.4%, and 40.7%, respectively. No apparent relationship was observed between the trough plasma ceritinib concentration and the response rate.

4.(ii).A.(7).2) Relationship between exposure and safety

In a foreign phase I study (Study CLDK378X2101), the incidences of gastrointestinal-related events and Grade ≥3 hepatic function disorder were high [see "4.(iv) Adverse events observed in clinical studies"]; and *in vitro* studies showed that ceritinib inhibits insulin-like growth factor 1 receptor and insulin receptor [see "3.(i).A.(1).1) Inhibitory activity against phosphorylation of various kinases" and "3.(i).A.(1).3) Anti-proliferative activity against cells transduced with various kinase fusion genes"]. For these reason, the relationship of the trough plasma ceritinib concentration and the incidence of adverse events (Grade ≥2 ALT increased, Grade ≥2 aspartate aminotransferase [AST] increased, Grade ≥2 total bilirubin increased, Grade ≥2 blood sugar increased, and Grade ≥3 gastrointestinal events) was evaluated based on the data from Study CLDK378X2101. The results indicated increases in the incidences of Grade ≥2 ALT increased, Grade ≥2 AST increased, and Grade ≥2 blood sugar increased with an elevation in the trough plasma ceritinib concentration.

4.(ii).B Outline of the review conducted by PMDA

4.(ii).B.(1) Difference in PK between Japanese and non-Japanese patients

The applicant's explanation of the differences in the PK of ceritinib between Japanese and non-Japanese patients:

Based on the PK data of ceritinib obtained from the Japanese phase I study (Study CLDK378X1101) [see "4.(ii).A.(2).1) Japanese phase I study"] and foreign phase I study (Study CLDK378X2101) [see "4.(ii).A.(2).2) Foreign phase I study"], differences in the PK of ceritinib between Japanese and non-Japanese patients were investigated. The C_{max} and $AUC_{0\text{-}24h}$ values following a single oral dose of ceritinib at 300 and 600 mg tended to be higher in non-Japanese patients than in Japanese patients, but the C_{max} and $AUC_{0\text{-}24h}$ values following administration of ceritinib at 750 mg as a single dose or multiple doses (Day 22) in non-Japanese patients were similar to those in Japanese patients.

In a global phase II study (Study CLDK378A2201), the trough plasma concentration (geometric mean [coefficient of variation]) following multiple oral doses of ceritinib 750 mg on Day 22 was 1200 ng/mL (37.3%) in Japanese patients and 960 ng/mL (69.9%) in non-Japanese patients. There were no apparent differences between the two subgroups.

Based on the above, no apparent differences have been observed in the PK of ceritinib between Japanese and non-Japanese patients.

PMDA accepted the applicant's explanation.

4.(ii).B.(2) Use of ceritinib in patients with hepatic impairment

No clinical study data on the PK of ceritinib in patients with hepatic impairment are available.

The applicant's explanation of the use of ceritinib in patients with hepatic impairment:

Hepatic impairment may affect the PK of ceritinib because the metabolism of ceritinib is shown to involve CYP3A [see "3.(ii).A.(3).1) *In vitro* metabolism"], and also because ceritinib is mainly excreted in feces [see "4.(ii).A.(1) Foreign phase I study"]. However, dose adjustment of ceritinib is unnecessary in patients with mild hepatic impairment, for the following reasons: (1) despite albumin concentration and ALT selected as significant covariates in the PPK analysis, there would be no clear difference in exposure to ceritinib between patients with normal hepatic function and patients with mild hepatic impairment [see "4.(ii).A.(5) Population pharmacokinetic (PPK) analysis"], and (2) no clear difference

in the incidence of adverse events was observed between patients with normal hepatic function and patients with mild hepatic impairment in clinical studies. However, ceritinib should be carefully used in patients with moderate to severe hepatic impairment, as ceritinib has not been used in these patient subgroups.

Based on the above, the "Careful Administration" section of the package insert will include precautionary advice on the use of ceritinib in patients with moderate to severe hepatic impairment. A clinical study in patients with moderate to severe hepatic impairment (Study CLDK378A2110) is currently ongoing, and its data are due in [redacted], 20[redacted].

PMDA's view:
The applicant's explanation is acceptable. The data from Study CLDK378A2110 should be communicated to healthcare professionals appropriately when they become available.

4.(iii) Summary of clinical efficacy and safety

4.(iii).A Summary of the submitted data

The applicant submitted the evaluation data on efficacy and safety, namely, the data from a total of 9 studies including 1 Japanese phase I study, 2 global phase II studies, and 6 foreign phase I studies.

List of clinical studies on efficacy and safety

Category of data	Study site	Study identifier	Phase	Participants	No. of enrolled patients	Outline of dosage regimens	Main endpoints
Evaluation data	Japan	CLDK378 X1101	I	Patients with *ALK*-positive advanced malignant tumor	19	Single oral dose of ceritinib at 300, 450, 600, or 750 mg on Day 1 and then QD oral dose from Day 4 onward	Safety PK
	Global	CLDK378 A2201	II	Patients with *ALK*-positive advanced or recurrent NSCLC previously treated with platinum-based chemotherapy and crizotinib	140	Ceritinib 750 mg QD oral dose	Efficacy Safety
		CLDK378 A2203	II	Patients with *ALK*-positive advanced or recurrent NSCLC who were previously untreated or previously treated with ≤3 chemotherapy regimens (except for crizotinib)	124	Ceritinib 750 mg QD oral dose	Efficacy Safety
	Foreign	CLDK378 X2101	I	Patients with *ALK*-positive advanced malignant tumor	304 (a) 59 (b) 245	(a) In the dose-escalation phase, single oral dose of ceritinib at 50, 100, 200, 300, 400, 500, 600, 700, or 750 mg on Day 1 and then QD oral dose from Day 4 onward (b) In the expansion phase, oral dose of ceritinib 750 mg QD	Efficacy Safety PK
		CLDK378 A2101	I	Healthy adult subjects	28	Single oral dose of ceritinib 500 mg under fasted conditions, or after a low- or high-fat meal	Safety PK
		CLDK378 A2104	I	Healthy adult subjects	19	Single oral dose of ceritinib 450 mg on Day 1 and Day 18, and oral dose of KCZ 200 mg twice daily for 14 days starting on Day 15	Safety PK
		CLDK378 A2105	I	Healthy adult subjects	6	Single oral dose of [^{14}C]ceritinib 750 mg	Safety PK

Category of data	Study site	Study identifier	Phase	Participants	No. of enrolled patients	Outline of dosage regimens	Main endpoints
		CLDK378 A2106	I	Healthy adult subjects	19	Single oral dose of ceritinib 750 mg on Day 1 and Day 21, and oral dose of RFP 600 mg QD for 14 days starting on Day 15	Safety PK
		CLDK378 A2108	I	Healthy adult subjects	24 (a) 12 (b) 12	(a) Single oral dose of ceritinib 750 mg (capsules) under fasted or fed conditions (b) Single oral dose of ceritinib 750 mg (capsules or tablets) under fasted conditions	Safety PK

QD, Once daily; PK, Pharmacokinetics; KCZ, Ketoconazole; RFP, Rifampicin

The clinical studies are summarized below.

Major non-fatal adverse events reported in the clinical studies are shown in "4.(iv) Adverse events reported in clinical studies" and pharmacokinetic data are presented in "4.(i) Summary of biopharmaceutic studies and associated analytical methods" and "4.(ii) Summary of clinical pharmacology studies."

Evaluation data

4.(iii).A.(1) Clinical pharmacology studies

The applicant submitted the data from 5 clinical pharmacology studies in healthy adult subjects [see "4.(i) Summary of biopharmaceutic studies and associated analytical methods" and "4.(ii) Summary of clinical pharmacology studies"]. In these studies, no deaths occurred during the study period.

1) Foreign phase I study (5.3.1.1-1, Study CLDK378A2101 [October to December 2012])
2) Foreign phase I study (5.3.3.4-1, Study CLDK378A2104 [June to September 2013])
3) Foreign phase I study (5.3.3.1-1, Study CLDK378A2105 [January to March 2013])
4) Foreign phase I study (5.3.3.4-2, Study CLDK378A2106 [May to July 2013])
5) Foreign phase I study (5.3.1.1-2, Study CLDK378A2108 [April to August 2014])

4.(iii).A.(2) Japanese clinical studies

Japanese phase I study (5.3.5.2-4, Study CLDK378X1101 [ongoing since June 2012 (data cut-off on [redacted], 20[redacted])])

An open-label, uncontrolled study was conducted at 3 centers in Japan to investigate the safety and pharmacokinetics of ceritinib in patients with *ALK*-positive advanced malignant tumor (target sample size, 18 subjects).

Ceritinib was orally administered on Day 1 as a single dose and then QD from Day 4 onward. The starting dose was 300 mg, and the dose for the next cohort was determined in the Bayesian Logistic Regression Model (BLRM) based on the toxicity findings. Treatment was continued until disease progression or the occurrence of unacceptable toxicity.

All of 19 subjects enrolled in the study (3 in the 300 mg group, 6 in the 450 mg group, 4 in the 600 mg group, and 6 in the 750 mg group) received ceritinib and were included in the safety analysis population.

During the first 24 days of treatment with ceritinib, 18 subjects* were assessed for dose limiting toxicity (DLT). DLTs occurred in 1 of 4 subjects in the 600 mg group (Grade 3 lipase increased) and 1 of 6 subjects in the 750 mg group (Grade 3 drug-induced liver injury). The maximum tolerated dose (MTD) of ceritinib was determined to be 750 mg QD orally.

Safety results included deaths reported in the 450 mg group during the treatment period or within 28 days after the end of treatment (2 of 6 subjects, 33.3%). Both subjects died due to disease progression, and a causal relationship to ceritinib was ruled out.

* One subject in the 450 mg group who died due to disease progression was excluded from DLT evaluation, because the exposure criteria or safety evaluation criteria were not met.

4.(iii).A.(3) Global clinical studies

4.(iii).A.(3).1) Global phase II study (5.3.5.2-1, Study CLDK378A2201 [ongoing since November 2012 (data cut-off on ■ ■, 20■)])

An open-label, uncontrolled study was conducted at 51 centers in 12 countries and regions including Japan to investigate the efficacy and safety of ceritinib in patients with *ALK*-positive advanced or recurrent NSCLC previously treated with platinum-based antineoplastic drugs and crizotinib[*1] (target sample size, 137 subjects).

Ceritinib was orally administered QD at a dose of 750 mg, and the treatment was continued until disease progression or the occurrence of unacceptable toxicity.

A total of 140 subjects were enrolled in the study to receive ceritinib and all the subjects were included in the Full Analysis Set (FAS) for efficacy analysis. The FAS was also the population used for safety analysis.

The primary efficacy endpoint was the overall response rate[*2] assessed by the investigator according to RECIST ver. 1.1. The results are shown in the table below.

*1 Patients with acquired resistance to crizotinib

*2 The threshold response rate of 25% was used based on the data from clinical studies in which docetaxel hydrate or pemetrexed sodium hydrate were administered to patients with advanced or recurrent NSCLC previously treated with chemotherapy (*J Clin Oncol.* 2000;18:2095-103, *J Clin Oncol.* 2000;18:2354-62, *J Clin Oncol.* 2004;22:1589-97).

Best overall response and overall response rate (assessed by the investigator, FAS, data cut-off on ■ ■, 20■)

	n (%) (N = 140)
Complete response (CR)	3 (2.1)
Partial response (PR)	49 (35.0)
Stable disease (SD)	56 (40.0)
Progressive disease (PD)	19 (13.6)
Not evaluable (NE)	13 (9.3)
Response (CR + PR)	52
(response rate [95% CI[*1]] %)	(37.1 [29.1, 45.7])
P value (one-sided)[*2]	<0.001

*1 Clopper-Pearson method

*2 Exact test based on binomial distribution, with one-sided significance level of 0.025.

Safety results included deaths reported during the treatment period or within 30 days after the end of treatment (17 of 140 subjects, 12.1%). Fifteen subjects died due to disease progression, and other causes of deaths were respiratory failure (1 subject) and pneumonia (1 subject). A causal relationship between pneumonia and ceritinib could not be ruled out.

4.(iii).A.(3).2) Global phase II study (5.3.5.2-2, Study CLDK378A2203 [ongoing since December 2012 (data cut-off on ■ ■, 20■)])

An open-label, uncontrolled study was conducted at 41 centers in 16 countries and regions including Japan to investigate the efficacy and safety of ceritinib in patients with *ALK*-positive advanced or recurrent NSCLC who had been untreated or previously treated with ≤3 chemotherapy regimens (except for crizotinib) (target sample size, 105 subjects).

Ceritinib was orally administered QD at a dose of 750 mg, and the treatment was continued until disease progression or the occurrence of unacceptable toxicity.

A total of 124 subjects were enrolled in the study to receive ceritinib and all the subjects were included in the FAS for efficacy analysis. The FAS was also the population used for safety analysis.

The the primary efficacy endpoint was the overall response rate* assessed by the investigator according to RECIST ver. 1.1. The results are shown in the table below.

* The threshold response rate of 35% was used based on the data from clinical studies in which patients with advanced or recurrent NSCLC were treated with platinum-base doublet chemotherapy (*Lancet.* 2009;373:1525-31, *J Clin Oncol.* 2012;30:3084-92).

Best overall response and overall response rate (assessed by the investigator, FAS, data cut-off on [redacted], 20[redacted])

	n (%) (N = 124)
Complete response (CR)	0
Partial response (PR)	79 (63.7)
Stable disease (SD)	32 (25.8)
Progressive disease (PD)	5 (4.0)
Not evaluable (NE)	8*1 (6.5)
Response (CR + PR)	79
(response rate [90% CI*2] %)	(63.7 [57.6, 68.7])
P value (one-sided)*3	<0.001

*1 Including 1 subject who was assessed as non-CR/non-PD according to the study protocol because of no measurable lesion at baseline.
*2 Uniformly minimum variance unbiased estimator according to Simon two-stage design (optimal design)
*3 *P* value according to Simon two-stage design (optimal design) with one-sided significance level of 0.05.

Safety results included deaths reported during the treatment period or within 30 days after the end of treatment (10 of 124 subjects, 8.1%). Eight subjects died due to disease progression, and other causes of deaths were pneumonia aspiration (1 subject) and cardiac tamponade (1 subject). A causal relationship to ceritinib was ruled out for both cases.

4.(iii).A.(4) Foreign clinical studies

Foreign phase I study (5.3.5.2-3, Study CLDK378X2101 [ongoing since January 2011 (data cut-off on [redacted], 20[redacted])])

An open-label, uncontrolled study was conducted at 20 centers overseas to investigate the efficacy, safety, and PK of ceritinib in patients with *ALK*-positive advanced malignant tumor (target sample size, 40 subjects for the dose-escalation phase and 310 subjects for the expansion phase).

In the dose-escalation phase of this study, ceritinib was orally administered on Day 1 as a single dose and then QD from Day 4 onward. The starting dose was 50 mg, and the dose for the next cohort was determined by BLRM based on the DLT findings. In the expansion phase of this study, ceritinib was orally administered QD at the recommended dose (RD) determined in the dose-escalation phase, and the treatment was continued until disease progression or the occurrence of unacceptable toxicity.

A total of 304 subjects*1 (59 subjects in the dose-escalation phase [2 in the 50 mg group, 2 in the 100 mg group, 3 in the 200 mg group, 3 in the 300 mg group, 14 in the 400 mg group, 10 in the 500 mg group, 10 in the 600 mg group, 5 in the 700 mg group, 10 in the 750 mg group], 245 subjects in the expansion phase) were enrolled in the study to receive ceritinib. All the subjects were included in the FAS for safety analysis. Of the subjects included the FAS, those with NSCLC who had started treatment with ceritinib ≥18 weeks before the data cut-off were evaluable for efficacy analysis.

In the dose-escalation phase, 54 subjects*2 were assessed for DLT during the first 24 days of treatment with ceritinib. DLTs were observed in 2 of 14 subjects in the 400 mg group (Grade 3 hypophosphataemia and Grade 3 transaminases increased, 1 subject each), 2 of 10 subjects in the 600 mg group (Grade 3 diarrhoea and Grade 3 dehydration, 1 subject each), and 2 of 8 subjects in the 750 mg group (Grade 3 diarrhoea and Grade 3 vomiting and Grade 2 diarrhoea, 1 subject each). Based on these findings, the MTD and RD of ceritinib were determined to be 750 mg QD orally.

Efficacy results showed that the response rate [95% CI], assessed by the investigator according to RECIST ver. 1.0, in subjects with NSCLC receiving ceritinib 750 mg was 61.8% [55.4, 67.9] (152 of 246 of subjects).

Safety results included deaths reported during the treatment period or within 28 days after the end of treatment. Deaths occurred in 1 of 2 subjects (50.0%) in the 100 mg group, 1 of 3 subjects (33.3%) in

the 200 mg group, 1 of 3 subjects (33.3%) in the 300 mg group, 4 of 14 subjects (28.6%) in the 400 mg group, 2 of 10 subjects (20.0%) in the 500 mg group, 2 of 10 subjects (20.0%) in the 600 mg group, 1 of 5 subjects (20.0%) in the 700 mg group, and 38 of 255 subjects (14.9%) in the 750 mg group. The following subjects died due to disease progression: 1 subject in the 100 group, 1 subject in the 200 group, 1 subject in the 300 group, 1 subject in the 500 group, 1 subject in the 700 mg group, 4 subjects in the 400 mg group, 2 subjects in the 600 mg group, and 24 subjects in the 750 mg group. Other causes of deaths were respiratory failure in 1 subject in the 500 mg group, and pneumonia in 3 subjects, respiratory failure in 2 subjects, and cardiac tamponade, gastric haemorrhage, euthanasia, general physical health deterioration, multi-organ failure, pulmonary tuberculosis, sepsis, interstitial lung disease, and pneumothorax in 1 subject each in the 750 mg group. A causal relationship to ceritinib could not be ruled out for multi-organ failure and interstitial lung disease.

*1 Of the 304 subjects, 246 with *ALK*-positive advanced or recurrent NSCLC received ceritinib 750 mg (163 subjects previously treated with crizotinib[*3]).
*2 The following subjects were excluded from DLT assessment because the exposure criteria and safety evaluation criteria were not met: 1 subject who discontinued the study treatment due to disease progression (in the 100 mg group), 1 subject who discontinued the study treatment due to disease progression (in the 500 mg group), 1 subject who died of respiratory failure (in the 500 mg group), and 1 subject who experienced sepsis and 1 subject who experienced dosing error (in the 750 mg group).
*3 Patients who acquired resistance or were intolerant to crizotinib

4.(iii).B Outline of the review conducted by PMDA

4.(iii).B.(1) Data for review

PMDA considers that pivotal clinical studies evaluating the efficacy and safety of ceritinib in the submitted data were the global phase II study (Study CLDK378A2201 [“Study A2201”]) and foreign phase I study (Study CLDK378X2101 [“Study X2101”]) in patients with *ALK*-positive advanced or recurrent NSCLC previously treated with crizotinib, and has determined to evaluate this application with a main focus on these studies. PMDA has determined to evaluate the efficacy and safety of ceritinib in Japanese patients mainly based on the data from Study A2201.

4.(iii).B.(2) Efficacy

As a result of the following review, PMDA has concluded that the submitted data has demonstrated a certain level of efficacy of ceritinib in patients with *ALK*-positive advanced or recurrent NSCLC previously treated with crizotinib.

4.(iii).B.(2).1) Efficacy endpoint and evaluation results

The applicant’s explanation of the efficacy endpoint of ceritinib and evaluation results:
In patients with advanced or recurrent NSCLC, reduced tumor volume led to alleviation of associated symptoms such as dyspnoea and pain (*JAMA.* 2003;290:2149-58, *J Thorac Oncol.* 2008;3:30-6). The achievement of clinical response in these patients is therefore considered of clinical significance.

The response rate in Study A2201 was significantly higher than the threshold response rate set based on the rates of response to the conventional therapies in patients with advanced or recurrent NSCLC with a history of chemotherapy [see “4.(iii).A. (3).1) Global phase II study”]. As a sensitivity analysis, a blinded independent review committee (BIRC) assessed the responses according to RECIST ver. 1.1 and reported the response rate [95% CI] of 34.3% [26.5, 42.8], which supported the results of the responses assessed by the investigator. In addition, the duration of response to ceritinib estimated by the Kaplan-Meier method (time from the date of confirmed complete response [CR] or partial response [PR] as assessed by the investigator to the date of progressive disease [PD] or death) [95% CI] was 9.2 months [5.6, not estimable], which was indicative of a sustained response.

The response rate in patients with *ALK*-positive advanced or recurrent NSCLC previously treated with crizotinib who received ceritinib at a dose of 750 mg in Study X2101 was assessed according to RECIST ver. 1.0 by the investigator and by BIRC. The results are shown in the table below.

Best overall response and overall response rate (data cut-off [redacted], 20[redacted])

	Investigator's assessment n (%) (N = 163)	BIRC's assessment n (%) (N = 163)
Complete response (CR)	3 (1.8)	3 (1.8)
Partial response (PR)	89 (54.6)	72 (44.2)
Stable disease (SD)	29 (17.8)	41 (25.2)
Progressive disease (PD)	16 (9.8)	18 (11.0)
Not evaluable (NE)	26 (16.0)	29 (17.8)
Response (CR + PR) (response rate [95% CI] %)	92 (56.4 [48.5, 64.2])	75 (46.0 [38.2, 54.0])

The applicant considered that a certain level of efficacy of ceritinib in patients with *ALK*-positive advanced or recurrent NSCLC previously treated with crizotinib was demonstrated by the above findings.

PMDA's view:
The true endpoint for patients with *ALK*-positive advanced or recurrent NSCLC is overall survival (OS). The relationship between response rate and OS is unclear. At present, therefore, it is difficult to assess the survival benefit of ceritinib in this patient population. However, the applicant claims that reduction of tumor volume has a certain clinical significance for this patient population, for reasons such as alleviation of associated symptoms attributable to progression of the tumor. The applicant's claim is understandable. Therefore, the efficacy of ceritinib can be evaluated based on the overall response rate.

Considering that ceritinib is an ALK inhibitor targeting a molecule responsible for proliferation of cancer cells (oncogenic driver), PMDA has comprehensively concluded that the data including the above-mentioned response rate has demonstrated a certain level of efficacy of ceritinib in patients with *ALK*-positive advanced or recurrent NSCLC previously treated with crizotinib.

4.(iii).B.(2).2) Efficacy in Japanese patients
The response rate [95% CI], assessed by the investigator according to RECIST ver. 1.1, in Japanese patients in Study A2201 was 45.8% [25.6, 67.2] (11 of 24 patients).

PMDA's view:
Although the efficacy evaluation of ceritinib in Japanese patients has a limitation due to the limited number of Japanese patients included in the relevant evaluation, ceritinib is expected to be effective in Japanese patients with *ALK*-positive advanced or recurrent NSCLC previously treated with crizotinib as well, because the response was observed in Japanese patients as in the case of the overall study population.

4.(iii).B.(3) Safety [for adverse events, see "4.(iv) Adverse events reported in clinical studies"]
Based on the assessment of safety data presented below, PMDA has reached the following conclusion: Adverse events requiring special attention during treatment with ceritinib are interstitial lung disease (ILD), hepatic function disorder, QT interval prolonged, nausea/vomiting/diarrhoea, hyperglycaemia/diabetes mellitus, bradycardia, pericarditis, infection, and pancreatitis. Patients on ceritinib should be monitored for the above adverse events.

Although due attention should be paid to the occurrence of the above adverse events in patients on ceritinib, the tolerability profile of ceritinib is acceptable if appropriate measures such as monitoring and management of adverse events and treatment interruption are taken by physicians with sufficient knowledge and experience in cancer chemotherapy, and if the safety management is ensured through strict monitoring, management, and treatment of serious adverse events such as ILD. However, information on the safety of ceritinib is very limited, and thus information should continue to be collected in the post-marketing setting. New safety information should be appropriately communicated to healthcare professionals when it becomes available [see "4.(iii).B.(6) Post-marketing investigations" and "4.(iii).B.(7) Post-marketing risk minimization activities"].

4.(iii).B.(3).1) Safety profile of ceritinib and differences in safety between Japanese and non-Japanese patients

The applicant's explanation of the safety profile of ceritinib:

The safety data from Study A2201, Study CLDK378A2203 (Study A2203), and patients treated with ceritinib 750 mg QD in Study CLDK378X2101 (Study X2101) (Study X2101-750 mg group) are summarized in the table below.

Summary of safety data (Study A2201, Study A2203, and Study X2101-750 mg group)

	n (%)		
	Study A2201 N = 140	Study A2203 N = 124	Study X2101-750 mg group N = 255*
Total	140 (100)	123 (99.2)	255 (100)
Grade ≥3 adverse events	96 (68.6)	80 (64.5)	208 (81.6)
Adverse events resulting in death	17 (12.1)	10 (8.1)	38 (14.9)
Serious adverse events	51 (36.4)	27 (21.8)	121 (47.5)
Adverse events leading to treatment discontinuation	10 (7.1)	9 (7.3)	26 (10.2)
Adverse events leading to treatment interruption or dose reduction	101 (72.1)	90 (72.6)	198 (77.6)

* Includes 9 non-NSCLC patients who received ceritinib 750 mg in the dose-escalation phase.

Adverse events with an incidence of ≥20% in any of Study A2201, Study A2203, or Study X2101-750 mg group are shown in the table below.

Adverse events with an incidence of ≥20% in any study (Study A2201, Study A2203, or Study X2101-750 mg group)

	n (%)					
System organ class Preferred term	Study A2201 N = 140		Study A2203 N = 124		Study X2101-750 mg group N = 255	
(MedDRA ver. 17.0)	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Total	140 (100)	96 (68.6)	123 (99.2)	80 (64.5)	255 (100)	208 (81.6)
Gastrointestinal disorders						
Diarrhoea	112 (80.0)	9 (6.4)	102 (82.3)	4 (3.2)	221 (86.7)	15 (5.9)
Nausea	111 (79.3)	9 (6.4)	92 (74.2)	4 (3.2)	211 (82.7)	15 (5.9)
Vomiting	87 (62.1)	6 (4.3)	83 (66.9)	6 (4.8)	157 (61.6)	12 (4.7)
Abdominal pain	43 (30.7)	2 (1.4)	41 (33.1)	0	98 (38.4)	3 (1.2)
Constipation	33 (23.6)	3 (2.1)	19 (15.3)	0	79 (31.0)	0
Abdominal pain upper	16 (11.4)	1 (0.7)	11 (8.9)	0	60 (23.5)	2 (0.8)
General disorders and administration site conditions						
Fatigue	46 (32.9)	9 (6.4)	40 (32.3)	7 (5.6)	109 (42.7)	13 (5.1)
Pyrexia	29 (20.7)	4 (2.9)	13 (10.5)	1 (0.8)	42 (16.5)	0
Investigations						
ALT increased	56 (40.0)	19 (13.6)	50 (40.3)	19 (15.3)	112 (43.9)	76 (29.8)
AST increased	42 (30.0)	7 (5.0)	38 (30.6)	9 (7.3)	83 (32.5)	25 (9.8)
Weight decreased	45 (32.1)	6 (4.3)	36 (29.0)	1 (0.8)	46 (18.0)	5 (2.0)
GGT increased	25 (17.9)	17 (12.1)	33 (26.6)	23 (18.5)	14 (5.5)	7 (2.7)
Blood ALP increased	21 (15.0)	4 (2.9)	25 (20.2)	8 (6.5)	45 (17.6)	13 (5.1)
Blood creatinine increased	20 (14.3)	0	26 (21.0)	0	43 (16.9)	0
Metabolism and nutrition disorders						
Decreased appetite	56 (40.0)	5 (3.6)	61 (49.2)	2 (1.6)	95 (37.3)	4 (1.6)
Nervous system disorders						
Headache	20 (14.3)	0	11 (8.9)	1 (0.8)	51 (20.0)	4 (1.6)
Respiratory, thoracic and mediastinal disorders						
Cough	26 (18.6)	0	21 (16.9)	0	73 (28.6)	0
Dyspnoea	25 (17.9)	7 (5.0)	17 (13.7)	1 (0.8)	63 (24.7)	11 (4.3)

ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; GGT, γ-glutamyltransferase; ALP, Alkaline phosphatase

Grade ≥3 adverse events with an incidence of ≥5% in Study A2201 were ALT increased (13.6%), gamma-glutamyltransferase (GGT) increased (12.1%), diarrhoea (6.4%), fatigue (6.4%), nausea (6.4%), AST increased (5.0%), and dyspnoea (5.0%). Those in in Study A2203 were GGT increased (18.5%), ALT increased (15.3%), AST increased (7.3%), blood alkaline phosphatase (ALP) increased (6.5%), fatigue (5.6%), and hyperglycaemia (5.6%). Those in Study X2101-750 mg group were ALT increased

(29.8%), AST increased (9.8%), lipase increased (6.3%), diarrhoea (5.9%), nausea (5.9%), hyperglycaemia (5.9%), fatigue (5.1%), blood ALP increased (5.1%), and anaemia (5.1%).

Serious adverse events with an incidence of ≥2% in Study A2201 were pyrexia (5.0%), dyspnoea (4.3%), pneumonia (3.6%), abdominal pain (2.1%), asthenia (2.1%), dehydration (2.1%), nausea (2.1%), non-cardiac chest pain (2.1%), pneumonitis (2.1%), and vomiting (2.1%). Those in Study A2203 were hyperglycaemia (2.4%), pericarditis (2.4%), and pneumonia (2.4%). Those in Study X2101-750 mg group were pneumonia (5.5%), convulsion (4.3%), dyspnoea (3.5%), pneumonitis (3.5%), hyperglycaemia (2.4%), nausea (2.4%), respiratory failure (2.0%), and pericardial effusion (2.0%).

Adverse events leading to treatment discontinuation with an incidence of ≥1% in Study A2201 were nausea (1.4%) and pneumonitis (1.4%). Such an adverse event in Study X2101-750 mg group was pneumonia (1.2%). No such events occurred in Study A2203.

Adverse events leading to treatment interruption or dose reduction with an incidence of ≥5% in Study A2201 were vomiting (26.4%), ALT increased (26.4%), nausea (22.9%), diarrhoea (17.1%), AST increased (14.3%), abdominal pain (5.0%), and fatigue (5.0%). Those in Study A2203 were ALT increased (29.0%), vomiting (16.1%), AST increased (16.1%), diarrhoea (11.3%), nausea (9.7%), and blood creatinine increased (7.3%). Those in Study X2101-750 mg group were ALT increased (30.6%), nausea (20.8%), AST increased (16.5%), diarrhoea (18.0%), vomiting (16.1%), fatigue (9.0%), abdominal pain (7.8%), decreased appetite (6.7%), and lipase increased (5.1%).

The applicant's explanation of the differences in safety of ceritinib between Japanese and non-Japanese patients:
A summary of safety in Japanese patients and non-Japanese patients in Study A2201 and Study A2203 is shown in the table below.

Summary of safety in Japanese and non-Japanese patients (Study A2201 and Study A2203)

	n (%)			
	Study A2201		Study A2203	
	Japanese N = 24	Non-Japanese N = 116	Japanese N = 19	Non-Japanese N = 105
Total	24 (100)	116 (100)	19 (100)	104 (99.0)
Grade ≥3 adverse events	16 (66.7)	80 (69.0)	13 (68.4)	67 (63.8)
Adverse events resulting in death	1 (4.2)	16 (13.8)	0	10 (9.5)
Serious adverse events	7 (29.2)	44 (37.9)	2 (10.5)	25 (23.8)
Adverse events leading to treatment discontinuation	2 (8.3)	8 (6.9)	1 (5.3)	8 (7.6)
Adverse events leading to treatment interruption or dose reduction	22 (91.7)	79 (68.1)	19 (100)	71 (67.6)

Adverse events with an incidence ≥15% higher in Japanese patients than in non-Japanese patients in Study A2201 and Study A2203 are shown in the table below.

Adverse events with an incidence ≥15% higher in Japanese patients than in non-Japanese patients (Study A2201)

Preferred term (MedDRA ver. 17.0)	n (%)			
	Japanese N = 24		Non-Japanese N = 116	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Total	24 (100)	16 (66.7)	116 (100)	80 (69.0)
Decreased appetite	16 (66.7)	1 (4.2)	40 (34.5)	4 (3.4)
Vomiting	20 (83.3)	1 (4.2)	67 (57.8)	5 (4.3)
Dermatitis acneiform	6 (25.0)	0	0	0
Blood ALP increased	7 (29.2)	1 (4.2)	14 (12.1)	3 (2.6)
Hepatic function abnormal	4 (16.7)	3 (12.5)	0	0
Hyperuricaemia	4 (16.7)	0	0	0
Neck pain	4 (16.7)	0	1 (0.9)	0

ALP, Alkaline phosphatase

Adverse events with an incidence ≥15% higher in Japanese patients than in non-Japanese patients (Study A2203)

Preferred term (MedDRA ver. 17.0)	n (%)			
	Japanese N = 19		Non-Japanese N = 105	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Total	19 (100)	13 (68.4)	104 (99.0)	67 (63.8)
Blood ALP increased	11 (57.9)	2 (10.5)	14 (13.3)	6 (5.7)
Blood creatinine increased	9 (47.4)	0	17 (16.2)	0
Nasopharyngitis	6 (31.6)	0	4 (3.8)	0
Hyperuricaemia	5 (26.3)	0	0	0
Decreased appetite	13 (68.4)	1 (5.3)	48 (45.7)	1 (1.0)
Hepatic enzyme increased	4 (21.1)	0	0	0
Hepatic function abnormal	4 (21.1)	4 (21.1)	0	0
Diarrhoea	19 (100)	0	83 (79.0)	4 (3.8)
Dysgeusia	4 (21.1)	0	1 (1.0)	0
Rash maculo-papular	4 (21.1)	1 (5.3)	1 (1.0)	0
White blood cell count decreased	4 (21.1)	0	2 (1.9)	0
Electrocardiogram QT prolonged	5 (26.3)	0	10 (9.5)	1 (1.0)

ALP, Alkaline phosphatase

Grade 3 adverse events with an incidence ≥5% higher in Japanese patients than in non-Japanese patients in Study A2201 were hepatic function abnormal (12.5% versus 0% in Japanese versus non-Japanese patients, respectively), hypokalaemia (12.5% vs. 0.9%), fatigue (12.5% vs. 5.2%), GGT increased (16.7% vs. 11.2%), pericarditis (8.3% vs. 0%), and constipation (8.3% vs. 0.9%). Those in Study A2203 were hepatic function abnormal (21.1% vs. 0%), rash maculo-papular (5.3% vs. 0%), GGT increased (26.3% vs. 17.1%), neutrophil count decreased (5.3% vs. 0%), pleurisy (5.3% vs. 0%), pericarditis (5.3% vs. 0%), photosensitivity reaction (5.3% vs. 0%), lymphocyte count decreased (5.3% vs. 0%), haematuria (5.3% vs. 0%), hypophosphataemia (5.3% vs. 0%), and non-cardiac chest pain (5.3% vs. 0%).

No fatal adverse events occurred more frequently in Japanese patients than in non-Japanese patients either in Study A2201 or in Study A2203.

Serious adverse events with an incidence ≥5% higher in Japanese patients than in non-Japanese patients were pericarditis (8.3% versus 0% in Japanese and non-Japanese patients, respectively) in Study A2201; and pericarditis (10.5% vs. 1.0%) and pleurisy (5.3% vs. 0%) in Study A2203.

Adverse events requiring treatment interruption or dose reduction with an incidence ≥15% higher in Japanese patients than in non-Japanese patients were nausea (45.8% versus 18.1% in Japanese versus non-Japanese patients, respectively), diarrhoea (37.5% vs. 12.9%) and hepatic function abnormal (16.7% vs. 0%) in Study A2201; and GGT increased (21.1% vs. 0%) and hepatic function abnormal (21.1% vs. 0%) in Study A2203.

Adverse events reported by ≥2 Japanese patients only in Study A2201 were dermatitis acneiform (6 subjects), hepatic function abnormal (4 subjects), hyperuricaemia (4 subjects), cancer pain (3 subjects), and procedural pain (2 subjects). Those in Study A2203 were hyperuricaemia (5 subjects), hepatic enzyme increased (4 subjects), hepatic function abnormal (4 subjects), dermatitis acneiform (2 subjects), hiccups (2 subjects), hypersensitivity (2 subjects), neutrophil count decreased (2 subjects), and pleurisy (2 subjects).

PMDA's view:
Although the incidence of Grade 3 adverse events and serious adverse events was high in Study A2201, Study A2203, and Study X2101-750 mg group, the incidence of adverse events resulting in death due to reasons other than disease progression was low. Therefore, the tolerability profile of ceritinib is acceptable if appropriate measures including dose adjustment such as dose reduction and interruption or discontinuation of treatment are taken by physicians with sufficient knowledge and experience in cancer chemotherapy, and if post-marketing safety measures are taken appropriately [see "4.(iii).B.(7) Post-marketing risk minimization activities"]. However, adverse events reported in the clinical studies

of ceritinib require special attention. Information on the adverse events should be communicated to healthcare professionals appropriately through the package insert and relevant materials.

Comparison of safety profiles between Japanese and non-Japanese patients has a limitation due to the small number of Japanese patients evaluated in Study A2201 and Study A2203, but some adverse events occurred more frequently in Japanese patients than in non-Japanese patients in the clinical studies. Information on the adverse events occurring in Japanese patients should be communication to healthcare professionals in a similar manner to the above.

The following section describes PMDA's evaluation of the common adverse events in Study A2201, Study A2203, and Study X2101-750 mg group, in light of the known adverse events with crizotinib and alectinib hydrochloride (alectinib), which are ALK inhibitors like ceritinib.

4.(iii).B.(3).2) ILD

The applicant's explanation of ILD in patients treated with ceritinib:

Adverse event terms included in the Standardised MedDRA Queries (SMQ) "Interstitial lung disease" and those coded to the MedDRA preferred term "acute lung injury" were tabulated as ILD-related events.

The incidence of ILD-related events in Study A2201, Study A2203, and Study X2101-750 mg group are shown in the table below.

Incidence of ILD-related events (Study A2201, Study A2203, and Study X2101-750 mg group)

Preferred term (MedDRA ver. 17.0)	n (%)					
	Study A2201 N = 140		Study A2203 N = 124		Study X2101-750 mg group N = 255	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
ILD-related events	3 (2.1)	1 (0.7)	2 (1.6)	0	12 (4.7)	9 (3.5)
Pneumonitis	3 (2.1)	1 (0.7)	1 (0.8)	0	9 (3.5)	7 (2.7)
ILD	0	0	1 (0.8)	0	2 (0.8)	2 (0.8)
Lung infiltration	0	0	0	0	1 (0.4)	0

ILD, Interstitial lung disease

ILD-related events leading to death occurred in 1 subject (0.4%) in Study X2101-750 mg group, and a causal relationship to ceritinib could not be ruled out. Serious ILD-related events occurred in 3 subjects (2.1%) in Study A2201 and 12 subjects (4.7%) in Study X2101-750 mg group. ILD-related events leading to treatment discontinuation occurred in 2 subjects (1.4%) in Study A2201, 1 subject (0.8%) in Study A2203, and 3 subjects (1.2%) in Study X2101-750 mg group. ILD-related events leading to treatment interruption or dose reduction occurred in 1 subject (0.7%) in Study A2201, 1 subject (0.8%) in Study A2203, and 8 subjects (3.1%) in Study X2101-750 mg group.

ILD-related events did not occur in Japanese patients either in Study A2201 or in Study A2203, but in the Japanese phase I study (Study CLDK378X1101 [Study X1101]), ILD-related events occurred in 1 of 19 subjects (5.3%). The event was non-serious Grade 1 pneumonitis, and the outcome was reported as "resolved."

Patients who experienced ILD-related events in Study A2201, Study A2203, Study X2101-750 mg group, and Study X1101 are shown in the table below.

List of patients with ILD-related events (Study A2201, Study A2203, Study X2101-750 mg group, and Study X1101)

Study	Sex	Age (years)	Race	Preferred term	Worst Grade	Serious or non-serious	Causal relationship	Time to onset (Day)	Duration (Day)	Action on ceritinib	Medication	Outcome
A2201	Female	5[redacted]	Asian	Pneumonitis	2	Serious	Yes	120	Ongoing	Discontinuation	Steroid	Not resolved
	Male	4[redacted]	Caucasian	Pneumonitis	2	Serious	No	70	18	Treatment interruption	Antimicrobial and antifungal drugs	Resolved
	Male	7[redacted]	Caucasian	Pneumonitis	4	Serious	Yes	22	13	Discontinuation	Steroid and antimicrobial drug	Resolved
A2203	Female	5[redacted]	Asian	Pneumonitis	1	Non-serious	Yes	142	11	Treatment interruption and dose reduction	None	Resolved
	Male	4[redacted]	Caucasian	ILD	2	Non-serious	Yes	155	Ongoing	Discontinuation	None	Not resolved
X2101	Male[*1]	2[redacted]	Asian	Pneumonitis	2	Serious	Yes	189	44	Treatment interruption and dose reduction	Steroid and antimicrobial drug	Resolved
	Female	7[redacted]	Asian	Pneumonitis	2	Serious	Yes	200	75	Treatment interruption	Antimicrobial drug	Resolved
	Female	7[redacted]	Asian	Pneumonitis	2	Serious	Yes	120	29	Treatment interruption and dose reduction	Antimicrobial drug	Resolved
				Pneumonitis	3	Serious	Yes	154	16	Discontinuation	Steroid and antimicrobial drug	Resolved
				Pneumonitis	2	Serious	Yes	179	Ongoing	None[*3]	Antimicrobial drug	Not resolved
	Female	3[redacted]	Caucasian	Pneumonitis	3	Serious	Yes	130	12	Treatment interruption and dose reduction	Steroid and antimicrobial drug	Resolved
	Female	5[redacted]	Caucasian	Pneumonitis	3	Serious	Yes	60	Unknown	Treatment interruption	Steroid and antimicrobial drug	Resolved
	Female	5[redacted]	Caucasian	Pneumonitis	4	Serious	No	85	146	None[*4]	Steroid	Not resolved[*6]
	Male	6[redacted]	Caucasian	Pneumonitis	3	Serious	Yes	36	Ongoing	None[*3]	Steroid and antimicrobial drug	Not resolved
	Male	5[redacted]	Caucasian	Pneumonitis	3	Serious	Yes	162	Unknown	Discontinuation	Steroid	Unknown
	Male[*2]	5[redacted]	Caucasian	ILD	3	Serious	Yes	36	26	Treatment interruption[*5]	Antimicrobial drug	Resolved
	Male	4[redacted]	Caucasian	ILD	4	Serious	Yes	23	20	Discontinuation	Steroid and antimicrobial drug	Death
	Female	5[redacted]	Caucasian	Lung infiltration	1	Serious	Yes	107	15	Treatment interruption and dose reduction	None	Resolved
	Male	6[redacted]	Negroid	Pneumonitis	3	Serious	Yes	261	9	Treatment interruption and dose reduction	Steroid and antimicrobial drug	Resolved
X1101	Male[*1]	5[redacted]	Japanese	Pneumonitis	1	Non-serious	Yes	255	Unknown	Treatment interruption	None	Resolved

ILD, Interstitial lung disease
*1 Patient with inflammatory myofibroblastic tumour.
*2 Patient with rectal cancer
*3 Developed after discontinuation of ceritinib.
*4 Ceritinib was discontinued due to disease progression. Coadministration of ceritinib and AUY922 was started 8 days after the discontinuation of ceritinib, but pneumonitis was aggravated to Grade 4, resulting in discontinuation of ceritinib and AUY922.
*5 Ceritinib was discontinued due to disease progression after interruption.
*6 Died of respiratory failure 22 days after discontinuation of ceritinib.

PMDA's view:

The incidence of ILD-related events in Japanese patients treated with ceritinib was not particularly higher than the incidence of the events noted in the clinical studies of crizotinib and alectinib, both of which are ALK inhibitors as with ceritinib (see "Review Report on Xalkori Capsules 200 mg, and Xalkori Capsules 250 mg, dated February 20, 2012" and "Review Report on Alecensa Capsules 20 mg, and Alecensa Capsules 40 mg, dated May 16, 2014"). However, the following findings have been reported: (a) serious ILD-related events including fatal outcomes occurred in patients treated with

ceritinib in foreign clinical studies; (b) the number of Japanese patients included in the safety evaluation of ceritinib was very limited; and (c) in the clinical studies of crizotinib, the incidence of ILD was higher in Japanese patients than in non-Japanese patients, and death occurred in some patients experiencing ILD (see "Review Report on Xalkori Capsules 200 mg and Xalkori Capsules 250 mg, dated February 20, 2012"). In light of these findings, the applicant should include appropriate precautions in the package insert and relevant materials to ensure that physicians assess patients for previous or concurrent ILD to carefully identify their eligibility for treatment with ceritinib before use, that the patients on ceritinib are continuously monitored for ILD, and that appropriate measures are taken if ILD occurs.

4.(iii).B.(3).3) Hepatic function disorder

The applicant's explanation of hepatic function disorder in patients treated with ceritinib:
Adverse event terms included in the MedDRA SMQ "Cholestasis and jaundice of hepatic origin," "Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions," "Hepatitis, non-infectious," and "Liver related investigations, signs and symptoms" were tabulated as events of hepatic function disorder.

The incidence of hepatic function disorder in Study A2201, Study A2203, and Study X2101-750 mg group are shown in the table below.

Incidence of hepatic function disorder (Study A2201, Study A2203, and Study X2101-750 mg group)

Preferred term (MedDRA ver. 17.0)	n (%)					
	Study A2201 N = 140		Study A2203 N = 124		Study X2101-750 mg group N = 255	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Hepatic function disorder	73 (52.1)	35 (25.0)	75 (60.5)	43 (34.7)	126 (49.4)	82 (32.2)
ALT increased	56 (40.0)	19 (13.6)	50 (40.3)	19 (15.3)	112 (43.9)	76 (29.8)
AST increased	42 (30.0)	7 (5.0)	38 (30.6)	9 (7.3)	83 (32.5)	25 (9.8)
GGT increased	25 (17.9)	17 (12.1)	33 (26.6)	23 (18.5)	14 (5.5)	7 (2.7)
Blood bilirubin increased	0	0	5 (4.0)	0	9 (3.5)	1 (0.4)
Transaminases increased	0	0	2 (1.6)	0	9 (3.5)	3 (1.2)
Hepatic function abnormal	4 (2.9)	3 (2.1)	4 (3.2)	4 (3.2)	0	0
Hepatic enzyme increased	3 (2.1)	1 (0.7)	4 (3.2)	0	0	0
Liver function test abnormal	2 (1.4)	0	3 (2.4)	1 (0.8)	1 (0.4)	0
Bilirubin conjugated increased	0	0	0	0	3 (1.2)	1 (0.4)
Ascites	0	0	0	0	2 (0.8)	0
Drug-induced liver injury	0	0	0	0	1 (0.4)	1 (0.4)
Hepatitis	0	0	2 (1.6)	1 (0.8)	0	0
Ammonia increased	0	0	1 (0.8)	0	0	0
Asterixis	1 (0.7)	0	0	0	0	0
Hepatic encephalopathy	1 (0.7)	1 (0.7)	0	0	0	0
Hepatitis cholestatic	0	0	0	0	1 (0.4)	1 (0.4)
Hepatocellular injury	1 (0.7)	1 (0.7)	0	0	0	0
Hepatotoxicity	1 (0.7)	0	0	0	0	0
Hyperbilirubinaemia	0	0	0	0	1 (0.4)	0
Ischaemic hepatitis	0	0	0	0	1 (0.4)	0
Jaundice	0	0	0	0	1 (0.4)	1 (0.4)

ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; GGT, γ-glutamyltransferase

No hepatic function disorder leading to death occurred. Serious hepatic function disorder occurred in 4 subjects (2.9%; hepatocellular injury, hepatic function abnormal, hepatic encephalopathy, ALT increased, and AST increased in 1 subject each [some subjects experienced more than one event]) in Study A2201; 1 subject (0.8%, hepatitis) in Study A2203; and 5 subjects (2.0%; ALT increased in 4 subjects, AST increased in 2 subjects, drug-induced liver injury and hepatitis cholestatic in 1 subject each [some subjects experienced more than one event]) in Study X2101-750 mg group. A causal relationship to ceritinib could not be ruled out for all cases in Study A2201 and ALT increased (2 subjects), and AST increased (1 subject), drug-induced liver injury (1 subject), and hepatitis cholestatic (1 subject) (some subjects experienced more than one event) in Study X2101-750 mg group. Hepatic function disorder leading to treatment discontinuation occurred in 1 subject (0.7%) in Study A2201, 1 subject (0.8%) in Study A2203, and 1 subject (0.4%) in Study X2101-750 mg group. Hepatic function disorder leading to treatment interruption or dose reduction occurred in 45 subjects (32.1%) in Study A2201, 50 subjects (40.3%) in Study A2203, and 85 subjects (33.3%) in Study X2101-750 mg group.

Hepatic function disorder meeting laboratory criteria of Hy's law (defined on the basis of the Guidance

for industry. Drug-Induced Liver Injury: Premarketing Clinical Evaluation. U.S. Department of Health and Human Services, Food and Drug Administration. July 2009) occurred in 1 subject (0.4%) in Study X2101-750 mg group. In this patient, a hepatic function disorder meeting laboratory criteria of Hy's law occurred on Day 543 of treatment with ceritinib (AST, >3 × upper limit of normal [ULN]; ALT, normal; total bilirubin, >2 × ULN; and ALP, <2 × ULN), but its causal relationship to ceritinib was ruled out. The treatment with ceritinib was therefore continued without specific measures to reduce the risk of hepatic function disorder, but laboratory parameters related to hepatic function returned to normal levels in 19 days.

PMDA's view:
Patients on ceritinib should be closely monitored for hepatic function disorder, because (1) serious hepatic function disorder possibly related to ceritinib occurred in the clinical studies; (2) the incidence of hepatic function disorder leading to treatment interruption or dose reduction was high; and (3) the incidence of hepatic function abnormal was higher in Japanese patients than in non-Japanese patients [see "4.(iii).B.(3).1) Safety profile of ceritinib and differences in safety between Japanese and non-Japanese patients"]. Therefore, information on hepatic function disorder reported in clinical studies should be appropriately communicated to healthcare professionals. In addition, the applicant should provide advice to healthcare professionals appropriately through the package insert and relevant materials containing information on details of hepatic function test employed in the clinical studies and criteria for treatment interruption, thereby ensuring that the hepatic function test is periodically performed in patients on ceritinib and that appropriate measures are taken if hepatic function disorder occurs.

4.(iii).B.(3).4) QT interval prolonged

The applicant's explanation of QT interval prolonged in patients treated with ceritinib:
Adverse event terms included in the MedDRA SMQ "Torsade de pointes/QT prolongation" were tabulated as QT interval prolonged.

The incidence of QT interval prolonged in Study A2201, Study A2203, and Study X2101-750 mg group are shown in the table below.

Incidence of QT interval prolonged (Study A2201, Study A2203, and Study X2101-750 mg group)

Preferred term (MedDRA ver. 17.0)	n (%)					
	Study A2201 N = 140		Study A2203 N = 124		Study X2101-750 mg group N = 255	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
QT interval prolonged	9 (6.4)	0	15 (12.1)	1 (0.8)	16 (6.3)	7 (2.7)
Electrocardiogram QT prolonged	9 (6.4)	0	15 (12.1)	1 (0.8)	10 (3.9)	3 (1.2)
Ventricular arrhythmia	0	0	1 (0.8)	0	0	0
Syncope	0	0	0	0	4 (1.6)	3 (1.2)
Cardio-respiratory arrest	0	0	0	0	1 (0.4)	1 (0.4)
Loss of consciousness	0	0	0	0	1 (0.4)	0

No QT interval prolonged leading to death occurred. Serious QT interval prolonged occurred in 2 subjects (0.8%, loss of consciousness and cardio-respiratory arrest in 1 subject each) in Study X2101-750 mg group, and a causal relationship between both events and ceritinib was ruled out. QT interval prolonged leading to treatment discontinuation occurred in 1 subject (0.8%) in Study A2203. QT interval prolonged leading to treatment interruption or dose reduction occurred in 1 subject (0.8%) in Study A2203 and 4 subjects (1.6%) in Study X2101-750 mg group.

The proportion of subjects who had QTc interval >500 ms and the incidence of an increase in QTc interval of >30 ms or >60 ms from baseline in subjects with evaluable electrocardiogram (ECG) are shown in the table below.

Incidence of QTcP and QTcF prolonged (Study A2201, Study A2203, and Study X2101-750 mg group)

	n (%)					
	Study A2201 N = 136		Study A2203 N = 123		Study X2101-750 mg group N = 254	
	QTcP	QTcF	QTcP	QTcF	QTcP	QTcF
Maximum QT interval						
>480 msec	3 (2.2)	3 (2.2)	6 (4.9)	6 (4.9)	10 (3.9)	7 (2.8)
>500 msec	0	0	1 (0.8)	1 (0.8)	0	0
Increase from baseline (max.)						
>30 msec	75 (55.1)	75 (55.1)	59 (48.0)	78 (63.4)	106 (41.7)	122 (48.0)
>60 msec	7 (5.1)	9 (6.6)	6 (4.9)	12 (9.8)	9 (3.5)	15 (5.9)

QTcP, Corrected QTc interval according to linear regression; QTcF, Corrected QTc interval according to Fridericia's formula

The analysis of the foreign post-marketing data (data cut-off on December 31, 2015) revealed 32 events of QT interval prolonged reported as serious adverse events (electrocardiogram QT prolonged [15 events], syncope and cardiac arrest [5 events each], loss of consciousness [4 events], and ventricular fibrillation, cardio-respiratory arrest, and sudden death [1 event each]). Of these, 10 events (cardiac arrest [5 events] and loss of consciousness, syncope, ventricular fibrillation, cardio-respiratory arrest, and sudden death [1 event each]) resulted in death.

PMDA's view:
Patients on ceritinib should be monitored for QT interval prolongation, because (1) QT interval prolonged occurred at a certain frequency in patients treated with ceritinib in the clinical studies and (2) serious or fatal QT interval prolonged was found in the foreign post-marketing data. Therefore, information on QT interval prolonged reported in clinical studies should be communicated to healthcare professionals. In addition, the applicant should provide advice to healthcare professionals appropriately through the package insert and relevant materials containing information on details of electrocardiography employed in the clinical studies and criteria for treatment interruption, thereby ensuring that electrolyte test and electrocardiography are periodically performed in patients on ceritinib and that appropriate measures are taken if QT interval prolongation occurs.

4.(iii).B.(3).5) Nausea, vomiting, and diarrhoea

The applicant's explanation of nausea, vomiting, and diarrhoea in patients treated with ceritinib:
Adverse event terms coded to the MedDRA preferred terms "nausea," "vomiting," and "diarrhoea" were tabulated.

The incidence of nausea, vomiting, and diarrhoea in Study A2201, Study A2203, and Study X2101-750 mg group are shown in the table below.

Incidence of nausea, vomiting, and diarrhoea (Study A2201, Study A2203, and Study X2101-750 mg group)

Preferred term (MedDRA ver. 17.0)	n (%)					
	Study A2201 N = 140		Study A2203 N = 124		Study X2101-750 mg group N = 255	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Nausea, vomiting, and diarrhoea	134 (95.7)	18 (12.9)	118 (95.2)	12 (9.7)	246 (96.5)	34 (13.3)
Nausea	111 (79.3)	9 (6.4)	92 (74.2)	4 (3.2)	211 (82.7)	15 (5.9)
Vomiting	87 (62.1)	6 (4.3)	83 (66.9)	6 (4.8)	157 (61.6)	12 (4.7)
Diarrhoea	112 (80.0)	9 (6.4)	102 (82.3)	4 (3.2)	221 (86.7)	15 (5.9)

There was no nausea, vomiting, or diarrhoea leading to death. Serious nausea, vomiting, and diarrhoea occurred in 5 subjects (3.6%; nausea and vomiting in 3 subjects each [some subjects experienced more than one event]) in Study A2201, 3 subjects (2.4%; nausea, vomiting, and diarrhoea in 1 subject each) in Study A2203, and 11 subjects (4.3%; nausea in 6 subjects, and vomiting and diarrhoea in 3 subjects each [some subjects experienced more than one event]) in Study X2101-750 mg group. A causal relationship to ceritinib could not be ruled out for all events in Study A2201 and Study A2203, and nausea, vomiting, and diarrhoea in 2 subjects each in Study X2101-750 mg group. Nausea, vomiting, and diarrhoea leading to treatment discontinuation occurred in 2 subjects (1.4%) in Study A2201 and 1 subject (0.4%) in Study X2101-750 mg group. Nausea, vomiting, and diarrhoea leading to treatment

interruption or dose reduction occurred in 52 subjects (37.1%) in Study A2201, 30 subjects (24.2%) in Study A2203, and 90 subjects (35.3%) in Study X2101-750 mg group.

PMDA's view:
Patients on ceritinib should be monitored for nausea, vomiting, and diarrhoea, because the adverse events occurred at a certain frequency in patients treated with ceritinib in the clinical studies, and a causal relationship to ceritinib could not be ruled out for some of serious adverse events (nausea, vomiting, and diarrhea). Information on nausea, vomiting, and diarrhoea reported in the clinical studies should be communicated to healthcare professionals appropriately through the package insert and relevant materials.

4.(iii).B.(3).6) Hyperglycaemia/diabetes mellitus

The applicant's explanation of hyperglycaemia/diabetes mellitus in patients treated with ceritinib:
Adverse event terms included in the MedDRA SMQ "Hyperglycaemia/new onset diabetes mellitus" and those coded to the MedDRA preferred terms "anti-GAD antibody positive," "anti-IA2 antibody positive," "anti-insulin antibody increased," "anti-insulin antibody positive," "anti-insulin receptor antibody increased," "anti-insulin receptor antibody positive," "anti-islet cell antibody positive," "anti-zinc transporter 8 antibody positive," "blood glucose abnormal," "blood glucose fluctuation," "blood insulin abnormal," "blood insulin decreased," "glucose tolerance decreased," "glucose tolerance test abnormal," "hypoinsulinaemia," "impaired insulin secretion," "increased insulin requirement," "insulin autoimmune syndrome," and "insulin tolerance test abnormal" were tabulated as hyperglycaemia/diabetes mellitus.

The incidence of hyperglycaemia/diabetes mellitus in Study A2201, Study A2203, and Study X2101-750 mg group are shown in the table below.

Incidence of hyperglycaemia/diabetes mellitus (Study A2201, Study A2203, and Study X2101-750 mg group)

Preferred term (MedDRA ver. 17.0)	n (%)					
	Study A2201 N = 140		Study A2203 N = 124		Study X2101-750 mg group N = 255	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Hyperglycaemia/diabetes mellitus	11 (7.9)	5 (3.6)	15 (12.1)	9 (7.3)	32 (12.5)	17 (6.7)
Hyperglycaemia	6 (4.3)	3 (2.1)	13 (10.5)	7 (5.6)	21 (8.2)	15 (5.9)
Diabetes mellitus	3 (2.1)	2 (1.4)	3 (2.4)	1 (0.8)	10 (3.9)	0
Blood glucose increased	1 (0.7)	0	0	0	2 (0.8)	0
Diabetic ketoacidosis	0	0	1 (0.8)	1 (0.8)	1 (0.4)	1 (0.4)
Blood glucose abnormal	0	0	0	0	1 (0.4)	0
Glucose tolerance impaired	0	0	0	0	1 (0.4)	1 (0.4)
Type 2 diabetes mellitus	1 (0.7)	0	0	0	0	0

There was no hyperglycaemia or diabetes mellitus leading to death. Serious hyperglycaemia/diabetes mellitus occurred in 5 subjects (4.0%; hyperglycaemia in 3 subjects, and diabetes mellitus and diabetic ketoacidosis in 1 subject each) in Study A2203 and 7 subjects (2.7%, hyperglycaemia in 6 subjects and diabetic ketoacidosis in 1 subject) in Study X2101-750 mg group. A causal relationship to ceritinib could not be ruled out for hyperglycaemia in 1 subject in Study A2203 and in 2 subjects in Study X2101-750 mg group. Hyperglycaemia/diabetes mellitus leading to treatment discontinuation occurred in 1 subject (0.8%) in Study A2203. Hyperglycaemia/diabetes mellitus leading to treatment interruption or dose reduction occurred in 3 subjects (2.4%) in Study A2203 and 7 subjects (2.7%) in Study X2101-750 mg group.

Serious hyperglycaemia/diabetes mellitus, hyperglycaemia/diabetes mellitus leading to treatment discontinuation, or hyperglycaemia/diabetes mellitus leading to treatment interruption or dose reduction occurred between Day 77 and Day 279 in Study A2203 and between Day 22 and Day 174 in Study X2101-750 mg group.

PMDA asked the applicant to explain the risk factors for hyperglycaemia/diabetes mellitus.

The applicant's response:
Grade ≥3 hyperglycaemia based on laboratory parameters were noted in 3 of 5 subjects (60.0%) with a history of diabetes mellitus or glucose tolerance abnormal and 12 of 132 subjects (9.1%) without such a history in Study A2201; 3 of 8 subjects (37.5%) with a history of diabetes mellitus or glucose tolerance abnormal and 7 of 114 subjects (6.1%) without such a history in Study A2203; and 12 of 22 subjects (54.5%) with a history of diabetes mellitus or glucose tolerance abnormal and 24 of 230 subjects (10.4%) without such a history in Study X2101-750 mg group. The risk ratio [95% CI] of Grade ≥3 hyperglycaemia based on laboratory parameters in subjects with such a history to those without such a history was 6.6 [2.69, 16.17] in Study A2201, 6.11 [1.94, 19.23] in Study A2203, and 5.23 [3.05, 8.95] in Study X2101-750 mg group. The possibility cannot be ruled out that ceritinib increases the risk of hyperglycaemia in patients with a history of diabetes mellitus or glucose tolerance abnormal. Grade ≥3 hyperglycaemia based on laboratory parameters were noted in 8 of 77 subjects (10.4%) who were on concurrent corticosteroids and 7 of 60 subjects (11.7%) who were not on concurrent corticosteroids in Study A2201; 4 of 56 subjects (7.1%) who were on concurrent corticosteroids and 6 of 66 subjects (9.1%) who were not on concurrent corticosteroids in Study A2203; and 22 of 128 subjects (17.2%) who were on concurrent corticosteroids and 14 of 124 subjects (11.3%) who were not on concurrent corticosteroids in Study X2101-750 mg group. The risk ratio [95% CI] of Grade ≥3 hyperglycaemia based on laboratory parameters in subjects on concurrent corticosteroids to those not on concurrent corticosteroids was 0.89 [0.34, 2.32] in Study A2201, 0.79 [0.23, 2.65] in Study A2203, and 1.52 [0.82, 2.84] in Study X2101-750 mg group. The applicant considers it difficult to determine whether there is an increased risk of hyperglycaemia resulting from use of concurrent corticosteroids.

PMDA's view:
Information on hyperglycaemia/diabetes mellitus reported in the clinical studies should be appropriately communicated to healthcare professionals, because serious hyperglycaemia/diabetes mellitus for which a causal relationship to ceritinib could not be ruled out occurred in the clinical studies. In addition, the applicant should provide advice to healthcare professionals appropriately through the package insert and relevant materials, thereby ensuring that blood glucose test is performed in patients on ceritinib and that appropriate measures are taken if hyperglycaemia/diabetes mellitus occurs.

4.(iii).B.(3).7) Bradycardia
The applicant's explanation of bradycardia in patients treated with ceritinib:
Adverse event terms included in the MedDRA SMQs "Bradyarrhythmia terms, nonspecific," "Conduction defects," and "Disorders of sinus node function" and those coded to the preferred term "syncope" were tabulated as bradycardia-related events.

Bradycardia-related events occurred in 10 of 140 subjects (7.1%; electrocardiogram QT prolonged in 9 subjects, bradycardia and bundle branch block right in 1 subject each [some subjects experienced more than one event]) in Study A2201, 17 of 124 subjects (13.7%; electrocardiogram QT prolonged in 15 subjects, sinus bradycardia and atrioventricular block in 1 subject each) in Study A2203, and 21 of 255 subjects (8.2%; electrocardiogram QT prolonged in 10 subjects, bradycardia, sinus bradycardia, and syncope in 4 subjects each [some subjects experienced more than one event]) in Study X2101-750 mg group. Grade ≥3 bradycardia-related events occurred in 1 subject (0.8%, electrocardiogram QT prolonged) in Study A2203 and 6 subjects (2.4%, electrocardiogram QT prolonged and syncope in 3 subjects each) in Study X2101-750 mg group. No serious or fatal bradycardia-related events occurred. Bradycardia-related events leading to treatment discontinuation occurred in 1 subject (0.8%, electrocardiogram QT prolonged) in Study A2203. Bradycardia-related events leading to treatment interruption or dose reduction occurred in 1 subject (0.8%) in Study A2203 and 4 subjects (1.6%) in Study X2101-750 mg group.

Bradycardia with a decrease in heart rate of >25% from baseline and to <50/min (ECG changes) occurred in 6 of 136 subjects (4.4%) in Study A2201, 6 of 123 subjects (4.9%) in Study A2203, and in 8 of 254 subjects (3.1%) in Study X2101-750 mg group.

In the 11 clinical studies of ceritinib including those submitted in the new drug application* (data cut-off on April 28, 2015), serious bradycardia-related events occurred in 6 subjects (electrocardiogram QT

prolonged in 4 subjects, syncope in 2 subjects, and nodal rhythm in 1 subject [some subjects experienced more than one event]). A causal relationship to ceritinib could not be ruled out for electrocardiogram QT prolonged in 4 subjects. No bradycardia-related events leading to death occurred.

The analysis of foreign post-marketing data (data cut-off on December 31, 2015) revealed 25 serious bradycardia-related events (electrocardiogram QT prolonged [15 events], syncope [5 events], bradycardia [3 events], and electrocardiogram PR shortened and nodal rhythm [1 event each]). Of these events, 2 events (bradycardia and syncope [1 event each]) resulted in death.

* A total of 11 studies (Studies X1101, X2101, X2103, A2109, A2201, A2203, A2301, A2303, A2402, AKR01T, and AUS10T) were included in the evaluation. The same applies hereinafter.

PMDA's view:
Bradycardia-related events were observed in the clinical studies and the foreign post-marketing data at a certain frequency, but most of them were electrocardiogram QT prolonged. No serious bradycardia-related events occurred in the clinical studies. However, bradycardia with a heart rate <50/min was reported in the studies. Bradycardia with a heart rate <50/min is considered to be a finding suggestive of possible syncope (Guidelines for Diagnosis and Management of Syncope [JCS 2012], Japanese Circulation Society) and is specified as an adverse event requiring special attention associated with use of crizotinib, which is an ALK inhibitor as with ceritinib (see "Review Report on Xalkori Capsules 200 mg and Xalkori Capsules 250 mg, dated February 20, 2012"). In light of the above findings, the applicant should provide information on the bradycardia-related events to healthcare professionals appropriately, and should continue collecting information on bradycardia. New safety information should be communicated to healthcare professionals appropriately if such information becomes available.

4.(iii).B.(3).8) Pericarditis

The applicant's explanation of pericarditis in patients treated with ceritinib:
Adverse event terms coded to the MedDRA preferred terms "cardiac tamponade," "Dressler's syndrome," "intrapericardial thrombosis," "pericardial calcification," "pericardial disease," "pericardial drainage," "pericardial effusion," "pericardial fibrosis," "pericardial haemorrhage," "pericardial rub," "pericarditis," "pericarditis adhesive," "pericarditis constrictive," "pericarditis uraemic," "pleuropericarditis," and "pneumopericardium" were tabulated as pericarditis-related events.

The incidence of pericarditis-related events in Study A2201, Study A2203, and Study X2101-750 mg group are shown in the table below.

Incidence of pericarditis-related events (Study A2201, Study A2203, and Study X2101-750 mg group)

Preferred term (MedDRA ver. 17.0)	n (%)					
	Study A2201 N = 140		Study A2203 N = 124		Study X2101-750 mg group N = 255	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Pericarditis-related events	9 (6.4)	7 (5.0)	6 (4.8)	3 (2.4)	18 (7.1)	9 (3.5)
Pericardial effusion	5 (3.6)	5 (3.6)	2 (1.6)	1 (0.8)	10 (3.9)	4 (1.6)
Pericarditis	4 (2.9)	2 (1.4)	3 (2.4)	1 (0.8)	8 (3.1)	3 (1.2)
Cardiac tamponade	0	0	1 (0.8)	1 (0.8)	2 (0.8)	2 (0.8)

Pericarditis-related events leading to death occurred in 1 subject (0.8%, cardiac tamponade) in Study A2203 and 1 subject (0.4%, cardiac tamponade) in Study X2101-750 mg group, and a causal relationship to ceritinib was ruled out for both events. Serious pericarditis-related events occurred in 4 subjects (2.9%, pericarditis and pericardial effusion in 2 subjects each) in Study A2201, 4 subjects (3.2%, pericarditis in 3 subjects and cardiac tamponade in 1 subject) in Study A2203, and 10 subjects (3.9%; pericardial effusion in 5 subjects, pericarditis in 4 subjects, and cardiac tamponade in 2 subjects [some subjects experienced more than one event]) in Study X2101-750 mg group. A causal relationship to ceritinib could not be ruled out for pericarditis in 2 subjects and pericardial effusion in 1 subject in Study A2201, pericarditis in 3 subjects in Study A2203, and pericarditis in 3 subjects and pericardial effusion in 1 subject in Study X2101-750 mg group. Pericarditis-related events leading to treatment discontinuation occurred in 2 subjects (1.6%) in Study A2203 and 1 subject (0.4%) in Study X2101-750 mg group. Pericarditis-related events leading to treatment interruption or dose reduction occurred in 5 subjects (3.6%) in Study A2201, 3 subjects (2.4%) in Study A2203, and 8 subjects (3.1%) in Study X2101-750 mg group.

In the 11 clinical studies of ceritinib including those submitted in the new drug application (data cut-off on April 28, 2015), serious pericarditis-related events occurred in 38 subjects (pericardial effusion in 20 subjects, pericarditis in 15 subjects, cardiac tamponade in 3 subjects, and pericardial haemorrhage and pleuropericarditis in 1 subject each [some subjects experienced more than one event]). A causal relationship to ceritinib could not be ruled out for pericarditis in 14 subjects, pericardial effusion in 4 subjects, and pericardial haemorrhage in 1 subject. Pericarditis-related events resulting in death occurred in 4 subjects (cardiac tamponade in 2 subjects, and pericardial effusion and pericardial haemorrhage in 1 subject each). A causal relationship to ceritinib could not be ruled out for pericardial haemorrhage in 1 subject.

The analysis of foreign post-marketing data (data cut-off on April 28, 2015) revealed 89 serious pericarditis-related events (pericardial effusion [47 events], pericarditis [31 events], cardiac tamponade [8 events], and pericardial haemorrhage, pericardial rub, and pleuropericarditis [1 event each]). Six pericarditis-related events (cardiac tamponade [3 events], pericardial effusion [2 events], and pericardial haemorrhage [1 event]) resulted in death.

PMDA's view:
Although pericarditis were observed at a certain frequency in the clinical studies and the foreign post-marketing data, it is difficult at present to determine the risk of pericarditis in patients on ceritinib because NSCLC patients may have pericarditis as a complication of the underlying disease. However, serious or fatal pericarditis-related events for which a causal relationship to ceritinib could not be ruled out occurred. Therefore, the applicant should provide information on the pericarditis-related events to healthcare professionals appropriately and should continue collecting information on the occurrence of pericarditis. New safety information should be communicated to healthcare professionals if such information becomes available.

4.(iii).B.(3).9) Infection
The applicant's explanation of infection in patients treated with ceritinib:
Adverse event terms classified into the MedDRA system organ class "Infections and infestations" were tabulated as events of infection.

Infection occurred in 57 of 140 subjects (40.7%) in Study A2201, 53 of 124 subjects (42.7%) in Study A2203, and 136 of 255 subjects (53.3%) in Study X2101-750 mg group. Grade ≥3 infection occurred in 14 subjects (10.0%) in Study A2201, 9 subjects (7.3%) in Study A2203, and 28 subjects (11.0%) in Study X2101-750 mg group. Infection resulting in death occurred in 1 subject (0.7%, pneumonia) in Study A2201 and 6 subjects (2.4%; pneumonia in 3 subjects, and sepsis, pulmonary tuberculosis, and septic shock in 1 subject each) in Study X2101-750 mg group. A causal relationship to ceritinib could not be ruled out for pneumonia in Study A2201. Serious infection occurred in 13 subjects (9.3%) in Study A2201, 10 subjects (8.1%) in Study A2203, and 33 subjects (12.9%) in Study X2101-750 mg group. A causal relationship to ceritinib could not be ruled out for infection in 7 subjects in Study A2201, 1 subject in Study A2203, and 1 subject in Study X2101-750 mg group. Infection leading to treatment discontinuation occurred in 2 subjects (1.4%) in Study A2201, 1 subject (0.8%) in Study A2203, and 4 subjects (1.6%) in Study X2101-750 mg group. Infection leading to treatment interruption or dose reduction occurred in 12 subjects (8.6%) in Study A2201, 11 subjects (8.9%) in Study A2203, and 25 subjects (9.8%) in Study X2101-750 mg group.

In the 11 clinical studies of ceritinib including those submitted in the new drug application (data cut-off on April 28, 2015), serious infection occurred in 123 subjects. A causal relationship to ceritinib could not be ruled out for infection in 12 subjects (pneumonia in 7 subjects, lung infection in 2 subjects, and enteritis infectious, infection, amoebic dysentery, Escherichia urinary tract infection, and Salmonella sepsis in 1 subject each [some subjects experienced more than one event]). Infection leading to death occurred in 22 subjects (pneumonia in 14 subjects, respiratory tract infection and septic shock in 2 subjects each, and lung infection, pulmonary tuberculosis, lung abscess, peritonitis, pneumonia klebsiella, klebsiella sepsis, and sepsis in 1 subject each [some subjects experienced more than one event]). A causal relationship to ceritinib could not be ruled out for pneumonia in 1 subject.

The analysis of foreign post-marketing data (data cut-off on December 31, 2015) revealed 315 events of serious infection. Of these, 60 events (pneumonia [23 events], sepsis [7 events], septic shock [5

events], lower respiratory tract infection, lung infection, peritonitis, and respiratory tract infection [2 events each], and abdominal sepsis, H1N1 influenza, Aspergillus infection, infection, influenza, klebsiella sepsis, listeriosis, atypical pneumonia, bacterial sepsis, pyelonephritis, soft tissue infection, urinary tract infection, lung abscess, abdominal infection, meningitis, pneumonia klebsiella, and pulmonary tuberculosis [1 event each]) resulted in death.

PMDA's view:
Although serious infection occurred at a certain frequency in the clinical studies, it is difficult at present to determine the risk of infection in patients on ceritinib because NSCLC patients may have infection with pneumonia or other infectious diseases as complications of the underlying disease. However, death resulting from infection for which a causal relationship to ceritinib could not be ruled out occurred. Therefore, the applicant should provide information on the pericarditis-related events to healthcare professionals appropriately and should continue collecting information on the occurrence of infection. New safety information should be communicated to healthcare professionals appropriately if such information becomes available.

4.(iii).B.(3).10) Pancreatitis
The applicant's explanation of pancreatitis in patients treated with ceritinib:
Adverse event terms coded to the MedDRA preferred terms "Cullen's sign," "Grey Turner's sign," "hereditary pancreatitis," "ischaemic pancreatitis," "oedematous pancreatitis," "pancreatic abscess," "pancreatic haemorrhage," "pancreatic necrosis," "pancreatic phlegmon," "pancreatic pseudocyst," "pancreatic pseudocyst drainage," "pancreatitis," "pancreatitis acute," "pancreatitis haemorrhagic," "pancreatitis necrotising," "pancreatitis relapsing," "pancreatorenal syndrome," "amylase abnormal," "amylase creatinine clearance ratio abnormal," "amylase increased," "blood trypsin increased," "hyperamylasaemia," "hyperlipasaemia," "lipase abnormal," "lipase increased," "lipase urine increased," "pancreatic enzyme abnormality," "pancreatic enzymes abnormal," and "pancreatic enzymes increased" were tabulated as pancreatitis-related events.

The incidence of pancreatitis-related events in Study A2201, Study A2203, and Study X2101-750 mg group are shown in the table below.

Incidence of pancreatitis-related events (Study A2201, Study A2203, and Study X2101-750 mg group)

Preferred term (MedDRA ver. 17.0)	n (%)					
	Study A2201 N = 140		Study A2203 N = 124		Study X2101-750 mg group N = 255	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Pancreatitis-related events	2 (1.4)	1 (0.7)	5 (4.0)	2 (1.6)	31 (12.2)	18 (7.1)
Amylase increased	1 (0.7)	0	5 (4.0)	2 (1.6)	18 (7.1)	8 (3.1)
Lipase increased	0	0	0	0	24 (9.4)	16 (6.3)
Pancreatitis	1 (0.7)	1 (0.7)	1 (0.8)	1 (0.8)	0	0
Hyperlipasaemia	0	0	0	0	1 (0.4)	0

No pancreatitis-related events resulting in death occurred. Serious pancreatitis-related events occurred in 1 subject (0.7%, pancreatitis) in Study A2201 and 1 subject (0.8%, pancreatitis) in Study A2203. A causal relationship to ceritinib was ruled out for both events. No pancreatitis-related events leading to treatment discontinuation occurred. Pancreatitis-related events leading to treatment interruption or dose reduction occurred in 1 subject (0.7%) in Study A2201, 1 subject (0.8%) in Study A2203, and 17 subjects (6.7%) in Study X2101-750 mg group.

Amylase increased and lipase increased reported as laboratory abnormalities in Study A2201, Study A2203, and Study X2101-750 mg group are shown in the table below.

Incidence of amylase or lipase increased (Study A2201, Study A2203, and Study X2101-750 mg group)

Laboratory abnormalities	n (%)					
	Study A2201* N = 140		Study A2203* N = 124		Study X2101-750 mg group N = 255	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Amylase increased	41 (29.3)	3 (2.1)	23 (18.5)	4 (3.2)	61 (23.9)	17 (6.7)
Lipase increased	-	-	-	-	75 (29.4)	28 (11.0)

* Lipase levels were not evaluated in Study A2201 or Study A2203.

In the 11 clinical studies of ceritinib (data cut-off on April 28, 2015), serious pancreatitis-related events occurred in 6 subjects (pancreatitis in 3 subjects,* lipase increased in 3 subjects, and amylase increased in 2 subjects [some subjects experienced more than one event]). A causal relationship to ceritinib could not be ruled out for lipase increased in 3 subjects, amylase increased in 2 subjects, and pancreatitis in 1 subject. No pancreatitis-related events leading to death occurred.

* A 54-year male enrolled in Study A2201. On Day 523 of treatment with ceritinib (after data cut-off for the submission), serious pancreatitis occurred. At the time of onset of pancreatitis, the subject had abdominal pain, amylase level of 1724 U/L (normal range, 30-110 U/L), and lipase level of 9664 IU/L (normal range, 23-300 IU/L) as well as inflammatory lesion in the pancreatic head detected by abdominal CT scan and ultrasonography. The baseline amylase level was 129 U/L (normal range, 28-100 U/L). The subject died of respiratory failure on the day following the onset of pancreatitis. A causal relationship between pancreatitis and ceritinib could not be ruled out, and a causal relationship between respiratory failure and ceritinib was ruled out.

The analysis of foreign post-marketing data (data cut-off on December 31, 2015) revealed 15 serious pancreatitis-related events (pancreatitis [9 events], lipase increased [4 events], and amylase increased [2 events]) occurred. No pancreatitis-related events leading to death.

PMDA's view:
Although amylase or lipase increased and pancreatitis-related events reported as laboratory abnormalities occurred at a certain frequency in clinical studies, serious pancreatitis occurred only in a very limited number of patients. Therefore, it is difficult to determine the risk of pancreatitis in patients on ceritinib. However, serious pancreatitis for which a causal relationship to ceritinib could not be ruled out was reported. In light of the above findings, the applicant should provide information on the laboratory abnormalities and pancreatitis-related events reported in clinical studies to healthcare professionals appropriately and should continue collecting information on the occurrence of pancreatitis-related events. New safety information should be communicated to healthcare professionals appropriately if such information becomes available. In addition, the applicant should provide advice to healthcare professionals appropriately through the package insert and relevant materials containing information on details of laboratory test employed in the clinical studies and criteria for dose interruption, thereby ensuring that tests for lipase or amylase are periodically performed in patients on ceritinib and that appropriate measures are taken if pancreatitis-related events occur.

4.(iii).B.(4) Clinical positioning and indication

The proposed indication of ceritinib is "*ALK*-positive, unresectable, advanced or recurrent non-small cell lung cancer resistant or intolerant to other ALK inhibitors," and the "Precautions for Indications" section includes the following:

- The efficacy and safety of ceritinib in adjuvant chemotherapy have not been established.
- Physicians should select patients eligible for ceritinib therapy after closely reading the "Clinical Studies" section to fully understand the efficacy and safety of ceritinib and carefully considering other treatment options.

On the basis of the review presented in "4.(iii).B.(2) Efficacy" and "4.(iii).B.(3) Safety" as well as the following considerations described in this section, PMDA has reached the following conclusion:
The proposed indication of ceritinib (*ALK*-positive, unresectable, advanced or recurrent non-small cell lung cancer resistant or intolerable to crizotinib) is appropriate. In addition, information on patients enrolled in Study A2201 and Study X2101 such as prior therapy and its outcome should be included in the "Clinical Studies" section of the package insert, and precautionary advise on the above content proposed by the applicant should also be included in the "Precautions for Indications" section.

4.(iii).B.(4).1) Clinical positioning, intended patient population, and indication of ceritinib

Foreign clinical practice guidelines and representative textbooks of clinical oncology published in and outside of Japan were searched for the use of ceritinib for unresectable, advanced or recurrent NSCLC. The guidelines found are shown below. No description about ceritinib was found in the Guideline for EBM-based diagnosis and management of lung cancer, Version 2015, edited by the Japanese Lung Cancer Society (Japanese Lung Cancer Society, 2015) ("Japanese guideline") or *New clinical oncology*, 4th version (Nankodo, 2015).

Clinical practice guidelines

- National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Non-Small Cell Lung Cancer ("NCCN guidelines") (v. 7.2015), USA: Ceritinib is recommended for patients with *ALK*-positive, unresectable, advanced or recurrent NSCLC resistant or intolerant to crizotinib (Category 2A*).

- National Cancer Institute Physician Data Query (NCI PDQ) (accessed on September 3, 2015), USA: Ceritinib is recommended for patients with *ALK*-positive, unresectable, advanced NSCLC resistant or intolerant to crizotinib.

  * Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Textbook

- DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology 10th edition (Lippincott Williams & Wilkins 2015, USA): Based on the results from Study X2101, ceritinib is one of the treatment options for patients with *ALK*-positive unresectable, advanced or recurrent NSCLC who have progressed after crizotinib.

On the basis of the clinical positioning and intended patient population of ceritinib, the applicant explained the indication as follows:

At present, clinical practice guidelines available in and outside Japan recommend crizotinib for chemotherapy-naïve patients with *ALK*-positive, unresectable, advanced or recurrent NSCLC. However, the development of new therapeutic drugs is awaited for the following reasons: (a) 25% to 35% of the patients did not respond to crizotinib, and the median progression-free survival was only 7.7 to 10.9 months (*N Engl J Med.* 2014;371:2167-77, *N Engl J Med.* 2013;368:2385-94), and (b) despite the fact that two-drug combination chemotherapy containing platinum antineoplastic drugs is recommended for non-responders to crizotinib (Japanese guideline), the median overall survival in patients treated with such therapy was 10 to 13 months (*N Engl J Med.* 2006;355:2542-50, *J Clin Oncol.* 2008;26:3543-51).

Under the above circumstances, Studies A2201 and X2101 demonstrated the clinical usefulness of ceritinib in patients with *ALK*-positive NSCLC previously treated with crizotinib. Ceritinib is therefore considered of clinical significance as one of the therapeutic options for this patient population.

Moreover, ceritinib may be used in patients with *ALK*-positive, unresectable, advanced or recurrent NSCLC previously treated with alectinib, an *ALK* inhibitor other than crizotinib, because ceritinib is expected to be effective in this patient population, in consideration of the following points:

- Of 7 patients with *ALK*-positive NSCLC previously treated with alectinib who were included in both the dose-escalation phase and expansion phase of Study X1101, 3 patients (42.9%) responded to ceritinib.
- Ceritinib inhibited proliferation of *ALK*-positive NSCLC cells with acquired resistance to alectinib in a non-clinical study [see "3.(i).B Mechanism of action and efficacy of ceritinib"].

Based on the above, the indication of ceritinib was defined as "*ALK*-positive, unresectable, advanced or recurrent non-small cell lung cancer resistant or intolerant to other ALK inhibitors." For identification of patients eligible for ceritinib therapy, physicians should fully understand clinical study data. Therefore, the "Precautions for Indications" section of the package insert includes a precautionary statement that therapies other than ceritinib should be carefully considered.

PMDA's view:
On the basis of the review presented in "4.(iii).B.(2) Efficacy" and "4.(iii).B.(3) Safety" as well as considerations in this section, the applicant's explanation of the clinical positioning of ceritinib (i.e. ceritinib is positioned as one of the therapeutic options for patients with *ALK*-positive, unresectable, advanced or recurrent NSCLC previously treated with crizotinib) is acceptable. Further, the intended patient population (patients previously treated with crizotinib) should be clearly defined in the indication, because at present ceritinib is not recommended for patients who have not previously received crizotinib but have been treated with alectinib, for the following reasons: (1) the inclusion criteria of Study A2201 only allowed crizotinib as prior ALK inhibitor therapy; and (2) the Japanese and foreign guidelines both recommend crizotinib as the first-line therapy for patients with *ALK*-positive, unresectable, advanced or recurrent NSCLC.

In addition, a global phase III study (Study CLDK378A2303) as a confirmatory study of ceritinib, is currently ongoing. The study intends to compare ceritinib with standard chemotherapy in patients with *ALK*-positive, unresectable, advanced or recurrent NSCLC previously treated with crizotinib and platinum-based chemotherapy. At present, no information on survival benefits is available. In light of the above facts, the following precautionary statement should be included in the "Precautions for Indications" section, as proposed by the applicant: the use of ceritinib should be carefully determined upon adequate consideration given to therapies other than ceritinib.

4.(iii).B.(4).2) *ALK* fusion gene testing
The applicant's explanation of the necessity of *ALK* fusion gene testing prior to use of ceritinib:
The inclusion criteria for Study A2201 specified that the Vysis ALK Break Apart FISH Probe Kit based on the Break Apart method should be used for *ALK* fusion gene testing. The intended patient population for ceritinib is patients with NSCLC previously treated with crizotinib, and these patients are supposed to have tested positive for *ALK* fusion gene using the Vysis ALK Break Apart FISH Probe Kit before starting crizotinib therapy. Therefore another *ALK* fusion gene testing is not necessary.

PMDA accepted the applicant's explanation.

4.(iii).B.(4).3) Efficacy and safety of ceritinib as an adjuvant chemotherapy
No clinical study data that support the efficacy and safety of ceritinib as an adjuvant chemotherapy are available. The applicant therefore explained that precautionary advice on this issue would be included in the "Precautions for Indications" section of the package insert.

PMDA accepted the applicant's explanation.

4.(iii).B.(5) Dosage and administration
The proposed dosage and administration of ceritinib is "The usual adult dosage is 750 mg of ceritinib administered orally once daily in the fasted state. The dose may be reduced according to the patient's condition." The "Precautions for Dosage and Administration" section states that administration of ceritinib in the fasted state is recommended to avoid the effect of food, and the section also includes the criteria for dose adjustment in patients experiencing any adverse drug reaction.

PMDA's view:
On the basis of the review presented in "4.(i).B.(1) Food effect" as well as the following considerations, the proposed dosage and administration of ceritinib ("The usual adult dosage is 750 mg of ceritinib administered orally once daily in the fasted state. The dose may be reduced according to the patient's condition.") is appropriate. In addition, the following precautionary advice should be included in the "Precautions for Dosage and Administration" section.

[Precautions for Dosage and Administration]
- Studies showed increases in the C_{max} and AUC of ceritinib administered after a meal. To avoid the effect of food, ceritinib should not be taken within 2 hours before and after a meal.

- Dose interruption, dose reduction, or treatment discontinuation due to adverse drug reactions should be considered based on the criteria shown below. Ceritinib should be discontinued in patients unable to tolerate ceritinib 300 mg daily.

Criteria for dose interruption, dose reduction, or discontinuation due to adverse drug reactions

	Criteria*	Dose adjustment of ceritinib
Interstitial lung disease (ILD)	Any Grade ILD	Discontinue ceritinib.
Hepatic function disorder	• Grade ≤1 elevation in AST or ALT with Grade 2 elevation in blood bilirubin • Grade 2 or 3 elevation in AST or ALT with Grade ≤1 elevation in blood bilirubin	Withhold ceritinib until recovery of AST, ALT, and blood bilirubin to Grade ≤1. Resume ceritinib at the previous dose level if recovery is seen within 7 days, or resume ceritinib with a 150 mg dose reduction if recovery is seen in >7 days.
	• Grade ≤1 elevation in AST or ALT with Grade 3 elevation in blood bilirubin • Grade ≥2 elevation in AST or ALT with blood bilirubin elevation to >1.5 × upper limit of normal (ULN) and ≤2 × ULN	Withhold ceritinib until recovery of AST, ALT, and blood bilirubin to Grade ≤1. Resume ceritinib with a 150 mg dose reduction if recovery is seen within 7 days. Discontinue if recovery is not seen within 7 days.
	• Grade 4 elevation in AST or ALT with Grade ≤1 elevation in blood bilirubin	Withhold ceritinib until recovery of AST and ALT to Grade ≤1. Resume ceritinib with a 150 mg dose reduction.
	• Grade 4 elevation in blood bilirubin • Grade ≥2 elevation in AST or ALT with blood bilirubin elevation to >2 × ULN	Discontinue ceritinib.
QT interval prolonged	QTc >500 msec on at least 2 separate ECGs	Withhold ceritinib until recovery to baseline or QTc <481 msec. Resume ceritinib with a 150 mg dose reduction.
	QTc >500 msec or a >60 msec increase in QTc interval from baseline and torsade de pointes, polymorphic ventricular tachycardia, or signs/symptoms of severe arrhythmia	Discontinue ceritinib.
Bradycardia	Symptomatic and serious bradycardia requiring medical intervention	Withhold ceritinib until recovery to asymptomatic bradycardia or to a heart rate of ≥60 bpm. Resume ceritinib with a 150 mg dose reduction.
	Life threatening bradycardia requiring urgent intervention	Discontinue ceritinib.
Nausea, vomiting, and diarrhoea	• Grade ≥3 • Intorelable nausea, vomiting or diarhoea despite use of optimal anti-emetic or anti-diarrheal agents	Withhold ceritinib until recovery to Grade ≤1. Resume ceritinib with a 150 mg dose reduction.
Hyperglycaemia	Persistent hyperglycaemia of >250 mg/dL even after optimal treatment	Withhold ceritinib until blood glucose is under control. Resume ceritinib with a 150 mg dose reduction.
Lipase or amylase elevation	Grade ≥3	Withhold ceritinib until recovery to Grade ≤1. Resume ceritinib with a 150 mg dose reduction.

* Severity grade according to CTCAE ver. 4

4.(iii).B.(5).1) Dosage and administration

The applicant's justification for the proposed dosage and administration:

On the basis of the results of the foreign phase I study (Study X2101), the MTD and RD of ceritinib were determined to be 750 mg QD orally [see "4.(iii).A.(4) Foreign phase I study"]. In addition, in the Japanese phase I study (Study X1101), the MTD and RD of ceritinib were determined to be 750 mg QD orally, as in the case of Study X2101 [see "4.(iii).A.(2) Japanese phase I study"].

This dosage was used in Study A2201, which demonstrated the clinical usefulness of ceritinib in patients with *ALK*-positive, unresectable, advanced or recurrent NSCLC previouly treated with crizotinib. Based on the design of this study, the proposed dosage and administration of ceritinib was selected.

PMDA accepted the applicant's explanation.

4.(iii).B.(5).2) Dose adjustment

The applicant's explanation of dose adjustment of ceritinib:

The protocol of Study A2201 specified criteria for dose adjustment of ceritinib according to the severity of adverse events, etc. The tolerability profile of ceritinib was acceptable as long as the criteria were met. The proposed "Precautions for Dosage and Administration" section of the package insert includes criteria for dose adjustment based on the above criteria. The criteria employed in Study A2201 were mondified for ILD, hepatic function disorder, and nausea, vomiting, and diarrhoea among the adverse drug reactions requiring dose adjustment. The modification was made for the following reasons:

- In the clinical study, subjects were allowed to resume ceritinib at a reduced dose after Grade 1 ILD had been alleviated. In light of the risk of aggravated ILD following resumption of ceritinib, the applicant considered that the criteria for dose adjustment should specify the discontinuation of ceritinib at the time of onset of ILD, irrespective of its severity.
- In general, serious hepatic injury occurs in approximately 10% of patients with hepatic function disorder meeting the Hy's Law criteria (Food and Drug Administration 2009). In light of this guidance, the applicant considered that the criteria for interruption of ceritinib due to hepatic function disorder can be defined based on the Hy's Law criteria. So far, all clinical studies of ceritinib have employed the criteria for dose adjustment based on the Hy's Law criteria.
- The applicant considered that the criteria for dose adjustment due to nausea, vomiting, and diarrhoea should be integrated.

In addition, on the basis of the safety information obtained from the clinical studies, the applicant considered that criteria for dose adjustment due to hyperglycaemia, pancreatitis, and bradycardia should be newly specified, and thus separate criteria for dose adjustment were established for hyperglycaemia, lipase or amylase increased, and bradycardia.

PMDA's view:

The applicant's explanation is generally acceptable. However, the criteria for treatment interruption, dose reduction, and treatment discontinuation due to hepatic function disorder should be established in line with the criteria employed in Study A2201, which demonstrated the clinical usefulness of ceritinib.

4.(iii).B.(6) Post-marketing investigations

The applicant's explanation of their proposed post-marketing surveillance plan for ceritinib:

The applicant plans an all-case drug use results survey which covers all patients treated with ceritinib to monitor the safety of ceritinib in the post-marketing clinical setting.

The key survey items consist of hepatotoxicity, QT prolonged, interstitial lung disease/pneumonitis, hyperglycaemia, gastrointestinal toxicity (nausea, vomiting, diarrhoea), and pancreatitis. These were selected as events of special concern that may occur as a consequence of pharmacological action of ceritinib, events frequently reported in clinical studies, and events that may affect continued treatment.

The planned sample size of 220 subjects has been set based on the incidence of QT prolonged (1.5%, 8 of 525 subjects), because the pooled analysis of Studies X2101, X1101, A2201, and A2203 (pooled safety analysis) revealed that QT prolonged was the least frequently reported Grade ≥3 adverse event among the key survey items.

The observation period has been set at 1 year, for the following reasons: (1) the pooled safety analysis revealed that most of the patients had the first onset of adverse events, including the key survey items, within 1 year after the start of treatment with ceritinib, and (2) there was no trend toward increased incidence of the adverse events at ≥1 year after the start of treatment.

PMDA's view:

Because information on the safety of ceritinib in Japanese patients is limited, the applicant should conduct a survey covering all patients treated with ceritinib for a specific period during the early post-marketing phase to collect information in a prompt and unbiased manner. New safety information should be communicated to healthcare professionals immediately when it becomes available.

The key survey items of the survey should include not only adverse events identified by the applicant but also bradycardia, pericarditis, infection, and diabetes mellitus, which are the adverse events requiring special attention in patients on ceritinib [see "4.(iii).B.(3) Safety"].

The planned sample size for the survey should be reconsidered, taking into account that the survey intends to compare post-marketing safety data with the incidence of adverse events in the currently available safety data (results from the above pooled safety analysis).

The observation period for the survey should be reconsidered in light of the time to onset of the adverse events additionally identified as the key survey items.

4.(iii).B.(7) Post-marketing risk minimization activities

The applicant's explanation of post-marketing risk minimization activities:

The post-marketing safety against the risk of ILD and related events must be ensured because (a) clinical experience with ceritinib is limited in Japan; (b) serious or fatal outcomes were observed in patients treated with ceritinib, as with the case of crizotinib, an approved ALK inhibitor; and (c) a phase III study of ceritinib is currently ongoing. To this end, the applicant plans to specify conditions for use of ceritinib (requirements for physicians and facilities, explanation to patients or their families by prescribing physicians, request to pharmacies for cooperation) as a part of its additional risk minimization activities.

PMDA's view:

The applicant's explanation is acceptable. Whether the validity period for conditions for use of ceritinib is extended should be considered at an appropriate timing such as submission of periodic safety update reports, in light of the latest information at that time.

4.(iv) Adverse events reported in clinical studies

Deaths reported in the clinical studies submitted for safety evaluation are described in "4.(iii) Summary of clinical efficacy and safety." Common adverse events other than death are summarized in the sections below.

4.(iv).(1) Japanese phase I study (Study CLDK378X1101)

Adverse events occurred in 19 of 19 subjects (100%), and adverse events for which a causal relationship to ceritinib could not be ruled out occurred in 19 of 19 subjects (100%). Adverse events with an incidence of ≥40% are shown in the table below.

Adverse events with an incidence of ≥40% in any group

System organ class Preferred term (MedDRA/J ver. 17.0)	n (%)							
	300 mg N = 3		450 mg N = 6		600 mg N = 4		750 mg N = 6	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Total	3 (100)	2 (66.7)	6 (100)	5 (83.3)	4 (100)	4 (100)	6 (100)	4 (66.7)
Blood and lymphatic system disorders								
Neutropenia	2 (66.7)	0	2 (33.3)	0	0	0	0	0
Leukopenia	2 (66.7)	0	1 (16.7)	0	0	0	0	0
Gastrointestinal disorders								
Nausea	3 (100)	0	6 (100)	0	4 (100)	0	5 (83.3)	0
Diarrhoea	3 (100)	0	2 (33.3)	0	4 (100)	0	5 (83.3)	0
Vomiting	1 (33.3)	0	6 (100)	0	4 (100)	0	3 (50.0)	0
Abdominal pain	2 (66.7)	0	1 (16.7)	0	1 (25.0)	0	2 (33.3)	0
Constipation	1 (33.3)	0	3 (50.0)	1 (16.7)	0	0	1 (16.7)	0
General disorders and administration site conditions								
Fatigue	0	0	2 (33.3)	0	2 (50.0)	0	3 (50.0)	0
Infections and infestations								
Nasopharyngitis	2 (66.7)	0	0	0	0	0	0	0
Investigations								
Blood creatinine increased	3 (100)	0	4 (66.7)	0	1 (25.0)	0	4 (66.7)	0
Weight decreased	0	0	1 (16.7)	0	2 (50.0)	0	0	0
Metabolism and nutrition disorders								
Decreased appetite	0	0	3 (50.0)	0	3 (75.0)	0	4 (66.7)	0
Hyperuricaemia	0	0	0	0	1 (25.0)	0	4 (66.7)	1 (16.7)
Nervous system disorders								
Headache	1 (33.3)	0	3 (50.0)	0	0	0	0	0
Dizziness	2 (66.7)	0	0	0	0	0	0	0
Skin and subcutaneous tissue disorders								
Rash	0	0	3 (50.0)	0	0	0	1 (16.7)	0

Serious adverse events occurred in 1 of 3 subjects (33.3%) in the 300 mg group, 5 of 6 subjects (83.3%) in the 450 mg group, 1 of 4 subjects (25.0%) in the 600 mg group, and 2 of 6 subjects (33.3%) in the 750 mg group. The serious adverse events were facial nerve disorder and tumour pain in 1 subject each (33.3%) in the 300 mg group; depressed level of consciousness, gait disturbance, hydrocephalus, pericarditis, pneumonia, and respiratory failure in 1 subject each (16.7%) in the 450 mg group; biliary tract infection, cholangitis, and cholangitis suppurative in 1 subject each (25.0%) in the 600 mg group; and drug-induced liver injury and hepatic function abnormal in 1 subject each (16.7%) in the 750 mg group. A causal relationship to ceritinib could not be ruled out for pericarditis in 1 subject in the 450 mg group, and drug-induced liver injury and hepatic function abnormal in 1 subject each in the 750 mg group.

Adverse events leading to treatment discontinuation occurred in 1 of 4 subjects (25.0%) in the 600 mg group and 1 of 6 subjects (16.7%) in the 750 mg group. The adverse events leading to treatment discontinuation were cholangitis and hepatic enzyme increased in 1 subject each (25.0%) in the 600 mg group and drug-induced liver injury in 1 subject (16.7%) in the 750 mg group. A causal relationship to ceritinib could not be ruled out for drug-induced liver injury.

4.(iv).(2) Global phase II study (Study CLDK378A2201)

Adverse events occurred in 140 of 140 subjects (100%) and adverse events for which a causal relationship to ceritinib could not be ruled out occurred in 135 of 140 subjects (96.4%). Adverse events with an incidence of ≥10% are shown in the table below.

Adverse events with an incidence of ≥10%

System organ class Preferred term (MedDRA/J ver. 17.0)	n (%) Ceritinib N = 140	
	All Grades	Grade ≥3
Total	140 (100)	96 (68.6)
Blood and lymphatic system disorders		
Anaemia	20 (14.3)	3 (2.1)
Gastrointestinal disorders		
Diarrhoea	112 (80.0)	9 (6.4)
Nausea	111 (79.3)	9 (6.4)
Vomiting	87 (62.1)	6 (4.3)
Abdominal pain	43 (30.7)	2 (1.4)
Constipation	33 (23.6)	3 (2.1)
Abdominal pain upper	16 (11.4)	1 (0.7)
General disorders and administration site conditions		
Fatigue	46 (32.9)	9 (6.4)
Pyrexia	29 (20.7)	4 (2.9)
Non-cardiac chest pain	23 (16.4)	2 (1.4)
Asthenia	22 (15.7)	6 (4.3)
Investigations		
ALT increased	56 (40.0)	19 (13.6)
Weight decreased	45 (32.1)	6 (4.3)
AST increased	42 (30.0)	7 (5.0)
GGT increased	25 (17.9)	17 (12.1)
Blood ALP increased	21 (15.0)	4 (2.9)
Blood creatinine increased	20 (14.3)	0
Metabolism and nutrition disorders		
Decreased appetite	56 (40.0)	5 (3.6)
Musculoskeletal and connective tissue disorders		
Back pain	18 (12.9)	1 (0.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Non-small cell lung cancer	15 (10.7)	15 (10.7)
Nervous system disorders		
Headache	20 (14.3)	0
Respiratory, thoracic and mediastinal disorders		
Cough	26 (18.6)	0
Dyspnoea	25 (17.9)	7 (5.0)
Skin and subcutaneous tissue disorders		
Rash	20 (14.3)	0

ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; GGT, γ-glutamyltransferase; ALP, Alkaline phosphatase

Serious adverse events occurred in 51 of 140 subjects (36.4%). The serious adverse events were pyrexia in 7 subjects (5.0%); dyspnoea in 6 subjects (4.3%); pneumonia in 5 subjects (3.6%); abdominal pain, asthenia, dehydration, nausea, non-cardiac chest pain, pneumonitis, and vomiting in 3 subjects each (2.1%); convulsion, malaise, pericardial effusion, pericarditis, pleural effusion, pleurisy, respiratory failure, and weight decreased in 2 subjects each (1.4%); and ALT increased, altered state of consciousness, aphasia, AST increased, blood creatinine increased, bone pain, brain oedema, constipation, coronary artery disease, cough, decreased appetite, disease progression, empyema, enteritis infectious, faecaloma, febrile neutropenia, gastrointestinal disorder, gastrointestinal toxicity, general physical health deterioration, hepatic encephalopathy, hepatic function abnormal, hepatocellular injury, hydronephrosis, intestinal perforation, lung disorder, lung infection, meningitis, metastases to lung, pain, pancreatitis, paraesthesia, pleural infection, pollakiuria, pubis fracture, pulmonary embolism, renal failure, respiratory tract infection, septic shock, spinal compression fracture, and viral pericarditis in 1 subject each (0.7%). A causal relationship to ceritinib could not be ruled out for pneumonia in 4 subjects, nausea and vomiting in 3 subjects each, abdominal pain, pericarditis, pneumonitis, and pyrexia in 2 subjects each, and pericardial effusion, constipation, gastrointestinal disorder, gastrointestinal toxicity, intestinal perforation, pain, hepatic function abnormal, hepatocellular injury, enteritis infectious, lung infection, pleural infection, ALT increased, AST increased, blood creatinine increased, weight decreased, decreased appetite, hepatic encephalopathy, renal failure, lung disorder, and pleurisy in 1 subject each.

Adverse events leading to treatment discontinuation occurred in 10 of 140 subjects (7.1%). The adverse events leading to treatment discontinuation were nausea and pneumonitis in 2 subjects each (1.4%), and cancer pain, empyema, faecaloma, fatigue, GGT increased, intestinal perforation, pneumonia, and vomiting in 1 subject each (0.7%). A causal relationship to ceritinib could not be ruled out for the above adverse events except for cancer pain, empyema, and faecaloma in 1 subject each.

4.(iv).(3) Global phase II study (Study CLDK378A2203)

Adverse events occurred in 123 of 124 subjects (99.2%) and adverse events for which a causal relationship to ceritinib could not be ruled out occurred in 122 of 124 subjects (98.4%). Adverse events with an incidence of ≥10% are shown in the table below.

Adverse events with an incidence of ≥10%

System organ class Preferred term (MedDRA/J ver. 17.0)	n (%) Ceritinib N = 124	
	All Grades	Grade ≥3
Total	123 (99.2)	80 (64.5)
Gastrointestinal disorders		
Diarrhoea	102 (82.3)	4 (3.2)
Nausea	92 (74.2)	4 (3.2)
Vomiting	83 (66.9)	6 (4.8)
Abdominal pain	41 (33.1)	0
Constipation	19 (15.3)	0
General disorders and administration site conditions		
Fatigue	40 (32.3)	7 (5.6)
Asthenia	18 (14.5)	2 (1.6)
Non-cardiac chest pain	16 (12.9)	1 (0.8)
Pyrexia	13 (10.5)	1 (0.8)
Investigations		
ALT increased	50 (40.3)	19 (15.3)
AST increased	38 (30.6)	9 (7.3)
Weight decreased	36 (29.0)	1 (0.8)
GGT increased	33 (26.6)	23 (18.5)
Blood creatinine increased	26 (21.0)	0
Blood ALP increased	25 (20.2)	8 (6.5)
Electrocardiogram QT prolonged	15 (12.1)	1 (0.8)
Metabolism and nutrition disorders		
Decreased appetite	61 (49.2)	2 (1.6)
Hyperglycaemia	13 (10.5)	7 (5.6)
Musculoskeletal and connective tissue disorders		
Back pain	19 (15.3)	1 (0.8)
Respiratory, thoracic and mediastinal disorders		
Cough	21 (16.9)	0
Dyspnoea	17 (13.7)	1 (0.8)
Skin and subcutaneous tissue disorders		
Rash	19 (15.3)	1 (0.8)

ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; GGT, γ-glutamyltransferase; ALP, Alkaline phosphatase

Serious adverse events occurred in 27 of 124 subjects (21.8%). The serious adverse events were hyperglycaemia, pericarditis, and pneumonia in 3 subjects each (2.4%); altered state of consciousness, fatigue, lung infection, and respiratory failure in 2 subjects each (1.6%); anal inflammation, asthenia, atypical pneumonia, bone pain, cardiac tamponade, cognitive disorder, diabetes mellitus, diabetic ketoacidosis, diarrhoea, encephalopathy, escherichia bacteraemia, headache, hepatitis, metastases to central nervous system, muscular weakness, nausea, neutropenia, nosocomial infection, oesophageal stenosis, pain, pancreatitis, Parkinson's disease, pleurisy, Pneumocystis jirovecii pneumonia, pneumonia aspiration, pneumothorax, post procedural infection, pulmonary embolism, pulmonary oedema, pyrexia, radiation oesophagitis, respiratory tract infection, stomatitis, toxicity to various agents, tracheal haemorrhage, tracheo-oesophageal fistula, vomiting, and weight decreased in 1 subject each (0.8%). A causal relationship to ceritinib could not be ruled out for pericarditis in 3 subjects, and diarrhoea, nausea, vomiting, asthenia, fatigue, lung infection, weight decreased, hyperglycaemia, altered state of consciousness, pleurisy, and respiratory failure in 1 subject each.

Adverse events leading to treatment discontinuation occurred in 9 of 124 subjects (7.3%). The adverse events leading to treatment discontinuation were AST increased, cardiac tamponade, electrocardiogram QT prolonged, hyperglycaemia, interstitial lung disease, Parkinson's disease, pericarditis, pneumonia aspiration, and respiratory tract infection in 1 subject each (0.8%). A causal relationship to ceritinib could not be ruled out for AST increased, electrocardiogram QT prolonged, hyperglycaemia, interstitial lung disease, and pericarditis in 1 subject each.

4.(iv).(4) Foreign phase I study (Study CLDK378X2101)

Adverse events occurred in 304 of 304 subjects (100%) and adverse events for which a causal relationship to ceritinib could not be ruled out occurred in 1 of 2 subjects (50.0%) in the 50 mg group, 0 of 2 subjects in the 100 mg group, 3 of 3 subjects (100%) in the 200 mg group, 2 of 3 subjects (66.7%) in the 300 mg group, 14 of 14 subjects (100%) in the 400 mg group, 9 of 10 subjects (90.0%) in the 500 mg group, 10 of 10 subjects (100%) in the 600 mg group, 5 of 5 subjects (100%) in the 700 mg group, and 246 of 255 subjects (96.5%) in the 750 mg group. Adverse events with an incidence of ≥40% are shown in the table below.

Adverse events with an incidence of ≥40% in any group (50-400 mg groups)

System organ class Preferred term (MedDRA/J ver17.0)	n (%)									
	50 mg N = 2		100 mg N = 2		200 mg N = 3		300 mg N = 3		400 mg N = 14	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Total	2 (100)	0	2 (100)	1 (50.0)	3 (100)	3 (100)	3 (100)	2 (66.7)	14 (100)	8 (57.1)
Gastrointestinal disorders										
Diarrhoea	0	0	0	0	2 (66.7)	0	1 (33.3)	1 (33.3)	9 (64.3)	1 (7.1)
Nausea	0	0	1 (50.0)	0	2 (66.7)	0	2 (66.7)	0	10 (71.4)	0
Vomiting	0	0	1 (50.0)	0	3 (100)	0	1 (33.3)	0	8 (57.1)	0
Dyspepsia	1 (50.0)	0	0	0	0	0	0	0	0	0
General disorders and administration site conditions										
Fatigue	1 (50.0)	0	1 (50.0)	1 (50.0)	1 (33.3)	0	0	0	5 (35.7)	0
Asthenia	0	0	1 (50.0)	0	1 (33.3)	1 (33.3)	1 (33.3)	0	2 (14.3)	0
Pain	1 (50.0)	0	0	0	1 (33.3)	0	0	0	0	0
Axillary pain	0	0	1 (50.0)	0	0	0	0	0	0	0
Investigations										
Blood lactate dehydrogenase increased	1 (50.0)	0	1 (50.0)	1 (50.0)	0	0	0	0	0	0
Musculoskeletal and connective tissue disorders										
Muscle spasms	1 (50.0)	0	0	0	0	0	0	0	0	0
Neck pain	0	0	1 (50.0)	0	0	0	0	0	0	0
Respiratory, thoracic and mediastinal disorders										
Cough	0	0	0	0	2 (66.7)	0	0	0	3 (21.4)	0
Dyspnoea	2 (100)	0	0	0	1 (33.3)	0	1 (33.3)	0	2 (14.3)	1 (7.1)
Productive cough	1 (50.0)	0	0	0	0	0	0	0	0	0
Metabolism and nutrition disorders										
Decreased appetite	0	0	1 (50.0)	1 (50.0)	1 (33.3)	0	0	0	0	0
Infections and infestations										
Bronchitis	1 (50.0)	0	0	0	1 (33.3)	1 (33.3)	0	0	0	0
Respiratory tract infection	0	0	1 (50.0)	0	0	0	0	0	0	0
Cystitis	1 (50.0)	0	0	0	0	0	0	0	0	0
Vulvovaginal candidiasis	1 (50.0)	0	0	0	0	0	0	0	0	0
Nervous system disorders										
Headache	1 (50.0)	0	0	0	1 (33.3)	0	0	0	2 (14.3)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)										
Alveolar rhabdomyosarcoma	0	0	1 (50.0)	1 (50.0)	0	0	0	0	0	0

Adverse events with an incidence of ≥40% in any group (500-750 mg groups)

System organ class Preferred term (MedDRA/J ver. 17.0)	n (%)							
	500 mg N = 10		600 mg N = 10		700 mg N = 5		750 mg N = 255	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Total	10 (100)	7 (70.0)	10 (100)	8 (80.0)	5 (100)	4 (80.0)	255 (100)	208 (81.6)
Gastrointestinal disorders								
Diarrhoea	7 (70.0)	1 (10.0)	8 (80.0)	1 (10.0)	4 (80.0)	0	221 (86.7)	15 (5.9)
Nausea	9 (90.0)	1 (10.0)	10 (100)	1 (10.0)	5 (100)	0	211 (82.7)	15 (5.9)
Vomiting	6 (60.0)	0	8 (80.0)	1 (10.0)	4 (80.0)	0	157 (61.6)	12 (4.7)
Constipation	3 (30.0)	0	4 (40.0)	0	2 (40.0)	0	79 (31.0)	0
General disorders and administration site conditions								
Fatigue	4 (40.0)	1 (10.0)	8 (80.0)	0	0	0	109 (42.7)	13 (5.1)
Asthenia	1 (10.0)	1 (10.0)	3 (30.0)	0	3 (60.0)	0	50 (19.6)	2 (0.8)
Investigations								
ALT increased	3 (30.0)	2 (20.0)	3 (30.0)	1 (10.0)	4 (80.0)	4 (80.0)	112 (43.9)	76 (29.8)
AST increased	2 (20.0)	0	2 (20.0)	0	3 (60.0)	3 (60.0)	83 (32.5)	25 (9.8)
Weight decreased	1 (10.0)	0	0	0	3 (60.0)	0	46 (18.0)	5 (2.0)
Musculoskeletal and connective tissue disorders								
Myalgia	0	0	0	0	2 (40.0)	0	9 (3.5)	0
Respiratory, thoracic and mediastinal disorders								
Dyspnoea	4 (40.0)	1 (10.0)	0	0	0	0	63 (24.7)	11 (4.3)
Oropharyngeal pain	1 (10.0)	0	2 (20.0)	0	2 (40.0)	0	14 (5.5)	0
Metabolism and nutrition disorders								
Decreased appetite	3 (30.0)	0	4 (40.0)	1 (10.0)	3 (60.0)	0	95 (37.3)	4 (1.6)
Nervous system disorders								
Dysgeusia	1 (10.0)	0	0	0	2 (40.0)	0	18 (7.1)	0

ALT, Alanine aminotransferase; AST, Aspartate aminotransferase

Serious adverse events occurred in 1 of 2 subjects (50.0%) in the 100 mg group, 1 of 3 subjects (33.3%) in the 200 mg group, 1 of 3 subjects (33.3%) in the 300 mg group, 7 of 14 subjects (50.0%) in the 400 mg group, 4 of 10 subjects (40.0%) in the 500 mg group, 7 of 10 subjects (70.0%) in the 600 mg group, 3 of 5 subjects (60.0%) in the 700 mg group, and 121 of 255 subjects (47.5%) in the 750 mg group. Serious adverse events reported by ≥2 subjects in any group were pneumonia in 14 subjects (5.5%); convulsion in 11 subjects (4.3%); dyspnoea and pneumonitis in 9 subjects each (3.5%); nausea and hyperglycaemia in 6 subjects each (2.4%); pericardial effusion and respiratory failure in 5 subjects each (2.0%); pericarditis, general physical health deterioration, ALT increased, dehydration, headache, and pneumothorax in 4 subjects each (1.6%); vomiting, diarrhoea, non-cardiac chest pain, pyrexia, ataxia, and pleural effusion in 3 subjects each (1.2%); and anaemia, atrial fibrillation, cardiac tamponade, constipation, abdominal pain, ileus, fatigue, bronchitis, lung infection, respiratory tract infection, sepsis, septic shock, urinary tract infection, AST increased, back pain, paraplegia, anxiety, pulmonary embolism, acute respiratory failure, interstitial lung disease, and pneumonia aspiration in 2 subjects each (0.8%) in the 750 mg group. A causal relationship to ceritinib could not be ruled out for pneumonitis in 8 subjects, pericarditis in 3 subjects, vomiting, diarrhoea, nausea, ALT increased, hyperglycaemia, and interstitial lung disease in 2 subjects each, and pericardial effusion, abdominal pain, fatigue, pneumonia, AST increased, dyspnoea, pleural effusion, and respiratory failure in 1 subject each in the 750 mg group.

Adverse events leading to treatment discontinuation occurred in 1 of 14 subjects (7.1%) in the 400 mg group, 2 of 10 subjects (20.0%) in the 600 mg group, and 26 of 255 subjects (10.2%) in the 750 mg group. The adverse events leading to treatment discontinuation were blood ALP increased in 1 subject (7.1%) in the 400 mg group; depressed level of consciousness, hyponatraemia, and pain in extremity in 1 subject each (10.0%) in the 600 mg group; and pneumonia in 3 subjects (1.2%), pneumonitis, respiratory failure, general physical health deterioration, and decreased appetite in 2 subjects each (0.8%); and dyspnoea, haemoptysis, interstitial lung disease, pleural effusion, pleuritic pain, pneumonia aspiration, pneumothorax, fatigue, performance status decreased, sepsis, cauda equina syndrome, haemorrhage intracranial, monoplegia, blood ALP increased, ALT increased, AST increased, weight decreased, cardiac tamponade, corneal infiltrates, nausea, hepatitis cholestatic, malignant neoplasm of thorax, and renal failure acute in 1 subject each (0.4%) in the 750 mg group. A causal relationship to ceritinib could not be ruled out for pain in extremity in 1 subject in the 600 mg group, and pneumonitis in 2 subjects, and interstitial lung disease, hepatitis cholestatic, ALT increased, AST increased, blood ALP increased, pleural effusion, pleuritic pain, nausea, corneal infiltrates, renal failure acute, and decreased appetite in 1 subject each in the 750 mg group.

4.(iv).(5) Foreign phase I study (Study CLDK378A2101)
Adverse events occurred in 17 of 28 subjects (60.7%), and adverse events for which a causal relationship to ceritinib could not be ruled out occurred in 9 of 28 subjects (32.1%). Adverse events with an incidence of ≥10% were diarrhoea in 7 subjects (25.0%), and nausea and headache in 4 subjects each (14.3%), all of which were Grade 1 events.

No serious adverse events occurred.

An adverse event leading to ceritinib discontinuation was blood creatine phosphokinase increased in 1 subject (3.6%), for which a causal relationship to ceritinib was ruled out.

4.(iv).(6) Foreign phase I study (Study CLDK378A2104)
Adverse events occurred in 11 of 19 subjects (57.9%), and adverse events for which a causal relationship to ceritinib could not be ruled out occurred in 5 of 19 subjects (26.3%). Adverse events with an incidence of ≥10% were abdominal pain in 3 subjects (15.8%), and diarrhoea, infrequent bowel movements, nausea, and vomiting in 2 subjects each (10.5%). All of these adverse events, except for Grade 2 nausea in 1 subject, were Grade 1 events.

Neither serious adverse events nor adverse events leading to treatment discontinuation occurred.

4.(iv).(7) Foreign phase I study (Study CLDK378A2105)
Adverse events occurred in 6 of 6 subjects (100%), and adverse events for which a causal relationship to ceritinib could not be ruled out occurred in 6 of 6 subjects (100%). Adverse events with an incidence of ≥10% were diarrhoea in 5 subjects (83.3%), abdominal discomfort and nausea in 3 subjects each (50.0%), dizziness, dry skin, flatulence, headache, myalgia, rhinorrhoea, sinus headache, skin odour abnormal, and sneezing in 1 subjects each (16.7%), all of which were Grade 1 events.

Neither serious adverse events nor adverse events leading to treatment discontinuation occurred.

4.(iv).(8) Foreign phase I study (Study CLDK378A2106)
Adverse events occurred in 15 of 19 subjects (78.9%), and adverse events for which a causal relationship to ceritinib could not be ruled out occurred in 14 of 19 subjects (73.7%). Adverse events with an incidence of ≥10% were nausea in 10 subjects (52.6%), diarrhoea in 8 subjects (42.1%), headache in 7 subjects (36.8%), abdominal pain and vomiting in 3 subjects each (15.8%), and dizziness in 2 subjects (10.5%), all of which were Grade 1 events.

Neither serious adverse events nor adverse events leading to treatment discontinuation occurred.

4.(iv).(9) Foreign phase I study (Study CLDK378A2108)
Adverse events occurred in 17 of 24 subjects (70.8%), and adverse events for which a causal relationship to ceritinib could not be ruled out occurred in 14 of 24 subjects (58.3%). Adverse events with an incidence of ≥10% were diarrhoea in 12 subjects (50.0%), nausea in 7 subjects (29.2%), headache in 4 subjects (16.7%), and vomiting in 3 subjects (12.5%). Cases of diarrhoea in 2 subjects were Grade 3 events.

Neither serious adverse events nor adverse events leading to treatment discontinuation occurred.

III. Results of Compliance Assessment Concerning the Data Submitted in the New Drug Application and Conclusion by PMDA

1. PMDA's conclusion on the results of document-based GLP/GCP inspections and data integrity assessment

Document-based compliance inspection and data integrity assessment were conducted in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics for the

data submitted in the new drug application. The inspection revealed a problem in Section 5.3.5.2-1 of the submitted documents. Because of a discrepancy among the sponsor's personnel in charge in terms of the interpretation of the criteria for dosing modification specified in the study protocol, deviation from the study protocol was not identified in a timely manner. The sponsor should have prepared an appropriate study protocol that would cause no discrepancy in the interpretation of the modification. In addition, the monitor should have confirmed that the study drug was administered at a dose modified as per the protocol amendment. Furthermore, the sponsor should have operated and maintained the quality assurance and quality control systems based on the standard operating procedures to ensure that the clinical study was conducted in accordance with the revised protocol. Although the above finding requiring corrective action was identified, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

2. PMDA's conclusion on the results of on-site GCP inspection

On-site GCP inspection was conducted in accordance with provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics for the data submitted in the new drug application (5.3.5.2-1, 5.3.5.2-2). As a result, PMDA confirmed that the studies were generally conducted in compliance with GCP. Thus, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application documents. Although overall evaluation of the studies is not significantly affected, the inspection revealed the following findings at a study site and the sponsor site. PMDA informed the heads of the concerned study sites and the applicant (sponsor) of these matters as findings requiring corrective action.

Findings requiring corrective action

Study site

- Deviation from the protocol (use of prohibited concomitant medications, non-compliance with rules for electrocardiography)

Sponsor

- Failure by the monitor to identify deviation from the study protocol (use of prohibited concomitant medications) in a timely manner.

IV. Overall Evaluation

Based on the submitted data, a certain level of the efficacy of ceritinib in patients with *ALK*-positive, unresectable, advanced or recurrent non-small cell lung cancer resistant or intolerant to crizotinib has been demonstrated and its safety is acceptable in view of its observed benefits. Ceritinib is a drug with a new active ingredient and is thought to suppress tumor growth by inhibiting ALK phosphorylation. Ceritinib is considered of clinical significance as an option for the treatment of *ALK*-positive, unresectable, advanced or recurrent non-small cell lung cancer resistant or intolerant to crizotinib. The indication of ceritinib and post-marketing investigations will be discussed at the Expert Discussion.

This application may be approved if ceritinib is not considered to have particular problems based on comments from the Expert Discussion.

Review Report (2)

February 15, 2016

I. Product Submitted for Registration

[Brand name]	Zykadia Capsules 150 mg
[Non-proprietary name]	Ceritinib
[Name of applicant]	Novartis Pharma K.K.
[Date of application]	June 24, 2015

II. Content of the Review

The comments from the Expert Discussion and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined in the following sections. The expert advisors for the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for registration, in accordance with the provisions of the "Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency" (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

(1) Efficacy

On the basis of the review presented in "4.(iii).B.(2) Efficacy" of the Review Report (1), PMDA has comprehensively concluded that ceritinib shows a certain level of efficacy in patients with anaplastic lymphoma kinase (ALK)-positive, unresectable, advanced or recurrent non-small cell lung cancer (NSCLC) previously treated with crizotinib in light of the facts that ceritinib is an ALK inhibitor targeting a molecule responsible for proliferation of cancer cells (oncogenic driver) and that the drug is used based on the evidence provided by molecular diagnosis, as well as on the basis of the data including the response rate shown in the global phase II study (Study CLDK378A2201 [Study A2201]) and the foreign phase I study (Study CLDK378X2101 [Study X2101]) in patients with *ALK*-positive, unresectable, advanced or recurrent NSCLC previously treated with crizotinib.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

(2) Safety

On the basis of the review presented in "4.(iii).B.(3) Safety" of the Review Report (1), PMDA has concluded that the adverse events requiring special attention for treatment with ceritinib are interstitial lung disease (ILD), hepatic function disorder, QT interval prolonged, nausea/vomiting/diarrhoea, hyperglycaemia/diabetes mellitus, bradycardia, pericarditis, infection, and pancreatitis.

In addition, PMDA has concluded that the tolerability profile of ceritinib is acceptable if appropriate measures such as monitoring and management of adverse events and treatment interruption are taken by physicians with sufficient knowledge and experience in cancer chemotherapy, and if the safety management is ensured through strict monitoring, management, and treatment of serious adverse events such as ILD.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

(3) Clinical positioning and indication

On the basis of the review presented in "4.(iii).B.(4) Clinical positioning and indication" of the Review Report (1), PMDA has concluded that the proposed indication of ceritinib (*ALK*-positive, unresectable, advanced or recurrent non-small cell lung cancer resistant or intolerant to crizotinib) is appropriate because ceritinib is positioned as one of the therapeutic options for patients with *ALK*-positive, unresectable, advanced or recurrent NSCLC previously treated with crizotinib. However, a global phase III study (Study CLDK378A2303) as a confirmatory study of ceritinib is currently ongoing and the study intends to compare ceritinib with standard chemotherapy in patients with *ALK*-positive, unresectable, advanced or recurrent NSCLC previously treated with crizotinib and platinum-based chemotherapy. At present, no information on survival benefits is available. Given the above facts, the

following precautionary statement should be included in the "Precautions for Indications" section of the package insert.

- The efficacy and safety of ceritinib in adjuvant chemotherapy have not been established.
- Physicians should select patients eligible for ceritinib therapy after closely reading the "Clinical Studies" section to fully understand the efficacy and safety of ceritinib and carefully considering other treatment options.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion. The following comment was raised from the expert advisors:

- It is desirable to provide healthcare professionals with the results of Study X2101 regarding the response rates in patients with *ALK*-positive, unresectable, advanced or recurrent NSCLC previously treated with crizotinib, analyzed for patient subgroups by the number of prior regimens.

In response to the above comment from the expert advisors, PMDA asked the applicant to explain the response rates analyzed for patient subgroups by the number of prior regimens.

The applicant's response:
In Study X2101, 163 patients with *ALK*-positive, unresectable, advanced or recurrent NSCLC previously treated with crizotinib received ceritinib at a dose of 750 mg. The response rate [95% CI] in patients treated with 1 prior regimens was 65.4% [44.3, 82.8] (17 of 26 subjects) and that in patients treated with ≥2 prior regimens was 54.7 [46.0, 63.3] (75 of 137 subjects). Patients treated with ≥2 prior regimens were further divided by the presence or absence of a history of platinum-based chemotherapy, and the response rates [95% CI] were 54.1% [45.3, 62.8] (72 of 133 subjects) and 75.0 [19.4, 99.4] (3 of 4 subjects), respectively.

PMDA's view:
Not only the results of Study X2101 regarding the response rates in patients with *ALK*-positive, unresectable, advanced or recurrent NSCLC previously treated with crizotinib but also the above-mentioned response rates for patient subgroups by the number of prior regimens should be communicated to healthcare professionals appropriately through information materials.

PMDA instructed the applicant to include the above issues in the "Indications" and "Precautions for Indications" sections, and the applicant responded that it would duly follow the instruction.

(4) Dosage and administration
On the basis of the review presented in "4.(iii).B.(5) Dosage and administration" of the Review Report (1), PMDA has concluded that the "Dosage and Administration" and the "Precautions for Dosage and Administration" sections should include the following statements.

[Dosage and Administration]
The usual adult dosage is 750 mg of ceritinib administered orally once daily in the fasted state. The dose may be reduced according to the patient's condition.

[Precautions for Dosage and Administration]
- Studies showed increases in the C_{max} and AUC of ceritinib administered after a meal. To avoid the effect of food, ceritinib should not be administered within 2 hours before and after a meal.
- Dose interruption, dose reduction, or treatment discontinuation due to adverse drug reactions should be considered based on the criteria shown below. Ceritinib therapy should be discontinued in patient unable to tolerate ceritinib 300 mg daily.

Criteria for dose interruption, dose reduction, or discontinuation due to adverse drug reactions

	Criteria*	Dose adjustment of ceritinib
Interstitial lung disease (ILD)	Any Grade ILD	Discontinue ceritinib.
Hepatic function disorder	• Grade ≤1 elevation in AST or ALT with Grade 2 elevation in blood bilirubin • Grade 2 or 3 elevation in AST or ALT with Grade ≤1 elevation in blood bilirubin	Withhold ceritinib until recovery of AST, ALT, and blood bilirubin to Grade ≤1. Resume ceritinib at the previous dose level if recovery is seen within 7 days, or resume ceritinib with a 150 mg dose reduction if recovery is seen in >7 days.
	• Grade ≤1 elevation in AST or ALT with Grade 3 elevation in blood bilirubin • Grade ≥2 elevation in AST or ALT with blood bilirubin elevation to >1.5 × upper limit of normal (ULN) and ≤2 × ULN	Withhold ceritinib until recovery of AST, ALT, and blood bilirubin to Grade ≤1. Resume ceritinib with a 150 mg dose reduction if recovery is seen within 7 days. Discontinue if recovery is not seen within 7 days.
	• Grade 4 elevation in AST or ALT with Grade ≤1 elevation in blood bilirubin	Withhold ceritinib until recovery of AST and ALT to Grade ≤1. Resume ceritinib with a 150 mg dose reduction.
	• Grade 4 elevation in blood bilirubin • Grade ≥2 elevation in AST or ALT with blood bilirubin elevation to >2 × ULN	Discontinue ceritinib.
QT interval prolonged	QTc >500 msec on at least 2 separate ECGs	Withhold ceritinib until recovery to baseline or QTc <481 msec. Resume ceritinib with a 150 mg dose reduction.
	QTc >500 msec or a >60 msec increase in QTc interval from baseline and torsade de pointes, polymorphic ventricular tachycardia, or signs/symptoms of severe arrhythmia	Discontinue ceritinib.
Bradycardia	Symptomatic and serious bradycardia requiring medical intervention	Withhold ceritinib until recovery to asymptomatic bradycardia or to a heart rate of ≥60 bpm. Resume ceritinib with a 150 mg dose reduction.
	Life threatening bradycardia requiring urgent intervention	Discontinue ceritinib.
Nausea, vomiting, and diarrhoea	• Grade ≥3 • Intorelable nausea, vomiting or diarhoea despite use of optimal anti-emetic or anti-diarrheal agents	Withhold ceritinib until recovery to Grade ≤1. Resume ceritinib with a 150 mg dose reduction.
Hyperglycaemia	Persistent hyperglycaemia of >250 mg/dL even after optimal treatment	Withhold ceritinib until blood glucose is under control. Resume ceritinib with a 150 mg dose reduction.
Lipase or amylase elevation	Grade ≥3	Withhold ceritinib until recovery to Grade ≤1. Resume ceritinib with a 150 mg dose reduction.

* Severity grade according to CTCAE ver. 4

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

PMDA instructed the applicant to include the above issues in the "Dosage and Administration" and "Precautions for Dosage and Administration" sections, and the applicant responded that it would duly follow the instruction.

(5) Draft risk management plan

The applicant plans an all-case drug use results survey which covers all patients treated with ceritinib to monitor the safety of ceritinib in the post-marketing clinical setting. The planned sample size of 220 patients and the observation period of 1 year were selected for the survey. The proposed key survey items are hepatotoxicity, QT prolonged, ILD/pneumonitis, hyperglycaemia, gastrointestinal toxicity (nausea, vomiting, diarrhoea), and pancreatitis.

On the basis of the review presented in "4.(iii).B.(6) Post-marketing investigations" of the Review Report (1), PMDA has concluded that the applicant should conduct post-marketing surveillance covering all patients treated with ceritinib for a specific period during the early post-marketing phase to collect safety information in a prompt and unbiased manner, and to provide the obtained safety information to healthcare professionals immediately, because currently available information on the

safety of ceritinib in Japanese patients is very limited. In addition, PMDA has reached the following conclusions on the plan of this survey:

- The key survey items should include not only adverse events identified by the applicant but also bradycardia, pericarditis, infection, and diabetes mellitus, which are the adverse events requiring special attention in patients on ceritinib.
- The planned sample size should be reconsidered, taking into account that the survey intends to compare post-marketing safety data with the incidence of adverse events in the currently available safety data from the clinical studies of ceritinib.
- The observation period for the survey should be reconsidered in light of the time to onset of the adverse events additionally identified as key survey items (i.e. the time-to-onset data from the clinical studies).

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

Based on the above discussion, PMDA instructed the applicant to reconsider the survey plan.

The applicant's response:
- The key survey items will include ILD, hepatic function disorder, QT interval prolonged, nausea/vomiting/diarrhoea, hyperglycaemia (including diabetes mellitus), bradycardia, pericarditis, infection, and pancreatitis.
- The planned sample size will be increased to 520 patients. This size is comparable to the total number of subjects who received ceritinib 750 mg once daily in the clinical studies of ceritinib in *ALK*-positive patients (Studies X2101, X1101, A2201, and A2203) whose results are currently available.
- The observation period will be 1 year as initially planned, in light of the time to onset of the adverse events additionally identified as key survey items (i.e. the time-to-onset data from the clinical studies).

PMDA's view:
The applicant's response about the survey plan is acceptable. However, the applicant should reconsider the sample size or plan a new survey if the survey reveals a new issue to be investigated.

On the basis of the above discussion and the review presented in "4.(iii).B.(7) Post-marketing risk minimization activities" of the Review Report (1), PMDA has concluded that the safety and efficacy specifications in the current draft risk management plan shown in the table below are appropriate, and the additional pharmacovigilance activities and risk minimization activities shown below should be implemented.

Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• ILD • Hepatic function disorder • QT interval prolonged • Nausea/vomiting/diarrhoea • Hyperglycaemia (including diabetes mellitus)	• Bradycardia • Pericarditis • Infection • Pancreatitis • Concomitant use of CYP3A inhibitors • Embryo-fetal toxicity	• Use in patients with hepatic impairment
Efficacy specification		
• Efficacy in routine clinical practice		

Summary of additional pharmacovigilance activities and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance • Specified drug use-results survey	• Disseminate data gathered during early post-marketing phase vigilance • Organize and distribute information materials for healthcare professionals • Organize and disseminate information materials for patients • Establish conditions for the use of the drug

Outline of specified drug use-results survey (draft)

Objective	To investigate the safety of ceritinib in routine clinical practice
Survey method	All-case survey using the central registration system
Population	All patients treated with ceritinib
Observation period	1 year
Planned sample size	520 patients
Main survey items	Key survey items: ILD, hepatic function disorder, QT interval prolonged, nausea/vomiting/diarrhoea, hyperglycaemia (including diabetes mellitus), bradycardia, pericarditis, infection, and pancreatitis Main survey items other than above: patient characteristics (sex, age, intended use of ceritinib, lung cancer stage classification, ECOG Performance Status, pregnancy status, medical history or complications, prior treatment of the primary disease, etc.), use status of ceritinib, concomitant medications and therapies, adverse events (including changes in laboratory parameters), etc.

III. Overall Evaluation

As a result of the above review, PMDA has concluded that ceritinib may be approved with the conditions presented below after the "Indications" and the "Dosage and Administration" sections are modified as below; on the premise that appropriate precautions are included in the package insert, information on the proper use of the product is disseminated adequately in the post-marketing setting, and the product is used by physicians with sufficient knowledge and experience in cancer chemotherapy in medical institutions capable of responding to medical emergencies. Since the product is designated as an orphan drug, the re-examination period is 10 years. The drug substance and drug product are classified as a powerful drug. The drug product is not categorized as a biological product or specified biological product.

[Indication] *ALK*-positive, unresectable, advanced or recurrent non-small cell lung cancer resistant or intolerable to crizotinib

[Dosage and administration] The usual adult dosage is 750 mg of ceritinib administered orally once daily in the fasted state. The dose may be reduced according to the patient's condition.

[Conditions for approval]

1. The applicant required to develop and appropriately implement a risk management plan
2. The applicant required to conduct a drug use-results survey covering all patients treated with the product during the early post-marketing phase in order to grasp the characteristics of such patients until data have been accumulated from a specific number of patients, because only a limited number of patients participated in the Japanese clinical studies. At the same time, the applicant should collect data on the safety and efficacy of the product without delay and take necessary measures to ensure the proper use of the product.
3. The applicant required to take necessary measures to ensure that the product is used only under the supervision of a physician experienced in the diagnosis of lung cancer and chemotherapy in a medical institution capable of managing the risks associated with

treatment, and by a supervising pharmacist with knowledge about the use of the product.

[Warnings]

1. Ceritinib should be administered only to patients who are eligible for treatment with ceritinib, under the supervision of a physician with sufficient knowledge and experience in cancer chemotherapy, in a medical institution with adequate facilities that can respond to medical emergencies. Patients or their family members should be fully informed of the benefits and risks of ceritinib, and informed consent should be obtained prior to the start of therapy.
2. Interstitial lung disease may occur in patients on ceritinib. Patients should therefore be monitored carefully for early symptoms of the disease (e.g., shortness of breath, dyspnoea, cough, and pyrexia) and should undergo chest CT or other examinations. If any abnormality is observed, appropriate measures, such as discontinuation of ceritinib, should be taken. In the initial treatment phase, patients should be hospitalized or supervised under equivalent conditions to be carefully monitored for serious adverse drug reactions such as interstitial lung disease.

[Contraindications]

Patients with a history of hypersensitivity to any components of the product

[Precautions for indications]

1. The efficacy and safety of ceritinib in adjuvant chemotherapy have not been established.
2. Physicians should select patients eligible for ceritinib therapy after closely reading the “Clinical Studies” section to fully understand the efficacy and safety of ceritinib and carefully considering other treatment options.

[Precautions for dosage and administration]

1. Studies showed increases in the C_{max} and AUC of ceritinib administered after a meal. To avoid the effect of food, ceritinib should not be administered within 2 hours before and after a meal.
2. Dose interruption, dose reduction, or treatment discontinuation due to adverse drug reactions should be considered based on the criteria shown below. Ceritinib therapy should be discontinued in patient unable to tolerate ceritinib 300 mg.

Criteria for dose interruption, dose reduction, or discontinuation due to adverse drug reactions

	Criteria*	Dose adjustment of ceritinib
Interstitial lung disease (ILD)	Any Grade ILD	Discontinue ceritinib.
Hepatic function disorder	• Grade ≤1 elevation in AST or ALT with Grade 2 elevation in blood bilirubin • Grade 2 or 3 elevation in AST or ALT with Grade ≤1 elevation in blood bilirubin	Withhold ceritinib until recovery of AST, ALT, and blood bilirubin to Grade ≤1. Resume ceritinib at the previous dose levels if recovery is seen within 7 days, or resume ceritinib with a 150 mg dose reduction if recovery is seen in >7 days.
	• Grade ≤1 elevation in AST or ALT with Grade 3 elevation in blood bilirubin • Grade ≥2 elevation in AST or ALT with blood bilirubin elevation to >1.5 × upper limit of normal (ULN) and ≤2 × ULN	Withhold ceritinib until recovery of AST, ALT, and blood bilirubin to Grade ≤1. Resume ceritinib with a 150 mg dose reduction if recovery is seen within 7 days. Discontinue if recovery is not seen within 7 days.
	• Grade 4 elevation in AST or ALT with Grade ≤1 elevation in blood bilirubin	Withhold ceritinib until recovery of AST and ALT to Grade ≤1. Resume ceritinib with a 150 mg dose reduction.
	• Grade 4 elevation in blood bilirubin • Grade ≥2 elevation in AST or ALT with blood bilirubin elevation to >2 × ULN	Discontinue ceritinib.
QT interval prolonged	QTc >500 msec on at least 2 separate ECGs	Withhold ceritinib until recovery to baseline or QTc <481 msec. Resume ceritinib with a 150 mg dose reduction.
	QTc >500 msec or a >60 msec increase in QTc interval from baseline and torsade de pointes, polymorphic ventricular tachycardia, or signs/symptoms of severe arrhythmia	Discontinue ceritinib.
Bradycardia	Symptomatic and serious bradycardia requiring medical intervention	Withhold ceritinib until recovery to asymptomatic bradycardia or to a heart rate of ≥60 bpm. Resume ceritinib with a 150 mg dose reduction.
	Life threatening bradycardia requiring urgent intervention	Discontinue ceritinib.
Nausea, vomiting, and diarrhoea	• Grade ≥3 • Intorelable nausea, vomiting or diarhoea despite use of optimal anti-emetic or anti-diarrheal agents	Withhold ceritinib until recovery to Grade ≤1. Resume ceritinib with a 150 mg dose reduction.
Hyperglycaemia	Persistent hyperglycaemia of >250 mg/dL even after optimal treatment	Withhold ceritinib until blood glucose is under control. Resume ceritinib with a 150 mg dose reduction.
Lipase or amylase elevation	Grade ≥3	Withhold ceritinib until recovery to Grade ≤1. Resume ceritinib with a 150 mg dose reduction.

* Severity grade according to CTCAE ver. 4