Report on the Deliberation Results

March 6, 2012
Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

[Brand name]	Xalkori Capsules 200 mg and 250 mg
[Non-proprietary name]	Crizotinib (JAN*)
[Applicant]	Pfizer Japan Inc.
[Date of application]	March 31, 2011

[Results of deliberation]
In the meeting held on February 29, 2012, 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 product is not classified as a biological product or a specified biological product, the re-examination period is 10 years, and both the drug substance and the drug product are classified as powerful drugs.

[Conditions for approval]
1. The applicant is required to conduct a drug use-results survey involving all patients treated with the product after the market launch until data from a certain number of patients have been accumulated in order to grasp the demographic information of the treated patients, since the product has been studied in only a limited number of patients in the Japanese clinical studies. At the same time, data on the safety and efficacy of the product should be collected without delay and necessary measures should be taken to ensure proper use of the product.

2. The applicant is required to take necessary measures to ensure that the product will be administered only under the supervision of a physician who is familiar with the diagnosis and chemotherapy treatment of lung cancer and is also fully capable of managing risks etc. associated with the product, at a medical institution with facilities that allow the physician to perform those duties, along with a supervising pharmacist (at a pharmacy) who is familiar with the chemotherapy and risk management.

**Japanese Accepted Name (modified INN)*

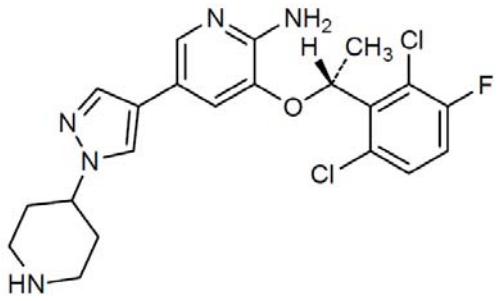
Review Report

February 20, 2012
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]	Xalkori Capsules 200 mg and 250 mg
[Non-proprietary name]	Crizotinib
[Name of applicant]	Pfizer Japan Inc.
[Date of application]	March 31, 2011
[Dosage form/Strength]	A capsule containing 200 or 250 mg Crizotinib
[Application classification]	Prescription drug (1) Drug with a new active ingredient

[Chemical structure]



Molecular formula: $C_{21}H_{22}Cl_2FN_5O$
Molecular weight: 450.34
Chemical name: 3-[(1*R*)-1-(2,6-Dichloro-3-fluorophenyl)ethoxy]-5-[1-(piperidin-4-yl)-1*H*-pyrazol-4-yl]pyridin-2-amine

[Items warranting special mention]
Orphan drug (Notification No. 0128-9 from the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW, dated January 28, 2011)

[Reviewing office] Office of New Drug V

Review Results

February 20, 2012

[Brand name] Xalkori Capsules 200 mg and 250 mg

[Non-proprietary name] Crizotinib

[Name of applicant] Pfizer Japan Inc.

[Date of application] March 31, 2011

[Results of review]
Based on the submitted data, it is concluded that the efficacy of the product in patients with anaplastic lymphoma kinase (*ALK*)-positive, unresectable, advanced or relapsed non-small-cell lung cancer has been demonstrated and its safety is acceptable in view of its observed benefits. The occurrence of pneumonitis, interstitial lung disease, QT prolonged, bradycardia, hepatotoxicity, visual disturbance, neutropenia/leukopenia, neuropathy, renal cyst, and photosensitivity, as well as the safety of the product in patients with hepatic impairment or severe renal impairment need to be further investigated via post-marketing surveillance.

As a result of its regulatory review, the Pharmaceuticals and Medical Devices Agency has concluded that the product may be approved for the following indication and dosage and administration with the following conditions for approval.

[Indication] *ALK*-positive, unresectable, advanced or relapsed non-small-cell lung cancer

[Dosage and administration] The usual adult dosage is 250 mg of crizotinib administered orally twice daily. The dose may be adjusted according to the patient's condition.

[Conditions for approval]
1. The applicant is required to conduct a drug use-results survey involving all patients treated with the product after the market launch until data from a certain number of patients have been accumulated in order to grasp the demographic information of the treated patients, since the product has been studied in only a limited number of patients in the Japanese clinical studies. At the same time, data on the safety and efficacy of the product should be collected without delay and necessary measures should be taken to ensure proper use of the product.
2. The applicant is required to take necessary measures to ensure that the product will be administered only under the supervision of a physician who is familiar with the diagnosis and chemotherapy treatment of lung cancer and is also fully capable of managing risks etc. associated with the product, at a medical institution with facilities that allow the physician to perform those duties, along with a supervising pharmacist (at a pharmacy) who is familiar with the chemotherapy and risk management.

Review Report (1)

January 17, 2012

I. Product Submitted for Registration

[Brand name]	Xalkori Capsules 200 mg and 250 mg
[Non-proprietary name]	Crizotinib
[Applicant]	Pfizer Japan Inc.
[Date of application]	March 31, 2011
[Dosage form/Strength]	A capsule containing 200 or 250 mg Crizotinib
[Proposed indication]	ALK-positive advanced non-small-cell lung cancer
[Proposed dosage and administration]	The usual adult dosage is 250 mg of crizotinib administered orally twice daily every day. The dose may be adjusted according to the patient's condition.

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

A summary of the submitted data and an outline of the review by the Pharmaceuticals and Medical Devices Agency (PMDA) are as shown below.

1. Origin or history of discovery and usage conditions in foreign countries etc.

1.(1) Drug overview

It is reported that, in non-small-cell lung cancer (NSCLC), the fusion of the gene encoding anaplastic lymphoma kinase (ALK) with echinoderm microtubule-associated protein-like 4 (EML4) etc. results from an inversion in the short arm of human chromosome 2 (2p), thereby generating fusion proteins (EML4-ALK), and that the fusion protein contributes to the growth and survival of cancer cells and neoplastic conversion of normal cells (e.g., *Nature*. 2007;448:561-6). It is reported that patients who have tumors positive for *ALK* fusion gene *(ALK* positive) account for 2% to 13% of all NSCLC patients (e.g., *Nature*. 2007;448:561-6).

Crizotinib was discovered by Pfizer Inc. (US) as a compound that inhibits tyrosine kinase (TK) of hepatocyte growth factor receptor (c-Met) in an ATP-competitive manner. Subsequently, crizotinib was shown to also inhibit ALK, its fusion proteins, and recepteur d'origine nantais (RON). Thus, crizotinib is considered to suppress tumor growth by inhibiting signal transduction through suppression of these TK activities.

1.(2) Development history etc.

A foreign phase I study in patients with advanced malignant tumor excluding leukemia (Study A8081001) was initiated in April 2006 by Pfizer Inc. (US). A global phase III study in *ALK*-positive NSCLC patients previously treated with chemotherapy (Study A8081007) was started in September 2009, and a global phase III study in chemotherapy-naïve patients with *ALK*-positive NSCLC (Study A8081014) was started in January 2011. Meanwhile, a global phase II study in *ALK*-positive NSCLC patients previously treated with chemotherapy including those who had been assigned to the control group in Study A8081007 (Study A8081005) was started in January 2010.

Based on the results of the above Studies A8081001 and A8081005, marketing application for crizotinib was submitted in March 2011 both in Japan and in the US and in July 2011 in the EU. In the US, accelerated approval for crizotinib was granted in August 2011 with the indications for "the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved

test. This indication is based on response rate. There are no data available demonstrating improvement in patient reported outcomes or survival with XALKORI."

As of December 2011, crizotinib is approved in the US and Korea with the indication for *ALK*-positive NSCLC.

Crizotinib has been designated as an orphan drug in January 2011 with the proposed indication for the treatment of "*ALK*-positive advanced non-small-cell lung cancer" (Designation No. [23 yaku] 238).

2. Data relating to quality

2.A Summary of the submitted data

2.A.(1) Drug substance

2.A.(1).1) Characterization

a. General properties

Crizotinib is a white to pale yellow powder. It is sparingly soluble in methanol, slightly soluble in acetonitrile, and slightly soluble or practically insoluble in neutral to alkaline aqueous solution. Crizotinib is non-hygroscopic. The melting point is approximately [redacted]°C, and the dissociation constant is [redacted] ([redacted] group) and [redacted] ([redacted] group). The partition coefficient in 1-octanol/water (pH 7.4) is 1.65. The specific rotation in methanol solution is [redacted]°. No crystalline polymorphism is identified.

b. Structure determination

The chemical structure of the drug substance is supported by ultraviolet-visible absorption spectrometry, infrared spectrophotometry (IR), nuclear magnetic resonance spectrometry (^{1}H-, ^{13}C-, [redacted], [redacted]-NMR), mass spectrometry, and [redacted] structural analysis.

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

a. Manufacturing process

The drug substance is synthesized using, as the starting materials, a solution of [redacted] in [redacted], [redacted], and [redacted].

A Quality by Design (QbD) approach is used to investigate the following:

- Genotoxic impurities
- Identification of [redacted], [redacted], [redacted], and [redacted] as critical quality attributes (CQAs)
- Identification of critical process parameters (CPPs) based on the quality risk assessment and design of experiments
- Development of design space

b. Control of critical process steps and critical intermediate

The process of [redacted] reaction has been defined as the critical process step. [redacted] is controlled as the critical intermediate to consistently ensure the quality of the drug substance.

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

The proposed specifications for the drug substance include content, description, identification (IR), purity (heavy metals, [redacted], related substances, residual solvents), residues on ignition, [redacted], and assay.

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

Long-term stability testing (25°C/60% RH, 12 months) and accelerated testing (40°C/75% RH, 6 months) were performed on 4 lots of the drug substance that were manufactured at the commercial scale, transferred into polyethylene bag ([redacted]), placed into [redacted], and tightly sealed. Results demonstrated the stability of crizotinib.

Photostability testing (providing an overall illumination of 1.2 million lx·h, an integrated near ultraviolet energy of 258 W·h/m^2) was performed. Results demonstrated the stability of crizotinib.

Based on the above results, a retest period of [redacted] months has been proposed for the drug substance when stored in [redacted] polyethylene bags placed in [redacted] at room temperature, in accordance with the "Guideline on the Evaluation of Stability Data" (PFSB/ELD Notification No. 0603004 dated June 3, 2003). The long-term testing is scheduled to be continued for up to [redacted] months.

2.A.(2) Drug product

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

The drug product is an immediate release capsule containing 200 or 250 mg of crizotinib. It also contains, as excipients, light anhydrous silicic acid, microcrystalline cellulose, anhydrous dibasic calcium phosphate, sodium starch glycolate, and magnesium stearate.

2.A.(2).2) Formulation development

As oral formulations for clinical studies, a powder in capsule*, an immediate release tablet, and a formulated capsule were used. Due to the [redacted] of crizotinib, it was practically impossible to achieve [redacted] required for [redacted] as [redacted]. Therefore, immediate release capsules, the commonly used dosage form, were selected as the drug product for marketing. It has been demonstrated by a bioequivalence study (Study A8081011) that the formulated capsule is biologically equivalent to the powder in capsule and to the immediate release tablet [see "4.(i).A.(4) Foreign phase I study"].

*: In the early stage clinical studies, [redacted] filled in capsules were used so that [redacted].

2.A.(2).3) Manufacturing process

The manufacturing process for the drug product consists of [redacted], [redacted], and [redacted] processes.

A QbD approach is used to mainly investigate the following:

- Identification of [redacted] and [redacted] as CQAs
- Identification of CPPs based on the quality risk assessment and design of experiments
- Development of design space
- Investigation of [redacted] conditions and of the effect of [redacted] using a model

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

The proposed specifications for the drug product include content, description (appearance), identification (liquid chromatography, UV), purity (degradation products), uniformity of dosage units, dissolution, and assay.

2.A.(2).5) Stability of drug product

Stability of the drug product was investigated by bracketing using formulated capsules (200 mg and 250 mg formulations) and [redacted] mg formulation which is [redacted] to the capsules. Long-term stability studies (25°C/60% RH and 30°C/75% RH, 12 months) and accelerated testing (40°C/75% RH, 6 months) were conducted for 3 lots each of [redacted] mg formulation and 250 mg formulation and 1 lot of 200 mg formulation. Results demonstrated the stability of crizotinib.

Using 1 lot each of [redacted] mg formulation and 250 mg formulation, photostability testing (exposed to light providing an overall illumination of 1.2 million lx·h and an integrated near ultraviolet energy of 258 W·h/m^2) was performed. Results demonstrated the stability of crizotinib.

Based on the above results, a shelf life of 24 months has been proposed for the drug product when stored in press-through package (PTP) of polyvinyl chloride film/aluminum foil 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 is scheduled to be continued for up to 36 months.

2.A.(3) Reference materials

The proposed specifications for the crizotinib reference material include purity ([redacted] method), description (appearance), identification ([redacted], [redacted]), purity ([redacted], [redacted]), [redacted], and [redacted].

2.B Outline of the review by PMDA

Based on the submitted data and the following reviews, PMDA has concluded that the quality of the drug product is appropriately controlled. The product has been developed using a QbD approach as described in "Revised Pharmaceutical Development" (PFSB/ELD Notification No. 0628-1 dated June 28, 2010).

Design space for [redacted] removal

The applicant investigated the method for removing [redacted] by the design of experiment and, as a result, found out that "[redacted]" and "[redacted]" were parameters with a relatively large effect in the [redacted] removal process and has developed a design space for [redacted] removal. However, only "[redacted]" was mentioned as the parameter constituting the design space and "[redacted]" was omitted from the description in the application.

PMDA asked the applicant to explain the reason for not including "[redacted]" in the application.

The applicant responded as follows:

[redacted] has been confirmed to significantly affect the amount of residual [redacted]. Therefore, [redacted] was defined as [redacted] in order to sufficiently [redacted] [redacted] before [redacted] and described in the application.

As regards [redacted], even if [redacted] exceeds [redacted], its effect on the residual [redacted] is considered to be minor (the figure below*).

*: In this figure, the area to the right of [redacted] shows that [redacted]. Regarding [redacted], it can be confirmed to conform to [redacted] by setting [redacted].

The design space of [redacted] and [redacted], where the amount of [redacted] is below [redacted]. The area surrounded by [redacted] indicates the verified acceptable range of [redacted] and [redacted].

Also, the following findings were identified from the study results newly obtained after the regulatory submission. Therefore, [redacted] was a "non-critical" process parameter that is unlikely to affect CQA and it was considered appropriate not to include [redacted] in the application.

- Even when the amount of residual [redacted] was [redacted] exceeding [redacted], [redacted] allowed it conform to [redacted] of residual [redacted].
- Even when [redacted] and [redacted] were changed to [redacted] and [redacted], respectively, the amount of residual [redacted] decreased to [redacted] removal [redacted] and conformed to the specifications of crizotinib.
- Within the usual operation range of [redacted], residual [redacted] conformed to [redacted] even if [redacted] was changed to [redacted].

PMDA concluded that it was inappropriate that, of the parameters constituting the design space indicating the interactions between parameters ("[redacted]" and "[redacted]"), only [redacted] which was identified as the parameter with a relatively large effect was described in the application while the other parameter [redacted] was not, and instructed the applicant to include [redacted] also in the application, to which the applicant agreed.

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) Tumor growth inhibition in NSCLC-derived cells expressing EML4-ALK (Report PF-02341066_06Oct[redacted]_192308, Report PF-02341066_06Oct[redacted]_192438)

***In vitro*:**

The effect of crizotinib (0.61-3333 nmol/L) to inhibit tumor growth was investigated using human non-small-cell lung cancer (NSCLC)-derived cell lines (NCI-H3122 cell line, NCI-H2228 cell line) expressing EML4-ALK fusion protein* (generated by fusion of echinoderm microtubule-associated protein-like 4 [EML4] and anaplastic lymphoma kinase [ALK]). As a result, crizotinib inhibited the growth of NCI-H3122 cell line and NCI-H2228 cell line in a concentration-dependent manner, with

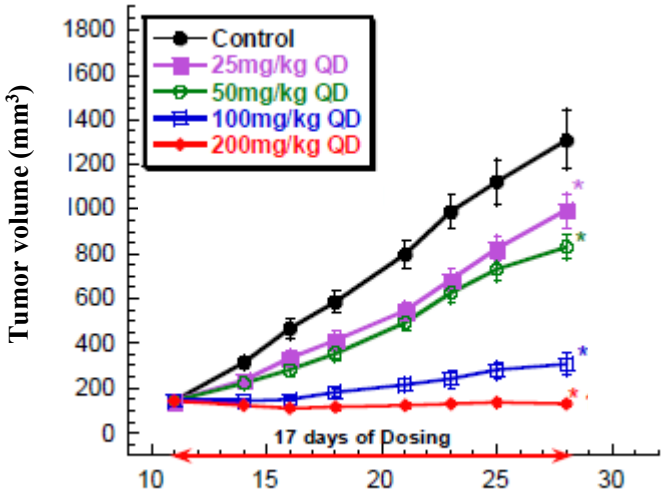
IC_{50} (mean ± standard deviation [SD]) of 54 ± 7 and 34 ± 2 nmol/L, respectively.

*: The following variants of EML4-ALK fusion protein are reported. NCI-H3122 cell line and NCI-H2228 cell line express variant 1 and variant 3, respectively.
- variant 1: fusion protein consisting of EML4 exon 13 and ALK exon 20
- variant 2: fusion protein consisting of EML4 exon 20 and ALK exon 20
- variant 3a: fusion protein consisting of EML4 exon 6 and ALK exon 20
- variant 3b: fusion protein consisting of EML4 exon 6 and ALK exon 20, with 10 more amino acid residues than variant 3a
- variant 3: variant 3a and variant 3b

***In vivo*:**
The effect of crizotinib to inhibit tumor growth was evaluated using athymic mice (nude mice) subcutaneously implanted with NCI-H3122 cell line. When the tumor volume reached the pre-specified size (11 days after implantation), crizotinib (25, 50, 100, 200 mg/kg) was administered orally once daily (QD) for 17 consecutive days. As a result, in the crizotinib groups, a statistically significant tumor growth inhibition was observed compared with the control (vehicle) group (the figure below). The tumor growth inhibition rate calculated using the following equation was 17%, 29%, 86%, and 100%, respectively, at 25, 50, 100, and 200 mg/kg of crizotinib.

$$\text{Tumor growth inhibition rate (\%)} = \left(1 - \frac{\text{increase in tumor volume from Days 12 to 28 after implantation in each dose group}}{\text{increase in tumor volume from Days 12 to 28 after implantation in control group}}\right) \times 100$$

Tumor growth inhibition of crizotinib (*in vivo*)



Mean ± standard error (SE), n = 9-12, *: $P < 0.05$ against the control group (Dunnett's test)

3.(i).A.(1).2) Mechanism of action of crizotinib
In human anaplastic large-cell lymphoma (ALCL), nucleophosmin (NPM) gene is reported to be fused with *ALK* gene (*J Cell Physiol*. 2004;199:330-58). Therefore, results of studies on NPM-ALK fusion protein (NPM-ALK) were also submitted as evaluation data.

i) Inhibition of phosphorylation
a. Study on recombinant ALK protein (Report PF-02341066_06Oct[redacted]_192308)
The effect of crizotinib to inhibit the phosphorylation of ALK tyrosine kinase (TK) was evaluated

using recombinant ALK protein by microfluidic mobility shift assay. As a result, crizotinib inhibited the phosphorylation of recombinant ALK TK in an ATP-competitive manner, with Ki (mean ± SD) of 0.5 ± 0.17 nmol/L.

b. Study on cell lines expressing ALK fusion protein (Report PF-02341066_06Oct[redacted]_192308)

The effect of crizotinib to inhibit the phosphorylation of ALK TK was studied using cell lines expressing ALK fusion protein by enzyme-linked immunosorbent assay (ELISA). IC_{50} values were as shown in the table below.

Inhibition of phosphorylation in cell lines expressing ALK fusion protein

Cell line	Type of ALK fusion protein expressed	IC_{50} (nmol/L)
NCI-H3122	EML4-ALK variant 1	63 ± 31
NCI-H2228	EML4-ALK variant 3	74 ± 23
NIH3T3/EML4-ALK variant 1*[1]	EML4-ALK variant 1	60
NIH3T3/EML4-ALK variant 2*[1]	EML4-ALK variant 2	69
NIH3T3/EML4-ALK variant 3a*[1]	EML4-ALK variant 3a	27
NIH3T3/EML4-ALK variant 3b*[1]	EML4-ALK variant 3b	41
Karpas299*[2]	NPM-ALK	35 ± 17

Mean ± SD [Note by PMDA: SD omitted for data of n = 2], n = 2-41, *1: Murine fibroblast-derived NIH3T3 cell line forced to express an EML4-ALK variant, *2: Human ALCL-derived cell line

c. Inhibitory effect of metabolites on ALK phosphorylation (Report PF-02341066_06Oct[redacted]_192308)

A lactam (PF-06260182) and *O*-dealkylated lactam (M2) are observed as crizotinib metabolites in human plasma [see "4.(ii).A.(1).2) Foreign phase I study"]. The activity of these metabolites and O-dealkylated crizotinib (M4) [Note by PMDA: In human plasma, only sulfate conjugates and glucuronide conjugates of M4, but not M4 itself, are detected] to inhibit the phosphorylation of ALK TK was evaluated using recombinant ALK protein by microfluidic mobility shift assay. For PF-06260182, each of the 2 diastereomers (PF-06270079, PF-06270080) was investigated. As a result, the Ki of PF-06270079 and PF-06270080 was 2.4 and 1.6 nmol/L, respectively, and Ki values of M2 and M4 were ≥2000 nmol/L.

The effects of crizotinib, PF-06270079, PF-06270080, M2, and M4 to inhibit the phosphorylation of EML4-ALK TK was evaluated using NCI-H3122 cell line and NCI-H2228 cell line. As a result, PF-06270079 and PF-06270080 inhibited the phosphorylation of EML4-ALK TK (the table below). In contrast, neither M2 nor M4 showed an inhibitory effect up to 10 μmol/L.

Inhibition of phosphorylation in EML4-ALK-expressing cell lines

	Cell line	Type of ALK fusion protein expressed	IC_{50} (nmol/L)	Activity ratio (metabolite/crizotinib)
Crizotinib	NCI-H3122	EML4-ALK variant 1	63 ± 31	—
PF-06270079			284 ± 182	3.7
PF-06270080			194 ± 118	2.5
Crizotinib	NCI-H2228	EML4-ALK variant 3	74 ± 23	—
PF-06270079			554 ± 102	7.5
PF-06270080			355 ± 66	5.0

Mean ± SD, n = 3-20

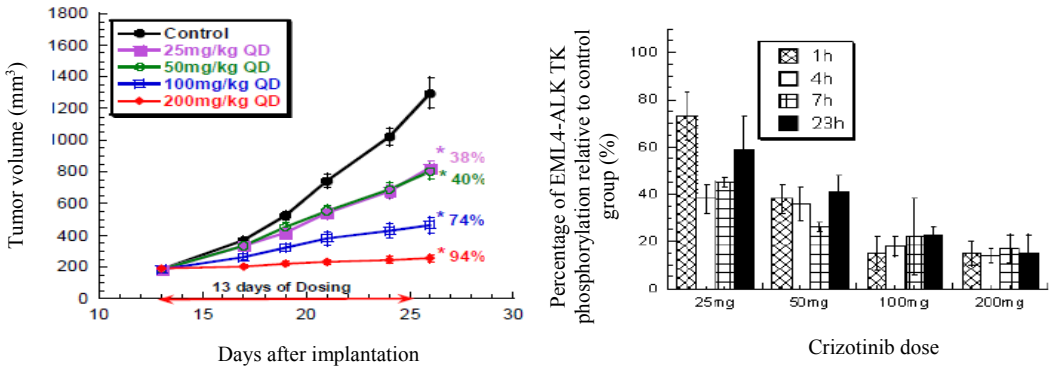
ii) Mechanism of tumor growth inhibition

a. Relationship between the inhibition of phosphorylation of ALK fusion protein TK and the tumor growth inhibition

NCI-H3122 cell line (Report PF-02341066_06Oct[redacted]_192438)

NCI-H3122 cell line was implanted subcutaneously in nude mice. Starting on the day when the tumor volume reached the pre-specified size, crizotinib (25, 50, 100, 200 mg/kg) was administered orally QD to the animals for 13 consecutive days and tumor diameter was measured. Also, phosphorylating state of EML4-ALK TK in the tumor mass at 1, 4, 7, and 23 hours on Day 13 of crizotinib administration was measured by ELISA. As a result, crizotinib showed statistically significantly greater inhibition of tumor growth compared with the control (vehicle) (the figure below, left). Also, a dose-dependent inhibition of EML4-ALK TK phosphorylation was observed (the figure below, right).

Activity of crizotinib to inhibit tumor growth and EML4-ALK TK phosphorylation (NCI-H3122 cell line)



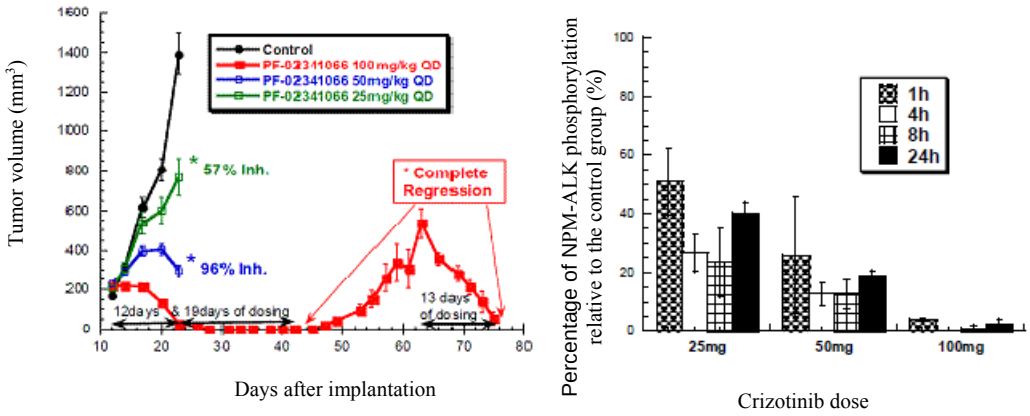
Mean ± SE, n = 10-12, *: $P < 0.0001$ against the control group (Dunnett's test). The numerical value on the horizontal axis of the graph for tumor volume represents the tumor growth inhibition rate (%) (= [1 – (increase in tumor volume from Day 13 to 26 after implantation in each dose group / increase in tumor volume from Day 13 to 26 after implantation in the control group)] × 100).

Karpas 299 cell line (Report PF-02341066-Pharm-002)

The relationship between the inhibition of NPM-ALK TK phosphorylation and the tumor growth inhibition by crizotinib was investigated using human ALCL-derived Karpas 299 cell line expressing NPM-ALK.

Karpas 299 cell line was implanted subcutaneously in severe combined immunodeficient (SCID) mice. Starting on the day when the tumor volume reached the pre-specified size, crizotinib was administered orally QD to the animals for 12 consecutive days (25, 50 mg) or for 31 consecutive days (100 mg/kg), and tumor diameter was measured. Also, phosphorylation state of NPM-ALK TK in the tumor mass at 1, 4, 8, and 24 hours post-dose on Day 4 of crizotinib administration was measured by ELISA. As a result, crizotinib showed statistically significantly greater inhibition of tumor growth compared with the control (vehicle) (the figure below, left). Also, a dose-dependent inhibition of NPM-ALK TK phosphorylation was observed (the figure below, right).

Activity of crizotinib to inhibit tumor growth and NPM-ALK phosphorylation (Karpas 299 cell line)



Mean ± SE, n = 3-12, PF-02341066: crizotinib, *: $P < 0.0001$ against the control group (Dunnett's test). The numerical value on the horizontal axis of the graph for tumor volume represents the tumor growth inhibition rate (%) (= [1 – (increase in tumor volume from Day 12 to 23 after implantation in each dose group / increase in tumor volume from Day 12 to 23 after implantation in the control group)] × 100).

The applicant explained as follows:
A complete regression of the tumor was observed in the crizotinib 100 mg/kg group. Although the tumor grew again after 31 days of crizotinib administration, the complete regression was observed again after re-administration of crizotinib at 100 mg/kg.

b. Effect on downstream signal-transducing molecules (Report PF-02341066_06Oct[redacted]_192438, PF-02341066-Pharm-002)

NCI-H3122 cell line was implanted subcutaneously in nude mice. Starting on the day when the tumor volume reached the pre-specified size, crizotinib (50, 100, 200 mg/kg) was administered orally QD to the animals for 4 consecutive days, and the phosphorylation state of STAT3, Akt1, and Erk1/2 proteins, which are signal transducing molecules downstream of EML4-ALK TK, in the tumor mass at 7 hours after the last dose of crizotinib was investigated by Western blotting. As a result, phosphorylation of these proteins tended to be inhibited by crizotinib in a dose-dependent manner at 50, 100, and 200 mg/kg, the dose range similar to that which showed tumor growth inhibition of crizotinib (25, 50, 100, 200 mg/kg) [see "3.(i).A.(1).1) Tumor growth inhibition in NSCLC-derived cells expressing EML4-ALK, *In vivo*"].

Similarly, the effect of crizotinib on downstream signal transducing molecules was investigated using nude mice subcutaneously implanted with Karpas 299 cell line. Results showed similar tendencies.

c. Effect on cell growth and apoptosis induction (Report PF-02341066_06Oct[redacted]_192308, PF-02341066-Pharm-001, Report PF-02341066_06Oct[redacted]_192438)

***In vitro*:**

In addition to the study using NCI-H3122 cell line and NCI-H2228 cell line [see "3.(i).A.(1).1) Tumor growth inhibition in NSCLC-derived cells expressing EML4-ALK, *In vitro*"], the tumor growth inhibition of crizotinib (0.6-2500 nmol/L) in Karpas 299 cell line was investigated. IC_{50} was 64.6 nmol/L.

Using Karpas 299 cell line and human ALCL-derived SU-DHL-1 cell line expressing NPM-ALK,

the effect of crizotinib on cell cycle and on apoptosis induction was evaluated by flow cytometry. As a result, crizotinib (50, 100, 200 nmol/L) increased the percentage of cells in the G0/G1 stage and the percentage of apoptosis-induced cells in a concentration-dependent manner.

Using NCI-H3122 cell line, the apoptosis-inducing effect (caspase 3/7 activity) of crizotinib (5-370 nmol/L) was studied by luciferase activity assay. EC_{50} (mean ± SD) was 110 ± 18 nmol/L.

***In vivo*:**
NCI-H3122 cell line was subcutaneously implanted in nude mice. Starting on the day when the tumor volume reached the pre-specified size, crizotinib (25, 50, 100, 200 mg/kg) was administered orally QD to the animals for 14 consecutive days. The cell growth in the tumor mass at 7 hours after the last dose of crizotinib was evaluated by immunohistochemical staining using anti-Ki67 antibody (the table below).

Effect on cell growth (*in vivo*)

Dose (mg/kg)	Ki67 score*1	Cell growth inhibition rate (%)*2
0 (control)	3.0 ± 0.00	—
25	3.1 ± 0.30	38
50	3.3 ± 0.45	40
100	2.5 ± 0.52	74
200	2.0 ± 0.71	94

Mean ± SD, n = 9-12, *1: The percentage of Ki67-positive cells in the tumor is expressed in score points (1: 0%-50%, 2: 51%-75%, 3: 76%-90%, 4: >90%), *2: The tumor growth inhibition rate after continuous oral administration of the same dose for 13 days to mice implanted with NCI-H3122 cell line (%) (= [1 – (increase in tumor volume from Day 13 to 26 after implantation in each dose group / increase in tumor volume from Day 13 to 26 after implantation in the control group)] × 100)

NCI-H3122 cell line was subcutaneously implanted in nude mice. Starting on the day when the tumor volume reached the pre-specified size, crizotinib (50, 100, 200 mg/kg) was administered orally QD to the animals for 4 consecutive days. Apoptosis induction in the tumor mass at 7 hours after the last dose of crizotinib was evaluated by Western blotting using anti-cleaved caspase 3 antibody (the table below).

Effect on apoptosis induction (*in vivo*)

Dose (mg/kg)	Signal intensity of anti-cleaved caspase 3 antibody (corrected for GAPDH)
0 (control)	0.255 ± 0.085
50	0.736 ± 0.177
100	1.704 ± 0.348
200	1.315 ± 0.344

Mean ± SE, n = 3

iii) Correlation between PK and PD (Report PF-02341066_06Oct[redacted]_192438, PF-02341066_01Oct[redacted]_124928, PF-02341066_13Oct[redacted]_213230)

In order to investigate the relationship between the inhibition by crizotinib of EML4-ALK phosphorylation and the plasma crizotinib concentration, NCI-H3122 cell line was subcutaneously implanted in nude mice. Starting on the day when the tumor volume reached the pre-specified size, crizotinib (25, 50, 100, 200 mg/kg) was administered orally QD to the animals for 4 or 14 consecutive days. Phosphorylation state of EML4-ALK TK in the tumor mass at 1, 4, 7, and 24 hours after the last dose of crizotinib was studied by ELISA. Hill function plots were constructed on the relationship between the rate of inhibition of EML4-ALK TK phosphorylation and the concentration of unbound crizotinib in plasma and subjected to analysis by the Link model (*Clin Pharmacol Ther*. 1979;25:358-71). As a result, EC_{50} (the concentration of unbound crizotinib in plasma) for inhibiting EML4-ALK phosphorylation after 4- and 14-day consecutive

administration was estimated to be 51 and 19 nmol/L, respectively.

In order to evaluate the relationship between the tumor growth inhibition of crizotinib and the plasma crizotinib concentration, NCI-H3122 cell line was subcutaneously implanted in nude mice and, starting on the day the tumor volume reached the pre-specified size, crizotinib (25, 50, 100, 200 mg/kg) was administered orally QD to the animals for 17 consecutive days, and the tumor growth inhibition was evaluated. The relationship between the tumor growth suppressive effect and the plasma crizotinib concentration was analyzed by the indirect response model (*Br J Clin Pharmacol*. 1998;45:229-39). As a result, EC_{50} (the concentration of unbound crizotinib in plasma) for tumor growth inhibition was estimated to be 23 nmol/L.

Based on the above, the applicant explained that EC_{50} of crizotinib for inhibiting EML4-ALK phosphorylation was comparable to that for inhibiting tumor growth, which suggests that inhibition of EML4-ALK TK phosphorylation is directly associated with tumor growth inhibition.

3.(i).A.(1).3) Inhibition of c-Met and RON functions

Crizotinib inhibits the phosphorylation of not only ALK but also hepatocyte growth factor receptor (c-Met) and recepteur d'origine nantais (RON), a kinase related to c-Met. Therefore, results of studies on the tumor growth inhibition of crizotinib mediated by its inhibition of c-Met and RON TK were also submitted. However, since the applicant explained that it was unknown to what extent the inhibition of c-Met and RON TK phosphorylation contributed to the tumor growth inhibition of crizotinib in *ALK*-positive NSCLC [see "3.(i).B.(2) Efficacy mediated by inhibition of c-Met and RON functions"], part of the study results with an unknown relationship with the present application is omitted from description.

Inhibition of angiogenesis (Report PF-02341066-Pharm-002)

Human gastric cancer-derived GTL-16 cell line with constitutively activated c-Met was subcutaneously implanted in nude mice and, starting on the day when the tumor volume reached the pre-specified size, crizotinib (12.5, 25, 50 mg/kg) was administered orally QD to the animals for 12 consecutive days. Vascular vessel density in the tumor mass at 4 hours after the last dose of crizotinib was investigated by immunohistochemical staining using anti-CD31 antibody. As a result, a dose-dependent decrease in vascular vessel density was observed.

The applicant explained that, in mice implanted with U87MG cell line, a cell line confirmed to express c-Met and its ligand hepatocyte growth factor (HGF), crizotinib had little or no effect on vascular vessel density.

Based on the above, the applicant explained as follows:
The results suggest that crizotinib inhibits tumor growth by the direct effect, i.e., suppression of growth or viability of tumor cells, and by the indirect effect, i.e., suppression of angiogenesis. However, the results also suggest that the inhibition of angiogenesis by crizotinib is dependent on the type of tumor.

3.(i).A.(2) Secondary pharmacodynamics (Report 901036, 8850568, 8850900_3, SP7610)

Effects of crizotinib on radioligand binding with a total of 66 types of receptors, ion channels, and transporters were investigated. As a result, the minimum concentration of crizotinib required to inhibit the binding of ligands to 11 types of receptors, 2 types of ion channels, and 2 types of transporters was in the low, single-degit micromolar range at the maximum.

Based on the above results, antagonistic activity of crizotinib to serotonin $(5\text{-HT})_{4E}$ receptor, 5-HT_7 receptor, and $\text{adrenaline}_{\alpha 1A}$ receptor was investigated. As a result, Kb values were 140 nmol/L, 2.2 μmol/L, and 40.7 nmol/L, respectively. Ki of crizotinib against the agonist-

binding site of 5-HT_{2B} receptor was 160 nmol/L, and IC_{50} of crizotinib against dopamine and serotonin transporter functions was 630 and 830 nmol/L, respectively.

In addition, the effect of crizotinib to inhibit 7 types of enzymes was investigated. As a result, IC_{50} of crizotinib against phosphodiesterase 4 and $p55^{fyn}$ kinase was 7.8 μmol/L and 290 nmol/L, respectively.

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

3.(i).A.(3).1) Effects on cardiovascular system

a. Effect on hERG current (Report PF02341066HERG [non-GLP study], Reference data)

Using human embryonic kidney HEK293 cell line expressing human ether-a-go-go related gene (hERG), the effect of crizotinib (0.1, 0.3, 1, 3, 10 μmol/L) on potassium ion current (I_{Kr}) was evaluated by the patch-clamp technique. As a result, crizotinib suppressed hERG current in a concentration-dependent manner, with IC_{20} and IC_{50} being 0.3 and 1.1 μmol/L, respectively.

b. Effect on calcium channel (Report PF02341066AORTA [non-GLP study], Reference data)

Using the thoracic descending aorta isolated from rats, the effect of crizotinib (0.1, 1, 10 μmol/L) on calcium-induced vascular contraction was studied by isometric tension measurement. As a result, crizotinib inhibited potassium chloride-induced vascular contraction in a concentration-dependent manner with IC_{50} of 0.83 μmol/L, suggesting the calcium channel inhibition of crizotinib.

c. Effect on L-type calcium channel (Report [redacted]-2796-01 [non-GLP study], Reference data)

Using the ventricular muscle cells isolated from guinea pigs, the effect of crizotinib (1, 3, 10, 30, 100 μmol/L) on L-type calcium channel was evaluated by the patch-clamp technique. As a result, crizotinib inhibited L-type calcium channel in a concentration-dependent manner, with IC_{50} of 14.6 μmol/L.

d. Effect on Nav1.5 sodium channel (Report PF02341066NA15, [non-GLP study], Reference data)

Using Chinese hamster ovary-derived CHO cell line forced to express Nav1.5 channel, the effect of crizotinib (0.3, 1, 3, 10 μmol/L) on Nav1.5 sodium channel was evaluated by the patch-clamp technique. As a result, crizotinib inhibited Nav1.5 sodium channel current in a concentration-dependent manner, with IC_{50} of 1.56 μmol/L.

e. Effect on the action potential of Purkinje fibers (Report PF02341066/IC/001[redacted])

Using the Purkinje fibers isolated from dog cardiac ventricle, the effect of crizotinib (0.01, 0.1, 1, 10 μmol/L) on the action potential of cardiac muscles was evaluated by measuring the resting membrane potential (RP), action potential amplitude (APA), maximum upstroke velocity (V_{max}), and action potential duration (APD_{50}, APD_{90}) during stimulation at 0.3, 1, and 3 Hz. As a result, RP (at 3 Hz), APD_{50} (at all frequencies), and APD_{90} (at 1 and 3 Hz) were statistically significantly decreased or shortened at crizotinib 10 μmol/L compared with the vehicle control group. The extent of the decrease in APD_{50} was greater at higher frequencies (maximum 18.4% decrease at 3 Hz). At ≤1 μmol/L, crizotinib had no statistically significant effect on the action potential of cardiac muscles.

f. Effects on hemodynamics and electrocardiogram (Report PF02341066/CG/003[redacted])

Crizotinib (0.134, 0.295, 1.192, 1.907 mg/kg) was administered intravenously over 10 minutes to 8 male anesthetized dogs, followed by intravenous administration (maintenance administration) for 25 minutes at 0.00939, 0.0207, 0.0834, and 0.134 mg/kg/min in each dose group, and effects

on arterial blood pressure, left ventricular pressure, monophasic action potential (MAP), and electrocardiogram (ECG) were evaluated. The experiment was conducted at the sinus rhythm or with heart rate pacing at 150, 160, 170, 180, 190, and 200 beats/min. At 5 minutes before the end of the maintenance administration, plasma crizotinib concentrations were measured. The mean concentration of unbound crizotinib in the plasma was 8, 24, 84, and 164 ng/mL, respectively, in each dose group [Note by PMDA: Following twice daily continuous administration of 250 mg crizotinib to Japanese patients, C_{max} of unbound crizotinib in the plasma under the steady state is 54 ng/mL].

In the groups with plasma unbound crizotinib concentration of ≥84 ng/mL, a statistically significant decrease in the heart rate (by up to 33 beats/min) and increase in the left ventricular end-diastolic pressure (by up to 3.47 mmHg) were observed compared with the vehicle control group. In the group with plasma unbound crizotinib concentration of 164 ng/mL, statistically significant decreases in myocardial contractile force and mean blood pressure were observed compared with the vehicle control group, but these were not major changes from baseline values. Also, a statistically significant decrease in diastolic blood pressure (by up to 7.5 mmHg) was observed. As regards ECG parameters, statistically significant increases in PR (by up to 16.3 msec), QRS (by up to 5 msec), and QT interval (by up to 35.5 msec) were observed in the groups with plasma unbound crizotinib concentration of ≥84 ng/mL compared with the vehicle control group. Under the sinus rhythm, a statistically significant increase in $MAPD_{100}$ was observed in the groups with plasma unbound crizotinib concentration of ≥84 ng/mL compared with the vehicle control group, whereas under pacing at 150 or 200 beats/min, no effect on $MAPD_{100}$ was observed.

3.(i).A.(3).2) Effects on the central nervous system

a. Effect on Nav1.1 sodium channel (Report PF02341066NA11 [non-GLP study], Reference data)

Using HEK293 cell line forced to express Nav1.1 channel*, the effect of crizotinib (0.3, 1, 3 μmol/L) on Nav1.1 sodium channel was evaluated by the patch-clamp technique. As a result, crizotinib inhibited Nav1.1 sodium channel current in a concentration-dependent manner. IC_{50} under closed gate condition and under inactivated condition was 0.85 and 0.87 μmol/L, respectively.

*: It is reported that Nav1.1 sodium channel plays an important role in depolarization to generate action potential in nerve cells and that its inhibition is associated with the induction of convulsive seizure (*Nature Neurosci*. 2006;9:1142-9). Therefore, the results of this study were submitted as the effect of crizotinib on the central nervous system.

b. Effect on nerve functions (Report 3660)

Crizotinib (10, 75, 500 mg/kg) was administered orally in a single dose to male rats (n = 8 per group) and animals were subjected to symptom observation (clinical signs, open-field test), neuromuscular function test, reflex response test, and activity test. In line with t_{max} (4.0-5.3 hours) observed after crizotinib administration in the single dose study in rats [see "3.(ii).A.(1).1) Single-dose administration"], monitoring for clinical signs was performed for 1 hour each immediately after administration and from 3 hours after crizotinib administration, and other open-field tests, etc., were performed at 4 hours after crizotinib administration.

In the 75 and 500 mg/kg groups, decreases in the total travel distance (decrease by an average of 33% and 48%, respectively, relative to the vehicle control group) and in the frequency of standing-up behavior (decrease by an average of 30% and 65%, respectively, relative to the vehicle control group) were observed. In the 500 mg/kg group, changes in clinical signs (salivation and dyspnea [2 animals each], soiled muzzle [1 animal], and decreased activity [1 animal]) were observed. No biologically significant changes were observed in neuromuscular function test,

reflex response, or body temperature.

3.(i).A.(3).3 Effect on respiratory system (Report 3622)
Crizotinib (10, 75, 500 mg/kg) was administered orally in a single dose to male rats (n = 8 per group), and effects on respiratory rate, tidal volume, and minute ventilation volume were studied by plethysmography. In line with t_{max} observed after crizotinib administration in the single dose study in rats, whole body plethysmography measurement was performed for 2 hours from 3 hours after crizotinib administration. At 5 hours post-dose, observation for clinical signs was also performed.

In the 75 mg/kg group, a statistically significant increase in the respiratory rate was observed during the period from 25 to 48 minutes after the start of measurement compared with the vehicle control group. In the 500 mg/kg group, the respiratory rate and minute ventilation volume decreased statistically significantly (decrease by an average of 47% and 28%, respectively, relative to the vehicle control group) and tidal volume increased statistically significantly (increase by an average of 64%) compared with the vehicle control group during the period from 1 to 24 minutes after the start of measurement. The statistically significant decrease in the respiratory rate and increase in tidal volume were also observed when averaged over a 2-hour observation period, whereas minute ventilation volume did not show any change from 24 minutes after the start of measurement. Clinical signs observed were dyspnea, soiled muzzle, and salivation in the 500 mg/kg group.

3.(i).B Outline of the review by PMDA
Based on the submitted data and on the following reviews, PMDA has concluded that crizotinib is expected to be effective in *ALK*-positive NSCLC and that information on the effect of the product on the cardiovascular system should be provided in an appropriate manner, as explained by the applicant.

3.(i).B.(1) Mechanism of action of crizotinib and its efficacy on *ALK*-positive NSCLC
The indication of crizotinib proposed in the application is *ALK*-positive NSCLC. However, primary pharmacodynamics studies documented in the submitted file were conducted using only NSCLC-derived cell lines expressing EML4-ALK. PMDA therefore asked the applicant to explain the types of genes that fuse with *ALK* gene in NSCLC (partner genes) and the reason why crizotinib was considered to be effective in *ALK*-positive NSCLC other than EML4-ALK.

The applicant responded as follows:
As partner genes for *ALK* gene in NSCLC, *TFG* gene (*Cell*. 2007;131:1190-203) and *KIF5B* gene (*Clin Can Res*. 2009;15:3143-9) have been reported in addition to *EML4* gene (*Nature*. 2007;448:561-6).

Taking account of the role of ALK fusion protein in the following oncogenic mechanism of *ALK*-positive NSCLC, crizotinib, the drug that inhibits TK of ALK, is expected to be effective in *ALK*-positive NSCLC regardless of the type of the partner gene.

[Role of ALK fusion protein in the oncogenic mechanism of NSCLC cells]
In transgenic mice forced to express *EML4-ALK* gene in alveolar epithelial cells by the promoter of Surfactant protein-C gene, hundreds of adenomas are observed in both lungs at 3 weeks after birth (*Proc Natl Acad Sci USA*. 2008;105:19893-7). This and other findings suggest that *EML4-ALK* fusion gene is an important oncogene driver of the oncogenesis (transformation) of *ALK*-positive NSCLC.

A TK domain in ALK exon 20 and a coiled-coil domain (capable of dimerization) at the N-terminus of EML4 are essential for this oncogenesis (transformation) process. It is believed that

EML4-ALK is dimerized constitutively via a coiled-coil domain, resulting in the activation of ALK TK (*Cancer Science*. 2008;99:2349-55), which in turn activates the signal transduction of PI3K/Akt (*Blood*. 2000;96:4319-27), STAT3 and RAS/Erk (*Clin Cancer Res*. 2011;17:2140-8) in the downstream of ALK, leading to cell growth enhancement and apoptosis inhibition.

These findings suggest that the partner gene of *ALK* gene in oncogenesis (transformation) is not limited to *EML4* gene and that fusion proteins generated by the fusion of *ALK* gene with *TFG*, *KIF5B*, *NPM* gene, etc., which have an oligomerization domain such as a coiled-coil domain in the N-terminus, induce oncogenesis (transformation) by the mechanism similar to that of EML4-ALK.

The ALK break apart FISH assay is recommended at the moment for detecting *ALK* fusion gene. This assay detects the breakage of *ALK* gene by the change in the distance between 2 probes located on opposite sides flanking the breakpoint of *ALK* gene. If the breakage of ALK gene has occurred, the assay is positive even for NSCLC with *ALK* gene fused with partner genes other than EML4.

PMDA considers as follows:
The explanation by the applicant is largely acceptable. However, ALK break apart FISH assay recommended by the applicant may also be positive for *ALK* fusion gene even if the partner gene does not have an oligomerization domain such as a coiled-coil domain in the N-terminus. It is unknown whether or not crizotinib is effective in patients with NSCLC with *ALK* gene fused with such a partner gene. In order to predict the efficacy of crizotinib and to select eligible patients in clinical use, it is critical to know whether or not crizotinib is effective in NSCLC with *ALK* gene fused with a partner gene without an oligomerization domain. Therefore, the applicant should actively investigate this issue and provide new findings in an appropriate manner.

3.(i).B.(2) Efficacy mediated by inhibition of c-Met and RON functions
Crizotinib is reported to inhibit the phosphorylation of not only ALK but also c-Met and RON TK [see "3.(i).A.(1).3) Inhibition of c-Met and RON functions"]. Therefore, PMDA asked the applicant to explain the expression status of c-Met and RON in *ALK*-positive NSCLC and contribution of the inhibition of c-Met and RON TK phosphorylation to the tumor growth inhibitory effect of crizotinib in *ALK*-positive NSCLC.

The applicant responded as follows:
At the moment, there are no reports on the expression status of c-Met or RON in *ALK*-positive NSCLC and, as a result, the contribution of the inhibition of c-Met and RON TK phosphorylation to the tumor growth inhibitory effect of crizotinib in *ALK*-positive NSCLC is unknown. However, in light of the reports that c-Met expression level is increased in NSCLC (*Pathol Oncol Res*. 2011:Jul 21 [DOI:10.1007/s12253-011-9430-7]) and that c-Met is involved in the angiogenesis during the tumor growth (*Cancer Lett*. 2005;225:1-26), crizotinib may indirectly inhibit tumor growth via angiogenesis suppression through inhibition of c-Met phosphorylation.

PMDA considers as follows:
Given that the inhibition of angiogenesis by crizotinib depends on the type of tumor, as explained by the applicant [see "3.(i).A.(1).3) Inhibition of c-Met and RON functions, Inhibition of angiogenesis"], the possibility of crizotinib indirectly inhibiting tumor growth in *ALK*-positive NSCLC via angiogenesis suppression through inhibition of c-Met TK phosphorylation remains only a speculation at the moment. The applicant is encouraged to investigate in future whether or not the inhibition of angiogenesis by crizotinib via inhibition of c-Met phosphorylation is associated with tumor growth inhibition in *ALK*-positive NSCLC, and thereby to elucidate the mechanism of action of crizotinib.

3.(i).B.(3) Mechanism of acquired resistance to crizotinib

The applicant explained the mechanism of acquired resistance to crizotinib based on published papers, etc., as follows:

In the foreign phase I study (Study A8081001), the mechanism of acquired resistance to crizotinib was investigated using the tissue of patients who had relapse after having responded markedly to crizotinib (*N Engl J Med*. 2010;363:1734-9). As a result, 2 gene mutations (4374G>A, 4493C>A), which had not been observed before crizotinib administration, were detected in a TK domain of *EML4-ALK* gene, suggesting that cysteine residue at position 1156 was replaced by tyrosine residue, or leucine residue at position 1196 by methionine residue (C1156Y and L1196M, respectively). In cell lines forced to express C1156Y or L1196M, the sensitivity to crizotinib decreased compared with that forced to express the wild type gene. C1156Y is distant from the ATP-binding site, suggesting that the residue endows the enzyme with resistance to crizotinib by an allosteric mechanism such as inhibition of the approach of crizotinib to the ATP-binding site. On the other hand, L1196M is located at the gate keeper position of the ATP-binding pocket, suggesting that methionine residue with a bulky side chain prevents crizotinib from binding to the active site of the enzyme, thereby rendering the enzyme resistant to crizotinib.

The applicant is also currently investigating the mechanism of acquired resistance to crizotinib, and results obtained so far suggest the possibility of resistance acquired by the following mechanisms: (i) mutations in TK domains other than C1156Y and L1196M and (ii) activation of signal transduction system other than ALK fusion protein, such as increase in the expression level of phosphorylated EGFR.

PMDA considers as follows:

The mechanism(s) of acquired resistance to crizotinib is important from the point of view of estimating the clinical efficacy of crizotinib and selecting eligible patients for crizotinib treatment. Therefore, the applicant should collect relevant information, including findings from further investigation by the applicant, and appropriately provide the information to the medical practice when new findings become available.

3.(i).B.(4) Findings observed in safety pharmacology studies

PMDA asked the applicant to explain the necessity of providing information on the findings observed in safety pharmacology studies and of exercising cautions in clinical use.

The applicant responded as follows:

By taking account of the results of the comparison between crizotinib concentrations wherein findings of interest were observed and plasma crizotinib concentration in clinical use, and of the occurrence of the findings of interest in other nonclinical and clinical studies, the applicant considered as follows regarding each of the findings.

[Effect on cardiovascular system]

IC_{20} of crizotinib to inhibit hERG current was 0.3 μmol/L (135 ng/mL), which was 2.5 times the C_{max} (54 ng/mL) of plasma unbound crizotinib under steady state in twice daily multiple dosing of crizotinib 250 mg to Japanese patients. In the study with anesthetized dogs, findings such as decreased heart rate, prolonged QT interval, and increased $MAPD_{100}$ (under sinus rhythm only) were observed at the plasma unbound crizotinib concentration of 84 ng/mL, which was 1.6 times the C_{max} achieved in clinical use.

Thus, taking account of the findings that QT interval prolonged, bradycardia, and sinus bradycardia for which a causal relationship to crizotinib could not be denied were observed in the toxicity studies [see "3.(iii).A.(2).6) One-month oral toxicity study in dogs" and "3.(iii).A.(2).7) Three-month oral toxicity study in dogs"] and in the clinical studies (Studies A8081001 and A8081005), the applicant will provide caution for QT interval prolonged and bradycardia via the

package insert, etc.

[Effect on the central nervous system]
Inhibition of Nav1.1 sodium channel was observed at a crizotinib concentration that was approximately 7 times higher than the C_{max} (54 ng/mL) in clinical use.

In the studies in rats, decreased spontaneous locomotor activity was observed at 75 mg/kg and changes in clinical signs at 500 mg/kg and, under these conditions, C_{max} of the plasma unbound crizotinib was 66.1 and 129 ng/mL, respectively, which was 1.2 and 2.4 times, respectively, the C_{max} in clinical use (54 ng/mL). In clinical studies, there were no reports suggestive of adverse events in the central nervous system. Neither was there any result suggesting the effect of crizotinib on the central nervous system in toxicity studies.

On the basis of the above results, the applicant considers that it is not necessary at the moment to exercise caution or provide the information regarding the findings observed in the studies on the central nervous system.

[Effect on the respiratory system]
In studies in rats, a decreased respiratory rate was observed in the 500 mg/kg group. However, changes in clinical signs were observed at the same dose in studies of the effect on the central nervous system, suggesting that the decreased respiratory rate was secondary to the changes in clinical signs. The increased tidal volume was considered to be caused by the decreased respiratory rate. The timing of the decreased minute ventilation volume did not coincide with t_{max} after crizotinib administration in rats, suggesting that the decrease was unlikely to be due to the direct effect of crizotinib. In the 500 mg/kg group, dyspnoea was observed in 2 animals, but the observed symptom showed deep and slow respiration and occurred in the same animals as those which showed a decreased respiratory rate and increased tidal volume, which suggests that the observed events were not adverse effects of crizotinib on the respiratory system. No adverse events corresponding to dyspnoea were observed in clinical studies, neither was there any result suggestive of the effect of crizotinib on the respiratory system in toxicological studies.

On the basis of the above, the applicant considers that it is not necessary at the moment to exercise caution or provide the information regarding the findings observed in the studies on the respiratory system.

PMDA accepted the response.

3.(ii) Summary of pharmacokinetic studies

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

The pharmacokinetics (PK) of crizotinib in animals was evaluated in rats, dogs, and monkeys. The binding of crizotinib to plasma protein, drug-metabolizing enzymes, transporters, etc. were studied using human and animal specimens.

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

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

Crizotinib was administered to male rats in a single oral dose (12.5, 25, 50 mg/kg) or single intravenous dose (1, 5 mg/kg), and plasma crizotinib concentrations were determined (the table below). After oral administration, plasma crizotinib reached C_{max} at 4.0 to 5.3 hours post-dose and was eliminated with $t_{1/2}$ of 6.6 to 13 hours. C_{max} and $AUC_{0-\infty}$ increased more than dose-proportionally at the doses of 12.5 and 25 mg/kg and increased almost dose-proportionally at the doses of 25 and 50 mg/kg. Bioavailability (BA) of crizotinib in 10 mmol/L hydrochloric acid solution was comparable to that in 0.5% methylcellulose suspension. The applicant explained that the more than dose-proportional increase in the exposure level observed at the doses of 12.5 and

25 mg/kg may be due to the saturation of metabolism in the gastrointestinal tract or in the liver after absorption or to the saturation of transporter-mediated efflux in the gastrointestinal tract, but the details are unknown. After intravenous administration, plasma crizotinib was eliminated in a multiphasic manner. Blood clearance was estimated to be comparable to plasma clearance based on the blood/plasma concentration ratio [see "3.(ii).A.(2).2) Plasma protein binding and distribution in blood cells"], and was 54% to 85% of the hepatic blood flow rate in rats (55.2 mL/min/kg, *Pharm Res.* 1993;10:1093-5). V_{SS} was greater than the total fluid volume (approximately 0.7 L/kg) in rats, suggesting a broad tissue distribution of crizotinib. The applicant explained that $t_{1/2}$ differed among different doses was attributed to the fact that in the 1 mg/kg group, plasma crizotinib concentration was below the detection limit at the last measuring timepoint, necessitating the calculation of $t_{1/2}$ based on different elimination phases among dose groups.

PK parameters of crizotinib (male rats, single-dose administration)

	Dose (mg/kg)	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0-\infty}$ (ng·h/mL)	$t_{1/2}$ (h)	BA*[1] (%)
p.o.	12.5*[2]	100 ± 40	4.0 ± 0.0	1100 ± 400	13 ± 8.0	26 ± 8
	25*[2]	410 ± 120	4.0 ± 0.0	4400 ± 1400	5.8 ± 0.4	49 ± 15
	25*[3]	530 ± 100	4.7 ± 1.2	5700 ± 800	10 ± 2.0	63 ± 9
	50*[2]	780 ± 200	5.3 ± 1.2	11,000 ± 300	6.6 ± 2.6	60 ± 19
i.v.	Dose (mg/kg)	CL (mL/min/kg)	V_{SS} (L/kg)	$AUC_{0-\infty}$ (ng·h/mL)	$t_{1/2}$ (h)	
	1*[4]	30 ± 8	2.9 ± 1.4	590 ± 180	2.3 ± 0.3	
	5*[2]	47 ± 6	24 ± 4	1800 ± 200	9.6 ± 1.0	

Mean ± SD, n = 3, *1: Calculated from $AUC_{0-\infty}$ (relative to $AUC_{0-\infty}$ after 5 mg/kg i.v. administration), *2: Administered in 10 mmol/L hydrochloric acid solution, *3: Administered in 0.5% methyl-cellulose suspension, *4: Administered in physiological saline solution

Crizotinib was administered to male dogs in a single oral dose (10 mg/kg) or single intravenous dose (1, 5 mg/kg), and the plasma crizotinib concentration was determined (the table below). After oral administration of crizotinib in 30% PEG400 solution, in 0.5% methylcellulose suspension, or in gelatin capsules, plasma crizotinib reached C_{max} at 1 to 4 hours post-dose and was eliminated with $t_{1/2}$ of 12 to 13 hours post-dose. BA was 38% to 66%. When crizotinib was administered intravenously, CL and V_{SS} were comparable between dose groups. Blood clearance was estimated to be comparable to plasma clearance based on the blood/plasma concentration ratio, and was 29% to 42% of the hepatic blood flow rate in dogs (30.9 mL/min/kg). V_{SS} was greater than the total body fluid in dogs (approximately 0.6 L/kg).

PK parameters of crizotinib (male dogs, single-dose administration)

	Dose (mg/kg)	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0-\infty}$ (ng·h/mL)	$t_{1/2}$ (h)	BA*[1] (%)
p.o.	10*[2]	360 ± 70	1 ± 0	5100 ± 900*[6]	12 ± 3	38 ± 8
	10*[3]	620 ± 370	4 ± 2	12,300 ± 7900	13 ± 2	66 ± 43
	10*[4,5]	620 ± 510	3 ± 3	9700 ± 6800	13 ± 2	52 ± 44
i.v.	Dose (mg/kg)	CL (mL/min/kg)	V_{SS} (L/kg)	$AUC_{0-\infty}$ (ng·h/mL)	$t_{1/2}$ (h)	
	1*[7]	13 ± 2	11 ± 2	1300 ± 200	12 ± 1	
	5*[2]	9.0 ± 0.7	13 ± 2	5900 ± 300	17 ± 4	

Mean ± SD, n = 3, *1: Calculated from $AUC_{0-\infty}$ (relative to $AUC_{0-\infty}$ after 5 mg/kg i.v. administration), *2: Administered in 30% PEG400 solution, *3: Administered in 0.5% methylcellulose suspension, *4: Administered in gelatin capsules, *5: n = 4, *6: AUC_{0-t}, *7: Administered in physiological saline solution

Crizotinib was administered to male monkeys in a single oral dose (20 mg/kg) or single intravenous dose (1, 5 mg/kg), and the plasma crizotinib concentration was determined (the table below). After oral administration, plasma crizotinib reached C_{max} at 6 hours post-dose and was eliminated with $t_{1/2}$ of 14 hours post-dose. After intravenous administration, CL and V_{SS} were comparable among the dose groups. Blood clearance was estimated to be 0.64 times the plasma clearance based on the blood/plasma concentration ratio, and was 43% to 50% of the hepatic blood flow rate in monkeys (43.6 mL/min/kg). V_{SS} was greater than the total body fluid (approximately 0.7 L/kg).

PK parameters of crizotinib (male monkeys, single-dose administration)

	Dose (mg/kg)	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0-\infty}$ (ng·h/mL)	$t_{1/2}$ (h)	BA*[1] (%)
p.o.	20*[2]	240 ± 110	6 ± 0	4100 ± 1800	14 ± 3	44 ± 19
i.v.	Dose (mg/kg)	CL (mL/min/kg)	V_{SS} (L/kg)	$AUC_{0-\infty}$ (ng·h/mL)	$t_{1/2}$ (h)	
	1*[3]	29 ± 5	13 ± 6	510 ± 130	7.9 ± 2.1	
	5*[4]	34 ± 4	13 ± 1	2400 ± 200	6.5 ± 0.2	

Mean ± SD, n = 3, *1: Calculated from $AUC_{0-\infty}$ (relative to $AUC_{0-\infty}$ after 5 mg/kg i.v. administration), *2: Administered in 0.5% methylcellulose suspension, *3: Administered in physiological saline solution, *4: Administered in 30% PEG400 solution

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

Crizotinib (10, 50, 150 mg/kg) was administered orally QD for 28 consecutive days to male and female rats, and plasma crizotinib concentrations were determined (the table below). Plasma crizotinib concentrations were higher in males than in females, with AUC_{0-24h} on Day 1 and 26 in males being 1.6 to 2.9 times that in females. AUC_{0-24h} and C_{max} increased almost dose-proportionally both in males and females. Repeated dose administration did not cause any marked increase in plasma crizotinib concentrations.

Crizotinib was administered orally QD for 90 consecutive days to male rats at 10, 30, or 100 mg/kg or to female rats at 10, 50, or 250 mg/kg, and plasma crizotinib concentrations were measured (the table below). The exposure level adjusted for dose tended to be higher in males compared with females. AUC_{0-24h} and C_{max} tended to increase more than dose-proportionally at low doses (males, 10 and 30 mg/kg; females, 10 and 50 mg/kg) and increased less than dose-proportionally at high doses (males, 30 and 100 mg/kg; females, 50 and 250 mg/kg). On Day 88 relative to Day 1, AUC_{0-24h} increased 1.8- to 4.5-fold (males) and 1.6- to 2.1-fold (females) and C_{max} increased 1.5- to 4.0-fold (males) and 1.1- to 2.1-fold (females), showing an increase in the exposure level of crizotinib following repeated administration.

The applicant explained that the higher exposure level of crizotinib in males compared with females was due to the sex difference in the activity of sulfotransferase which is considered to be involved in the metabolism of crizotinib to sulfate conjugate (M19) [see "3.(ii).A.(3) Metabolism"].

PK parameters of crizotinib*[1] (male and female rats, repeated-dose administration)

Study	Date of measurement	Dose (mg/kg/day)	Sex	n	t_{max} (h)	C_{max} (ng/mL)	AUC_{0-24h} (ng·h/mL)
One-month oral dose study	Day 1	10	Male	3	2.67 ± 1.15	218 ± 27.3	1800 ± 111
			Female	3	2.67 ± 2.31	88.3 ± 79.7	800 ± 703
		50	Male	3	4.00 ± 0.00	1040 ± 184	13,900 ± 2600
			Female	3	1.33 ± 1.15	624 ± 541	4750 ± 4130
		150	Male	3	10.0 ± 12.2	1500 ± 183	29,900 ± 3470
			Female	3	2.00 ± 0.00	1060 ± 66.6	14,700 ± 1020
	Day 26	10	Male	3	2.00 ± 0.00	254 ± 131	2160 ± 721
			Female	3	2.00 ± 0.00	219 ± 32	1070 ± 192
		50	Male	3	4.00 ± 0.00	898 ± 198	13,500 ± 3760
			Female	3	2.67 ± 1.15	881 ± 336	8350 ± 2570
		150	Male	3	2.67 ± 1.15	3240 ± 1030	41,600 ± 14,900
			Female	3	2.00 ± 0.00	1290 ± 246	14,400 ± 3440
3-month oral dose study	Day 1	10	Male	*[2]	4	84.9	835
			Female	*[2]	2	87.9	588
		30	Male	*[2]	4	564	5900
		50	Female	*[2]	2	721	6130
		100	Male	*[2]	7	1350	20,500
		250	Female	*[2]	1	978	15,300
	Day 88	10	Male	*[2]	4	343	3750
			Female	*[2]	4	120	1060
		30	Male	*[2]	4	1290	14,300
		50	Female	*[2]	4	813	10,100
		100	Male	*[2]	4	2090	37,600
		250	Female	*[3]	4	2090	32,700

Mean ± SD or mean, *1: Administered in 0.5% methylcellulose suspension, *2: 3 animals/measuring timepoint (blood samples were collected from different animals at each measuring timepoint), *3: 2 animals/measuring timepoint

In the above 3-month oral administration study in rats, the plasma concentrations of 2 diastereomers (PF-06270079, PF-06270080) of the metabolite lactam (PF-06260182) were determined. As a result, on Day 88 of crizotinib administration at 30, 100, 50, and 250 mg/kg, AUC_{0-24h} of PF-06270079 was 1250, 3700, 2150, and 3390 ng·h/mL, respectively, and AUC_{0-24h} of PF-06270080 was 559, 1710, 1190, and 1680 ng·h/mL, respectively.

Crizotinib (1, 6, 20 mg/kg) was administered orally QD for 28 consecutive days to male and female dogs, and plasma crizotinib concentrations were determined (the table below). AUC_{0-24h} and C_{max} were similar between males and females on all measurement days, and increased almost dose-proportionally. On Day 28 compared with Day 1, AUC_{0-24h} (all animals) increased 2.2- to 3.4-fold and C_{max} (all animals) increased 2.0- to 2.6-fold.

Crizotinib (1, 5, 25 mg/kg) was administered orally QD for 91 consecutive days to male and female dogs, and plasma crizotinib concentrations were determined (the table below). AUC_{0-24h} and C_{max} tended to increase more than dose-proportionally at the doses of 1 and 5 mg/kg and increased less than dose-proportionally at the doses of 5 and 25 mg/kg. On Day 91 compared with Day 1, AUC_{0-24h} (all animals) increased 2.2- to 3.1-fold and C_{max} (all animals) increased 1.8- to 2.2-fold.

PK parameters of crizotinib* (male and female dogs, repeated-dose administration)

Study	Day of measurement	Dose (mg/kg/day)	Sex	n	t_{max} (h)	C_{max} (ng/mL)	AUC_{0-24} (ng·h/mL)
1-month oral dose study	Day 1	1	Male	3	2.00 ± 0.00	31.8 ± 8.28	534 ± 169
			Female	3	2.00 ± 0.00	37.1 ± 4.14	517 ± 56.6
			All	6	2.00 ± 0.00	34.4 ± 6.53	526 ± 113
		6	Male	3	3.33 ± 3.21	266 ± 90.5	4080 ± 1440
			Female	3	1.33 ± 0.577	260 ± 122	3210 ± 972
			All	6	2.33 ± 2.34	263 ± 96.3	3650 ± 1200
		20	Male	3	1.00 ± 0.00	946 ± 347	11,900 ± 4190
			Female	3	1.67 ± 0.577	757 ± 159	9050 ± 4450
			All	6	1.33 ± 0.516	851 ± 263	10,500 ± 4170
	Day 28	1	Male	3	3.33 ± 1.15	68.6 ± 12.4	1130 ± 304
			Female	3	3.00 ± 1.73	105 ± 49.8	1560 ± 598
			All	6	3.17 ± 1.33	86.8 ± 38.1	1350 ± 486
		6	Male	3	2.33 ± 1.53	608 ± 229	9220 ± 3100
			Female	3	1.33 ± 0.577	437 ± 118	6540 ± 1390
			All	6	1.83 ± 1.17	523 ± 188	7880 ± 2600
		20	Male	3	1.67 ± 0.577	2590 ± 789	43,800 ± 13,800
			Female	3	3.00 ± 1.73	1860 ± 594	28,300 ± 6000
			All	6	2.33 ± 1.37	2220 ± 741	36,100 ± 12,800
3-month oral dose study	Day 1	1	Male	5	2.6 ± 1.3	40.4 ± 12.9	518 ± 149
			Female	5	2.0 ± 0.0	44.8 ± 13.1	502 ± 118
			All	10	2.3 ± 0.95	42.6 ± 12.5	510 ± 127
		5	Male	5	1.2 ± 0.45	300 ± 250	3930 ± 3220
			Female	5	1.4 ± 0.55	322 ± 63.1	4150 ± 686
			All	10	1.3 ± 0.48	311 ± 172	4040 ± 2200
		25	Male	5	1.6 ± 1.3	739 ± 655	9270 ± 7490
			Female	5	1.8 ± 1.3	889 ± 442	12,800 ± 6620
			All	10	1.7 ± 1.3	814 ± 532	11,100 ± 6920
	Day 91	1	Male	5	3.0 ± 1.4	78.8 ± 16.6	1220 ± 277
			Female	5	3.2 ± 1.1	82.6 ± 4.12	1280 ± 119
			All	10	3.1 ± 1.2	80.7 ± 11.6	1250 ± 204
		5	Male	5	4.0 ± 2.1	614 ± 238	10,200 ± 3740
			Female	5	1.6 ± 1.3	475 ± 64.2	7570 ± 1720
			All	10	2.8 ± 2.1	545 ± 180	8900 ± 3080
		25	Male	5	4.8 ± 3.0	1440 ± 547	25,900 ± 10,100
			Female	5	6.0 ± 2.2	2200 ± 748	43,400 ± 13,700
			All	10	5.4 ± 2.6	1820 ± 737	34,600 ± 14,600

Mean ± SD, *: Administered in 0.5% methylcellulose suspension

Crizotinib (50 mg/kg) was administered orally QD for 28 consecutive days to male and female monkeys. Although the study was conducted in a limited number of animals, AUC_{0-24h} and C_{max} were similar between males and females, and increased with repeated administration (the table below).

PK parameters of crizotinib*[1]
(male and female monkeys, 50 mg/kg QD, repeated-dose administration)

Day of measurement	Sex	n	t_{max} (h)	C_{max} (ng/mL)	AUC_{0-24} (ng·h/mL)
1	Male	2	17 ± 9.9	1130 ± 212	19,800 ± 4170
	Female	2[*2]	14 ± 15	818 ± 795	14,600 ± 16,100
28	Male	2	5.5 ± 6.4	2730 ± 170	58,100 ± 2330
	Female	1	24	2560	39,900

Mean ± SD, *1: Administered in 0.5% methylcellulose suspension, *2: Vomiting was observed in 1 animal at 3 to 8 hours post-dose.

In all animal species, the exposure level after repeated administration tended to be higher than that predicated based on $t_{1/2}$ after single-dose administration. In humans, CL decreased by multiple administration, and the decrease was considered to be due to the inhibition of CYP3A, the main metabolic enzyme of crizotinib, by crizotinib itself [see "4.(ii).A.(2).1) Foreign phase I study"]. The applicant explained that although the main crizotinib-metabolizing enzyme and the effect of crizotinib on the enzyme in animals are unknown, the increase in the exposure level after repeated administration may be caused by a mechanism similar to that after multiple administration in humans.

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

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

^{14}C-labeled crizotinib (10 mg/kg) was administered orally in a single dose to pigmented male rats, and tissue distribution of radioactivity was investigated. At 1 hour post-dose, which was the first measuring timepoint, the radioactivity was distributed widely in tissues. The tissue radioactivity reached the maximum level at 4 to 8 hours post-dose in most of the tissues, while the radioactivity in the ocular tissues, uvea, Harderian gland, and pituitary gland reached the maximum level at 48 to 96 hours post-dose. In agreement with the large distribution volume of crizotinib [see "3.(ii).A.(1).1) Single-dose administration"], radioactivity levels in most tissues were higher than that in the blood (C_{max} 165 ng eq/g). Particularly high levels of radioactivity were observed in the liver, uvea, adrenals, small intestine, and pituitary gland (C_{max} was 12,900, 8300, 7900, 7670, and 7380 ng eq/g, respectively) among tissues other than feces. In many tissues, radioactivity level remained up to 48 hours post-dose. At 168 hours post-dose, which was the last measuring timepoint, radioactivity was detected at a level exceeding the lower limit of quantitation (45 ng eq/g) in 17 out of 51 tissues examined, while in tissues other than melanin-containing tissues, pituitary gland, and testis, radioactivity levels decreased to ≤10% of C_{max}. At all measuring timepoints, radioactivity levels in the brain and the spinal cord were less than or equal to the lower limit of quantitation, which suggested that crizotinib and its metabolites hardly cross the blood-brain barrier.

In the above study, radioactivity was eliminated from the ocular tissues only gradually with $t_{1/2}$ of 24 days (576 hours), but the radioactivity levels decreased over time, suggesting that the binding to the ocular tissues was reversible. The applicant explained that the radioactivity showed a marked affinity to melanin-containing tissues such as the uvea and pigmented skin, which was caused by the reversible binding of crizotinib, a lipophilic basic compound, to melanin (*Pharm Res*. 1990;7:935-41).

3.(ii).A.(2).2) Plasma protein binding and distribution in blood cells

Crizotinib (225, 2250, 9000 ng/mL) was incubated with plasma samples of mice, rats, rabbits, dogs, monkeys, and humans, and binding to plasma proteins was evaluated by equilibrium dialysis. As a result, the plasma protein binding rate (mean at each concentration) was 95.3% to 97.2%, 90.3% to 97.1%, 89.4% to 96.2%, 95.5% to 95.8%, 86.3% to 97.0%, and 88.7% to 94.2%, respectively, in mice, rats, rabbits, dogs, monkeys, and humans, showing no clear dose-dependency.

Crizotinib (450 mg/mL) was incubated with human serum albumin (40 mg/mL) or α_1-acid glycoprotein (0.8 mg/mL), and the binding rates were 93.8% and 73.7%, respectively. The applicant explained that in the human body, crizotinib is mostly bound to serum albumin.

The metabolite lactam (PF-06260182) and its 2 diastereomers, PF-06270079 and PF-06270080 (both 0.5 or 5 μmol/L), were incubated in rat or human plasma. As a result, the plasma binding rates (mean of all concentration) of PF-06260182, PF-06270079, and PF-06270080 were 98.3%, 98.7%, and 97.8%, respectively, in rats and 93.8%, 94.6%, and 94.1%, respectively, in humans.

^{3}H-labeled crizotinib (45, 450, 4500 ng/mL) was incubated in the blood samples of mice, rats, dogs, monkeys, and humans. As a result, the blood/plasma concentration ratios of the radioactivity (mean at each concentration) in mice, rats, dogs, monkeys, and humans were 0.65 to 1.10, 0.88 to 1.16, 0.80 to 1.34, 1.37 to 1.88, and 1.01 to 1.16, respectively. The ratio was slightly higher in monkeys than in other animal species, while the ratio was close to 1 in all other animal species within the concentration range examined.

After oral administration of ^{14}C-labeled crizotinib to rats, dogs, and humans, the blood/plasma concentration ratios of the radioactivity (mean at each measuring timepoint) in rats, dogs, and humans were 0.63 to 1.03, 0.75 to 0.95, and 0.62 to 0.76, respectively.

The applicant explained that these results suggest that, in mice, rats, dogs, and humans, crizotinib is distributed roughly evenly in the blood cells and in the plasma.

3.(ii).A.(2).3) Placental transfer and fetal distribution

The applicant explained as follows:

Placental transfer or fetal distribution of crizotinib was not evaluated. However, in toxicity studies for effects on embryo-fetal development in rats and rabbits, effects on fetuses (e.g., decrease in fetal weight) were observed [see "3.(iii).A.(5) Reproductive and developmental toxicity"]. Therefore, crizotinib or its metabolites may cross the placenta.

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

3.(ii).A.(3).1) *In vivo*

^{14}C-labeled crizotinib (10 mg/kg) was administered orally in a single dose to male and female rats, and metabolites in the plasma, urine, feces, and bile were evaluated. In the plasma (at 1-8 hours post-dose), unchanged crizotinib (ratio relative to total plasma radioactivity, 53% in males and 44% in females), lactam (PF-06260182) generated by oxidization of piperidine ring (8%, 16%, respectively), nitrone (M21) (14%, 9%, respectively), and sulfate conjugate (M19) (3%, 18%, respectively) were detected. Neither unchanged crizotinib nor metabolites were detected in urine. In feces, unchanged crizotinib (ratio relative to dose, 79% in males and 60% in females) and M19 (1%, 24%, respectively) were detected. In bile, M19 (7%, 47%, respectively), glucuronide conjugate of O-dealkylated form (M1, 7%, 3%, respectively; M20, 3%, <1%, respectively), O-dealkylated form of PF-06260182 (M2) (3%, <1%, respectively), and sulfate conjugate of M2 (M8) (9%, 10%, respectively) were detected. The applicant explained that M19 was formed in a greater amount in females than in males, possibly due to the sex difference in sulfotransferase activity (*Curr Drug Metab*. 2010;11:296-306).

^{14}C-labeled crizotinib (10 mg/kg) was administered orally in a single dose to male and female dogs, and metabolites in the plasma, urine, and feces were evaluated. In the plasma (at 1-24 hours post-dose), unchanged crizotinib (ratio relative to plasma radioactivity, 59% in males, 71% in females), M21 (8%, 5%, respectively), hydroxylated form (M15) (not detected, 3%, respectively), N-dealkylated form (M16) (3%, not detected, respectively), and dicarbonyl form (M17/M18) (3%, not detected, respectively) of PF-06260182 were detected. Neither unchanged crizotinib nor metabolites were detected in urine. In feces, unchanged crizotinib (ratio relative to dose, 47% in males and 70% in females) and M17/M18 (3%, 3%, respectively) were detected. In the plasma, PF-06260182 was detected only as a trace metabolite, with the amount formed being lower than that observed in rats and humans. The applicant explained that it is likely to be associated with the low aldehyde oxidase activity in dogs (*Eur J Drug Metab Pharmacokinet.* 1987;12:307-10).

^{14}C-labeled crizotinib (250 mg) was administered orally in a single dose to healthy adult male subjects, and metabolites in the plasma, urine, and feces were evaluated. In the plasma (at 1-96 hours post-dose), unchanged crizotinib (ratio relative to plasma radioactivity, 33%) and PF-06260182 (10%) were detected. In urine, unchanged crizotinib (ratio relative to dose, 2%) and

M8 (5%) were detected and, in feces, unchanged crizotinib (54%) was detected. In the plasma, urine, and feces, the following trace metabolites were also detected: M2, hydroxylated form (M6) and O-dealkylated form (M4) of M2, M1, sulfate conjugate (M3), hydroxylated form/glucuronide conjugate (M5), and cysteine conjugate (M9) of M4.

3.(ii).A.(3).2) ***In vitro***

In liver cells of rats, dogs, monkeys, and humans, the intrinsic clearance of crizotinib (1 μmol/L) was 19, 9.9, 32, and 5.8 mL/min/kg, respectively. In rats, dogs, and monkeys, the hepatic clearance was estimated to be 16, 8.6, and 23 mL/min/kg, respectively, which was similar to *in vivo* blood clearance [see "3.(ii).A.(1).1) Single-dose administration"].

Crizotinib (5 μmol/L) was incubated with liver cells of rats, dogs, monkeys, or humans, hydroxylated form of piperidine ring (M13), M21, and PF-06260182 were detected as major metabolites. In addition, ^{3}H-labeled crizotinib (10 μmol/L) was incubated with rat or human liver S9 fraction, M13, M21, PF-06260182, and M19 (rats only) were detected as metabolites. In rats, sex difference was observed in metabolite formation. Thus, M21 and PF-06260182 were the main metabolites in male rats, whereas M19 was the main metabolite and neither M21 nor PF-06260182 was detected in female rats. No glutathione conjugate was detected in any of the studies.

Based on the above results, the applicant explained that oxidation of piperidine ring and sulfate conjugation resembled the results of *in vivo* studies, whereas O-dealkylation reaction was not detected *in vitro*.

Crizotinib (1 μmol/L) was incubated with human liver microsomes in the presence of inhibitors of CYP isoforms (1A2, 2C8, 2C9, 2C19, 2D6, 3A4). As a result, the metabolism of unchanged crizotinib was inhibited by 84% and 17%, respectively, by inhibitors of CYP3A4 and 2D6.

Crizotinib (1 μmol/L) was incubated with human liver microsomes in the presence of inhibitors of CYP isoforms (1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4, 3A5). As a result, metabolism to M4 was inhibited by 99% and 14%, respectively, by inhibitors of CYP3A4 and 2C19, and metabolism to PF-06260182 was inhibited by 59% by the inhibitor of CYP3A4. Metabolism to PF-06260182 in the presence of the cytosol containing aldehyde oxidase was inhibited by 88%, 19%, 15%, and 14%, respectively, by the inhibitors of CYP3A4, 2D6, 2C8, and 2C19.

Crizotinib (1 μmol/L) was incubated with recombinant human CYP isoforms (1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4, 3A5) and metabolism to M4 and PF-06260182 was investigated. As a result, M4 was detected only when crizotinib was incubated with CYP3A4, whereas PF-06260182 was observed when crizotinib was incubated with any of the CYP isoforms excluding CYP2C8. When the cytosol was added in the incubation mixture, PF-06260182 was observed with all CYP isoforms.

Crizotinib (1 μmol/L) was incubated with human liver microsomes or with recombinant human CYP isoforms (1A2, 2C9, 2C19, 2D6, 3A4, 2B6, 2C8). As a result, the contribution rate of CYP3A4, 2C19, and 2D6 to crizotinib metabolism was estimated to be 99.4%, 0.5%, and 0.1%, respectively.

Crizotinib (1 μmol/L) was incubated with recombinant CYP3A4 or 3A5, the intrinsic clearance was 0.51 and 0.09 μL/min/pmol P450, respectively.

On the basis of the above results, the applicant explained as follows:
CYP3A4/5 may be mainly involved in the metabolism of crizotinib. As regards the metabolism to PF-06260182 (lactam), the main metabolite in human plasma, piperidine ring is oxidized mainly by CYP3A4/5 (and by CYP2C8, 2C19, and 2D6 to more or less extent) to form an imine

intermediate, which is then further oxidized by aldehyde oxidase, resulting in the formation of lactam (*Curr Drug Metab*. 2000;1:357-89). Metabolism to M4, the O-dealkylated form, is presumed to be catalyzed mainly by CYP3A4. In humans, plasma PF-06260182 concentration increased after concomitant use with ketoconazole and decreased after concomitant use with rifampicin [see "4.(ii).A.(3) Drug-drug interaction studies"]. These findings suggest that CYP3A4 is involved in the metabolism of PF-06260182 to M2 (O-dealkylation).

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

3.(ii).A.(4).1) Urinary and fecal excretion

^{14}C-labeled crizotinib (10 mg/kg) was administered orally in a single dose to male and female rats, and urinary and fecal excretion of the radioactivity was determined. The radioactivity was mainly excreted in feces. The fecal excretion rate (percentage of dose) up to 168 hours post-dose was 99.6% and 98.4%, respectively, in males and females, and the urinary excretion rate 3.2% and 2.2%, respectively.

^{14}C-labeled crizotinib (10 mg/kg) was administered orally in a single dose to male and female dogs, and urinary and fecal excretion of the radioactivity was determined. The radioactivity was mainly excreted in feces. The fecal excretion rate (percentage of dose) up to 168 hours post-dose was 62.4% and 85.3%, respectively, in males and females, and the urinary excretion rate 2.1% and 2.2%, respectively. Vomiting occurred after crizotinib administration in 1 of 2 males and in 2 of 2 females, and 33.5% of the radioactivity was recovered from the vomit in the male, and 0.1% and 8.0% in each of the 2 females.

3.(ii).A.(4).2) Biliary excretion

^{14}C-labeled crizotinib (10 mg/kg) was administered orally in a single dose to bile duct cannulated male and female rats, and biliary, urinary, and fecal excretion of the radioactivity was determined. The biliary, urinary, and fecal excretion rates (percentage of dose) of the radioactivity up to 48 hours post-dose was 37.8%, 5.6%, and 53.3%, respectively, in males and 61.9%, 2.5%, and 35.1% in females, with the biliary excretion rate being higher in females than in males.

The applicant explained that, in all animal species studied, the urinary excretion rate of the radioactivity was low, and unchanged crizotinib was not detected in rat bile [see "3.(ii).A.(3).1) *In vivo*], which indicates that crizotinib is eliminated mainly by hepatic metabolism.

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

No study on the excretion of crizotinib in milk was conducted, and it is therefore unknown whether crizotinib is excreted in milk or not. The applicant explained that the following Caution will be provided in the package insert: "use of this drug should be avoided in nursing women and, if the use of the drug is absolutely necessary, breast feeding should be discontinued during treatment."

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

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

Substrates of CYP isoforms (1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A) were incubated with human liver microsomes in the presence of crizotinib (0.1-30 μmol/L). IC_{50} of crizotinib against CYP2B6, 2C9, and 3A (felodipine oxidation and testosterone 6β- hydroxylation) was 22, 23, 8.2 and 7.3 μmol/L, respectively, and more than 30 μmol/L against CYP1A2, 2C8, 2C19, 2D6, and 3A (midazolam 1'-hydroxylation) demonstrating the potent inhibitory effect of crizotinib against CYP3A.

Crizotinib (0.3-10 μmol/L) was preincubated with human liver microsomes in the presence of NADPH for up to 40 minutes. As a result, crizotinib inhibited CYP3A activity in a time-dependent manner, with the maximum rate constant for enzyme inactivation (k_{inact}) and Ki being 0.11 min^{-1}

and 3.0 μmol/L, respectively.

Based on the above, the applicant explained as follows:
These results suggest the possibility that crizotinib may cause pharmacokinetic drug interactions mediated by CYP3A. On the other hand, the steady-state C_{max} of crizotinib following twice-daily (BID) administration of crizotinib 250 mg to humans was 1.3 μmol/L (concentration of unbound form, 0.12 μmol/L). Comparison of the C_{max} with IC_{50} suggests that crizotinib is unlikely to cause drug-drug interactions via CYP1A2, 2B6, 2C8, 2C9, 2C19, or 2D6.

3.(ii).A.(5).2) Enzyme induction
Human liver cells were treated with crizotinib (0.25-7 μmol/L) for 3 days, and CYP1A2 and 3A4 activities and *CYP3A4* gene expression level (mRNA) were investigated. At the maximum crizotinib concentration (7 μmol/L), the enzymatic activities of CYP1A2 and 3A4 were 1.2 to 2.1 and 0.18 to 1.0 times, respectively, that of the vehicle control. In contrast, *CYP3A4* gene expression level increased in a concentration-dependent manner, with EC_{50} being 0.47 to 3.1 μmol/L and 6.4 to 29-fold increase in E_{max}. The applicant explained that the failure of CYP3A4 activity to increase in spite of the increase in *CYP3A4* gene expression level was possibly due to the time-dependent inhibition of CYP3A4 activity by crizotinib.

3.(ii).A.(5).3) Transporters
a. Transporters that transport crizotinib as a substrate
In dog kidney-derived cell line MDCK cell engineered to overexpress P-glycoprotein (P-gp), the efflux ratio ($P_{appB\rightarrow A}/P_{appA\rightarrow B}$) of crizotinib (0.1-50 μmol/L) was 33.6 to 3.9 at ≤20 μmol/L, which was higher than the ratio observed in non-P-gp expressing cells, whereas it decreased to 1.3 at 50 μmol/L, which suggested that crizotinib was a substrate of P-gp and that P-gp-mediated efflux becomes saturated with the increase in crizotinib concentration. In light of the findings that BA of crizotinib in humans is 43%, that the urinary excretion rate of unchanged crizotinib in humans is only 2.4%, and that results of the studies in the "3.(ii).A.(4) Excretion" section suggest that biliary excretion is not the major excretion route of crizotinib, the applicant explained that pharmacokinetic interaction is unlikely to occur between crizotinib and other drugs that affect P-gp, during the process of absorption from the gastrointestinal tract or elimination from the body.

In MDCK cells forced to express human breast cancer resistance protein (BCRP), $P_{appB\rightarrow A}/P_{appA\rightarrow B}$ of crizotinib (0.1-50 μmol/L) was 0.65 to 1.28, suggesting that crizotinib does not serve as a substrate for BCRP.

Uptake of crizotinib (1 or 25 μmol/L) into human liver cells was not significantly inhibited by rifamycin SV (100 μmol/L), an organic anion transporter polypeptide (OATP) inhibitor (maximum inhibition 11% at crizotinib 1 μmol/L), suggesting that OATP is not involved in the uptake of crizotinib into human liver cells.

b. Inhibition of transporters by crizotinib
Using human colon cancer-derived cell line Caco-2 cells, the inhibitory effect of crizotinib (0.1-20 μmol/L) on the efflux of digoxin (5 μmol/L), a P-gp substrate, was evaluated. As a result, crizotinib inhibited the efflux of digoxin in a concentration-dependent manner, showing a 69% inhibition at 20 μmol/L. IC_{50} was 5.8 μmol/L, and the steady-state C_{max} (0.12 μmol/L) of unbound crizotinib following administration of crizotinib 250 mg BID to humans was approximately a fiftieth of the IC_{50}. In contrast, crizotinib concentration in the gastrointestinal tract after oral administration of crizotinib 250 mg is 2220 μmol/L (calculated as "dose/250 mL"), which is approximately 400 times the IC_{50}. Therefore, the applicant explained that crizotinib in combination with a P-gp substrate may possibly increase the plasma concentration of the P-gp substrate.

Using MDCK cells forced to express BCRP, the inhibitory effect of crizotinib (0.01-30 μmol/L) on the efflux of topotecan (2 μmol/L), a substrate of BCRP, was investigated. The maximum inhibition of topotecan achieved by crizotinib was 42%, precluding the calculation of IC_{50}.

Using HEK293 cells forced to express OATP1B1 or OATP1B3, the inhibitory effect of crizotinib (0.001-100 μmol/L against OATP1B1, 0.01-100 μmol/L against OATP1B3) on the uptake of pravastatin (10 μmol/L), a substrate of OATP1B1, and rosuvastatin (5 μmol/L), a substrate of OATP1B3, was investigated. Crizotinib inhibited the uptake of both substrates in a concentration-dependent manner, showing 71% and 54% inhibition, respectively, at 100 μmol/L. IC_{50} was 48 and 44 μmol/L, respectively. Based on the steady-state C_{max} (0.12 μmol/L) of unbound crizotinib and the estimated crizotinib concentration in the liver (0.48 μmol/L) following crizotinib 250 mg BID administration to humans, the applicant explained that crizotinib is unlikely to cause pharmacokinetic interactions due to the inhibition of OATP1B1 or OATP1B3.

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

Based on the submitted data and on the following reviews, PMDA has concluded that the applicant's discussions on the absorption, distribution, metabolism, excretion, and pharmacokinetic interactions are largely acceptable, except the tissue distribution and pharmacokinetic interactions described below.

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

Crizotinib and its metabolites are shown to remain in melanin-containing tissues such as the uvea and pigmented skin for a long time [see "3.(ii).A.(2).1) Tissue distribution"]. PMDA asked the applicant to discuss (i) the possibility of crizotinib and its metabolites accumulating in melanin-containing tissues following crizotinib 250 mg BID administration to humans and (ii) differences observed between Japanese and foreign subjects in adverse events possibly related to the distribution of crizotinib in melanin-containing tissues.

The applicant responded as follows:
In the tissue distribution study in pigmented rats, $t_{1/2}$ of radioactivity was 576 hours in the ocular tissues, 133 hours in the pigmented skin, while $t_{1/2}$ in the uvea could not be calculated because of insufficient measuring timepoints in the elimination phase. Given the slow elimination rate of the radioactivity from melanin-containing tissues, crizotinib or its metabolites may accumulate in melanin-containing tissues when crizotinib is administered daily in clinical use. However, due to the limited number of subjects in each ethnic group enrolled in the foreign phase I study (Study A8081001) and the global phase II study (Study A8081005), no conclusion could be drawn regarding the difference between Japanese and foreign subjects in adverse events possibly related to the distribution in melanin-containing tissues (e.g., photosensitivity, visual disturbance).

As regards visual disturbance observed in clinical studies of crizotinib [see "4.(iii).B.(3).3) Visual disturbance"], although the measurement of dark adaptation response showed a decrease in the amplitude of b-waves in the 4-week electroretinography study in rats [see "3.(iii).A.(7).3) Four-week electroretinography (ERG) study in rats"], both bipolar cells and Müller cells which generate b-waves are cells that make up the retina and do not contain melanin granules. These findings suggest that the distribution of crizotinib or its metabolites in the uvea, a melanin-containing tissue, is not related to the delay in b-waves.

PMDA considers as follows:
Since it is suggested that crizotinib or its metabolites are potentially distributed in melanin-containing tissues such as the uvea and pigmented skin for a long time, attention should be paid to adverse events such as eye and skin disorders associated with the distribution of crizotinib or its metabolites in these tissues in clinical use. Also, information on adverse events possibly related

to the distribution in melanin-containing tissues should be collected, including the presence or absence of difference between Japanese and foreign patients and, when a new finding becomes available, the information should be appropriately supplied to the medical practice. The mechanism of visual disturbance caused by crizotinib has not been elucidated [3.(iii).B.(2) Visual disturbance"], with the relationship between visual disturbance and the distribution of crizotinib or its metabolite in the uvea remaining unknown.

The tissue distribution study using pigmented rats showed the distribution of crizotinib or its metabolite in the liver, small intestine, and pituitary gland at high concentrations. Regarding the liver, increases in hepatic enzymes such as ALT and AST were observed in toxicological studies [see "3.(iii).A.(2) Repeat-dose toxicity"] and clinical studies [see "4.(iii).B.(3).4) Hepatic impairment"], and death caused by hepatic failure occurred in Study A8081005. As regards the small intestine and the pituitary gland, phospholipidosis was observed as a pathological change in toxicological studies. Therefore, attention should be paid to the effects on these tissues in the clinical use of crizotinib.

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

The applicant explained that 2 study results related to enzyme inhibition and induction by crizotinib were obtained after the regulatory submission.

PMDA is currently making inquiries to the applicant about the details of these study results.

3.(iii) Summary of toxicology studies

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

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

No single-dose toxicity study was conducted, but the acute toxicity was evaluated in a 2-day oral toxicity study in rats and in a dose escalation toxicity study in dogs.

3.(iii).A.(1).1) Two-day toxicity study in rats

Crizotinib (monohydrochloride, 0 or 2000 mg/kg/day*) was administered orally for 2 days to SD rats (n = 3/sex/dose). One female in the crizotinib group was moribund-sacrificed on Day 2 because of aggravation of systemic conditions.

Based on the above, the approximate lethal dose of crizotinib (monohydrochloride) was determined to be 2000 mg/kg/day*.

*: Expressed in terms of crizotinib

3.(iii).A.(1).2) Dose escalation toxicity study in dogs

Crizotinib (10, 25, 40 mg/kg/day) was administered orally to beagle dogs (n = 1/sex/group) on Days 1, 5, and 8. After 40 mg/kg administration, the male showed bloody vomiting, diarrhoea, decreased neutrophil count, and decreased lymphocyte count. Necropsy showed reddening of the small and large intestines, and histopathological examination showed diffuse congestion of the small and large intestines, luminal mucus accumulation in the small intestine accompanied by the infiltration of neutrophils, and clear change of liver cells.

Based on the above, crizotinib 40 mg/kg/day was considered to be a dose that causes acute toxicity.

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

3.(iii).A.(2).1) Twenty eight-day oral toxicity study in mice

Crizotinib (dihydrochloride; 0, 40, 200 mg/kg/day*) was administered orally for 28 consecutive days to female C57BL6 mice (n = 5 per group). Clinical chemistry showed high aspartate aminotransferase (AST) level, high alanine aminotransferase (ALT) level, and low serum

triglyceride level in the ≥40 mg/kg groups.

Based on the above, the maximum tolerated dose of crizotinib (dihydrochloride) was determined to be 200 mg/kg/day*.

*: Expressed in terms of crizotinib

3.(iii).A.(2).2) Seven-day oral toxicity study in rats

Crizotinib (monohydrochloride, 0, 50, 150, 500 mg/kg/day*) was administered orally for 7 consecutive days to SD rats (n = 3/sex/dose). On Day 4, 1 male in the 500 mg/kg group was found dead and all other animals in the same group were moribund-sacrificed on Day 4 because of aggravation of systemic conditions. (i) Changes in clinical signs observed were abnormal breath sounds in the 50 and 150 mg/kg groups, somnolence, dyspnoea, and oral discharge in the ≥150 mg/kg groups, and diarrhoea and decreased body weight in the 500 mg/kg group; (ii) hematology findings included low white blood cell count, low lymphocyte count, high neutrophil count, and high monocyte count observed in both males and females of the 500 mg/kg group; (iii) clinical chemistry showed high serum ALT, AST and high creatine kinase levels in both males and females of the 500 mg/kg group; and (iv) histopathological examination showed decreased lymphocytes in the spleen and gut-associated lymphoid tissue, thymic atrophy, decreased cell density in the bone marrow, decreased extramedullary haemopoiesis in the spleen, single cell necrosis in the follicular antrum and granular layer, decreased secretory granules and single cell necrosis in the submaxillary gland, edema, enhanced keratinization, and erosion/ulcer of the submucosal tissue in the anterior stomach, and glandular hyperplasia and inflammation of the glandular stomach.

Based on the above, crizotinib (monohydrochloride) 500 mg/kg/day* was considered to be a dose that causes acute toxicity, and 150 mg/kg/day* as the maximum tolerated dose.

*: Expressed in terms of crizotinib

3.(iii).A.(2).3) Twenty eight-day oral toxicity study in monkeys

Crizotinib (50 mg/kg/day) was administered orally for 28 consecutive days to cynomolgus monkeys (n = 2/sex), and effects on the visual system and systemic toxicity were evaluated in an exploratory manner. On Day 21, one female was moribund-sacrificed because of aggravation of systemic conditions. The moribund-sacrificed animal showed erosion/ulcer in the cecum, haematological changes (anemia, high white blood cell count, low platelet cell count), and clinical chemistry changes (low serum total protein and albumin). In the surviving animals, (i) changes in clinical signs observed were diarrhoea/loose stools, decreased food intake, and decreased body weight, (ii) hematology findings included low reticulocyte count, low neutrophil count, left-shift of neutrophil nuclei, depletion of cytosolic granules in neutrophil precursor cells, increased macrophages and bone marrow cell fragments in the bone marrow, and basic deposit in osteoclasts; (iii) clinical chemistry showed high serum ALT and AST levels, and (iv) histopathological examination showed decreased cell density of erythroid and myeloid cells in the bone marrow. There were no abnormal findings in the ophthalmological examination or in the histopathological examination of the eyes and the optic nerves.

Based on the above, crizotinib 50 mg/kg/day was considered to be a dose that causes toxicity.

3.(iii).A.(2).4) One-month oral toxicity study in rats

Crizotinib (0, 10, 50, 150 mg/kg/day) was administered orally for 28 consecutive days to SD rats (n = 10/sex/dose). (i) Changes in clinical signs observed were increased salivation (males and females in the ≥50 mg/kg groups), reduced body weight gain (males in the 150 mg/kg group), and decreased food intake (males in the 150 mg/kg group). (ii) Hematology findings included decreased

prothrombin time (males in the ≥50 mg/kg groups), decreased activated partial thromboplastin time (males and females in the ≥50 mg/kg groups), high platelet count (males in the ≥50 mg/kg groups), high neutrophil count (males in the ≥50 mg/kg groups and females in the 150 mg/kg group), and high monocyte count (males in the 150 mg/kg group), and morphological changes in lymphocytes manifested as vacuolization (males in the 150 mg/kg group). (iii) Clinical chemistry showed high serum ALT, AST, and γ-glutamyl transpeptidase (GGT) levels in males and high serum ALT levels in females in the 150 mg/kg group. (iv) Urinalysis showed low urine pH in males in the ≥50 mg/kg groups. (v) Histopathological examination showed vacuolization of renal tubules in the renal cortex, decreased lymphocytes in the spleen, gut-associated lymphoid tissue, and peripheral lymph nodes, and thymic atrophy in males in the ≥50 mg/kg groups, and degeneration of pachytene spermatocytes in the testis, decreased cell density of myeloid and erythroid cells in the bone marrow, decreased bone formation and diaphyseal trabecular bones in primary sponge bone of the growing long bones, and atrophy of the prostate gland and the vesicular gland in males in the 150 mg/kg group. The vacuolization of lymphocytes and vacuole formation in renal tubules were considered to be changes reflecting phospholipidosis [see "3.(iii).A.(2).5) Three-month oral toxicity study in rats with a 2-month recovery].

On the basis of the above results, the no-observed-adverse-effect level (NOAEL) of crizotinib was determined to be 10 mg/kg/day in males and 50 mg/kg/day in females. The mean exposure level ($AUC_{0\text{-}24h}$ on Day 26) at NOAEL was 2.16 μg·h/mL in males and 8.35 μg·h/mL in females, which was 0.5 and 1.8 times, respectively, the clinical exposure level.†

†: AUC_{τ} = 4590 ng·h/mL (observed in twice daily multiple oral dose of 250 mg in Japanese patients with cancer). Same applies hereafter.

3.(iii).A.(2).5) Three-month oral toxicity study in rats with a 2-month recovery

Crizotinib was administered orally for 90 consecutive days to SD rats (n = 15/sex/dose), and reversibility after a 57-day withdrawal period was investigated. Crizotinib was administered at 0, 10 (low dose), 30 (medium dose), or 100 (high dose) mg/kg/day to males and at 0, 10 (low dose), 50 (medium dose), or 250 (high dose) mg/kg/day to females. Four females in the high dose group died (3 rats due to error in administration, 1 rat due to unknown reason). (i) Changes in clinical signs observed were sporadic decreases in skin elasticity in the crizotinib groups and reduced body weight gain and decreased food intake in the high dose group. (ii) Hematology findings included low reticulocyte count (males), high white blood cell count (females), high monocyte count (females), high neutrophil count (males and females), high platelet count (males and females), and vacuolization of lymphocytes, in the high dose group. (iii) Clinical chemistry showed high serum ALT (males in the medium and high dose groups, females in the high dose group), high serum AST (males in the high dose group), and high alkaline phosphatase (ALP) (females in the high dose group). (iv) Histopathological examination showed vacuole formation in several tissues (bile duct epithelium, epithelial cells of small and large intestine, adenohypophysial cells, glandular epithelial cells of prostate gland), histiocytosis and occurrence of foamy macrophages in lung and mesenteric lymph node, aggravation of spontaneous cardiomyopathy, fragmentation of bone marrow cells, lymphocyte lysis in the thymus, and swelling of acinar cells in the submaxillary gland in the medium and high dose groups. The vacuole formation in the bile duct and the duodenal epithelial and foamy macrophages in the mesenteric lymph node were considered to be due to the accumulation of phospholipids based on the transmission electron microscopic analysis and by immunostaining of adipophilin. Since no other toxicological findings secondary to phospholipidosis were observed, phospholipidosis was considered to be of little toxicological significance. All of the above findings resolved or tended to resolve after a 2-month withdrawal period.

Based on the above, NOAEL of crizotinib was determined to be 10 mg/kg/day in males and 50

mg/kg/day in females. The exposure level ($AUC_{0\text{-}24h}$ on Day 88) at NOAEL was 3.75 μg·h/mL in males and 10.10 μg·h/mL in females, which was 0.8 and 2.2 times, respectively, the clinical exposure level.

3.(iii).A.(2).6) One-month oral toxicity study in dogs

Crizotinib (0, 1, 6, 20 mg/kg/day) was administered orally for 28 consecutive days to beagle dogs (n = 3/sex). (i) Changes in clinical signs observed were diarrhoea, vomiting, and salivation in males and females in the ≥6 mg/kg groups and QTc interval prolongation in 1 male in the 20 mg/kg group. (ii) Hematology findings suggested decreased peroxidase activity of neutrophils in males and females in the 20 mg/kg group. (iii) Clinical chemistry showed a tendency of decreased serum albumin in both males and females in the ≥6 mg/kg groups. (iv) Necropsy and histopathological examination showed low thymus weight in males and females in the ≥6 mg/kg groups and decreased cell density in the thymus in males in the 20 mg/kg group.

Based on the above, NOAEL of crizotinib was determined to be 6 mg/kg/day. The exposure level ($AUC_{0\text{-}24h}$ on Day 28) at NOAEL was 9.22 μg·h/mL in males and 6.54 μg·h/mL in females, which was 2.0 and 1.4 times, respectively, the clinical exposure level.

3.(iii).A.(2).7) Three-month oral toxicity study in dogs

Crizotinib (0, 1, 5, 25 mg/kg/day) was administered orally by gavage for 91 consecutive days to beagle dogs (n = 5/sex), and reversibility after 57-day withdrawal was investigated. (i) Changes in clinical signs and ECG observed were abnormal feces (loose stools, mucous stools, watery stools) and vomiting in males and females in the ≥5 mg/kg groups and salivation and QTc interval prolongation in both males and females in the 25 mg/kg group. (ii) Hematology findings included low erythroid parameters, high white blood cell count, high lymphocyte count, high monocyte count, high platelet count, and high fibrinogen in both males and females in the 25 mg/kg group. (iii) Clinical chemistry showed high serum ALT, AST, ALP, and GGT in males, and high serum AST in females, and low serum albumin in both males and females in the 25 mg/kg group. There were no histopathological findings related to the administration of crizotinib.

Based on the above results, the NOAEL of crizotinib was determined to be 5 mg/kg/day. The exposure level ($AUC_{0\text{-}24h}$ on Day 91) at NOAEL was 10.20 μg·h/mL in males and 7.57 μg·h/mL in females, which was 2.2 and 1.6 times, respectively, the clinical exposure level.

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

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

Reverse mutagenicity of crizotinib was investigated using *S. typhimurium* (TA98, TA100, TA1535, TA1537) and *E. coli* (WP2*uvrAp*KM101). As a result, crizotinib was considered to have no reverse mutagenicity.

3.(iii).A.(3).2) Chromosomal aberration assay in human lymphocytes

After 3 hours of treatment with crizotinib, polyploid cells were increased in a concentration-dependent manner in the absence of metabolic activation system, while cells with chromosomal aberrations were increased significantly and polyploid cells were increased in a concentration-dependent manner in the presence of metabolic activation system. After 24 hours of treatment with crizotinib, polyploid cells were increased in a concentration-dependent manner in the absence of a metabolic activation system.

As decribed above, crizotinib significantly increased the number of polyploid cells and slightly increased chromosomal aberrations (breakage).

3.(iii).A.(3).3) *In vitro* micronucleus assay with centromere analysis

Centromere analysis was performed using Chinese hamster ovary (CHO)-derived cells. After 24 hours of treatment with crizotinib a 3- to 4-fold increase in binucleated cells containing micronuclei was observed in the absence of metabolic activation system. However, only the frequency of binucleated cells containing centromere staining-positive micronucleus increased, while the percentage of binucleated cells containing centromere staining-negative micronucleus did not increase.

Based on the above, the applicant considered that the crizotinib-induced micronucleus formation was due to the induction of heteroploidy.

3.(iii).A.(3).4) Micronucleus assay in rats

Crizotinib (0, 125, 250, 500, 1000 mg/kg/day) was administered orally for 2 days to SD rats (n = 5/sex/dose). In the ≥250 mg/kg groups, the increased incidences of micronucleated polychromatic erythrocytes and orthochromatic erythrocytes were noted in males, but not in females, which was potentially due to the lower exposure level in females relative to males.

An additional study was conducted in which crizotinib (0, 25, 100, 250 mg/kg/day) was administered orally for 2 days to male SD rats (n = 5 per group). In the 250 mg/kg group, a significant increase (2-fold increase compared with control group) in the incidence of micronucleated polychromatic erythrocytes was observed, while no such increase was observed in the ≤100 mg/kg groups.

Based on the above, the no observed effect level regarding micronucleus formation in males was determined to be 100 mg/kg/day.

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

Since crizotinib is intended to be used for treatment of patients with advanced cancer, no carcinogenicity test was performed according to "Guideline on Nonclinical Evaluation of Antineoplastic Drugs" (PFSB/ELD Notification No. 0604-1 dated June 4, 2010).

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

3.(iii).A.(5).1) Oral dose range-finding study on embryo-fetal development in rats

Crizotinib (0, 50, 250, 500 mg/kg/day) was administered orally every day to pregnant SD rats (n = 6 per group) from Gestation day 6 to 17. All animals in the 500 mg/kg group were moribund-sacrificed on Gestation day 12 because of exacerbation of clinical signs, decreased body weight, and decreased food intake. In the 50 and 250 mg/kg groups, reduced body weight gain was observed. Maternal animals in the control, 50 mg/kg, and 250 mg/kg groups underwent caesarean section on Gestation day 21. Low fetal body weight was observed in the 250 mg/kg group as the fetal abnormality.

3.(iii).A.(5).2) Study on embryo-fetal development in rats

Crizotinib (0, 10, 50, 200 mg/kg/day) was administered orally to pregnant SD rats (n = 20 per group) every day from Gestation day 6 to 17. In the 200 mg/kg group, 1 animal showed piloerection, colored nasal discharge, decreased body weight, and decreased food intake, and was therefore moribund-sacrificed on Gestation day 12. In the 200 mg/kg group, maternal animals showed reduced body weight gain and decreased food intake and, at caesarean section, low pregnant uterus weight. No crizotinib-related change was observed in the number of luteal bodies, the number of implantations, the number of resorptions, and the fetal survival rate. Findings observed in fetuses were low fetal body weight, skeletal variations (unossification of metatarsal bone, defective ossification of lumbar vertebrae, and wavy ribs) in the 200 mg/kg group.

On the basis of the above results, the NOAEL of crizotinib was determined to be 50 mg/kg/day

for general conditions of maternal animals and for embryo-fetal development and 200 mg/kg/day for the fertility of maternal animals. Mean $AUC_{0\text{-}24h}$ in the 50 mg/kg group on Gestation day 17 was 4980 ng·hr/mL, which was 1.1 times the clinical exposure level.

3.(iii).A.(5).3) Oral dose range-finding study on embryo-fetal development in rabbits

Crizotinib (0, 25, 75, 175, 350 mg/kg/day) was administered orally to pregnant NZW rabbits (n = 6 per group) every day from Gestation day 7 to 19. Maternal animals in the ≥175 mg/kg groups showed exacerbation of clinical signs, decreased body weight, and decreased food intake, and even death occurred in some animals, whereupon surviving animals in the 350 mg/kg group were moribund-sacrificed on Gestation day 9 and those in the 175 mg/kg group, on Gestation day 12. No crizotinib-related changes were observed in fetuses.

3.(iii).A.(5).4) Embryo-fetal development in rabbits

Crizotinib (0, 10, 25, 60 mg/kg/day) was administered orally to pregnant NZW rabbits (n = 20 per group) every day from Gestation day 7 to 19. No crizotinib-related change was observed in the general conditions of maternal animals, the number of luteal bodies, the number of implantations, the number of resorptions, and the fetal survival rate. As a finding on fetuses, a decreasing tendency of fetal body weight was observed in the 60 mg/kg group. Since the weight deviated from the range of the historical data, it was considered to be a toxicity finding. No crizotinib-related change was observed in the external appearance, skeletons, or visceral organs of fetuses.

On the basis of the above results, the NOAEL of crizotinib was determined to be 60 mg/kg/day for the general condition and the fertility of maternal animals and 25 mg/kg/day for embryo-fetal development. Mean $AUC_{0\text{-}24h}$ in the 25 mg/kg group on Gestation day 19 was 2730 ng·hr/mL, which was 0.6 times the clinical exposure level.

3.(iii).A.(6) Local tolerance

Physiological saline, crizotinib solution (0.5 or 5 mg/mL), or the solvent for crizotinib preparation for intravenous injection (50 mmol/L acetic acid-sodium acetate buffer solution [pH 4.4], osmolarity 312 mOsm/kg) was administered into the auricular vein, or to the perivascular area, of female rabbits (n = 3 per group), to investigate local tolerance. In the crizotinib groups and the vehicle group, redness or discoloration was observed at the site of the intravenous injection and the perivascular injection site. Histopathological examination showed inflammatory cell infiltration, oedema, haemorrhage, and localized necrosis. The findings at the perivascular injection site in the crizotinib 5 mg/mL group were more severe than those in other groups.

Based on the above, crizotinib and the solvent used in the preparation for intravenous injection were considered to have local irritant effects.

3.(iii).A.(7) Other toxicity studies

3.(iii).A.(7).1) *In vitro* phototoxicity

In the *in vitro* neutral red uptake study using Balb/c 3T3 mouse-derived fibroblasts (clone 31), IC_{50} of crizotinib without and with UVA (wavelength 365 nm) irradiation was 2.723 μg/mL and 0.804 μg/mL, respectively. The photo-irritation-factor (PIF) and mean photo effect (MPE) of crizotinib was 3.4 and 0.1, respectively.

Based on the above results, crizotinib was considered to be possibly phototoxic.

3.(iii).A.(7).2) *In vitro* hemocompatibility assay

a. *In vitro* hemocompatibility test using rabbit blood

Crizotinib preparation for intravenous injection (5 mg/mL) or the vehicle was diluted with

physiological saline and subjected to a test for hemolytic action by the method of Dacie. As a result, the applicant considered that neither crizotinib nor the vehicle, at the dilution ratio of ≤10%, had a toxicologically significant hemolytic effect on the whole blood of rabbits.

b. *In vitro* hemocompatibility assay using human blood

Crizotinib preparation for intravenous injection (5 mg/mL) or the vehicle was mixed with human whole blood, and subjected to test for hemolytic action according to the method of Reed and Yalkowsky. As a result, crizotinib was hemolytic when mixed with the blood in a 1:10 to 1:4 ratio, whereas the vehicle had no hemolytic effect.

3.(iii).A.(7).3) Four-week electroretinography (ERG) study in rats

Crizotinib (0, 100 mg/kg/day) was administered orally to male Long Evans rats (n = 8 per group) every day for 4 weeks. In addition to the usual ophthalmological examination, ERG (response under dark adaptation, light adaptation response, response under light adaptation, flicker response under light adaptation, dark adaptation response) was performed in the morning (2-4 hours post-dose) or in the afternoon (6-8 hours post-dose) on Days 15 and 29. Significant decreases in the amplitude of b-waves were observed at 16 minutes after the start of measurement of dark adaptation response on Day 15 and at 32 minutes after the start of measurement of dark adaptation response on Day 29, compared with the control group. In contrast, crizotinib had no effect on b-waves after dark adaptation for 2 hours in either case. Also, crizotinib had no effect on the latent time of b-waves at any measuring timepoint.

3.(iii).A.(7).4) Toxicity study on impurities

A 1-month repeated dose toxicity study was conducted in rats in order to evaluate the toxicity of 4 types of impurities (related substances A, B, C, D) that are contained in excess of qualification threshold in drug substance. The toxicity findings observed in this study were comparable to those in the 1-month repeated dose toxicity study in rats [see "3.(iii).A.(2).4) One-month oral toxicity study in rats"], with the toxicity of these 4 impurities not exceeding that of crizotinib.

Based on the above, the applicant considered that the above 4 impurities, even if present at the upper specification limits, would pose few safety problems.

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

Based on the submitted data and the following reviews, PMDA has concluded that, although there is no safety range for crizotinib, it may be used clinically, given the seriousness of the disease of patients for whom crizotinib is indicated. However, caution is necessary in using crizotinib clinically because (i) pathological changes without visceral toxicity such as phospholipidosis are observed in the gastrointestinal tract, lung, and lymphatic tissues, (ii) ERG in rats showed decreased amplitude of b-waves, suggesting the possibility that crizotinib has a pharmacological effect on the retinal function, (iii) ECG in dogs showed QTc interval prolongation, and (iv) an *in vitro* study suggested the possibility of phototoxicity.

3.(iii).B.(1) Immunotoxicity

Although no immunotoxicity study was conducted, decreased peroxidase activity of neutrophils was observed in dogs [see "3.(iii).A.(2).6) One-month oral toxicity study in dogs"], depletion of granules in precursor cells was observed in cynomolgus monkeys [see "3.(iii).A.(2).3) Twenty eight-day oral toxicity study in monkeys"], and vacuolization of lymphocytes was observed in rats [see "3.(iii).A.(2).5) Three-month oral toxicity study in rats]. Therefore, PMDA asked the applicant to explain the effect of crizotinib on the immune function.

The applicant responded as follows:

As regards the decrease in peroxidase activity of neutrophils, it appears that inhibition of c-Met

TK by crizotinib transiently suppressed bone marrow, causing a decrease in neutrophil count, which, in return, enhanced hematopoietic capacity in a compensatory manner and, as a result, the percentage of immature neutrophils increased in the peripheral blood during the process of the recovery of neutrophil cont.

As for the depletion of granules in neutrophil precursor cells, in light of the observation that the left-shift of neutrophil nuclei was observed, the depletion of granules in neutrophil precursor cells observed in cynomolgus monkeys was the change similar to decreased peroxidase activity of neutrophils observed in dogs.

Vacuolization of lymphocytes is considered to be due to phospholipidosis. Histopathological examination of lymphatic tissues such as the thymus, lymph nodes, and spleen did not show any findings that suggest the vacuolization of lymphocyte would affect the function of lymphocytes.

Based on the above, the applicant claims that crizotinib is unlikely to have any significant effect on immunological functions.

PMDA accepted the applicant's response.

3.(iii).B.(2) Visual disturbance

Visual disturbance was observed in the clinical studies of crizotinib [see "4.(iii).B.(3).3) Visual disturbance"]. PMDA asked the applicant to explain the relationship between the pharmacological action of crizotinib and the decrease in the amplitude of b-waves observed in the measurement of dark adaptation response in the ERG test in rats [see "3.(iii).A.(7).3) Four-week electroretinography (ERG) study in rats"].

The applicant responded as follows:

Given the following findings, the possibility cannot be excluded that inhibition by crizotinib of ALK and c-Met tyrosine kinases causes the decrease in the amplitude of b-waves, resulting in visual disturbance. However, since crizotinib had no effect on a-waves in the ERG test in rats, the relationship between the pharmacological action of crizotinib and the decrease in the amplitude of b-waves is unknown at the moment.

- The concentration of unbound crizotinib in the vitreous body is inferred to be approximately 106 ng/mL (235 nmol/L), a concentration sufficiently high for exhibiting its pharmacological effect (Study report [redacted]GR201).
- a-waves and b-waves in ERG are derived from the photoreceptor layer (rod cells, cone cells) and the inner granular layer (bipolar cells, Müller cells), respectively (*Handbook of physiological sciences, vol. 9: Sensory physiology.* 1st ed. Igaku-Shoin Ltd.; 1989).
- c-Met protein is expressed in the photoreceptor layer, and ALK protein is expressed in the retina (e.g., inner granular layer, ganglion cell layer, photoreceptor layer) (in-house document of the applicant).
- Hepatocyte growth factor has a protective effect against organic damage (apoptosis) that occurs in the photoreceptor layer and the inner granular layer (*Invest Ophthalmol Vis Sci.* 2004;45:4174-82, *Invest Ophthalmol Vis Sci.* 2002;43:528-36).

Taking into account that the mechanism and risk factors for crizotinib-induced visual disturbance are unknown, PMDA considers that the mechanism of the toxicity, etc. should be continuously investigated and examined and information should be appropriately provided to the medical practice.

3.(iii).B.(3) Phototoxicity

Taking account of the findings that (i) an *in vitro* phototoxicity study suggested potential phototoxicity of crizotinib [see "3.(iii).A.(7).1) *In vitro* phototoxicity"], and (ii) Grade 1

photosensitivity reaction for which a causal relationship to crizotinib could not be denied occurred in 1 of 255 patients with *ALK*-positive NSCLC enrolled in the clinical studies (Studies A8081001 and A8081005), PMDA has concluded that information on phototoxicity should be provided appropriately to the medical practice after the market launch [see "4.(iii).B.(3).10) Photosensitivity"].

4. Clinical data

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

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

4.(i).A.(1) Analytical methods

4.(i).A.(1).1) Assay for quantitation of crizotinib

Concentrations of crizotinib and metabolite PF-06260182 in human plasma were measured separately by LC/MS/MS.

4.(i).A.(1).2) Test for *ALK* fusion gene

Presence or absence of anaplastic lymphoma kinase (ALK) fusion gene in tumor tissue was tested mainly by the fluorescence *in situ* hybridization method (FISH) developed at Massachusetts General Hospital (MGH) (i.e., MGH FISH-CTA method) among multiple clinical trial assay (CTA) methods in the foreign phase I study (Study A8081001), and by ALK break apart FISH, for which application has been submitted as an *in vitro* diagnostic by Abbott Japan Co., Ltd., in global phase II study (Study A8081005). In MGH FISH-CTA and ALK break apart FISH, 2 separate regions on *ALK* gene locus on the short arm of human chromosome 2 (2p) were allowed to hybridize with DNA probes labeled with mutually different fluorescent dyes, and translocation or inversion (*ALK* fusion gene) in *ALK* gene locus was searched for based on the presence or absence of split signals (2 fluorescent dyes are detected at separate regions).

4.(i).A.(2) Foreign phase I study (5.3.1.1.1, Study A8081010 [August to September 2010])

A cross-over study was conducted in 14 healthy adult subjects in which an immediate release tablet of crizotinib (250 mg) was administered in a single oral dose under fasting conditions or single intravenous dose (50 mg) over 2 hours to evaluate the absolute bioavailability (BA). PK parameters obtained were as shown in the table below, and the absolute BA of crizotinib following oral administration, calculated from dose-adjusted $AUC_{0-\infty}$ (adjusted geometrical mean), was 43%. In addition, Vz following intravenous administration was markedly greater than the plasma volume. The applicant explained that the results suggested the wide distribution of crizotinib in tissues.

PK parameters following oral administration (immediate release tablet) and intravenous administration

Route of administration	Dose	$AUC_{0-\infty}$ (ng·h/mL)	AUC_{last} (ng·h/mL)	CL/F*1 (L/h)	C_{max} (ng/mL)	t_{max}*2 (h)	Vz/F*1 (L)	$t_{1/2}$*3 (h)
p.o.	250 mg	2321 (34)	2250 (35)	108 (32)	99.6 (28)	5.0 (4.0, 6.0)	4478 (35)	29.0 (10)
i.v.	50 mg	1067 (18)	1007 (18)	46.8 (18)	155 (19)	1.9 (1.0, 2.0)	1772 (18)	38.9 (16)

Geometrical mean (coefficient of variation [CV], %), n = 14, *1: CL or Vz in intravenous administration, *2: Median (range), *3: Arithmetic mean (CV%)

4.(i).A.(3) Foreign phase I study (5.3.1.2.1, Study A8081008 [July to August 2009])

A cross-over study was conducted in 24 healthy adult subjects to which a powder in capsule or immediate release tablet of crizotinib (250 mg) was administered orally in a single dose under fasting conditions to study the BA of the immediate release tablet relative to the powder in capsule.

The ratio of adjusted geometrical mean (immediate release tablet/powder in capsule) [90% confidence interval (CI)] was 92.43% [84.86%, 100.68%] for $AUC_{0-\infty}$, 92.61% [84.84%, 101.09%] for AUC_{last}, and 98.91% [90.18%, 108.48%] for C_{max}.

Plasma concentrations of 2 diastereomers (PF-06270079, PF-06270080) of the lactam (PF-06260182), a metabolite, were determined in 4 subjects. As a result, $AUC_{0-\infty}$ of PF-06270079 and PF-06270080 was 451 and 277 ng·h/mL, respectively, with the $AUC_{0-\infty}$ of PF-06270079 being 1.6 times that of PF-06270080.

4.(i).A.(4) Foreign phase I study (5.3.1.2.2, Study A8081011 [August to November 2010])

A cross-over study was conducted in 36 healthy adult subjects to which an immediate release tablet, a powder in capsule, or a formulated capsule of crizotinib (250 mg) was administered orally in a single dose under fasting conditions, or a formulated capsule of crizotinib (250 mg) was administered orally in a single dose after a high fat diet, to evaluate the following: (i) the bioequivalence (BE) between the formulated capsule and the immediate release tablet, and between the formulated capsule and the powder in capsule and (ii) the effect of food intake on the PK of crizotinib following the administration of the formulated capsule.

Results of the comparison of BE between dosage forms were as shown below.The ratios of the adjusted geometric means and 90% CIs for both $AUC_{0-\infty}$ and C_{max} was within the range (80%-125%) of BE stipulated by the protocol.

Comparison of BE between dosage forms

Comparison	Ratio of adjusted geometrical mean [90% CI]		
	$AUC_{0-\infty}$	AUC_{last}	C_{max}
Formulated capsule/immediate release tablet	99.56 [91.49, 108.33]	99.60 [91.30, 108.66]	106.97 [96.55, 118.51]
Formulated capsule/powder in capsule	106.93 [98.26, 116.35]	107.56 [98.58, 117.35]	111.32 [100.47, 123.33]

n = 35

Following administration of the formulated capsule under fasting conditions (n = 35) or after a high fat diet (n = 36), the ratio of the adjusted geometrical mean (fed administration/fasted administration) [90% CI] was 85.76% [78.88%, 93.25%] for $AUC_{0-\infty}$, 85.52% [78.45%, 93.22%] for AUC_{last}, and 86.22% [77.89%, 95.43%] for C_{max}, with each parameter showing an approximately 14% decrease after fed administration. In contrast, t_{max} (median) was approximately 5.0 hours after fasted administration and after fed administration and $t_{1/2}$ (arithmetic mean) was 34.9 and 35.4 hours, respectively, with both parameters being similar regardless of food intake.

4.(i).A.(5) Foreign phase I study (5.3.5.2.1, Study A8081001 [April 2006 to ongoing (data cut-off, September 15, 2010; database snapshot, November 1, 2010)])

In the recommended dose cohort in Study A8081001 described in "4.(ii).A.(2).1) Foreign phase I study," a powder in capsule of crizotinib (250 mg) was administered orally in a single dose to 13 subjects (12 subjects included in PK analysis) under fasted conditions or after a high fat diet on Day 1 of Cycle 1 or 7 days before (Day –7), and the effect of food intake on the PK of crizotinib was evaluated in an exploratory manner. As a result, the ratio of the adjusted geometrical mean [90% CI] after fasted administration (n = 10-12) versus fed administration (n = 8-11) was 84.64% [65.11%, 110.05%] for AUC_{0-24} and 87.65% [69.23%, 110.98%] for C_{max}.

4.(i).A.(6) Applicant's discussions

4.(i).A.(6).1) Comparison of BE between dosage forms

The oral dosage forms mainly used in clinical studies of crizotinib were powder in capsules (10,

50, 100 mg), immediate release tablets (50, 100 mg), and formulated capsules (150, 200, 250 mg*). The immediate release tablets were used in the Japanese phase I study (Study A8081022), the powder in capsules and the immediate release tablets were used in the foreign phase I study (Study A8081001), and the immediate release tablets were used in the global phase II study (Study A8081005). Results of Study A8081011 showed the bioequivalence of the formulated capsule (250 mg × 1) with the immediate release tablet and with the powder in capsule (50 mg × 1, 100 mg × 2). Results of the *in vitro* dissolution test also showed the bioequivalence of crizotinib content in each dosage form.

*: Only 200 and 250 mg capsules have been applied for approval.

4.(i).A.(6).2) Food effect on PK of crizotinib

In the exploratory study using the powder in capsule in Study A8081001, 90% CI of the ratio (fed administration/fasted administration) of the adjusted geometric mean exceeded the acceptance criterion (80%-125%) for BE both for $AUC_{0\text{-}24}$ and for C_{max}, but the results suggested that intake of a high fat diet did not markedly affect the exposure level of crizotinib. Therefore, in subsequent clinical studies (including Studies A8081001 and A8081005), crizotinib could be administered regardless of the condition of food intake.

The formulated capsule was used in Study A8081011, both AUC and C_{max} of crizotinib decreased by 14% after intake of a high fat diet. However, the changes of these PK parameters were smaller than the inter-individual variability of AUC and C_{max} (CV 36%-44%) under steady state in daily administration of crizotinib 250 mg BID in Study A8081001. 90% CI of the ratio (fed administration/fasted administration) of the adjusted geometrical mean was roughly within the range of 80% to 125%, both for AUC and for C_{max}. Based on the above, the applicant considered that the changes in PK parameters by a high fat diet were not clinically significant decreases and that the formulated capsule may be administered regardless of the condition of food intake.

4.(i).A.(6).3) Effect of antacids on PK of crizotinib

The solubility of crizotinib depends on pH; it is highly soluble in aqueous solution of low pH. Since concomitant use with antacids was permitted in clinical studies in patients with malignant tumor, the effect of antacids on the PK of crizotinib was evaluated in the analysis of population pharmacokinetics (PPK analysis) [see "4.(ii).A.(4).1) Population pharmacokinetic (PPK) analysis"]. As a result, the present data set did not contain sufficient data for evaluating the effect of famotidine and ranitidine (H_2 receptor blockers) or pantoprazole (proton pump inhibitor) on the k_a of crizotinib, whereas the results of the analysis suggested that proton pump inhibitors esomeprazole, omeprazole, and lansoprazole, when concomitantly using with crizotinib, were highly likely to decrease k_a of crizotinib by >20%. However, the distribution of the inter-individual variability of CL/F following concomitant use with a proton pump inhibitor, estimated by the final model of PPK analysis, did not show any clear difference from that observed following concomitant use without a proton pump inhibitor. Therefore, the applicant considered that the change in the CL/F of crizotinib by concomitant use with proton pump inhibitors is extremely small and that the decrease in k_a caused by the concomitant use with a proton pump inhibitor has a minor effect on AUCss after multiple administration.

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

Effect of pH in the gastrointestinal tract on the PK of crizotinib

Taking account of the pH-dependency of the solubility of crizotinib, the absorption of crizotinib may be decreased in patients with achlorhydria or patients with low gastric acid due to the medications. Despite such a possibility, the applicant explained that concomitant use with antacids has a minor effect on the AUCss of crizotinib, based on the results of the PPK analysis.

PMDA considers that the data so far obtained from the clinical studies provided only limited

information on the effect of pH within the gastrointestinal tract on the PK of crizotinib and that the applicant's explanation was only speculative. Thus, PMDA asked the applicant to explain the plan to conduct a study on drug interactions with antacids.

The applicant responded as follows:
The applicant plans to conduct a cross-over study to evaluate the drug interactions with proton pump inhibitors in healthy adult subjects, according to the instructions of the U.S. Food and Drug Administration (FDA). The clinical study report will be completed in September 2013.

PMDA considers that as soon as the results of the above study become available, the information should be provided appropriately to the medical practice.

4.(ii) Summary of clinical pharmacology studies

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

PK of crizotinib in healthy adult subjects and patients with malignant tumor including NSCLC with translocation or inversion of *ALK* gene locus (*ALK*-positive) was investigated after administration of crizotinib alone or in combination with ketoconazole, rifampicin, or midazolam.

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

4.(ii).A.(1).1) Japanese phase I study (5.3.3.1.1, Study A8081022 [December 2010 to January 2011])

Crizotinib (150, 250, 400 mg) was administered orally in a single dose to 18 healthy adult male subjects under fasting conditions, and plasma concentrations of unchanged crizotinib and the metabolite PF-06260182 were determined (the table below). Unchanged crizotinib in the plasma reached C_{max} at 5 hours post-dose, after which it was eliminated in a multiphasic manner with $t_{1/2}$ of 29.1 to 41.1 hours. $AUC_{0-\infty}$ and C_{max} increased more than dose-proportionally at the doses of 150 and 250 mg, and increased dose-proportionally at the doses of 250 and 400 mg. The applicant explained the reason that the more than dose-proportional increase observed at 250 mg may have been due to the weaker inhibitory effect of crizotinib on CYP3A at 150 mg than at 250 mg [see "3.(ii).A.(5).1) Enzyme inhibition"], or to the inter-individual variability because of the limited number of subjects studied.

The peak plasma PF-06260182 level was reached (C_{max}) at 5 to 6 hours post-dose, and $AUC_{0-\infty}$ and C_{max} increased with dose as was the case with unchanged crizotinib. The ratio of $AUC_{0-\infty}$ of PF-06260182 to that of unchanged crizotinib after administration of crizotinib at 150, 250, and 400 mg was 0.126, 0.137, and 0.154, respectively, and the ratio for C_{max} was 0.237, 0.235, and 0.226, respectively, with both $AUC_{0-\infty}$ and C_{max} ratios being comparable among different doses.

PK parameters of unchanged crizotinib and metabolite PF-06260182

Analyte	Dose (mg)	$AUC_{0-\infty}$ (ng·h/mL)	AUC_{last} (ng·h/mL)	C_{max} (ng/mL)	t_{max}*1 (h)	$t_{1/2}$*2 (h)	CL/F (L/h)	V_Z/F (L)
Unchanged crizotinib	150	1423 (32)	1339 (34)	70.5 (35)	5.0 (5.0-6.0)	41.1 (16)	105 (31)	6170 (43)
	250	3806 (33)	3732 (33)	156 (31)	5.0 (4.0-6.0)	29.9 (13)	65.7 (43)	2811 (56)
	400	6569 (31)	6386 (31)	236 (25)	5.0 (5.0-6.0)	29.1 (12)	60.9 (27)	2545 (35)
PF-06260182	150	181 (50)*3	188 (41)	17.2 (34)	5.0 (4.0-6.0)	–	–	–
	250	536 (46)	527 (46)	37.6 (44)	5.0 (4.0-6.0)	–	–	–
	400	1046 (48)	1034 (48)	54.9 (26)	6.0 (5.0-8.0)	–	–	–

Geometric mean (CV.%), n = 6, *1: Median (range), *2: Arithmetic mean (CV%), *3: n = 4

4.(ii).A.(1).2) Foreign phase I study (5.3.3.1.2, Study A8081009 [March to April 2010])

Crizotinib oral suspension (250 mg) containing ^{14}C-labeled form was administered orally in a single dose to 6 healthy adult male subjects under fasting conditions, and mass balance was evaluated. The total recovery rate of radioactivity (ratio relative to dose) up to 5 and 20 days post-

dose was 77.9% and 85.2%, respectively. The fecal and urinary excretion rates of total radioactivity up to 20 days post-dose were 63.1% and 22.2%, respectively, and the fecal and urinary excretion rates of unchanged crizotinib were 54% and 2.3%, respectively. The applicant explained that crizotinib is considered to be eliminated mainly by metabolism in the liver and in the gastrointestinal tract, and the results suggested the involvement of the elimination pathway other than metabolism, including biliary excretion, and also suggested the involvement of the kidney in the elimination of the metabolite.

The peak plasma radioactivity level was reached (C_{max}) at 5.0 hours post-dose, which was close to the t_{max} of unchanged crizotinib. The ratios of AUC_{last} and C_{max} of unchanged crizotinib to those of the radioactivity were 0.12 and 0.25, respectively, suggesting the presence of metabolites in plasma (the table below). Radioactivity concentration in red blood cells (AUC_{last}, 3641 ng eq·h/mL; C_{max}, 175 ng eq/mL) was lower than plasma radioactivity concentration, indicating the limited distribution of unchanged crizotinib and metabolites in red blood cells. $t_{1/2}$ of unchanged crizotinib was longer than that observed in Study A8081022 and other studies. The applicant explained the difference that unchanged crizotinib in plasma is eliminated in a multiphasic manner and, in the present study, the concentration of unchanged crizotinib was measurable for a longer period of time compared with other studies, which resulted in the calculation of $t_{1/2}$ based on a different elimination phase. Based on the findings that the $t_{1/2}$ of the radioactivity level in plasma was long and that the recovery rate of radioactivity from the plasma was low, the applicant explained that the results suggested that crizotinib or metabolites were irreversibly bound to plasma proteins, etc., but the details were unclear.

PK parameters of unchanged crizotinib and radioactivity in plasma

Analyte	$AUC_{0-\infty}$ (ng·h/mL)*1	AUC_{last} (ng·h/mL)*1	C_{max} (ng/mL)*1	t_{max}*2 (h)	$t_{1/2}$*3 (h)	CL/F (L/h)
Unchanged crizotinib	2777 (38)	2686 (40)	109 (46)	3.0 (2.0, 6.0)	94.0 (15)	90.1 (26)
Radioactivity	29,000, 29,600*4	22,830 (11)	436 (19)	5.0 (3.0, 6.0)	134, 178*4	8.61, 8.44*4

Geometric mean (CV%), n = 6, *1: ng eq·h/mL (AUC) or ng eq/mL(C_{max}) for PK parameters of radioactivity, *2: Median (range), *3: Arithmetic mean (CV%), *4: n = 2 (values in individual subjects are given)

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

4.(ii).A.(2).1) Foreign phase I study (5.3.5.2.1, Study A8081001 [April 2006 to ongoing (data cut-off, September 15, 2010; database snapshot, November 1, 2010)])

This study consisted of (i) dose escalation cohort and (ii) recommended dose cohort [see "4.(iii).A.(3) Foreign clinical studies"]. In this study, crizotinib was administered in a single dose on Day -7 to patients who had received crizotinib in the dose escalation cohort and to Asian patients, to evaluate the PK after single dose. Initially, it had been specified that crizotinib be administered under fasting conditions. However, based on the results of the exploratory study on the food effect on the PK of crizotinib [see "4.(i).A.(5) Foreign phase I study"], the protocol was amended and, as a result, crizotinib administration on and after Day 1 of Cycle 2 (4 weeks for 1 cycle) was allowed regardless of the condition of food intake. In addition, the subsequent amendment allowed administration regardless of the condition of food intake from the start of administration.

a. Dose escalation cohort

Crizotinib was administered orally once daily (QD) (50, 100, 200 mg) or twice daily (BID) (200, 250, 300 mg) to 38 patients with malignant tumor except leukemia (37 patients included in PK analysis), and plasma crizotinib concentration was investigated (the table below).

PK parameters of crizotinib (dose escalation cohort)

	Dose					
	50 mg QD	100 mg QD	200 mg QD	200 mg BID	250 mg BID	300 mg BID
Measuring timepoint	Day -7 (single dose administration)					
n	3	0	8	5	9	1
t_{max} (h)*[1]	2.0 (1.8, 4.1)	–	4.1 (1.1, 6.0)	4.0 (4.0, 4.1)	4.0 (1.0, 9.0)	2.02
C_{max} (ng/mL)	24.2 (36)	–	67.6 (60)	55.7 (46)	87.0 (34)	130
AUC_{τ} (ng·h/mL)	137 (8)	–	659 (66)	338 (46)	558 (33)	863
$AUC_{0-\infty}$ (ng·h/mL)	274 (21)	–	1378 (69)	729, 1230*[4]	1817 (33)	2320
CL/F (L/h)	182 (21)	–	145 (156)	163, 274*[4]	138 (32)	129
V_Z/F (L)	13,144 (32)	–	10,010 (183)	12,600, 20,500*[4]	9230 (30)	8510
$t_{1/2}$ (h)*[2]	50.2 (12)	–	49.5 (28)*[3]	51.7, 53.5*[4]	47.1 (16)*[5]	45.7
Measuring timepoint	Day 1 of Cycle 1 (single dose)					
n	0	4	0	2	0	5
t_{max} (h)*[1]	–	2.5 (1.0, 4.0)	–	4.0, 4.0	–	4.0 (2.1, 8.0)
C_{max} (ng/mL)	–	54.9 (56)	–	63.3, 65.0	–	114 (36)
AUC_{τ} (ng·h/mL)	–	458 (34)	–	357, 413	–	764 (50)
Measuring timepoint	Day 15 of Cycle 1 (multiple dose)					
n	3	4	8	4	5	4
t_{max} (h)*[1]	2.0 (1.0, 4.0)	2.5 (0.0, 6.1)	4.1 (1.0, 6.0)	5.0 (2.1, 8.0)	4.0 (1.0, 6.1)	5.0 (4.0, 6.2)
C_{max} (ng/mL)	24.4 (52)	85.7 (69)	149 (27)	189 (48)	327 (25)	420 (48)
C_{trough} (ng/mL)*[1]	7.47 (4.81, 10.8)	30.6 (23.5, 52.4)	44.1 (30.8, 160)	132, 183*[4]	259 (159, 356)*[6]	279 (183, 403)
AUC_{τ} (ng·h/mL)	206 (64)	1087 (37)	2047 (48)	1780 (61)	3084 (32)	4067 (55)
CL/F (L/h)	243 (63)	91.8 (27)	97.8 (44)	112 (61)	81.0 (28)	73.7 (42)
Cumulative coefficient*[1]	1.61 (0.72, 2.89)	2.36 (2.20, 2.61)	2.80 (1.12, 25.8)	4.85 (3.74, 18.7)	4.53 (4.36, 8.70)	4.87 (3.39, 7.47)
Measuring timepoint	Day 1 of Cycle 2 (multiple dose)					
n	3	3	5	3	5	3
t_{max} (h)*[1]	1.0 (1.0, 4.0)	4.0 (2.0, 4.0)	4.0 (2.0, 4.2)	4.0 (4.0, 4.0)	4.0 (4.0, 6.0)	4.1 (4.0, 9.0)
C_{max} (ng/mL)	48.0 (21)	134 (49)	146 (34)	239 (12)	328 (25)	475 (43)
C_{trough} (ng/mL)*[1]	8.75 (7.39, 31.5)	29.7 (23.4, 45.1)*[6]	29.4 (0.631, 38.1)	110, 178*[4]	229 (228, 378)*[7]	255 (6.10, 274)
AUC_{τ} (ng·h/mL)	426 (40)	1596 (31)	1719 (63)	2256 (13)	3054 (32)	3240, 4100*[4]
CL/F (L/h)	117 (51)	62.6 (26)	116 (51)	88.5 (14)	81.8 (25)	73.3,92.6*[4]
Cumulative coefficient*[1]	3.79 (1.98, 3.97)	3.39 (3.14, 3.83)	1.62 (1.46, 3.13)	4.65 (4.18, 4.88)	5.27 (3.73, 8.77)	3.94 (3.75, 4.13)

Geometric mean (CV%), *1: Median (range), *2: Arithmetic mean (CV%), *3: n = 7, *4: n = 2, *5: n = 8, *6: n = 4, *7: n = 3

b. Recommended dose cohort

Crizotinib (250 mg) was administered orally BID to 174 patients (167 patients included in PK analysis) with *ALK*-positive NSCLC, *ALK*-negative NSCLC, or other malignant tumor (e.g., malignant tumor that grows in a c-Met gene-dependent manner, malignant tumor [other than NSCLC] that grows in *ALK* fusion gene-dependent manner), and plasma crizotinib concentration was investigated (the table below). The applicant explained that no clear difference in PK parameters was observed after single dose of crizotinib among patients with *ALK*-positive NSCLC (118 patients included in PK analysis), patients with *ALK*-negative NSCLC (4 patients), and patients with other malignant tumors (45 patients), although there were only a limited number of patients with *ALK*-negative NSCLC. In 1 Japanese patient with *ALK*-positive NSCLC, crizotinib was administered in oral suspension (prepared by suspending the powder in capsule in hot water) on Day 1 to 8 in Cycle 1 because of dysphagia. In this patient, only t_{max} and C_{max} was obtained among PK parameters on Day 1 in Cycle 1, which were 8.03 hours and 86.6 ng/mL, respectively.

PK parameters of crizotinib (recommended dose cohort)

	Single dose		Multiple dose	
	Day -7	Day 1 of Cycle 1	Day 15 of Cycle 1	Day 1 of Cycle 2
Patients analyzed	Overall population (167 patients)			
n	46	98	24	18
t_{max} (h)*[1]	4.0 (2.0, 9.3)	4.1 (1.0, 9.1)	4.0 (0.0, 9.0)	4.0 (0.0, 9.0)
C_{max} (ng/mL)	108 (38)	98.9 (45)	411 (44)	478 (38)
C_{trough} (ng/mL)*[1]	0.0 (0.0, 32.6)*[3]	0.0 (0.0, 517)*[4]	319 (1.57, 1,030)*[5]	301 (3.17, 849)*[6]
AUC_{τ} (ng·h/mL)	742 (40)	663 (45)*[7]	3880 (36)*[8]	4164 (38)*[9]
$AUC_{0-\infty}$ (ng·h/mL)	2489 (51)*[10]	–	–	–
CL/F (L/h)	100 (50)*[10]	–	64.5 (56)*[8]	60.1 (44)*[9]
V_Z/F (L)	5946 (63)*[10]	–	–	–
$t_{1/2}$ (h)*[2]	42.4 (21)*[11]	–	–	–
Cumulative coefficient*[1]	–	–	4.84 (3.06, 13.1)*[12]	4.78 (2.75, 15.4)*[13]
Patients analyzed	Patients with *ALK*-positive NSCLC (118 patients)			
n	39	63	10	10
t_{max} (h)*[1]	4.0 (2.0, 9.3)	4.1 (1.0, 9.1)	5.1 (0.0, 9.0)	5.0 (2.0, 9.0)
C_{max} (ng/mL)	109 (37)	99.9 (48)	493 (16)	559 (25)
C_{trough} (ng/mL)*[1]	BLQ*[14]	0.0 (0.0, 517)*[15]	334 (1.57, 861)*[16]	306 (3.43, 797)*[17]
AUC_{τ} (ng·h/mL)	751 (38)	676 (45)*[18]	4717 (9)*[19]	4490 (23)*[20]
$AUC_{0-\infty}$ (ng·h/mL)	2510 (50)*[21]	–	–	–
CL/F (L/h)	99.6 (46)*[21]	–	53.0 (9)*[19]	55.7 (21)*[20]
V_Z/F (L)	6,101 (64)*[21]	–	–	–
$t_{1/2}$ (h)*[2]	43.7 (20)*[22]	–	–	–
Cumulative coefficient*[1]	–	–	6.06 (3.62, 13.1)*[23]	4.75 (2.75, 15.4)*[19]

Geometric mean (CV%), BLQ: Below the limit of quantitation, *1: Median (range), *2: Arithmetic mean (CV%), *3: n = 43, *4: n = 160, *5: n = 109, *6: n = 91, *7: n = 88, *8: n = 19, *9: n = 16, *10: n = 29, *11: n = 31, *12: n = 16, *13: n = 13, *14: n = 36, *15: n = 115, *16: n = 76, *17: n = 66, *18: n = 56, *19: n = 7, *20: n = 8, *21: n = 25, *22: n = 27, *23: n = 6

The applicant explained as follows, based on the results of studies on (i) the dose escalation cohort and on (ii) the recommended dose cohort:

- After a single oral dose of crizotinib 250 mg under fasting conditions, plasma crizotinib concentration reached C_{max} at 4 hours post-dose, after which it was eliminated in a multiphasic manner with $t_{1/2}$ of 42.4 to 47.1 hours.
- Following daily administration of crizotinib at the dose of 250 mg BID (recommended clinical dose), AUC_{τ} and C_{max} on Day 15 of Cycle 1 were similar to those on Day 1 of Cycle 2, which suggested that the plasma crizotinib concentration reached the steady state by Day 15 of Cycle 1.
- CL/F values on Day 15 of Cycle 1 and on Day 1 of Cycle 2 were lower compared with Day -7, showing a decrease by multiple dose, which suggested that it was difficult to predict the exposure level under steady state from the PK after the single dose. In light of the finding that crizotinib inhibited CYP3A in a time-dependent manner [see "3.(ii).A.(5).1) Enzyme inhibition"], the observed decrease in CL/F was considered to be due to the auto-inhibition of crizotinib metabolism.
- After single-dose administration (Day -7, and Day 1 of Cycle 1), $AUC_{0-\infty}$ and C_{max} increased roughly in proportion to dose. C_{max} increased less than dose-proportionally at 100 and 200 mg, which was probably caused by the inter-individual variability due to the limited number of patients studied.
- In multiple-dose administration (Day 15 of Cycle 1), both $AUC_{0-\infty}$ and C_{max} increased roughly in proportion to dose, whereas AUC_{τ} and C_{max} increased more than dose-proportionally after administration of 50 and 100 mg QD and after administration of 200 and 250 mg BID. The more than dose-proportional increase observed after administration at 50 and 100 mg may have been due to the inter-individual variability or to the weaker

inhibitory effect of crizotinib on CYP3A by 50 mg QD administration than by 100 mg QD administration.

- Following single oral dose of crizotinib (250 mg) to patients with malignant tumor (Day -7 of this study) and to healthy adult subjects (Studies A8081016, A8081008, A8081011, A8081010, and A8081022), $AUC_{0-\infty}$ was 1817 to 2489 ng·h/mL and 2192 to 3806 ng·h/mL, respectively, and C_{max} was 87.0 to 108 ng/mL and 100 to 156 ng/mL, respectively, showing no clear difference in crizotinib exposure level between healthy adult subjects and patients with malignant tumor.

4.(ii).A.(2).2) Foreign phase II study (5.3.5.2.2, Study A8081005 [January 2010 to ongoing (data cut-off, September 15, 2010; database snapshot, October 29, 2010)])

Crizotinib (250 mg) was administered orally BID for 3 weeks in each cycle to 136 patients with *ALK*-positive NSCLC who had received at least 1 chemotherapy regimen (85 patients included in PK analysis), and plasma concentrations of unchanged crizotinib and PF-06260182 were determined. The applicant explained that the median trough concentration on Day 1 of Cycles 2, 3, and 5 was 280, 255, and 242 ng/mL, respectively, with unchanged crizotinib and 58.6, 54.9, and 66.5 ng/mL, respectively, with PF-06260182, showing that the plasma concentrations of both unchanged crizotinib and PF-06260182 reached the steady state within Cycle 1.

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

4.(ii).A.(3).1) Drug interaction study with ketoconazole (5.3.3.4.1, Study A8081015 [July to September, 2010])

Crizotinib was administered to 15 healthy adult subjects alone or in combination with ketoconazole, a CYP3A4/5 inhibitor to investigate drug-drug interactions between crizotinib and ketoconazole. During the crizotinib monotherapy, crizotinib (150 mg) was to be administered orally in a single dose under fasting conditions. During the concomitant use with ketoconazole, ketoconazole (200 mg) was to be administered orally BID for 16 days and, on Day 4, crizotinib (150 mg) was to be administered orally in a single dose under fasting conditions. The exposure levels of unchanged crizotinib and PF-06260182 increased during the concomitant use with ketoconazole, compared with the crizotinib monotherapy. The ratio of the adjusted geometrical mean (concomitant use/crizotinib alone) [90% CI] of $AUC_{0-\infty}$, AUC_{last}, and C_{max} was 3.16 [2.86, 3.50], 3.28 [2.96, 3.64], and 1.44 [1.26, 1.64], respectively, for unchanged crizotinib, and 5.17 [4.58, 5.84], 5.20 [4.60, 5.87], and 1.61 [1.43, 1.82], respectively, for PF-06260182.

4.(ii).A.(3).2) Drug interaction study with rifampicin (5.3.3.4.2, Study A8081016 [July to October, 2010])

Crizotinib was administered to 15 healthy adult subjects alone or in combination with rifampicin, a CYP3A4/5 inducer to investigate drug-drug interactions between crizotinib and rifampicin. During the crizotinib monotherapy, crizotinib (250 mg) was to be administered orally in a single dose under fasting conditions. During the concomitant use with rifampicin, rifampicin (600 mg) was to be administered orally QD for 14 days and, on Day 9, crizotinib (250 mg) was to be administered orally in a single dose under fasting conditions. The exposure levels of unchanged crizotinib and PF-06260182 decreased during the concomitant use with rifampicin, compared with the crizotinib monotherapy. The ratio of the adjusted geometrical mean (concomitant use/crizotinib alone) [90% CI] of $AUC_{0-\infty}$, AUC_{last}, and C_{max} was 0.182 [0.161, 0.205], 0.176 [0.155, 0.200], and 0.315 [0.264, 0.375], respectively, for unchanged crizotinib, and 0.0575 [0.0486, 0.0681], 0.0549 [0.0464, 0.0649], and 0.110 [0.0902, 0.135], respectively, for PF-06260182.

4.(ii).A.(3).3) Drug interactions with midazolam (5.3.5.2.1, Study A8081001 [April 2006 to ongoing (data cut-off, September 15, 2010; database snapshot, November 1, 2010)])

In Study A8081001 described in "4.(ii).A.(2).1) Foreign phase I study," midazolam, a substrate for CYP3A4/5, was administered alone or in combination with crizotinib to 9 patients in the dose escalation cohort (4 patients in the 100 mg QD group, 5 patients in the 300 mg BID group) and to 14 patients in the recommended dose cohort to investigate the effect of crizotinib on the PK of midazolam (the table below). Midazolam (2 mg) was to be administered orally in a single dose under fasting conditions on Day -7 and on Day 1 of Cycle 2 (after 28-day daily administration of crizotinib). The exposure level of midazolam was increased after concomitant use with crizotinib relative to midazolam alone. The applicant explained that the extent of the increase was greater after administration of crizotinib 250 or 300 mg BID relative to administration of crizotinib 100 mg QD, which suggested that crizotinib inhibited CYP3A in a dose-dependent manner.

Effect of crizotinib on PK of midazolam

Crizotinib dose	n		Ratio of adjusted geometrical mean [90% CI] (%) (Day 1 of Cycle 2/Day -7)	
	Day -7	Day 1 of Cycle 2	$AUC_{0-\infty}$	C_{max}
100 mg QD	4	3	2.16 [1.61, 2.90]	1.32 [0.97, 1.80]
250 mg BID	14	8	3.65 [2.63, 5.07]	2.02 [1.39, 2.92]
300 mg BID	5	2	3.50 [1.41, 8.68]	2.39 [1.72, 3.32]

4.(ii).A.(4) Effects of covariates on PK of crizotinib

4.(ii).A.(4).1) Population pharmacokinetic (PPK) analysis

In order to investigate the factors causing the variations of the PK of crizotinib, a preliminary PPK analysis was performed based on PK data of 250 subjects (3184 measuring points) who received daily crizotinib 250 mg BID in Study A8081001 or Study A8081005, using a 2-compartment model including the first-order absorption process, lag time, and CL/F decrease on and after Day 2 of Cycle 1. In the final model, the following covariates were selected: body weight, ECOG PS, ethnicity, and sex for CL; body weight for the distribution volume of the central compartment, clearance between compartments, and distribution in the peripheral compartment; and concomitantly administered proton pump inhibitor and H_2 receptor blocker for k_a. Of these, body weight had the greatest effect on the AUCss of crizotinib, which decreased with the increase with body weight. The applicant explained that although AUCss of patients weighing 30 and 130 kg was 1.4 and 0.78 times, respectively, that of the patient with the reference body weight (70 kg), taking account of the inter-individual variability (CV 36%) of AUCss, the variation in the exposure level of crizotinib based on body weight does not have any clinical significance.

4.(ii).A.(4).2) Investigation based on the results of Study A8081001 (recommended dose cohort)

Effects of age, sex, body weight, and ethnicity on the exposure level of crizotinib were investigated based on the AUC and C_{max} observed in the recommended dose cohort of Study A8081001 following a single dose (Day -7, Day 1 of Cycle 1) or following multiple dose (Day 15 of Cycle 1) of crizotinib 250 mg BID. $AUC_{0-\infty}$ after single dose and AUC_{τ} and C_{max} after multiple dose were higher in female subjects than in male subjects. However, based on the observations that there was a correlation between the exposure level of crizotinib and body weight [see "4.(ii).A.(4).1) Population pharmacokinetic (PPK) analysis"] and that the body weight was lower in females than in males, the observed differences are considered to be due to the difference in the body weight. AUC_{τ} and C_{max} following multiple dose were higher in Asian subjects than in non-Asian subjects [see "4.(ii).B.(1) Difference in PK of crizotinib between Japanese and foreign patients"]. In contrast, no clear correlation was observed between crizotinib exposure level and age or body weight in this study. The applicant explained that as opposed to patients in PPK analysis, patients in Study A8081001 (recommended dose cohort) had a narrow range of body weight distribution, which was the cause for the failure to detect the correlation between crizotinib exposure level and body weight.

4.(ii).A.(5) Effects of crizotinib on QT interval

In order to investigate the effects of crizotinib on the heart rate (RR interval) and QT interval, a population pharmacokinetics (PPK)/pharmacodynamics (PD) analysis was performed based on 964 pairs of data on the plasma crizotinib concentrations and the ECG data obtained from 326 subjects in Studies A8081001 and A8081005. The relationship between crizotinib and RR or QTc interval was described using a linear mixed effect model. As a result, RR interval and QTcS interval (QTc interval adjusted for the correction factor estimated for each study) showed a tendency to increase with the increase of plasma crizotinib concentrations. It was estimated that, at the C_{max} (478 ng/mL) under the steady state after administration of crizotinib 250 mg BID (recommended clinical dose), heart rate [90% CI] decreased by 15.9 [14.3, 17.5] beats/min and QTcS interval [90% CI] increased by 3.4 [0.9, 5.8] msec. Based on the above, the applicant explained that crizotinib at the recommended clinical dose is unlikely to cause clinically significant QT interval prolonged.

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

4.(ii).B.(1) Difference in PK of crizotinib between Japanese and foreign patients

The applicant explained the difference in PK of crizotinib between Japanese and foreign subjects, as follows:

AUC_τ and C_{max} following administration of crizotinib 250 mg BID in Study A8081001 were higher in Japanese patients compared with non-Asian patients (the table below). The difference in the exposure level decreased after adjustment for body surface area and for body weight, which suggests that body size contributed to the observed difference in the exposure level between Japanese and non-Asian patients.

PK parameters of crizotinib (Study A8081001, recommended dose cohort, Day 15 of Cycle 1)

Patients	n	Before adjustment		After adjustment for body surface area		After adjustment for body weight	
		C_{max}	AUC_τ	C_{max}	AUC_τ	C_{max}	AUC_τ
Non-Asian	11	322 (67)	3137 (55)*1	318 (58)	3067 (47)*1	315 (52)	3039 (41)*1
Asian	13	506 (23)	4696 (11)*2	439 (22)	3974 (14)*2	393 (23)	3460 (21)*2
Japanese	5	485 (21)	4590 (10)	422 (23)	3996 (17)	372 (28)	3525 (24)
Korean	8	519 (25)	4805 (12)*3	450 (22)	3953 (13)*3	407 (22)	3397 (20)*3

Geometric mean (CV%); Unit of C_{max}, ng/mL; unit of AUC_τ; ng·h/mL; *1: n = 9, *2: n = 10, *3: n = 5

PMDA considers as follows:

Since only a limited number of Japanese patients were subjected to the analysis of PK, there is a certain limitation in the comparison of PK of crizotinib. However, as explained by the applicant, the results appear to suggest that the exposure level of crizotinib is higher in Japanese patients compared with non-Asian patients because of the difference in body weight, etc. Nevertheless, in Studies A8081001 and A8081005 which investigated the efficacy and safety of crizotinib, the tolerability and a certain efficacy in Japanese patients were confirmed, albeit in a limited number of patients studied [see "4.(iii).B.(2).2) Efficacy in Japanese patients" and "4.(iii).B.(3).1) Safety profile of crizotinib and difference between Japanese and foreign patients"]. Therefore, a daily administration of crizotinib 250 mg BID as the recommended dosage regimen can be selected for Japanese patients. However, given that there were adverse events that occurred at different frequencies between Japanese and foreign patients [see "4.(iii).B.(3).1) Safety profile of crizotinib and difference between Japanese and foreign patients"], information should be provided precisely to the medical practice regarding the difference in PK between Japanese and foreign patients. Also, since the comparison of PK between Japanese and foreign patients was based on a limited number of study data, information allowing the comparison of the ethnic difference of the PK of crizotinib should be continuously collected and the cause and the mechanism of the difference should be investigated.

4.(ii).B.(2) Drug-drug interactions

The applicant explained the possibility of CYP3A-mediated pharmacokinetic interactions, as follows:

1) Concomitant use with a CYP3A inhibitor or inducer

Concomitant use with ketoconazole or rifampicin was shown to increase or decrease, respectively, the exposure level following a single dose of crizotinib [see "4.(ii).A.(3) Drug-drug interaction studies"]. CL/F after multiple dose was decreased by the auto-inhibition of crizotinib metabolism, which suggests that the extent of the effect of CYP3A inhibitors and inducers on the exposure level of crizotinib at steady state may be different from that following a single dose administration. At the moment, there is no established recommended method for crizotinib dose adjustment in concomitant use with a CYP3A inhibitor or inducer. Therefore, concomitant use of crizotinib with potent CYP3A inhibitors such as ketoconazole and potent CYP3A inducers such as rifampicin should be avoided.

2) Concomitant use with CYP3A substrates

Multiple administration of crizotinib increased the exposure level of midazolam, a CYP3A substrate, following a single-dose administration [see "4.(ii).A.(3).3) Drug interactions with midazolam"]. Therefore, caution is required when crizotinib is concomitantly administered with a drug that is metabolized mainly by CYP3A. In particular, concomitant use with a CYP3A substrate with a narrow therapeutic range, such as pimozide, should be avoided.

According to the instructions of the FDA, the following studies will be conducted: (i) study on the effect of a potent CYP3A inhibitor (ketoconazole) on the PK in multiple administration of crizotinib (clinical study report scheduled to be completed in July 2015) and (ii) a study on the effect of a potent CYP3A inducer (rifampicin) on the PK in multiple administration of crizotinib (clinical study report scheduled to be completed in July 2015).

PMDA considers as follows:

Since ketoconazole and rifampicin are shown to affect the exposure level of crizotinib after a single-dose administration, it is desirable to avoid concomitant use of crizotinib with a potent CYP3A inhibitor or inducer. Also, since multiple administration of crizotinib increases the exposure level of midazolam, it is desirable to avoid concomitant use of crizotinib with a CYP3A substrate with a narrow therapeutic range. The above information, therefore, should be provided appropriately to the medical practice via the package insert, etc. In addition, it has been suggested that, after multiple administration, CL/F decreases due to the auto-inhibition of crizotinib. Therefore, as soon as the results of the above studies (i) and (ii) become available, the information should be provided appropriately to the medical practice.

4.(ii).B.(3) Effect of hepatic and renal impairment on PK of crizotinib

PMDA asked the applicant to explain the effect of hepatic and renal impairment on the PK of crizotinib.

The applicant responded as follows:

No clinical studies were conducted on subjects with hepatic or renal impairment. Since both Studies A8081001 and A8081005 included only a limited number of patients with hepatic or renal impairment, it is unknown how hepatic or renal impairment affects the PK of crizotinib. Since crizotinib is eliminated mainly by metabolism in the liver, hepatic impairment may possibly affect the PK of crizotinib. In contrast, the renal excretion rate of unchanged crizotinib is minimal (2.3% of the dose), which suggests that renal impairment has a minor effect on the PK of crizotinib.

According to the instructions of the FDA, the following studies will be conducted to evaluate the effects of hepatic impairment and severe renal impairment on the PK of crizotinib:

(a) A clinical study in patients with hepatic impairment (clinical study report scheduled to be

completed in January 2014)
In approximately 50 malignant tumor patients with normal hepatic function or mild, moderate, or severe hepatic impairment, classified by blood total bilirubin level and aspartate transferase level, crizotinib will be administered every day at a dose adjusted for hepatic function, and the effect of hepatic impairment on the PK of crizotinib will be investigated.

(b) A clinical study in patients with severe renal impairment (clinical study report scheduled to be completed in October 2012)
In 16 subjects with normal renal function (creatinine clearance ≥90 mL/min) or with severe renal impairment (creatinine clearance <30 mL/min), crizotinib 250 mg will be administered in a single dose and the effect of severe renal impairment on the PK of crizotinib will be investigated.

PMDA considers as follows:
As explained by the applicant, the exposure level of crizotinib may increase in patients with hepatic impairment and renal impairment may affect the PK of crizotinib, albeit to a limited extent. However, since no study data are available to support these explanations, it remains unknown whether or not, or to what extent if any, hepatic or renal impairment affects the PK of crizotinib. Therefore, as soon as the results of the planned clinical studies in patients with hepatic impairment and those with renal impairment become available, the information should be provided precisely to the medical practice.

4.(ii).B.(4) QT prolonged

The applicant explained that crizotinib administration is unlikely to cause clinically significant QT interval prolonged [see "4.(ii).A.(5) Effects of crizotinib on QT interval"].

PMDA considers that the study data suggest that QT interval prolongs with the increase in plasma crizotinib concentration. PMDA's conclusion on the crizotinib-induced QT prolonged based on incidences of QT prolonged in the clinical studies will be described in "4.(iii).B.(3).8) QT prolonged" section.

4.(ii).B.(5) Relationship between exposure level of crizotinib and its efficacy or safety

PMDA asked the applicant to explain the relationship between the exposure level of crizotinib and its efficacy or safety.

The applicant responded as follows:
Based on the results of Studies A8081001 and A8081005, the relationship between the exposure levels of crizotinib (estimated mean plasma concentration [C_{AVGss}] and observed C_{trough}) and its efficacy or safety was investigated in a preliminary manner. Efficacy was evaluated based on the objective response rate (logistic regression) and on the progression-free survival (PFS) (Cox proportional hazards model), and safety was evaluated based on the occurrences of pneumonitis, neutropenia, and fatigue, and on the ALT increased (all analyzed by logistic regression).

4.(ii).B.(5).1) Relationship between exposure level of crizotinib and its efficacy

A statistically significant relationship was observed between the exposure level of crizotinib (Log C_{AVGss}, Log C_{trough}) and the objective response rate, with the objective response rate increasing with the increase in the exposure level. In Study A8081001, when the patient population was divided into 6 groups based on C_{trough}, the odds ratio [95% CI] of the objective response rate of the overall population (median C_{trough} 284 ng/mL) to that of the group with the lowest exposure rate (median C_{trough} 174 ng/mL) was estimated to be 2.15 [1.19, 3.86]. In Study A8081005, when the patient population was divided into 6 groups based on C_{AVGss}, the odds ratio [95% CI] of the objective response rate of the overall population (median C_{AVGss} 296 ng/mL) to that of the group with lowest exposure level (median C_{AVGss} 191 ng/mL) was estimated to be 1.69 [1.01, 2.28].

In Study A8081001, PFS tended to increase with the increase in the exposure level of crizotinib (Log C_{trough}), but the correlation was not statistically significant. In Study A8081005, available data were insufficient, precluding the analysis using PFS as the index.

4.(ii).B.(5).2) Relationship between crizotinib exposure level and its safety

Neither Study A8081001 nor Study A8081005 showed any clear relationship between the exposure level and adverse events investigated. However, because of the limited number of patients studied, no conclusion was derived regarding the relationship between the exposure level of crizotinib and its safety.

PMDA considers that since the above results were obtained from a preliminary analysis based on a limited number of data, information on the relationship between the exposure level of crizotinib and its efficacy or safety should be continuously collected.

4.(iii) Summary of clinical efficacy and safety

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

As the efficacy and safety evaluation data, the results from a total of 9 studies including 1 Japanese phase I study, 1 global phase II study including Japan, and 7 foreign phase I studies were submitted. As the reference data, the results from 1 global phase III clinical study including Japan were submitted.

List of clinical studies on efficacy and safety

Data category	Region	Study	Phase	Study population	No. of subjects enrolled	Summary of dosage regimen of crizotinib	Major endpoint
Evaluation	Japan	A8081022	I	Healthy adult male subjects	18	Single oral dose of 150, 250, or 400 mg under fasting conditions	Safety PK
	Global	A8081005	II	Patients with *ALK*-positive advanced or relapsed NSCLC who had received ≥1 chemotherapy regimen	148	Daily oral dose of 250 mg BID	Efficacy Safety PK
	Foreign	A8081001	I	[Dose escalation cohort] • Patients with advanced malignant tumor except leukemia [Recommended dose cohort] • Patients with *ALK*-positive advanced or relapsed NSCLC • Patients with *ALK* fusion gene-negative advanced or relapsed NSCLC • Patients with c-Met gene-dependent malignant tumor, *ALK* fusion gene-dependent malignant tumor other than NSCLC, etc.	212	[Dose escalation cohort] Daily oral dose of 50, 100, or 200 mg QD, or daily oral dose of 200, 250, or 300 mg BID [Recommended dose cohort] Daily oral dose of 250 mg BID	Safety PK Efficacy
		A8081010	I	Healthy adult subjects	14	Single intravenous dose of 50 mg, or single oral dose of 250 mg under fasting conditions	BA PK Safety
		A8081008	I	Healthy adult subjects	24	Single oral dose of 250 mg in the powder in capsule or in the immediate release tablet under fasting conditions	BA PK Safety
		A8081011	I	Healthy adult subjects	36	Single oral dose of 250 mg in the immediate release tablet, in the powder in capsule, or in the formulated capsule under fasting conditions, or single oral dose of 250 mg in the formulated capsule after a high fat diet	BE PK Safety
		A8081009	I	Healthy adult male subjects	6	Single oral dose of ^{14}C-labeled crizotinib (250 mg) under fasting conditions	PK Safety
		A8081015	I	Healthy adult subjects	15	Single oral dose of 150 mg under fasting conditions, or daily oral dose of ketoconazole 200 mg BID for 16 days and, on Day 4, single oral dose of crizotinib 150 mg under fasting conditions	PK Safety
		A8081016	I	Healthy adult subjects	15	Single oral dose of 250 mg under fasting conditions, or daily oral dose of rifampicin 600 mg QD for 14 days and, on Day 9, single oral dose of crizotinib 250 mg under fasting conditions	PK Safety
Reference	Global	A8081007	III	Patients with *ALK*-positive advanced or relapsed NSCLC who had received 1 chemotherapy regimen (containing platinum antitumor agent)	36*	Daily oral dose of 250 mg BID	Efficacy Safety

ALK: Anaplastic lymphoma kinase, NSCLC: Non-small cell lung cancer, PK: Pharmacokinetic, QD: Once daily, BID: Twice daily, BA: Bioavailability, BE: Bioequivalence, *: Number of subjects receiving crizotinib

The outline of each clinical study was as described below.

Major adverse events other than deaths reported in each clinical study are described in "4.(iv) Adverse events observed in clinical studies," and PK data in "4.(i) Summary of biopharmaceutic studies and associated analytical methods" and in "4.(ii) Summary of clinical pharmacology studies."

[Evaluation data]
In the global phase II study (Study A8081005) and the foreign phase I study (Study A8081001) submitted, the last visit of patients was September 15, 2010 (data cut-off date). However, it took 6 weeks to confirm the completeness of the data obtained up to the cut-off date, and data obtained from patients who visited the office during the period were added to the database. As a result, the data available on October 29, 2010 (Study A8081005) or November 1, 2010 (Study A8081001) were recorded as a "database snapshot," and the clinical study report was prepared based on these data.

Regarding the global phase II study (Study A8081005), the foreign phase I study (Study A8081001), and the global phase III study (Study A8081007), a "60-day update report" prepared approximately 60 days after the regulatory submission was additionally submitted. Unless specified otherwise, the following description is based on the study results submitted in the application.

(1) Clinical pharmacology studies
A total of 7 clinical pharmacology studies in healthy adult subjects were submitted [see "4.(i) Summary of biopharmaceutic studies and associated analytical methods" and "4.(ii) Summary of clinical pharmacology studies"]. No death occurred during the study period of these studies.

1) Japanese phase I study
(5.3.3.1.1, Study A8081022 [December 2010 to January 2011])
2) Foreign phase I study
(5.3.1.1.1, Study A8081010 [August to September, 2010])
3) Foreign phase I study
(5.3.1.2.1, Study A8081008 [July to August, 2009])
4) Foreign phase I study
(5.3.1.2.2, Study A8081011 [August to November, 2010])
5) Foreign phase I study
(5.3.3.1.2, Study A8081009 [March to April, 2010])
6) Foreign phase I study
(5.3.3.4.1, Study A8081015 [July to September, 2010])
7) Foreign phase I study
(5.3.3.4.2, Study A8081016 [July to October, 2010])

(2) Global study
Global phase II study (5.3.5.2.2, Study A8081005 [January 2010 to ongoing (data cut-off date, September 15, 2010; database snapshot, October 29, 2010)])

An open-label, uncontrolled study was conducted at 57 centers in 12 countries and regions, including Japan, to evaluate, in an exploratory manner, the efficacy and safety of crizotinib in patients with *ALK*-positive, locally advanced or metastatic (advanced or relapsed) NSCLC who had been treated with ≥1 chemotherapy regimen (target sample size of 250).

Crizotinib (250 mg) was to be administered orally BID every day. The administration could be continued until any of the following occurred; aggravation of the tumor, aggravation of the

clinical condition, unacceptable toxicity, consent withdrawal, and noncompliance with protocol. However, even if the patient met any of the above discontinuation criteria, administration of crizotinib could be continued if the clinical benefit for the patient outweighed the risk, according to the opinion of the investigator.

Of 148 subjects enrolled in the study by the timepoint of database snapshot preparation, 136 patients who were confirmed to have received ≥1 dose of crizotinib were included in the safety analysis set. Of them, patients who underwent tumor evaluation at least once ≥6 weeks after the first dose, patients who discontinued the study, patients who had disease progression, and patients who died, at the timepoint of database snapshot preparation, a total of 76 subjects were included in the efficacy analysis set.

As regards efficacy, the best overall response and the objective response rate (evaluated by the investigator), the primary endpoints, were as shown in the following table.

Best overall response and objective response rate*
(evaluated by investigator, RECIST, efficacy analysis set)

Best overall response	Number of patients (%) (n = 76)
Complete response	0 (0)
Partial response	23 (30.3)
Stable disease	38 (50.0)
Progressive disease	7 (9.2)
Not evaluable	8 (10.5)
No. of responders (objective response rate)	23 (30.3)
[95%CI]	[20.2, 41.9]

*: At the timepoint of database snapshot preparation

As regards safety, 9 subjects died during the study period (during crizotinib administration or by 28 days after the last dose). The causes of the deaths were disease progression in 2 subjects and death unexplained, pneumonia, pneumonitis, sepsis, septic shock, pyothorax, and pulmonary embolism/death in 1 subject each. Of which, a causal relationship to crizotinib could not be ruled out for pneumonitis and death unexplained (1 subject each).

In the 60-day update report including patients who were enrolled in the study after database snapshot preparation, death occurred in 26 of 261 subjects during the study period (during crizotinib administration or by 28 days after the last dose). The causes of the deaths in 17 subjects other than 9 subjects described above were disease progression for 13 subjects, chronic obstructive pulmonary disease/arteriosclerosis/disease progression, dyspnoea, pneumonia, and hypoxia for 1 subject each. A causal relationship to crizotinib was ruled out for all of these adverse events.

(3) Foreign clinical studies

Foreign phase I study (5.3.5.2.1, Study A8081001 [April 2006 to ongoing (data cut-off, September 15, 2010; database snapshot, November 1, 2010)])

An open-label, uncontrolled study was conducted at 8 centers in 3 foreign countries in patients with advanced malignant tumor excluding leukemia (target sample size of 40), to evaluate the efficacy, safety, and PK of crizotinib (15 Japanese patients living in Japan were enrolled in this study at centers in foreign countries). Initially, the study had been planned as a dose titration study in patients with advanced malignant tumor excluding leukemia. However, pursuant to the report that production of the fusion protein (EML4-ALK) consisting of ALK and echinoderm microtubule-associated protein-like 4 (EML4) contributes to the growth and viability of cancer cells and to neoplastic transformation of normal cells, the *ALK*-positive, advanced or relapsed NSCLC cohort (*ALK*-positive NSCLC cohort) was added to evaluate the efficacy and safety of

the recommended crizotinib dose determined in the dose escalation cohort among patients with *ALK*-positive NSCLC. Furthermore, in order to evaluate the justification of diagnostic test results by FISH, the *ALK*-negative, advanced or relapsed NSCLC cohort (*ALK*-negative NSCLC cohort), consisting of NSCLC patients who tested negative for *ALK* fusion gene, was added as a patient group to be treated with crizotinib. As a result, patients were enrolled in the study in excess of the target sample size and assigned to the following recommended dose cohorts.

[Recommended dose cohorts]
- *ALK*-positive NSCLC cohort
- *ALK*-negative NSCLC cohort
- Other cohort (malignant tumor that grows in a c-Met gene-dependent manner, malignant tumor that grows in an *ALK* fusion gene-dependent manner other than NSCLC, etc.)

In the dose escalation cohort, crizotinib was to be administered orally QD (50, 100, 200 mg) or BID (200, 250, 300 mg) every day. In the recommended dose cohorts, crizotinib (250 mg) was to be administered orally BID.

Of 212 subjects enrolled in the study by the timepoint of database snapshot preparation (38 subjects in the dose escalation cohort, 119 subjects in the *ALK*-positive NSCLC cohort, 5 subjects in the *ALK*-negative NSCLC cohort, 50 subjects in the other cohort), 204 subjects (excluding 2 subjects in the dose escalation cohort and 6 subjects in the other cohort) who received at least 1 dose of crizotinib on or after Day 1 of Cycle 1, excluding patients who participated only in the single-dose administration period before the start of the Cycle 1 (Day -7) were included in the safety analysis set. Of 119 subjects in the safety analysis set in the *ALK*-positive NSCLC cohort, patients who underwent tumor evaluation at least once ≥6 weeks after the first dose, patients who discontinued the study, patients who had disease progression, and patients who died, at the timepoint of database snapshot preparation, a total of 116 subjects were included in the efficacy analysis set.

As regards efficacy, the best overall response and the objective response rate (evaluated by the investigator), the primary endpoints, were as shown in the following table.

Best overall response and objective response rate*
(evaluated by investigator, RECIST, efficacy analysis set)

Best overall response	Number of patients (%) (N = 116)
Complete response	2 (1.7)
Partial response	69 (59.5)
Stable disease	31 (26.7)
Progressive disease	6 (5.2)
Not evaluable	8 (6.9)
Number of responders (objective response rate)	71 (61.2)
[95%CI]	[51.7, 70.1]

*: At the timepoint of database snapshot preparation

As regards safety, death occurred in a total of 29 subjects during the study period (during crizotinib administration and up to 28 days after the last dose): (a) 3 subjects in the dose escalation cohort, (b) 13 subjects in the *ALK*-positive NSCLC cohort, (c) 2 subjects in the *ALK*-negative NSCLC cohort, and (d) 11 subjects in the other cohort. The deaths were caused by (a) disease progression (2 subjects) and respiratory failure (1 subject) in the dose escalation cohort; (b) disease progression (8 subjects), hypoxia, respiratory failure, pulmonary haemorrhage, pneumonia, and unknown cause (1 subject each) in the *ALK*-positive NSCLC cohort; (c) disease progression and pneumonia (1 subject each) in the *ALK*-negative NSCLC cohort; and (d) disease progression, respiratory failure, pleural effusion, pneumonia, and myocardial infarction (1 subject

each) in the other cohort. Of which, a causal relationship to crizotinib could not be ruled out for the death of unknown cause (1 subject) in the *ALK*-positive NSCLC cohort.

According to the 60-day update report including patients enrolled in the study after database snapshot preparation, a total of 39 deaths occurred during the study period (during crizotinib administration and up to 28 days after the last dose): (a) 4 of 36 subjects in the dose escalation cohort, (b) 19 of 136 subjects in the *ALK*-positive NSCLC cohort, (c) 4 of 25 subjects in the *ALK*-negative NSCLC cohort, and (d) 12 of 56 subjects in the other cohort. The causes of deaths in subjects other than the 29 subjects described above were (a) disease progression (1 subject) in the dose escalation cohort; (b) disease progression (4 subjects), disseminated intravascular coagulation and pneumonia (1 subject each) in the *ALK*-positive NSCLC cohort; (c) disease progression and cardio-respiratory arrest (1 subject each) in the *ALK*-negative NSCLC cohort; and (d) renal failure acute/septic shock (1 subject) in the other cohort. Of which, a causal relationship to crizotinib could not be ruled out for disseminated intravascular coagulation (1 subject) in the *ALK*-positive NSCLC cohort.

[Reference data]
Global phase III study (5.3.5.1.1, Study A8081007 [September 2009 to ongoing (data cut-off, [redacted], 20[redacted])])
An open-label, randomized, parallel group comparative study was conducted in 12 countries and regions including Japan in patients with *ALK*-positive advanced or relapsed NSCLC who had received 1 chemotherapy regimen including a platinum antineoplastic agent (target sample size of 318), in order to evaluate the efficacy and safety of crizotinib.

As of the time of the data cut-off, crizotinib was administered at least once to a total of 36 subjects enrolled in the study, and none of the subjects in the crizotinib group died.

According to the 60-day update report including patients enrolled in the study after data cut-off, death occurred in 5 of 71 subjects during the study period (during crizotinib and up to 28 days after the last dose). The deaths were caused by disease progression, cardiac arrest/respiratory failure, infection/acute respiratory distress syndrome, pneumonia, and interstitial lung disease in 1 subject each. Of which, a causal relationship to crizotinib could not be ruled out for cardiac arrest/respiratory failure and interstitial lung disease (1 subject each).

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

4.(iii).B.(1) Clinical positioning of crizotinib

The applicant explained the clinical positioning of crizotinib as follows:
In transgenic mice forced to express echinoderm microtubule-associated protein-like 4 (EML4)-*ALK* gene in alveolar epithelial cells by the promoter of surfactant protein-C gene, a numerous number of adenocarcinoma arose in both lungs of all animals within several weeks after birth, indicating that ALK fusion protein has a potent oncogenic and tumor growth-promoting activity (e.g., *Proc Natl Acad Sci USA*. 2008;10:19893-7). These study results suggest that, in *ALK*-positive NSCLC, ALK fusion protein is the principal cause of NSCLC and cancer cell growth. Crizotinib is being developed based on the rationale that it suppresses the growth of *ALK*-positive NSCLC by inhibiting tyrosine kinase (TK) of ALK. In fact, (a) crizotinib exhibited an anti-tumor effect in non-clinical studies and (b) In clinical studies, crizotinib showed a clinically significant marked tumor-shrinking effect in patients with *ALK*-positive advanced or relapsed NSCLC, including 2 cases of complete response [see "4.(iii).B.(2).1) Efficacy evaluation"]. Based on these and other results, crizotinib is expected to be effective in patients with *ALK*-positive advanced or relapsed NSCLC.

Currently, there are no approved drugs for patients with *ALK*-positive advanced or relapsed NSCLC that can be selected based on the evidence of molecular diagnosis. The standard treatment

method for these patients is chemotherapy containing platinum antineoplastic agents, as are the cases with patients with other advanced or relapsed NSCLC. However, there are *ALK*-positive patients for whom the pertinent chemotherapy is not indicated. In Study A8081001, crizotinib showed an objective response rate of 78.6% (11 of 14 patients) in patients with ECOG PS of 2, a patient group who are generally known to be poorly responsive to chemotherapy (*J Thorac Oncol*. 2010;5:620-30) [see "4.(iii).B.(2).1) Efficacy evaluation"].

Given the finding that crizotinib may cause the risk of life-threatening events including pneumonitis, interstitial lung disease (ILD), and QT prolonged, for which a causal relationship to crizotinib could not be ruled out although the incidences are low [see "4.(iii).B.(3) Safety"], caution should be provided adequately regarding the risk of crizotinib in the Warnings section, etc., of the package insert. However, crizotinib is considered to be a drug of high medical need for patients with *ALK*-positive, advanced or relapsed NSCLC, with the novel mechanism of action targeting the signal transduction molecule critical for tumor growth.

PMDA has confirmed the descriptions on crizotinib in various diagnosis and treatment guidelines and textbooks in Japan and other countries, as follows:

- U.S. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology Non-Small Cell Lung Cancer (v.2.2012):
  Crizotinib may be very effective in patients with *ALK*-positive NSCLC. If diagnosis of *ALK*-positive advanced or relapsed NSCLC (adenocarcinoma) is made by FDA-approved FISH, crizotinib is the first-choice drug.
- *DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology 9th edition* (Lippincott Williams & Wilkins 2011, PA, USA), which is one of the internationally acclaimed textbook on clinical oncology used by clinical oncologists in and outside Japan:
  ALK fusion protein was found to be a potent oncogene driver causing NSCLC (adenocarcinoma). This was supported by the finding in the phase I study of crizotinib that the drug was dramatically effective in patients with NSCLC with *EML-ALK* fusion gene. Currently, a phase III comparative study is ongoing in patients with *ALK*-positive NSCLC.
- *New Clinical Oncology*, 2nd revised edition (Japanese Society for Medical Oncology ed., Nankodo Co., Ltd., 2009):
  EML4-ALK fusion protein is expressed in approximately 4% of patients with NSCLC (adenocarcinoma), suggesting that *EML4-ALK* fusion gene is the major cause of the carcinogenesis. In light of the finding that imatinib mesilate, an ABL TK inhibitor, is markedly effective against chronic myeloid leukemia with *BCR-ABL* fusion gene, ALK TK inhibitors are expected to be effective against *EML4-ALK*-positive NSCLC.
- Guidance for ALK Gene Testing in Lung Cancer Patients, ver. 1.2 (Biomarker Committee, The Japan Lung Cancer Society, 2011):
  BCR-ABL fusion gene causes chronic myeloid leukemia, while imatinib mesilate, an ABL TK inhibitor, is known to have a strong anti-tumor effect. It is suggested that, in a similar manner, ALK TK inhibitors will be very effective against *EML4-ALK*-positive NSCLC.

PMDA considers as follows:
There is a certain limit in the evaluation of crizotinib based on the clinical study data submitted in the present application, for the following reasons. The clinical positioning of crizotinib relative to existing NSCLC treatment methods that are used for patients with *ALK*-positive NSCLC is a subject for future investigation.

- The submitted evaluation data do not contain a comparative study that was conducted using overall survival (OS), etc., as an efficacy index.
- In the pivotal studies, the foreign phase I study in patients with *ALK*-positive advanced or relapsed NSCLC (Study A8081001), and the global phase II study in patients with *ALK*-positive advanced or relapsed NSCLC who had received ≥1 chemotherapy regimen (Study

A8081005), no hypothesis was formulated for efficacy, let alone setting of the target sample size or the timing of the evaluation to test the hypothesis.

On the other hand, taking account of fact that crizotinib targets TK of ALK fusion protein, the oncogene driver responsible for carcinogenesis and growth of *ALK*-positive NSCLC, and given the pathology of the target disease and the characteristics of the pharmacological action of crizotinib, crizotinib can be positioned as a treatment option for patients diagnosed with *ALK*-positive advanced or relapsed NSCLC regardless of history of chemotherapy although, at the moment, there is only limited information on the tumor-shrinking effect of crizotinib. Currently, there are no approved drugs for patients with *ALK*-positive advanced or relapsed NSCLC that can be selected based on the evidence of molecular diagnosis. The standard treatment method for these patients is chemotherapy containing platinum antineoplastic agents, as are the cases with patients with other advanced or relapsed NSCLC. However, there are *ALK*-positive patients for whom the pertinent chemotherapy is not indicated. In addition, there are no or only limited treatment options for *ALK*-positive NSCLC that have become aggravated after chemotherapy containing platinum antineoplastic agents. By taking this situation into account, PMDA has reached the comprehensive conclusion that crizotinib has a certain clinical significance for *ALK*-positive NSCLC.

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

Based on the following review on Studies A8081001 and A8081005 submitted as the evaluation data, PMDA has concluded that crizotinib is effective to a certain extent for patients with *ALK*-positive advanced or relapsed NSCLC.

4.(iii).B.(2).1) Efficacy evaluation

The applicant explained the efficacy of crizotinib as follows:

Patients with advanced or relapsed NSCLC generally have accompanying clinical symptoms such as dyspnoea and pain. In order to improve these accompanying symptoms, it is important to reduce the tumor volume and to take effect. In fact, in a clinical study in patients with advanced or relapsed NSCLC, it was reported that accompanying clinical symptoms improved in patients who responded to the treatment (*JAMA*. 2003;290:2149-58, *J Thorac Oncol*. 2008;3:30-6).

In Studies A8081001 and A8081005, the best overall response and the objective response rate assessed by the independent organization were as shown in the following table, which supported the best overall response and the objective response rate assessed by the investigator [see "4.(iii).A.(2) Global phase II study (Study A8081005)" and "4.(iii).A.(3) Foreign phase I study (Study A8081001)"].

Best overall response and objective response rate*
(assessed by independent organization, RECIST, efficacy analysis set†)

Best overall response	Study A8081001	Study A8081005
	Number of patients (%) (N = 105)	Number of patients (%) (N = 46)
Complete response	0 (0)	0 (0)
Partial response	55 (52.4)	13 (28.3)
Stable disease	31 (29.5)	19 (41.3)
Progressive disease	10 (9.5)	6 (13.0)
Not evaluable	9 (8.6)	8 (17.3)
Responders (objective response rate) [95% CI]	55 (52.4) [42.4, 62.2]	13 (28.3) [16.0, 43.5]

*: At the timepoint of database snapshot preparation, †: The population defined based on the assessment of the independent organization instead of the investigator

In Study A8081001, patients with *ALK*-positive advanced or relapsed NSCLC were enrolled in the study regardless of the previous treatment history. Despite the fact that 62.2% (73 of 116 patients) of these patients had received ≥2 chemotherapy regimens (the table below), crizotinib reduced the tumor size in patients with *ALK*-positive NSCLC, with the objective response rate [95% CI] of 61.2% [51.7%, 70.1%] and the median response duration of 48 weeks [35.9 weeks, unconfirmed]. Furthermore, at the timepoint of database snapshot preparation, PFS (median) [95% CI], 6-month survival rate [95% CI], and 1-year survival rate [95% CI] in Study A8081001 were 10 months [8.2 months, 14.7 months], 90.0% [82.7%, 94.4%], and 80.5% [70.9%, 87.2%], respectively.

Best overall response and objective response rate*
(Study A8081001, assessed by investigator, RECIST, efficacy analysis set)

		No. of responders	Objective response rate [95% CI] (%)
Efficacy analysis population (N = 116)		71	61.2 [51.7, 70.1]
ECOG PS	0 (39)	21	53.8 [37.2, 69.9]
	1 (62)	39	62.9 [49.7, 74.8]
	2 (14)	11	78.6 [49.2, 95.3]
	3 (1†)	0	0
No. of previous treatment regimens	0 (15)	12	80.0 [51.9, 95.7]
	1 (28)	16	57.1 [37.2, 75.5]
	2 (21)	13	61.9 [38.4, 81.9]
	3 (22)	13	59.1 [36.4, 79.3]
	4 (16)	10	62.5 [35.4, 84.8]
	5 (6)	3	50.0 [11.8, 88.2]
	6 (4)	1	25.0 [0.6, 80.6]
	7 (4)	3	75.0 [19.4, 99.4]

*: At the timepoint of database snapshot preparation, †: ECOG PS1 at the screening but changed to ECOG PS3 at baseline (Day 1 of administration)

These results showed that in patients with *ALK*-positive advanced or relapsed NSCLC, crizotinib achieved an objective response rate far surpassing that achieved by the existing standard treatment, regardless of the number of previous treatment regimens, suggesting the clinical usefulness of crizotinib.

As regards the results of the objective response rate in Study A8081005 at the timepoint of database snapshot preparation, (i) the median treatment duration was 9.0 weeks (range, 0.1-36.1 weeks) in contrast to 31.9 weeks (range, 0.7-101.7 weeks) in Study A8081001, and (ii) 119 of 136 subjects (87.5%) were still being treated with crizotinib in Study A8081005. In the 60-day

update report of Study A8081005, 133 of 136 subjects were included in the efficacy analysis set. The median treatment duration was 22.3 weeks (range, 0.9-53.1 weeks), and the best overall response and the objective response rate were as shown below.

Best overall response and objective response rate* (Study A8081005, RECIST, efficacy analysis set)

Best overall response	Number of patients (%)	
	Assessed by investigator (N = 133)	Assessed by independent organization (N = 105)
Complete response	1 (< 1.0)	1 (< 1.0)
Partial response	67 (50.4)	43 (41.0)
Stable disease	45 (33.8)	40 (38.1)
Progressive disease	10 (7.5)	11 (10.5)
Not evaluable	10 (7.5)	10 (9.5)
Responders (objective response rate) [95% CI]	68 (51.1) [42.3, 59.9]	44 (41.9) [32.3, 51.9]

*: 60-day update report

PMDA considers as follows:
The relationship between the response to crizotinib and OS in patients with *ALK*-positive advanced or relapsed NSCLC is unclear, making it practically impossible to evaluate the life-prolonging effect of crizotinib in these patients at the moment. The clinical study data submitted in the present application were obtained from exploratory studies with the primary objective of estimating the objective response rate and not from studies that had pre-defined the target sample size, the timing of evaluation, etc., to evaluate the efficacy. As a result, the results obtained from these studies may overestimate the efficacy.

However, crizotinib targets the oncogene driver responsible for tumor growth. By taking into consideration (i) the results of nonclinical studies [see "3.(i).B.(1) Mechanism of action of crizotinib and its efficacy on *ALK*-positive NSCLC"], (ii) the finding that results of Studies A8081001 and A8081005 suggested the effectiveness of crizotinib in patients with *ALK*-positive advanced or relapsed NSCLC, and (iii) the observation that crizotinib reduced the tumor size in patients with *ALK*-positive NSCLC regardless of the number of previous treatment regimens, PMDA has reached the comprehensive conclusion that crizotinib is expected to be effective to a certain extent for patients with *ALK*-positive advanced or relapsed NSCLC.

Information should be provided in the package insert, etc., that, in the application, efficacy of crizotinib was evaluated mainly based on the objective response rate and no information is available on the life-prolonging effect, and that whether or not to administer crizotinib should be carefully determined upon thorough consideration of other treatment options [see "4.(iii).B.(4) Indications"].

4.(iii).B.(2).2) Efficacy in Japanese patients
In Study A8081001, the objective response rate in Japanese patients was as shown in the following table.

Best overall response and objective response rate*
(Study A8081001, assessed by investigator, RECIST, efficacy analysis set)

Best overall response	Number of patients (%)	
	Overall population (N = 116)	Japanese population (N = 15)
Complete response	2 (1.7)	0 (0)
Partial response	69 (59.5)	14 (93.3)
Stable disease	31 (26.7)	0 (0)
Progressive disease	6 (5.2)	0 (0)
Not evaluable	8 (6.9)	1 (6.7)
Responders (objective response rate) [95% CI]	71 (61.2) [51.7, 70.1]	14 (93.3) [68.1, 99.8]

*: At the timepoint of database snapshot preparation

PMDA considers as follows:
Although the objective response rate in Japanese patients may be higher than that in the overall population of Study A8081001, since only a limited number of Japanese patients were evaluated for the efficacy of crizotinib, it is unknown at the moment whether or not the objective response rate is higher in Japanese patients than in foreign patients. However, based on the results of the nonclinical studies and on Study A8081001 which suggested the favorable response of Japanese patients to the treatment as was the case with the overall population [see "4.(iii).B.(2).1) Efficacy evaluation"], PMDA has concluded that crizotinib has a certain level of efficacy for Japanese patients with *ALK*-positive advanced or relapsed NSCLC.

4.(iii).B.(3) Safety [see "4.(iv) Adverse events observed in clinical studies" for adverse events]

Based on the following review, PMDA has concluded that caution should be exercised against the following adverse events in administering crizotinib: ILD, visual disturbance (e.g., diplopia, photopsia, vision blurred, visual field defect, visual impairment, vitreous floaters), hepatic impairment, blood disorder, neuropathy, QT prolonged, bradycardia, thromboembolism, photosensitivity, and complicated renal cyst.

In using crizotinib, attention should be paid to the occurrence of these adverse events. PMDA considers that crizotinib is tolerable provided that (a) appropriate measures such as monitoring and control of adverse events and dose adjustment such as dose interruption, dose reduction, and discontinuation are taken by physicians with adequate knowledge and experience in cancer chemotherapy and (b) the safety of patients is ensured by the most careful attention to serious adverse events such as ILD and by their control and preventive measures. Because of the extremely limited safety information currently available in Japan, information should be continuously collected after the market launch and new safety information should be provided promptly and appropriately to the medical practice.

4.(iii).B.(3).1) Safety profile of crizotinib and difference between Japanese and foreign patients

The applicant explained the safety profile of crizotinib and its difference between Japanese and foreign patients, as follows:
In the *ALK*-positive NSCLC cohort of Study A8081001 and in Study A8081005, adverse events reported by ≥10% of either Japanese or foreign patients were as shown in the following table.

Adverse events reported by ≥10% of either Japanese or foreign patients in *ALK*-positive NSCLC cohort*† (Study A8081001)

MedDRA PT	Number of subjects (%)					
	ALK-positive NSCLC cohort				*ALK*-negative NSCLC cohort and other cohort (N = 49)	
	Foregin subjects (N = 104)		Japanese subjects (N = 15)			
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	102 (98.1)	39 (37.5)	15 (100)	7 (46.7)	47 (95.9)	26 (53.1)
Nausea	51 (49.0)	1 (1.0)	8 (53.3)	0	28 (57.1)	2 (4.1)
Visual impairment	47 (45.2)	0	10 (66.7)	0	15 (30.6)	0
Diarrhoea	47 (45.2)	1 (1.0)	10 (66.7)	0	16 (32.7)	0
Vomiting	42 (40.4)	1 (1.0)	6 (40.0)	0	25 (51.0)	1 (2.0)
Constipation	37 (35.6)	1 (1.0)	8 (53.3)	0	17 (34.7)	0
Oedema peripheral	32 (30.8)	1 (1.0)	6 (40.0)	0	7 (14.3)	0
Dizziness	27 (26.0)	0	6 (40.0)	0	10 (20.4)	0
Fatigue	27 (26.0)	3 (2.9)	3 (20.0)	0	17 (34.7)	0
Decreased appetite	22 (21.2)	1 (1.0)	6 (40.0)	0	0	0
ALT increased	21 (20.2)	8 (7.7)	0	0	0	0
Dyspnoea	19 (18.3)	5 (4.8)	0	0	9 (18.4)	4 (8.2)
Rash	18 (17.3)	0	3 (20.0)	0	2 (4.1)	0
AST increased	17 (16.3)	5 (4.8)	0	0	0	0
Pyrexia	14 (13.5)	0	5 (33.3)	0	4 (8.2)	0
Cough	14 (13.5)	1 (1.0)	1 (6.7)	0	2 (4.1)	0
Dyspepsia	13 (12.5)	0	1 (6.7)	0	3 (6.1)	0
Upper respiratory tract infection	13 (12.5)	0	0	0	0	0
Arthralgia	13 (12.5)	2 (1.9)	0	0	1 (2.0)	1 (2.0)
Headache	12 (11.5)	1 (1.0)	2 (13.3)	0	1 (2.0)	0
Back pain	12 (11.5)	0	1 (6.7)	0	2 (4.1)	0
Insomnia	12 (11.5)	0	0	0	2 (4.1)	0
Nasopharyngitis	9 (8.7)	0	5 (33.0)	0	1 (2.0)	0
Paraesthesia	9 (8.7)	0	2 (13.3)	0	1 (2.0)	0
Abdominal pain upper	8 (7.7)	0	4 (26.7)	0	4 (8.2)	0
Hypoaesthesia	5 (4.8)	0	2 (13.3)	0	2 (4.1)	0
Neutropenia	3 (2.9)	1 (1.0)	3 (20.0)	3 (20.0)	1 (2.0)	1 (2.0)
Haemoptysis	3 (2.9)	0	3 (20.0)	0	3 (6.1)	1 (2.0)
Asthenia	3 (2.9)	0	2 (13.3)	0	4 (8.2)	1 (2.0)
Oropharyngeal pain	3 (2.9)	0	2 (13.3)	0	2 (4.1)	0
Toothache	0	0	2 (13.3)	0	0	0

*: At the timepoint of database snapshot preparation, †: NCI-CTCAE ver. 3.0

Adverse events reported by ≥10% of either Japanese or foreign patients *† (Study A8081005)

MedDRA PT	Number of subjects (%)			
	Foreign subjects (N = 130)		Japanese subjects (N = 6)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	118 (90.8)	43 (33.1)	6 (100)	1 (16.7)
Nausea	66 (50.8)	1 (0.8)	3 (50.0)	0
Vomiting	56 (43.1)	2 (1.5)	3 (50.0)	0
Visual impairment	43 (33.1)	0	5 (83.3)	0
Diarrhoea	43 (33.1)	0	5 (83.3)	0
Constipation	37 (28.5)	1 (0.8)	0	0
Fatigue	36 (27.7)	2 (1.5)	0	0
Oedema peripheral	33 (25.4)	1 (0.8)	0	0
Decreased appetite	28 (21.5)	1 (0.8)	1 (16.7)	0
Dyspnoea	22 (16.9)	7 (5.4)	0	0
Dizziness	18 (13.8)	0	0	0
Cough	18 (13.8)	2 (1.5)	0	0
Dysgeusia	16 (12.3)	0	3 (50.0)	0
ALT increased	13 (10.0)	6 (4.6)	1 (16.7)	0
Headache	13 (10.0)	0	0	0
AST increased	9 (6.9)	1 (0.8)	1 (16.7)	0

MedDRA PT	Number of subjects (%)			
	Foreign subjects (N = 130)		Japanese subjects (N = 6)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Oedema	6 (4.6)	0	1 (16.7)	0
Blood ALP increased	4 (3.1)	0	1 (16.7)	0
Sinus bradycardia	3 (2.3)	0	1 (16.7)	0
Pruritus	3 (2.3)	0	1 (16.7)	0
QT prolonged	1 (0.8)	1 (0.8)	2 (33.3)	0
Palpitations	1 (0.8)	0	1 (16.7)	0
Thrombosis	1 (0.8)	0	1 (16.7)	1 (16.7)
Hepatic function abnormal	0	0	2 (33.3)	0
Eye pain	0	0	1 (16.7)	0
Cheilitis	0	0	1 (16.7)	0
Gastric ulcer	0	0	1 (16.7)	0
Platelet count decreased	0	0	1 (16.7)	1 (16.7)
Peripheral motor neuropathy	0	0	1 (16.7)	0
Menstruation irregular	0	0	1 (16.7)	0
Photosensitivity	0	0	1 (16.7)	0

*: At the time of database snapshot preparation, †: NCI-CTCAE ver. 4.0

Adverse events reported by ≥30% of both Japanese and foreign patients were nausea, visual impairment, diarrhoea, vomiting, constipation, and oedema peripheral in the *ALK*-positive NSCLC cohort of Study A8081001; and nausea, vomiting, visual impairment, and diarrhoea in Study A8081005. Thus, the main adverse events were common to both Japanese and foreign patients.

Adverse events reported at a ≥10% higher incidence in Japanese patients than in foreign patients were visual impairment, diarrhoea, constipation, dizziness, decreased appetite, pyrexia, nasopharyngitis, abdominal pain upper, neutropenia, haemoptysis, asthenia, oropharyngeal pain, and toothache in the *ALK*-positive NSCLC cohort of Study A8081001; and visual impairment, diarrhoea, dysgeusia, oedema, blood ALP increased, sinus bradycardia, pruritus, QT prolonged, palpitations, thrombosis, hepatic function abnormal, eye pain, cheilitis, gastric ulcer, platelet count decreased, peripheral motor neuropathy, menstruation irregular, and photosensitivity in Study A8081005.

As regards adverse events of Grade ≥3, haematotoxicity (e.g., neutropenia [3 of 15 subjects (20.0%) in the *ALK*-positive NSCLC cohort of Study A8081001] and thrombocytopenia [1 of 6 subjects (16.7%) in Study A8081005]) in Japanese patients and non-haematological toxicity (e.g., ALT increased, AST increased, fatigue) in foreign patients tended to occur more frequently.

However, given the limited number of Japanese patients studied, the safety profile is unlikely to significantly differ between Japanese and foreign patients.

PMDA considers as follows:
Because of the extremely small number of Japanese patients subjected to the study of safety after crizotinib administration, there is a limitation to the comparison of the safety profile of crizotinib and the incidence of adverse events between Japanese and foreign patients. Notwithstanding such a limitation, it is of note that the following adverse events occurred in ≥2 Japanese patients and their incidence was ≥ 10% higher in Japanese patients than in foreign patients: visual impairment, diarrhoea, constipation, dizziness, decreased appetite, pyrexia, nasopharyngitis, abdominal pain upper, neutrophil decreased, haemoptysis, asthenia, oropharyngeal pain, toothache, dysgeusia, QT prolonged, and hepatic function abnormal. Also, the incidence of ILD tended to be higher in Japanese patients than in foreign patients [see "4.(iii).B.(3).2).a Incidences and its characteristic features"]. Thus, PMDA has concluded that although it is necessary to appropriately provide information to the medical practice regarding these differences, crizotinib is tolerable in Japanese

patients provided that appropriate measures such as dose adjustment including dose reduction, dose interruption, and discontinuation are taken by physicians with adequate knowledge and experience in cancer chemotherapy and that post-marketing safety measures are taken in an appropriate manner [see "4.(iii).B.(3).2).c Post-marketing safety measures" and "4.(iii).B.(7) Actions to minimize risk after the market launch"].

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

a Incidences and its characteristic features

The applicant explained the incidence of ILD after crizotinib administration and its image and clinical characteristics as follows, based on the results of clinical studies so far available:

In the combined data of the safety analysis set in the *ALK*-positive NSCLC cohort of Study A8081001 and in Study A8081005 (at the timepoint of database snapshot preparation) (combined *ALK*-positive NSCLC data), ILD occurred in 5 of 255 subjects (2.0%) and the timing for each events was shown in the table below. Pfizer Inc. convened an independent review committee (IRC) consisting of pulmonologists, clinical oncologists, and radiologists, and evaluated the incidence of ILD in 46 patients who experienced Grade ≥3 adverse events with a potentially elevated risk for ILD. As a result, a causal relationship to crizotinib could not be ruled out for the 3 cases of ILD, which was consistent with the conclusion reached by investigators that the causal relationship to crizotinib could not be ruled out for 3 of 4 cases. In each of Studies A8081001 and A8081005, 1 patient was reported who was diagnosed with radiation pneumonitis by the IRC although the effect of crizotinib was unknown (The patient in Study A8081001 completed radiation therapy 1 month before the start of crizotinib administration and developed dyspnoea at 28 days after the start of administration. The patient in Study A8081005 completed radiation therapy 19 days before the start of crizotinib administration and developed dyspnoea at 29 days after the start of administration).

Patients who had ILD* (combined *ALK*-positive NSCLC data)

Study	Sex	Age	Race	Event	Day of occurrence	Duration (days)	Grade	Causal relationship to crizotinib		Treated by crizotinib	Intervening treatment	Outcome
								Investigator's assessment	IRC's assessment			
A8081001	Male	4[redacted]	Caucasian	Pneumonitis	12	>18	4	Yes	Yes	Discontinued	Yes (corticoid used)	Not recovered
	Male	4[redacted]	Caucasian	Pneumonitis	53	11	3	Yes	No	Not treated	Yes (corticoid used)	Recovered
A8081005	Female	8[redacted]	Caucasian	Pneumonitis	6	17	3	Yes	Yes	Discontinued	Yes (corticoid used)	Recovered
	Male	5[redacted]	Caucasian	Pneumonitis	20	1	5	Yes	Yes	Not treated	Yes (corticoid not used)	Death
	Male	7[redacted]	Caucasian	Pneumonitis	41	60	2	No	NA	Not treated	Yes (corticoid used)	Recovered

NA: Not available, *: At the timepoint of database snapshot preparation

During the period from the date of database snapshot preparation until December 6, 2011, ILD in 8 additional patients was reported as serious adverse events in Studies A8081005 and A8081007, and 4 patients of them were Japanese (the table below), suggesting the possible difference in the incidence between Japanese and foreign patients. However, no conclusion can be drawn regarding the difference at the moment because of the limited number of patients studied. Autopsy of a Japanese patient (6[redacted] years old, female) showed a histological picture of diffuse alveolar damage, a finding reported to be characteristic to ILD that is poorly responsive to steroids and highly lethal (*Br J Cancer*. 2004;91 Suppl 2:S18-23).

Patients who had ILD (from the date of database snapshot preparation up to December 6, 2011)

Study	Sex	Age	Country	Event	Day of occurrence	Duration (days)	Grade	Causal relationship to crizotinib		Treated by crizotinib	Intervening treatment	Outcome
								Investigator's assessment	IRC's assessment			
A8081005	Female	6[redacted]	U.S.	Pneumonitis	17	73	NA	Yes	NA	Discontinued	Yes (corticosteroid used)	Recovered
	Female	6[redacted]	Taiwan	Pneumonitis	43	16	NA	Yes	NA	Discontinued	Yes (corticosteroid used)	Recovered
	Female	4[redacted]	Japan	Interstitial lung disease	44	43	NA	Yes	NA	Discontinued	Unknown	Recovered
	Male	4[redacted]	U.S.	Pneumonitis	97	7	NA	Yes	NA	Not treated	Unknown	Recovered
	Male	3[redacted]	China	Interstitial lung disease	313	6	NA	No	NA	Discontinued	Unknown	Death
A8081007	Female	3[redacted]	Japan	Interstitial lung disease	66	18	NA	Yes	NA	Discontinued	Yes (corticosteroid not used)	Recovered
	Female	6[redacted]	Japan	Interstitial lung disease	10	12	NA	Yes	NA	Discontinued	Yes (corticosteroid used)	Death
	Male	3[redacted]	Japan	Pneumonitis	9	13	NA	Yes	NA	Discontinued	Yes (corticosteroid used)	Death

NA: Not available

Although no consistent tendency could be found in the image or clinical characteristics of ILD caused by crizotinib, ILD tended to develop within a relatively early period after the start of administration (within 1 month in 6 of 13 patients, within 2 weeks in 4 patients of them). As regards the outcome, 8 of 13 patients recovered after treatment with corticosteroid, etc., whereas 4 of 13 patients died. No information regarding the treatment for ILD is available for 3 of 13 patients.

In Studies A8081001 and A8081005, radiation pneumonitis was reported in 1 patient each. In these 2 patients, administration of crizotinib was continued after the onset of radiation pneumonitis and the IRC concluded that the effect of crizotinib on the disease was unknown. Therefore, the applicant considers that, at the moment, it is not necessary to exercise caution against progression or relapse of radiation pneumonitis in patients with past or current radiation pneumonitis.

PMDA, based on the findings that fatal ILD occurred after crizotinib administration in patients including Japanese patients and that the incidence of ILD may be higher in Japanese patients than in foreign patients, asked the applicant to have chest CT images evaluated by the IRC for all Japanese patients who received crizotinib in clinical studies.

The applicant responded as follows:
The IRC evaluated the chest CT images of all Japanese patients with evaluable images at the timepoint of February 1, 2011 (15 patients in Study A8081001, 6 patients in Study A8081005, 37 patients in Study A8081007). As a result, inflammatory findings in the lung were observed in 9 of 15 patients in Study A8081001, in 5 of 6 patients in Study A8081005, and in 17 of 37 patients in Study A8081007. Among them, 2 patients in Study A8081001 had no inflammatory findings before the start of crizotinib administration but, after administration, developed pulmonary inflammation for which a causal relationship to crizotinib could not be ruled out (the table below).

Patients who had no inflammatory findings before the start of crizotinib administration but developed pulmonary inflammation after crizotinib administration (as of February 1, 2011, IRC assessment, Japanese patients)

Study	Sex	Age	History of radiation therapy	Day of occurrence	Duration (days)	Day of disappearance	Respiratory adverse event
A8081001	Female	4[redacted]	Whole-brain irradiation, chest	303	539	NA	Nasopharyngitis (Grade 1) Dyspnoea exertional (Grade 1, persisting from 187 days before crizotinib administration)
A8081001	Female	3[redacted]	12th thoracic vertebra- 3rd lumbar vertebra	51	78	134	Nasopharyngitis (Grade 1)

NA: Not available

PMDA considers as follows:
Death occurred in 2 of 4 Japanese patients who developed ILD after the timepoint of database snapshot preparation, which suggests that ILD is one of the adverse events requiring special attention during the treatment with crizotinib. Therefore, it is critical to provide caution to healthcare professionals and medical institutions in charge of prescribing crizotinib and to provide caution to patients (education for patients) to ensure safety in using crizotinib after the market launch [see "4.(iii).B.(3).2).c Post-marketing safety measures" and "4.(iii).B.(7) Actions to minimize risk after the market launch"].

A histological picture of diffuse alveolar damage was observed in Japanese patients after crizotinib. This information should be provided to the medical practice using appropriate materials, etc. At the same time, information on the clinical characteristics of ILD, such as information on the time of onset after crizotinib and on the response to ILD therapy which is scarcely available at the moment, should be continuously collected after the market launch, and new information, whenever it becomes available, should be appropriately provided [see "4.(iii).B.(6) Post-marketing investigations"].

In addition, since patients undergoing crizotinib treatment are supposed to have received radiation therapy in the past, information that radiation pneumonitis occurred in some patients during crizotinib treatment should be provided in an appropriate manner, and at the same time, information on the relationship between crizotinib administration and occurrence of radiation pneumonitis, when new information becomes available after the market launch, should be provided in an appropriate manner [see "4.(iii).B.(6) Post-marketing investigations"].

b. Mechanism of occurrence and factors predicting the occurrence
The applicant explained the mechanism of the occurrence of ILD, factors predicting the occurrence, etc., as follows:
In the 3-month repeated dose toxicity study in rats, foamy macrophages due probably to phospholipidosis were observed in multiple organs including the lung (bile duct, intestine, pituitary gland, prostate gland, lung, mesenteric lymph node) [see "3.(iii).A.(2).5) Three-month oral toxicity study in rats"], but they were reversible changes and were considered not to be adverse findings. Also, crizotinib did not have any effect on the respiratory system in safety pharmacology studies or other toxicological studies.

In the clinical studies, among 5 cases of ILD in the combined *ALK*-positive NSCLC data, chest CT showed pulmonary nodule, ground-glass opacity, and thickening of alveolar septa in 1 patient before the diagnosis of ILD. In another patient, findings suggestive of past lung disease were not observed. In the remaining 3 patients of the combined *ALK*-positive NSCLC data and in 8 patients reported after a database snapshot preparation, no chest CT data before diagnosis of ILD were

available, precluding the determination of the presence or absence of lung disease

Thus, at the moment, neither the mechanism of crizotinib-induced ILD nor factors predicting ILD are known.

PMDA considers as follows:
Although the relationship between the history of lung disease and the risk of ILD is unclear, in view of the following observations, whether or not to administer crizotinib to patients with a history of ILD should be carefully determined with due consideration given to the risks and benefits of each patient. Also, it is important to continuously collect and evaluate information on factors predicting the occurrence of ILD after the market launch in order to ensure the proper use of crizotinib.

- The mechanism of crizotinib-induced ILD is unknown.
- History of ILD is generally considered to be a factor predicting ILD (*J Clin Oncol*. 2006;24:2549-56, *Am J Respir Crit Care Med*. 2008;177:1348-57).
- Since patients with history of ILD were excluded from Studies A8081001 and A8081005, there is no use experience of crizotinib in patients with a history of ILD.

c Post-marketing safety measures
Based on the review in "4.(iii).B.(3).2).(a) Incidences and its characteristic features" section, PMDA asked the applicant to explain the plan for post-marketing safety measures against crizotinib-induced ILD.

The applicant responded as follows:
As a safety measure against ILD after the market launch, the following cautions will be provided using the package insert and other materials. Physicians who use crizotinib will be requested (i) to explain in plain language to patients who use crizotinib and their family members "the initial symptoms of ILD," "precautions while taking crizotinib," and "the fact that some patients died while taking crizotinib," and administer crizotinib after receiving the informed consent, and (ii) to determine the appropriateness of using crizotinib, including the history of ILD, when registering the patients in the all-case surveillance.

[To healthcare professionals and medical institutions]
- ILD may occur after administration of crizotinib.
- During crizotinib administration, patients should be carefully asked about the initial symptoms of ILD (e.g., exertional breathlessness, dyspnoea, cough, pyrexia) and carefully monitored for objective findings such as chest auscultation. If a subjective or objective finding was observed, patients should be closely examined such as by periodical chest CT examination (once every month for the first 2 months after the start of crizotinib, followed by examination on as-needed basis) and treated without delay.
- If ILD has occurred during crizotinib administration and its causal relationship to crizotinib cannot be ruled out, the administration of crizotinib should be discontinued and appropriate measures should be taken.
- Given that patients with a history of ILD tended to have a high risk for ILD when treated with other antineoplastic agents, whether or not to administer crizotinib to patients with a history of ILD should be carefully determined and, in administering crizotinib, extreme caution should be exercised such as by carefully monitoring the patients during crizotinib administration.

[To patients]
- If any of subjective symptoms suggestive of ILD (e.g., exertional breathlessness, dyspnoea, cough, pyrexia) were observed, patients should promptly consult a physician at a medical

institution.
- The patients should always carry an emergency contact number so that patients can promptly consult a physician at a medical institution.

PMDA accepted the applicant's explanation.

4.(iii).B.(3).3) Visual disturbance

The applicant explained crizotinib-induced visual disturbance (collective term for the following MedDRA preferred terms: diplopia, photopsia, vision blurred, visual field defect, visual impairment, vitreous floaters) as follows:

The details of the incidences of visual disturbance in the *ALK*-positive NSCLC cohort of Study A8081001 and in Study A8081005 were as shown in the following table

Visual disturbance* (Studies A8081001 and A8081005)

MedDRA PT	Number of patients (%)			
	Study A8081001† (N = 119)		Study A8081005 (N = 136)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Diplopia	2 (1.7)	0	3 (2.2)	0
Photopsia	10 (8.4)	0	7 (5.1)	0
Vision blurred	4 (3.4)	0	3 (2.2)	0
Visual field defect	3 (2.5)	0	2 (1.5)	0
Visual impairment	57 (47.9)	0	48 (35.3)	0
Vitreous floaters	2 (1.7)	0	3 (2.2)	0

*: At the time of database snapshot preparation, †: *ALK*-positive NSCLC cohort

The applicant considers that crizotinib-induced visual disturbance is controllable and crizotinib administration may be continued after the occurrence of the event, for the following reasons: (i) most of the cases of visual disturbance observed were mild in severity, (ii) visual disturbance did not necessitate the discontinuation of crizotinib administration in any of the affected patients, and (iii) dose interruption was required in 2 patients and continued administration did not aggravate visual disturbance. However, the applicant will provide information and caution to medical institutions, patients, and their family members by means of the package insert, etc., regarding the following: (i) visual disturbance may occur, (ii) ophthalmological examination should be considered as necessary, and (iii) caution should be exercised in driving and operating machinery.

PMDA asked the applicant to explain the results of ophthalmological examination performed on patients who developed visual disturbance in clinical studies.

The applicant responded as follows:

Among patients who experienced visual disturbance in Study A8081005, only 29 patients underwent biomicroscopy, fundoscopy, and visual acuity test. Results showed no clinically significant changes compared with the baseline. After visual disturbance was observed in Study A8081001, ophthalmological examination was introduced as a mandatory screening test, and data are currently being collected.

Although results of nonclinical studies suggest that crizotinib affects the speed of dark adaptation, the mechanism of visual disturbance is unknown.

PMDA considers as follows:

Although crizotinib-induced visual disturbance is tolerable with severity Grade of only 1 or 2, caution is required for the following reasons: (i) the incidence is high, (ii) neither the mechanism of the occurrence nor the risk factors are known [see "3.(iii).B.(2) Visual disturbance"], and (iii) reversibility of the disorder after multiple administration of crizotinib and long-term safety are

unknown. Therefore, it is necessary to appropriately exercise caution about visual disturbance induced by crizotinib and, in the post-marketing surveillance, to collect information not only on the incidence of visual disturbance but also on the clinical characteristics (e.g., time to onset, symptom duration, signs of aggravation) [see "4.(iii).B.(6) Post-marketing investigations"].

4.(iii).B.(3).4) Hepatic impairment

The applicant explained crizotinib-induced hepatic impairment as follows:

In the *ALK*-positive NSCLC cohort of Study A8081001 and in Study A8081005, the incidences of adverse events related to hepatic impairment were as shown in the following table.

Hepatic impairment*(Studies A8081001 and A8081005)

MedDRA PT	Number of subjects (%)							
	Study A8081001†				Study A8081005			
	All subjects (N = 119)		Japanese (N = 15)		All subjects (N = 136)		Japanese (N = 6)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
ALT increased	21 (17.6)	8 (6.7)	0	0	14 (10.3)	6 (4.4)	1 (16.7)	0
AST increased	17 (14.3)	5 (4.2)	0	0	10 (7.4)	1 (0.7)	1 (16.7)	0
ALP increased	9 (7.6)	1 (0.8)	0	0	5 (3.7)	0	1 (16.7)	0
γ-GTP increased	0	0	0	0	1 (0.7)	0	0	0
Hepatic enzyme increased	0	0	0	0	1 (0.7)	1 (0.7)	0	0
Hepatic function abnormal	0	0	0	0	2 (1.5)	0	2 (33.3)	0
Liver function test abnormal	1 (0.8)	1 (0.8)	0	0	1 (0.7)	1 (0.7)	0	0
Transaminases increased	1 (0.8)	0	0	0	0	0	0	0

*: At the timepoint of database snapshot preparation, †: ALK-positive NSCLC cohort

During the study period, aggravation of ALT increased to Grade ≥3 from baseline (Grade ≤2) occurred in 6 of 113 subjects (5.3%) in Study A8081001 and in 5 of 121 subjects (4.1%) in Study A8081005, and aggravation of AST increased in 3 of 113 subjects (2.7%) in Study A8081001 and in 2 of 121 subjects (1.7%) in Study A8081005. Hepatic failure or hepatic failure-induced death did not occur at the timepoint of database snapshot preparation, whereas, in Study A8081005, hepatic failure developed in 2 patients by December 23, 2011 (1 subject on Day 24, 1 subject on Day 36) and died. Also, ALT increased (>3-fold the upper limit of normal) and total bilirubin increased (>2-fold the upper limit of normal) without ALP increased (hepatic impairment possibly fulfilling Hy's Law, the index for drug-induced liver disorder) simultaneously occurred in 1 patient in Study A8081001 at the timepoint of database snapshot preparation and in 2 patients in Study A8081005 by December 23, 2011.

Taking account of the occurrence of fatal hepatic failure, etc., PMDA is currently asking the applicant's view on the cautions to be exercised against crizotinib-induced hepatic impairment after the market launch.

In light of the findings that administration of crizotinib caused hepatic impairment and that some patients died because of hepatic failure, PMDA considers it necessary to perform blood tests, etc., periodically and to pay attention to hepatic impairment.

4.(iii).B.(3).5) White blood cell decreased

The applicant explained crizotinib-induced white blood cell decreased as follows:

The incidence of white blood cell deceased in the *ALK*-positive NSCLC cohort of Study A8081001 and in Study A8081005 was as shown in the following table.

White blood cell decreased* (Studies A8081001 and A8081005)

Hematology parameter	Number of patients (%)					
	Highest Grade after administration†					
	Study A8081001§			Study A8081005		
	No. of patients evaluated	Grade 3	Grade 4	No. of patients evaluated	Grade 3	Grade 4
Neutrophil count (absolute number)	114	3 (2.6)	1 (0.9)	120	3 (2.5)	2 (1.7)
White blood cell count	114	2 (1.8)	0	120	3 (2.5)	0
Lymphocytes (absolute number)	112	11 (9.8)	2 (1.8)	120	9 (7.5)	2 (1.7)

*: At the timepoint of database snapshot preparation, †: Aggravation to CTCAE Grade ≥3 from Grade ≤2 (by the highest CTCAE Grade after administration), §: *ALK*-positive NSCLC cohort

None of the patients who experienced white blood cell decreased discontinued crizotinib medication. Dose reduction was required in 1 patient (neutropenia) in Study A8081005, and dose interruption was necessary in 4 patients (neutropenia) in Study A8081001 and in 4 patients (neutropenia or leukopenia) in Study A8081005.

In neither study, neutropenia was reported as a serious adverse event or the cause of death. No febrile neutropenia occurred, while fungal infection related to Grade 4 neutropenia was observed in 1 patient.

White blood cell decreased, neutropenia in particular, occurred after crizotinib administration. If infection is observed, blood tests (blood cell counting, differential white blood cell counting), etc., should be performed and, in the event of Grade 3/4 haematotoxicity, appropriate measures such as dose interruption, dose reduction, or discontinuation should be taken.

Since crizotinib causes white blood cell decreased, PMDA considers it necessary to perform periodical blood test, etc., during crizotinib administration and to pay attention to leukopenia.

4.(iii).B.(3).6) Neuropathy

The applicant explained crizotinib-induced neuropathy (collective term for the following MedDRA preferred terms: burning sensation, hypoaesthesia, hypoaesthesia facial, neuralgia, neuropathy peripheral, paraesthesia, peripheral motor neuropathy, peripheral sensory neuropathy, sensory disturbance) as follows:

The incidences of neuropathy in the *ALK*-positive NSCLC cohort of Study A8081001 and in Study A8081005 were as shown in the following table. Neuropathy developed and did not resolve in 15 of 24 patients (62.5%) in Study A8081001 and in 18 of 24 patients (75.0%) in Study A8081005.

Neuropathy*(Studies A8081001 and A8081005)

MedDRA PT	Number of patients (%)			
	Study A8081001† (N = 119)		Study A8081005 (N = 136)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Burning sensation as a whole	213 (11)	1 (0.8)	215 (11.0)	0
Burning sensation	2 (1.7)	0	2 (1.5)	0
Hypoaesthesia	7 (5.9)	0	2 (1.5)	0
Hypoaesthesia facial	1 (0.8)	0	1 (0.7)	0
Neuralgia	1 (0.8)	0	1 (0.7)	0
Neuropathy peripheral	8 (6.7)	1 (0.8)	8 (5.9)	0
Paraesthesia	11 (9.2)	0	5 (3.7)	0
Peripheral motor neuropathy	0	0	1 (0.7)	0
Peripheral sensory neuropathy	1 (0.8)	0	7 (5.1)	0
Sensory disturbance	1 (0.8)	0	0	0

*: At the timepoint of database snapshot preparation, †: *ALK*-positive NSCLC cohort

Since more than half of patients who developed neuropathy in Studies A8081001 and A8081005 did not recover from the disorder, PMDA asked the applicant to explain the mechanism of the occurrence of neuropathy and its reversibility.

The applicant responded as follows:
Since crizotinib is considered to hardly cross the blood-brain barrier, with little distribution in the central nervous system [see "3.(ii).A.(2).1) Tissue distribution"]. Neuropathy appears to occur mostly in the peripheral system, but the mechanism of the occurrence is unknown.

As regards the observation that neuropathy did not resolve in more than half of the patients who experienced the disorder, the continuing crizotinib administration is likely to be a contributing factor as both Studies A8081001 and A8081005 are still ongoing.

Taking account of the findings that most of the patients enrolled in both studies have a history of chemotherapy containing a platinum antineoplastic agent, and that it is not clear how the history of treatment with a platinum antineoplastic agent affects the development of crizotinib-induced neuropathy, the applicant will continue to collect information on crizotinib-induced neuropathy.

PMDA considers as follows:
Since crizotinib administration causes neuropathy at a relatively high frequency, and the mechanism of the occurrence of neuropathy and its reversibility are unknown, caution is required. Therefore, PMDA has concluded that appropriate caution should be exercised regarding the occurrence of crizotinib-induced neuropathy.

Although the applicant explained that the ongoing study is the reason for the non-recovery of neuropathy in many patients in Studies A8081001 and A8081005, reversibility of neuropathy is unknown at the moment. Therefore, PMDA has concluded that not only the incidence of neuropathy but also information on clinical characteristics such as reversibility should be collected after the market launch [see "4.(iii).B.(6) Post-marketing investigations"].

4.(iii).B.(3).7) Thromboembolism

The applicant explained crizotinib-induced thromboembolism as follows:
The incidences of thromboembolism in the *ALK*-positive NSCLC cohort of Study A8081001 and in Study A8081005 were as shown in the following table.

Thromboembolism* (Studies A8081001 and A8081005)

MedDRA PT	Number of subjects (%)			
	Study A8081001† (N = 119)		Study A8081005 (N = 136)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Deep vein thrombosis	4 (3.4)	3 (2.5)	3 (2.2)	2 (1.5)
Pulmonary thrombosis	1 (0.8)	0	0	0
Thrombosis	0	0	2 (1.5)	1 (0.7)
Vena cava thrombosis	1 (0.8)	1 (0.8)	0	0
Pulmonary embolism	6 (5.0)	5 (4.2)	1 (0.7)	1 (0.7)
Peripheral embolism	1 (0.8)	1 (0.8)	1 (0.7)	0

*: At the timepoint of database snapshot preparation, †: *ALK*-positive NSCLC cohort

Thromboembolism-related deaths or serious adverse events observed were pulmonary embolism in 4 subjects, vena cava thrombosis in 1 patient, and deep vein thrombosis in 1 subject in Study A8081001; and thrombosis in 1 subject and fatal pulmonary embolism in 1 subject in Study A8081005.

At the moment, crizotinib is not considered to have a high risk of causing thromboembolism, and therefore there is no plan to exercise any special caution after the market launch. However, the applicant will pay attention to the clinical course of the event and to reports of new cases, thereby to continuously consider the necessity of providing caution in the package insert, etc.

PMDA considers as follows:
Since crizotinib caused thromboembolism, resulting in death or serious conditions, caution is required. Therefore, caution should be provided appropriately using materials, etc., about crizotinib-induced thromboembolism which resulted in death or serious conditions in some patients. Also, information on crizotinib-induced thromboembolism should be collected after the market launch, and new information, if available, should be provided in an appropriate manner.

4.(iii).B.(3).8) QT prolonged

The applicant explained crizotinib-induced QT prolonged as follows;
In patients in the *ALK*-positive NSCLC cohort of Study A8081001 or in Study A8081005, the maximum QTcF interval and the maximum change from baseline were as shown in the following table.

**Maximum QTcF interval and the maximum change from baseline*
(Studies A8081001 and A8081005†)**

Maximum QTcF interval	Number of subjects (%)	
	Study A8081001 (N = 118)	Study A8081005 (N = 133)
< 450 msec	104 (88.1)	119 (89.5)
≥450≤ and < 480 msec	12 (10.2)	9 (6.8)
≥480 and < 500 msec	1 (0.8)	3 (2.3)
≥500 msec	1 (0.8)	2 (1.5)
Maximum change from baseline	Number of patients (%)	
	Study A8081001 (N = 106)	Study A8081005 (N = 128)
< 30 msec	93 (87.7)	112 (87.5)
≥30 and < 60 msec	9 (8.5)	11 (8.6)
≥60 msec	4 (3.8)	5 (3.9)

*: At the timepoint of database snapshot preparation, †: Patients with evaluable ECG data in *ALK*-positive NSCLC cohort of Study A8081001 or in Study A8081005

QT prolonged regarded as an adverse event was observed in 1 of 119 subjects (0.8%) in the *ALK*-positive NSCLC cohort of Study A8081001 and in 3 of 136 subjects (2.2%) in Study A8081005, and Grade ≥3 QT prolonged was observed only in 1 subject in Study A8081005. There were no deaths, serious adverse events, or adverse events leading to study drug discontinuation in either of the studies. In Study A8081007, however, a serious case, albeit asymptomatic, was reported.

Taking account of the above results, the applicant will continue to collect information on the incidence of QT prolonged via the post-marketing surveillance.

PMDA asked the applicant to explain the incidence of QT prolonged with clinical symptoms or electrolyte abnormality.

The applicant responded as follows:
No QT prolonged with clinical symptoms was observed. As regards QT prolonged accompanied by electrolyte abnormality, of 4 patients who developed QT prolonged in Study A8081005, (a) Grade 1 and 3 sodium decreased, Grade 3 potassium decreased, Grade 1 magnesium increased, and Grade 2 calcium decreased was reported by 1 patient; (b) Grade 1 sodium increased in 1 patient; and (c) Grade 1 and 2 calcium decreased in 1 patient. In the remaining 1 patient, blood samples were not collected, precluding electrolyte analysis.

PMDA considers as follows:
Since crizotinib caused QT prolonged, resulting in serious conditions in some patients, caution is required. Therefore, information on crizotinib-induced QT prolonged should be collected via the post-marketing surveillance, and caution should be exercised appropriately about the necessity of periodically monitoring patients such as by ECG and electrolyte analysis during crizotinib administration.

4.(iii).B.(3).9) Bradycardia

The applicant explained crizotinib-induced bradycardia as follows:
Bradycardia (collective term for MedDRA preferred terms bradycardia and sinus bradycardia) was observed in 8 of 119 subjects (6.7%) in the *ALK*-positive NSCLC cohort of Study A8081001 and in 5 of 136 subjects (3.7%) in Study A8081005. The clinical characteristics of the observed bradycardia were as shown in the table below. The minimum pulse rate during the study period was <50 beats per minute in 16 of 114 patients (14.0%) in the *ALK*-positive NSCLC cohort of Study A8081001 and in 9 of 124 patients (7.3%) in Study A8081005.

Bradycardia-associated symptoms, dizziness, syncope, fatigue, shortness of breath, headache, and nausea, occurred simultaneously with bradycardia in 8 of 8 patients (100%) in Study A8081001 and in 3 of 6 patients (50.0%) in Study A8081005. Blood pressure decreased (systolic blood pressure <90 mmHg, diastolic blood pressure <50 mmHg, systolic blood pressure lower than baseline by ≥30 mmHg, or diastolic blood pressure lower than baseline by ≥20 mmHg) occurred simultaneously with bradycardia in 4 of 8 patients (50.0%) in Study A8081001 and in 1 of 6 patients (16.7%) in Study A8081005.

Based on the above results, the applicant will provide information using materials, etc., on the incidence of bradycardia in clinical studies and continue to collect information via the post-marketing surveillance.

**Clinical characteristics of patients with bradycardia or sinus bradycardia*
(Studies A8081001 and A8081005)**

	Study A8081001† (N = 119)	Study A8081005 (N = 136)
Number of affected patients (%)	8 (6.7)	5 (3.7)
Mean onset day [SD] (day)	39.3 [34.3]	25.6 [9.2]
Median onset day [max., min.] (day)	31.5 [1.0, 113.0]	22.0 [20.0, 42.0]
Mean duration [SD] (days)	234.5 [185.7]	41.8 [45.1]
Median duration [min., max.] (days)	190.0 [30.0, 532.0]	24.0 [1.0, 118.0]
Number of patients who recovered (%)	2 (25.0)	1 (20.0)

*: At the time of database snap shot preparation, †: *ALK*-positive NSCLC cohort

Since bradycardia may be associated with clinical symptoms and blood pressure decreased, albeit with a low incidence, caution is required. Therefore, PMDA accepted the explanation of the applicant.

4.(iii).B.(3).10) Photosensitivity

The applicant explained crizotinib-induced photosensitivity as follows:
Results of the *in vitro* phototoxicity test suggested the possibility of crizotinib-induced photosensitivity [see "3.(iii).A.(7).1) *In vitro* phototoxicity"], and Grade 1 photosensitivity occurred in 1 subject in Study A8081005. Therefore, in subsequent clinical studies, patients were advised, as precautions against photosensitivity, to avoid sun bathing, long-time direct exposure to sun light, and sunburn during the study period, and to wear a long sleeve and use sunscreen lotion to protect the skin from exposure to sunlight. After the market launch, the applicant will provide information on the incidence of photosensitivity and measures taken against photosensitivity in the clinical studies, using materials, etc.

PMDA accepted the explanation of the applicant. However, information on crizotinib-induced photosensitivity should be continuously collected via the post-marketing surveillance [see "4.(iii).B.(6) Post-marketing investigations"], and when new findings become available, information should be provided in an appropriate manner.

4.(iii).B.(3).11) Complicated renal cyst

Crizotinib-induced complicated renal cyst was not included in the data submitted for application, whereas during the review process, cases of serious complicated renal cyst (3 patients in Study A8081005, 1 patient in Study A8081007) were reported. Therefore, PMDA asked the applicant to explain the relationship between complicated renal cyst and crizotinib.

The applicant responded as follows:
Up to the end of June, 2011, 4 cases of complicated renal cyst were reported as serious adverse events by the investigator (2 patients of them had renal cyst from before the start of crizotinib administration). Of these, 1 patient continued to receive the same dose of crizotinib, whereas administration was discontinued, temporarily withdrawn, and continued at a reduced dose, respectively, in 1 each of the remaining patients. The adverse event resolved or improved in 2 of 4 patients but remained unresolved in the remaining 2 patients as of the time of the report. As subjective symptoms possibly related to renal cyst, flank pain and pyrexia associated with chills were observed in 1 patient each. There were no reports of urine analysis abnormal or renal impairment. Biopsy performed in 2 patients did not show any findings suggestive of malignant tumor of the kidney.

Although there is a report of the relationship between renal cyst and HGF/c-Met signal transduction (*J Urol*. 2004;171:2166-70), the relationship between the pharmacological action of crizotinib and the mechanism of onset of renal cyst has not been elucidated at the moment. Therefore, the applicant will provide caution using the package insert, etc., and collect information on the incidence of complicated renal cyst via the post-marketing surveillance.

PMDA accepted the applicant's explanation.

4.(iii).B.(4) Indications

The proposed indication for crizotinib was "ALK-positive advanced non-small cell lung cancer," and the Precautions for the Indications section in the proposed package insert contained the following descriptions:

[Precautions for Instructions]

- Crizotinib should be administered to patients who are diagnosed as *ALK* positive by pathologists or testing facilities with adequate experience.
- The efficacy and safety of crizotinib in adjuvant therapy has not been established.

Based on the review described in "4.(iii).B.(1) Clinical positioning of crizotinib," "4.(iii).B.(2) Efficacy," "4.(iii).B.(3) Safety," and the following review described in this section, PMDA considers that the indications for crizotinib should be "*ALK*-positive, unresectable, advanced or relapsed non-small cell lung cancer" for the following reasons: (i) crizotinib is expected to be effective for *ALK*-positive advanced or relapsed NSCLC and (ii) proposed indications should clearly state because efficacy of crizotinib in adjuvant therapy has not been investigated and crizotinib is thus indicated only for patients with "unresectable" cancer. Also, since it is currently unknown how crizotinib affects the survival period of these patients [see "4.(iii).B.(2) Efficacy"], PMDA has concluded that this finding should be added to the above precautions proposed by the applicant.

4.(iii).B.(4).1) Choice between crizotinib and existing standard chemotherapy

The standard treatment for advanced or relapsed NSCLC is chemotherapy containing platinum antineoplastic agent. Therefore, PMDA asked the applicant to explain the choice between crizotinib and the existing standard chemotherapy.

The applicant responded as follows:

The objective response rate to crizotinib of chemotherapy-naïve patients with *ALK*-positive advanced or relapsed NSCLC was 80% (12 of 15 patients), albeit evaluated in only a limited number of patients [see "4.(iii).B.(2).1) Efficacy evaluation"]. These results far surpassed the objective response rate (15%-32%) obtained with the standard therapy for chemotherapy-untreated advanced or relapsed NSCLC thus far reported (*N Engl J Med*. 2006;3552542-50, *J Clin Oncol*. 2008;26:3543-51, *N Engl J Med*. 2002;346:92-8, *J Clin Oncol*. 2004;22:785-94, *J Clin Oncol*. 2005;23:5892-9, *J Clin Oncol*. 2001;19:3210-8). Therefore, the applicant considers that crizotinib is qualified as a choice for the treatment of patients diagnosed with *ALK*-positive NSCLC.

In patients with chemotherapy-treated *ALK*-positive advanced or relapsed NSCLS, the objective response rate to crizotinib far exceeded that to the existing standard treatment regardless of the number of previous treatment regimens. Therefore, the applicant considers that crizotinib is qualified as a standard treatment for patients with *ALK*-positive advanced or relapsed NSCLC.

PMDA considers as follows:

As of the time of the submission, (i) efficacy of crizotinib has not been demonstrated using OS as the index in randomized comparative clinical studies, in either chemotherapy-untreated or treated patients [see "4.(iii).B.(2) Efficacy"], and (ii) life-threatening adverse events such as ILD were observed [see "4.(iii).B.(3) Safety"]. Therefore, the applicant's assertion that the crizotinib is qualified as a standard treatment for patients diagnosed with *ALK*-positive NSCLC is not well-supported by evidence and inappropriate at the moment.

The clinical positioning of crizotinib and the choice between crizotinib and other antineoplastic agents in patients with chemotherapy-untreated or treated *ALK*-positive advanced or relapsed NSCLC will be further clarified by the 2 global phase III studies (in chemotherapy-untreated patients [Study A8081014] and in chemotherapy-treated patients [Study A8081007]) currently being conducted with the aim of comparing the efficacy and safety of crizotinib between these patient groups.

4.(iii).B.(4).2) Test for *ALK* fusion gene

At the moment, there is no widely used test method for *ALK* fusion gene. Therefore, the applicant considered that the test should be performed by pathologists or testing facilities with sufficient experience, and proposed to include, in the Precautions for Indications of the package insert, the statement that "Crizotinib should be administered to patients who are diagnosed as *ALK* positive by pathologists or testing facilities with adequate experience."

The applicant also explained the test for *ALK* fusion gene as follows [see "4.(i).A.(1).2) Test for *ALK* fusion gene"]:
MGH FISH-CTA test or other CTA test was used in 99 of 119 patients enrolled in Study A8081001. In 45 patients found positive by CTA test other than MGH FISH-CTA test, the test was repeated using the MGH FISH-CTA method. As a result, the positive agreement rate was 91.1% (41 of 45 patients).

In Studies A8081005 and A8081007, ALK break apart FISH test, for which application has been filed as an *in vitro* diagnostic by Abbott Japan Co., Ltd., was used. At the same time, a test for correlation between MGH FISH-CTA test and ALK break apart FISH test was performed by Abbott Japan Co., Ltd. and by Abbott Molecular Inc. (MGH FISH-CTA test also was performed in patients enrolled in Study A8081005). As a result, the positive agreement rate was 95.12%, the negative agreement rate was 94.61%, and the total agreement rate was 94.78%.

Given the above results, although there is no established standard test for *ALK* fusion gene, the patient population diagnosed as *ALK* positive by MGH FISH-CTA test and the population diagnosed as *ALK* positive by ALK break apart FISH test can be regarded as identical. Therefore, it is appropriate to select patients who are expected to respond to crizotinib by ALK break apart FISH, the test method under application by Abbott Japan Co., Ltd.

In addition to FISH, it is technically possible to diagnose *ALK* fusion gene by a high-sensitive immunohistochemical method or by reverse transcription polymerase chain reaction. In future, the most appropriate test may be selected with consideration given to the type and amount of the sample, the cost of the test, etc. "Guidance for ALK Gene Testing in Lung Cancer Patients" has recently been published by the Biomarker Committee of the Japan Lung Cancer Society. The applicant will draw up an appropriate manual for the test for *ALK* fusion gene by also taking account of the guidance, and thereby provide information to the medical practice to assist selecting appropriate patients who are expected to respond to crizotinib.

PMDA considers as follows:
PMDA accepted the applicant's explanation about the test for *ALK* fusion gene. However, the above guideline requires that patients should be confirmed to be positive by at least 2 testing methods, and the testing method for selecting patients responsive to crizotinib will be revised based on new findings available in future. The result of the test for *ALK* fusion gene is critical in judging the appropriateness of administering crizotinib, and the selection of such patients should be based on the most up-to-date knowledge. Therefore, the applicant should continue to collect information on the test for *ALK* fusion gene and to provide useful information, if available, to the medical practice in an appropriate manner.

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

PMDA considers as follows:

As a result of the following review, the dosage and administration of crizotinib should be "The usual adult dosage is 250 mg of crizotinib administered orally twice daily. The dose may be adjusted according to the patient's condition," as proposed by the applicant. It is appropriate to provide the criteria for rendering dose interruption, dose reduction or treatment discontinuation according to the adverse event in the Precautions for Dosage and Administration section.

4.(iii).B.(5).1) Dose and administration of crizotinib

The applicant explained the rationale for the dosage and administration of crizotinib as follows:

In the dose escalation cohort* of Study A8081001, Grade 3 fatigue, a dose-limiting toxicity (DLT), was observed in 2 of 6 patients in the 300 mg BID group, whereupon further dose increase was cancelled according to the protocol, and the study was conducted in a total of 8 patients in the 250 mg BID group. Since no DLT was observed in this dose group, the dose 250 mg BID was determined to be the MTD and selected as the dosage regimen in the recommended dose cohort of Study A8081001 and in Study A8081005. Results confirmed the efficacy and safety of crizotinib in patients with *ALK*-positive advanced or relapsed NSCLC. Therefore, the dosage and administration of crizotinib was determined as "250 mg administered orally twice daily."

*: When the study on 200 mg QD was completed, daily dosing frequency was changed from QD to BID in order to continue the dose increase while decreasing the incidence and grade of nausea and vomiting. In all, 6 types of dosage regimens (50 mg QD, 100 mg QD, 200 mg QD, 200 mg BID, 300 mg BID, 250 mg BID) were examined. In the 200 mg QD group, Grade 3 ALT increased, a DLT, was observed in 1 of 8 patients.

PMDA, based on the findings that crizotinib showed a certain level of efficacy and was tolerated in patients receiving crizotinib 250 mg BID in the recommended dose cohort of Study A8081001 and in Study A8081005, accepted the explanation of the applicant.

4.(iii).B.(5).2) Criteria for dose reduction and interruption and discontinuation of crizotinib

The criteria for dose reduction and interruption and discontinuation of crizotinib in the proposed package insert were as follows:

[Precautions for Dosage and Administration]

Dose interruption, dose reduction, or discontinuation of crizotinib due to adverse drug reations should be done, interrupted or discontinued with consideration given to the following criteria. When administration is continued at a reduced dose, the dose should be reduced by 1 level depending on the symptom and severity of the adverse reaction (dose level, initial 250 mg dose twice daily → 200 mg twice daily → 250 mg once daily).

Adverse drug reaction	Grade[1]			
	1	2	3	4
Hematological[2]	Continue the same dose.		Withdraw crizotinib until the symptom improves to Grade ≤2. After recovery, resume the administration at the same dose as before the withdrawal.	Withdraw crizotinib until the symptom improves to Grade ≤2. After recovery, resume the administration starting from 200 mg twice daily.[3]
ALT or AST increased with Grade ≤1 blood bilirubin increased	Continue the same dose.		Withdraw crizotinib until the symptom improves to Grade ≤1, or to baseline. After recovery, resume the administration starting from 200 mg twice daily.[4]	
ALT or AST increased with Grade 2 to 4 blood bilirubin increased (excluding patients with cholestasis or haemolysis)	Continue the same dose.	Discontinue the administration.		
Pneumonitis, interstitial lung disease[5]	Discontinue the administration.			
QT interval prolonged	Continue the same dose.		Withdraw crizotinib until the symptom improves to Grade ≤1. After recovery, resume the administration starting from 200 mg twice daily.[4]	Discontinue the administration.

1: NCI-CTCAE. 2: Except lymphopenia (only not accompanied by clinical events such as opportunistic infection). 3: In case of relapse, withdraw the administration until the symptom improves to Grade ≤2. After recovery, resume the administration starting with 250 mg once daily. If a Grade 4 event relapses, discontinue the administration. 4: In case of relapse, withdraw crizotinib until the symptom improved to Grade ≤1. After recovery, resume the administration starting with 250 mg once daily. If a Grade 3 or 4 event relapses, discontinue the administration. 5: Other than those caused by the progression of NSCLC, other lung disease, infection, or radiation therapy.

The applicant explained the rationale for setting the method for dose reduction and the criteria for dose reduction and interruption and discontinuation in the proposed package insert, as follows:
In the initial plan for crizotinib dose reduction at the beginning of Studies A8081001 and A8081005, the first reduced level was 200 mg BID and the second reduced level was 150 mg BID. However, in the ongoing clinical studies, the first reduced dose is set at 200 mg BID and the second reduced dose 250 mg QD, for the following reasons:

- Results of Studies A8081001 and A8081005 suggested that crizotinib can be continued safely by reducing the dose to 150 mg BID.
- A simulation of pharmacokinetics at 250 mg QD and 150 mg BID using the basic model obtained from the PPK analysis [see "4.(ii).A.(4).1) Population pharmacokinetic (PPK) analysis"] suggests that, when crizotinib is administered at 250 mg QD, (i) plasma crizotinib concentration over time is expected to be similar to, and not exceed, that achieved by 150 mg BID, and (ii) the trough plasma concentration of crizotinib is expected to exceed the effective plasma concentration predicted from the nonclinical pharmacokinetic model.

The data submitted in the application do not contain the information obtained by administering crizotinib according to the dose reduction method described in the proposed package insert (200 mg BID at the first dose reduction level, 250 mg QD at the second dose reduction level). However, given the above reasoning, there should be no difference in the efficacy or safety between 250 mg QD and 150 mg BID. Therefore, the applicant considered that it was appropriate to describe "the first dose reduction level is 200 mg BID, and the second dose reduction level is 250 mg QD" in the package insert.

As regards the criteria for dose reduction and interruption and discontinuation, the criteria described in the proposed package insert and those used in the clinical studies were different regarding "pneumonitis, interstitial lung disease," "nonhaematological toxicity (as a whole)," "left ventricular contractile dysfunction," and "visual disturbance." Since "pneumonitis, interstitial lung disease" requires more strict safety management than in clinical studies, "pneumonitis, interstitial lung disease" of all Grades is handled as an adverse reaction that meets the discontinuation criteria in the proposed package insert. In contrast, "left ventricular contractile dysfunction" was not observed in the clinical studies, and "nonhaematological toxicity (as a whole)" and "visual disturbance" were mostly mild or moderate in severity, only rarely requiring dose interruption, dose reduction, or discontinuation of crizotinib, allowing continued administration with the standard symptomatic treatments. Therefore, no criteria were set for these adverse events in the proposed package insert.

PMDA considers as follows:
The applicant's explanation of the criteria for dose reduction and interruption and discontinuation are largely acceptable. However, regarding the method for dose reduction (200 mg BID at the first dose reduction, 250 mg QD at the second dose reduction), since there are no patients who reduced the dose from 200 mg BID to 250 mg QD, including those in the ongoing clinical studies, the safety and efficacy of continued crizotinib administration using this dose reduction method is unknown. Therefore, information on the specific method in dose reduction should be provided by materials. Also, the fact that the dose interruption criteria had been set for "nonhaematological toxicity (as a whole)," "left ventricular contractile dysfunction," and "visual disturbance" in clinical studies should be informed using materials, together with the detailed information.

4.(iii).B.(6) Post-marketing investigations
The applicant explained the plan for the post-marketing surveillance as follows:
The applicant plans to conduct a post-marketing surveillance in all patients treated with crizotinib (all-case surveillance) in order to identify the incidences of adverse drug reactions of crizotinib under routine use of the drug after the market launch and factors affecting the safety and efficacy, and to investigate the necessity of an additional post-marketing surveillance or a clinical study.

The priority surveillance items will include the following: ILD, QT prolonged, bradycardia, hepatotoxicity, visual disturbance, neutropenia/leukopenia, neuropathy, and renal cyst.

The target number of patients to be analyzed was determined as follows. Thus, among adverse events observed in Studies A8081001 and A8081005, serious and treatment-related ILD (assessed by investigators) occurred with an incidence of 1.6% (4 of 255 patients). By focusing on ILD, the target number of patients was set at 200 to allow the detection, at the probability of ≥95%, of at least 1 case of an event with an incidence of 1.5%. In Japan, approximately 300 patients are expected to be diagnosed with *ALK*-positive advanced or relapsed NSCLC within the first year after the market launch, and approximately 200 patients of them are expected to be treated with crizotinib. Therefore, the applicant predicts that it is possible to register 200 patients within 1 year after the start of registration for the post-marketing surveillance.

The observation period was set at 52 weeks from Day 1 of crizotinib administration based on the following observations: (i) in Study A8081001, the median treatment duration in Japanese patients was 42.9 weeks and the median response duration was 48.1 weeks, and (ii) in Studies A8081001 and A8081005, most adverse events, including those defined as the priority items, occurred within 1 year after the start of crizotinib administration. In case crizotinib administration is continued for >52 weeks, the clinical course will be followed up to 104 weeks (2 years).

PMDA considers as follows:

Since the data submitted in the application contain only a limited amount of information on the safety of crizotinib in Japanese patients, it is necessary to promptly collect relevant information. Therefore, the post-market surveillance should be conducted involving all patients treated with crizotinib.

As regards the plan for the surveillance proposed by the applicant, among adverse events requiring caution in administering crizotinib, ILD in particular may occur with a higher incidence in Japanese patients than in foreign patients, and some of the patients who developed ILD died [see "4.(iii).B.(3).2) ILD"]. Therefore, the number of patients analyzed should be re-examined so that predicting factors for ILD can be identified in the all-case surveillance. The maximum observation period may be set at 52 weeks, as planned by the applicant. However, the follow-up of patients treated with crizotinib for >52 weeks should be performed separately from the all-case surveillance so that the final results of the all-case surveillance can be obtained promptly. In addition, it is necessary to analyze the information obtained from the all-case surveillance at an early stage and, based on the results of the analysis, to readjust the plan for the surveillance.

The surveillance plan should be designed to make sure that the following information on the priority items of the all-case surveillance be collected:

- Characteristic features of ILD (e.g., patient background, imaging findings, severity, time to onset and outcome, outcome, treatment given, response to the treatment, predicting factors)
- Clinical characteristics of visual disturbance (e.g., time to onset, symptom duration, signs of aggravation)
- Safety of crizotinib in patients with hepatic impairment
- Safety of crizotinib in patients with severe renal impairment
- Clinical characteristics of neuropathy (e.g., reversibility)
- Incidence and clinical characteristics of photosensitivity (e.g., reversibility)

4.(iii).B.(7) Actions to minimize risk after the market launch

The applicant explained the measures to take to minimize risk after the market launch, as follows: In the clinical studies, crizotinib-related serious ILD occurred and resulted in death in some patients. Therefore, the applicant plans to carry out the following actions to minimize risk after the market launch: (i) to set the requirements for medical institutions and to control the distribution of the product, (ii) to promote confirmation of patient background at the advance registration for the all-case surveillance and proper use, and (iii) to provide information to healthcare professionals and patients using materials [see "4.(iii).B.(3).2).c Post-marketing safety measures"].

As regards (i) above, for "requirements for medical institutions," since crizotinib should be used only in patients who are judged as appropriate under the supervision of physicians with sufficient knowledge and experience of cancer chemotherapy at medical institutions capable of coping with emergencies, participating hospitals will be limited to "regional core centers for cancer treatment" or other equivalent medical institutions. As regards "distribution control," the applicant plans to supply, or permit the use of, crizotinib only to institutions that have closed the contract pertaining to the all-case surveillance and received the information on the proper use of crizotinib.

Since crizotinib is an oral product, PMDA asked the applicant to explain the safety measures for dispensing pharmacies, especially measures to be taken for prescription from medical institutions that do not meet the requirements for using crizotinib and therefore have not received the proper use information.

The applicant responded as follows:
The applicant plans to construct a system in which the delivery of crizotinib to each dispensing pharmacy is started only after it is confirmed that the prescription is issued by a medical institution

qualified to use crizotinib. In addition, the applicant will request physicians who use crizotinib to provide the patient with the material proving that the patient has received the explanation for the proper use of crizotinib (treatment confirmation sheet). The applicant will request the pharmacy the following: if a patient without the "treatment confirmation sheet" presents the prescription for crizotinib to a pharmacy, the pharmacy will provide the applicant with the information on the medical institution that has issued the prescription. Based on the information provided by the pharmacy, the applicant will confirm whether or not the medical institution meet the requirements for the use of crizotinib and, if such is the case, will conclude a contract for all-case surveillance [Note by PMDA: Crizotinib is dispensed even to patients without the "treatment confirmation sheet"].

PMDA considers as follows:
Taking account of the following, the actions to minimize risk planned by the applicant is acceptable: (i) since the target molecule of crizotinib is different from that of existing antineoplastic agents, the safety profile of crizotinib may be different from those of the existing antineoplastic agents, and (ii) among adverse events requiring caution in administering crizotinib, ILD in particular may occur with a higher incidence in Japanese patients than in foreign patients, and resulted in death in some of patients.

4.(iv) Adverse events observed in clinical studies
Among clinical study data submitted for safety evaluation, deaths were described under "4.(iii) Summary of clinical efficacy and safety" section, while major adverse events other than death were as follows.

4.(iv).(1) Japanese phase I study (Study A8081022)
Adverse events were observed in 2 of 6 subjects (33.3%) in the 150 mg group, in 0 of 6 subjects in the 250 mg group, and in 1 of 6 subjects (16.7%) in the 400 mg group. Adverse events for which a causal relationship to crizotinib could not be ruled out were observed in 2 of 6 subjects (33.3%) in the 150 mg group.

There were no adverse events reported by ≥2 subjects in any group, serious adverse events, or adverse events leading to crizotinib discontinuation in any dose groups.

4.(iv).(2) Global phase II study (Study A8081005)
Adverse events were observed in 124 of 136 subjects (91.2%). Adverse events for which a causal relationship to crizotinib could not be ruled out were observed in 115 of 136 subjects (84.6%). Adverse events reported by ≥10% of subjects were as shown in the table below.

Adverse events (incidence of ≥10%)

Adverse events classified by system organ class (MedDRA version 13.0)	Number of patients (%)	
	Crizotinib group (N = 136)	
	All Grades	Grade ≥3
All adverse events	124 (91.2)	44 (32.4)
Eye disorders	75 (55.1)	0
Visual impairment	48 (35.3)	0
Gastrointestinal disorders	108 (79.4)	5 (3.7)
Nausea	69 (50.7)	1 (0.7)
Vomiting	59 (43.4)	2 (1.5)
Diarrhoea	48 (35.3)	0
Constipation	37 (27.2)	1 (0.7)
General disorders and administration site conditions	66 (48.5)	9 (6.6)
Fatigue	36 (26.5)	2 (1.5)
Oedema peripheral	33 (24.3)	1 (0.7)
Investigations	31 (22.8)	11 (8.1)
ALT increased	14 (10.3)	6 (4.4)
Metabolism and nutrition disorders	43 (31.6)	7 (5.1)
Decreased appetite	29 (21.3)	1 (0.7)
Nervous system disorders	60 (44.1)	1 (0.7)
Dysgeusia	19 (14.0)	0
Dizziness	18 (13.2)	0
Respiratory, thoracic and mediastinal disorders	46 (33.8)	10 (7.4)
Dyspnoea	22 (16.2)	7 (5.1)
Cough	18 (13.2)	2 (1.5)

Serious adverse events were observed in 29 of 136 subjects (21.3%), including dyspnoea and pneumonia in 4 subjects each (2.9%), pyrexia in 3 subjects (2.2%), pneumonitis, dysphagia, death unexplained, cough, and disease progression in 2 subjects each (1.5%), palpitations, supraventricular tachycardia, ileus, oesophagitis, general physical health deterioration, oedema peripheral, cellulitis, lung infection, pyothorax, sepsis, septic shock, femoral neck fracture, hepatic enzyme increased, bursitis, pathological fracture, hypoxia, pneumothorax, pulmonary embolism, respiratory failure, haematoma, and thrombosis in 1 subject each (0.7%). Among these, a causal relationship to crizotinib could not be ruled out for dyspnoea and pneumonitis in 2 subjects each, palpitations, supraventricular tachycardia, dysphagia, death unexplained, oedema peripheral, lung infection, hepatic enzyme increased, cough, and haematoma in 1 subject each.

Adverse events leading to crizotinib discontinuation were observed in 9 of 136 subjects (6.6%), which included disease progression and pneumonitis in 2 subjects (1.5%), ALT increased, death unexplained, dyspnoea, nausea, and sepsis in 1 subject each (0.7%). Of these, a causal relationship to crizotinib could not be ruled out for pneumonitis in 2 subjects, ALT increased, death unexplained, dyspnoea, and nausea in 1 subject each.

4.(iv).(3) Foreign phase I study (Study A8081001)

4.(iv).(3).1) Dose escalation cohort

Adverse events were observed in all treatment groups: 3 subjects in the 50 mg QD group, 4 subjects in the 100 mg QD group, 8 subjects in the 200 mg QD group, 7 subjects in the 200 mg BID group, 8 subjects in the 250 mg BID group, and 6 subjects in the 300 mg BID group. Adverse events for which a causal relationship to crizotinib could not be ruled out were observed in 3 of 3 subjects (100%), 4 of 4 subjects (100%), 7 of 8 subjects (87.5%), 5 of 7 subjects (71.4%), 7 of 8 subjects (87.5%), and 6 of 6 subjects (100%), respectively.

Adverse events reported by ≥2 subjects in any group were diarrhoea, vomiting, fatigue, and dyspnoea in 2 subjects each (66.7%) in the 50 mg QD group; nausea and pyrexia in 3 subjects each (75.0%), vomiting, fatigue, decreased appetite, and dehydration in 2 subjects each (50.0%)

in the 100 mg QD group; nausea in 6 subjectts (75.0%), vomiting in 5 subjects (62.5%), decreased appetite in 4 subjects (50.0%), fatigue and back pain in 3 subjects each (37.5%), anaemia, abdominal pain upper, diarrhoea, dyspepsia, upper respiratory tract infection, and dizziness in 2 subjects each (25.0%) in the 200 mg QD group; nausea and vomiting in 4 subjects each (57.1%), fatigue in 3 subjects (42.9%), abdominal pain, constipation, oedema peripheral, bronchitis, decreased appetite, pain in extremity, dyspnoea, and haemoptysis in 2 subjects each (28.6%) in the 200 mg BID group; vomiting in 5 subjects (62.5%), fatigue in 4 subjects (50.0%), constipation, nausea, and dehydration in 3 subjects each (37.5%), diarrhoea, disease progression, and decreased appetite in 2 subjects each (25.0%) in the 250 mg BID group; and decreased appetite in 4 subjects (66.7%), dyspepsia, nausea, fatigue, and dyspnoea in 3 subjects each (50.0%), constipation, and blood ALP increased in 2 subjects each (33.3%) in the 300 mg BID group. Of these, anaemia, decreased appetite, and back pain in 1 subject each in the 200 mg QD group, vomiting and haemoptysis in 1 subject each in the 200 mg BID group, disease progression in 2 subjects, diarrhoea and fatigue in 1 subject each in the 250 mg BID group, and fatigue in 2 subjects, blood ALP increased, and dyspnoea in 1 subject each in the 300 mg BID group were Grade ≥3 adverse events.

Serious adverse events occurred in 0 of 3 subjects, 0 of 4 subjects, 1 of 8 subjects (12.5%), 2 out of 7 subjects (28.6%), 4 of 8 subjects (50.0%), and 2 of 6 subjects (33.3%), respectively, in the 50 mg QD group, the 100 mg QD group, the 200 mg QD group, the 200 mg BID group, the 250 mg BID group, the 300 mg BID group. Serious adverse events include small intestinal obstruction in 1 subject (12.5%) in the 200 mg QD group, haemoptysis and spinal cord compression in 1 subject each (14.3%) in the 200 mg BID group, disease progression in 2 subjects (25.0%), anaemia, diarrhoea, vomiting, dehydration, chest pain, and bronchitis in 1 subject each (12.5%) in the 250 mg BID group, and respiratory failure and disease progression in 1 subject each (16.7%) in the 300 mg BID group. A causal relationship to crizotinib was ruled out for all of the serious adverse events.

Adverse events leading to crizotinib discontinuation were observed in 0 of 3 subjects in the 50 mg QD group, 0 of 4 subjects in the 100 mg QD group, 0 of 8 subjects in the 200 mg QD group, 1 of 7 subjects (14.3%) in the 200 mg BID group, 2 of 8 subjects (25.0%) in the 250 mg BID group, and 1 of 6 subjects (16.7%) in the 300 mg BID group. They include spinal cord compression in 1 subject (14.3%) in the 200 mg BID group, deep vein thrombosis and blood bilirubin increased in 1 subject each (12.5%) in the 250 mg BID group, and fatigue in 1 subject (16.7%) in the 300 mg BID group. Of these, a causal relationship to crizotinib could not be ruled out for blood bilirubin increased in 1 subject in the 250 mg BID group and fatigue in 1 subject in the 300 mg BID group.

4.(iv).(3).2) *ALK*-positive NSCLC cohort

Adverse events were observed in 117 of 119 subjects (98.3%), and adverse events for which a causal relationship to crizotinib could not be ruled out were observed in 114 of 119 subjects (95.8%). Adverse events reported by ≥10% of subjects were as shown in the table below.

Adverse events (incidence of ≥10%)

Adverse events classified by system organ class (MedDRA version 13.0)	Number of subjects (%)	
	Crizotinib group (N = 119)	
	All Grades	Grade ≥3
All adverse events	117 (98.3)	46 (38.7)
Eye disorders	76 (63.9)	0
Visual impairment	57 (47.9)	0
Gastrointestinal disorders	108 (90.8)	4 (3.4)
Nausea	59 (49.6)	1 (0.8)
Diarrhoea	57 (47.9)	1 (0.8)
Vomiting	48 (40.3)	1 (0.8)
Constipation	45 (37.8)	1 (0.8)
Dyspepsia	14 (11.8)	0
Abdominal pain upper	12 (10.1)	0
General disorders and administration site conditions	80 (67.2)	13 (10.9)
Oedema peripheral	38 (31.9)	1 (0.8)
Fatigue	30 (25.2)	3 (2.5)
Pyrexia	19 (16.0)	0
Infections and infestations	50 (42.0)	10 (8.4)
Nasopharyngitis	14 (11.8)	0
Upper respiratory tract infection	13 (10.9)	0
Investigations	41 (34.5)	11 (9.2)
ALT increased	21 (17.6)	8 (6.7)
AST increased	17 (14.3)	5 (4.2)
Metabolism and nutrition disorders	39 (32.8)	5 (4.2)
Decreased appetite	28 (23.5)	1 (0.8)
Musculoskeletal and connective tissue disorders	48 (40.3)	5 (4.2)
Arthralgia	13 (10.9)	2 (1.7)
Back pain	13 (10.9)	0
Nervous system disorders	71 (59.7)	7 (5.9)
Dizziness	33 (27.7)	0
Headache	14 (11.8)	1 (0.8)
Psychiatric disorders	23 (19.3)	3 (2.5)
Insomnia	12 (10.1)	0
Respiratory, thoracic and mediastinal disorders	56 (47.1)	15 (12.6)
Cough	15 (12.6)	1 (0.8)
Dyspnoea	19 (16.0)	5 (4.2)
Skin and subcutaneous tissue disorders	45 (37.8)	0
Rash	21 (17.6)	0

Serious adverse events were observed in 33 of 119 subjects (27.7%), which included disease progression in 8 subjects (6.7%), pneumonia in 6 subjects (5.0%), pulmonary embolism in 4 subjects (3.4%), pneumonitis, constipation, pyrexia, and syncope in 2 subjects each (1.7%), and anaemia, oesophageal ulcer, death unexplained, bacteraemia, cellulitis, infection, nasal abscess, pleural infection, renal abscess, urosepsis, ankle fracture, hip fracture, subcutaneous haematoma, ALT increased, liver function test abnormal, arthralgia, chondrocalcinosis pyrophosphate, rhabdomyolysis, convulsion, drug abuse, bronchial obstruction, dyspnoea, hypoxia, pulmonary haemorrhage, respiratory failure, deep vein thrombosis, and vena cava thrombosis in 1 subject each (0.8%). Among these, a causal relationship to crizotinib could not be ruled out for pneumonitis in 2 subjects, constipation, oesophageal ulcer, renal abscess, ALT increased, and liver function test abnormal in 1 subject each.

Adverse events leading to crizotinib discontinuation were observed in 8 of 119 subjects (6.7%). They include pneumonitis in 2 subjects (1.7%), death unexplained, ALT increased, disease progression, respiratory failure, pulmonary haemorrhage, and pneumonia in 1 subject each (0.8%). Of these, a causal relationship to crizotinib could not be ruled out for pneumonitis in 2 subjects and ALT increased in 1 subject.

4.(iv).(3).3) *ALK*-negative NSCLC cohort

Adverse events were observed in 4 of 5 subjects (80.0%), and adverse events for which a causal relationship to crizotinib could not be ruled out were observed in 3 of 5 subjects (60.0%). Adverse events reported by ≥2 subjects were visual impairment and diarrhoea in 2 subjects each (40.0%), all of which were Grade 1 in severity.

Serious adverse events and adverse events leading to crizotinib discontinuation were observed in 2 of 5 subjects (40.0%). They include disease progression and pneumonia in 1 subject each (20.0%), and their causal relationship to crizotinib was ruled out.

4.(iv).(3).4) Other cohort

Adverse events were observed in 43 of 44 subjects (97.7%), and adverse events for which a causal relationship to crizotinib could not be ruled out were observed in 41 of 44 subjects (93.2%). Adverse events reported by ≥10% of subjects were as shown in the table below.

Adverse events (incidence of ≥10%)

Adverse events classified by system organ class (MedDRA version 13.0)	Number of subjects (%)	
	Crizotinib group (N = 44)	
	All Grades	Grade ≥3
All adverse events	43 (97.7)	24 (54.5)
Blood and lymphatic system disorders	7 (15.9)	4 (9.1)
Anaemia	5 (11.4)	3 (6.8)
Eye disorders	15 (34.1)	0
Visual impairment	13 (29.5)	0
Gastrointestinal disorders	39 (88.6)	5 (11.4)
Constipation	10 (22.7)	0
Diarrhoea	17 (38.6)	0
Nausea	27 (61.4)	2 (4.5)
Vomiting	24 (54.5)	1 (2.3)
General disorders and administration site conditions	30 (68.2)	11 (25.0)
Disease progression	7 (15.9)	7 (15.9)
Fatigue	17 (38.6)	0
Oedema peripheral	7 (15.9)	0
Metabolism and nutrition disorders	16 (36.4)	2 (4.5)
Decreased appetite	11 (25.0)	0
Nervous system disorders	20 (45.5)	0
Dizziness	10 (22.7)	0
Respiratory, thoracic and mediastinal disorders	19 (43.2)	9 (20.5)
Dyspnoea	9 (20.5)	4 (9.1)

Serious adverse events were observed in 21 of 44 subjects (47.7%), including disease progression in 7 subjects (15.9%), anaemia, pneumonia, and dyspnoea in 3 subjects each (6.8%), pleural effusion in 2 subjects (4.5%), and myocardial infarction, autoimmune thyroiditis, small intestinal obstruction, fat necrosis, pain, pyrexia, influenza, lower respiratory tract infection, wrist fracture, failure to thrive, arthralgia, pain in extremity, confusional state, haemoptysis, hypoxia, pulmonary embolism, and respiratory failure in 1 subject each (2.3%). Of these, a causal relationship to crizotinib could not be ruled out for anaemia in 3 subjects, and autoimmune thyroiditis, arthralgia, and pain in extremity in 1 subject each.

Adverse events leading to crizotinib discontinuation were observed in 9 of 44 subjects (20.5%), including dyspnoea and disease progression in 2 subjects each (4.5%), nausea, autoimmune thyroiditis, respiratory failure, vomiting, and pneumonia in 1 subject each (2.3%). Of these, a causal relationship to crizotinib could not be ruled out for nausea, autoimmune thyroiditis, and vomiting in 1 subject each.

4.(iv).(4) Foreign phase I study (Study A8081010)

Adverse events were observed in 8 of 14 subjects (57.1%) during the intravenous administration period and in 5 of 14 subjects (35.7%) during the oral administration period, and adverse events for which a causal relationship to crizotinib could not be ruled out were observed in 5 of 14 subjects (35.7%) in each of both periods.

Adverse events reported by ≥2 subjects in either administration period were diarrhoea and catheter site pain in 2 subjects each (14.3%) in the intravenous administration period and diarrhoea in 4 subjects (28.6%) in the oral administration period. All events were mild in severity.

There were no serious adverse events or adverse events leading to crizotinib discontinuation in either administration period.

4.(iv).(5) Foreign phase I study (Study A8081008)

Adverse events were observed in 7 of 24 subjects (29.2%) during the treatment of the powder in capsule and in 8 of 24 subjects (33.3%) during the treatment of the immediate release tablet, and adverse events for which a causal relationship to crizotinib could not be ruled out were observed in 6 of 24 subjects (25.0%) and in 8 of 24 subjects (33.3%), respectively.

Adverse events reported by ≥2 subjects in either period were nausea in 3 subjects (12.5%) during the treatment of the powder in capsule, and nausea in 4 subjects (16.7%) and diarrhoea in 3 subjects (12.5%) during the treatment of the immediate release tablet. Of these, nausea in 1 subject during the treatment of the immediate release tablet was rated as moderate in severity, while other events were rated as mild.

There were no serious adverse events or adverse events leading to crizotinib discontinuation in either treatment period.

4.(iv).(6) Foreign phase I study (Study A8081011)

Adverse events were observed in 21 of 35 subjects (60.0%) during the treatment of the immediate release tablet, in 24 of 36 subjects (66.7%) during the treatment of the powder in capsule, in 20 of 35 subjects (57.1%) during the treatment of the formulated capsule (under fasting conditions), and in 21 of 36 subjects (58.3%) during the treatment of the formulated capsule (after meal). Adverse events for which a causal relationship to crizotinib could not be ruled out were observed in 19 of 35 subjects (54.3%), 22 of 36 subjects (61.1%), 20 of 35 subjects (57.1%), and 18 of 36 subjects (50.0%), respectively.

Adverse events reported by ≥3 subjects in either period were diarrhoea in 9 subjects (25.7%), nausea in 5 subjects (14.3%), headache in 4 subjects (11.4%), and fatigue in 3 subjects (8.6%) during the treatment of the immediate release tablet; diarrhoea in 13 subjects (36.1%), nausea in 10 subjects (27.8%), fatigue and headache in 5 subjects each (13.9%), and nasopharyngitis in 3 subjects (8.3%) during the treatment of powder in capsule; diarrhoea in 13 subjects (37.1%) and headache in 4 subjects (11.4%) during the treatment of the formulated capsule (under fasting conditions); and diarrhoea in 13 subjects (36.1%), nausea in 5 subjects (13.9%), and headache in 3 subjects (8.3%) during the treatment of the formulated capsule (after meal). Of these, headache in 2 subjects during the treatment of the immediate release tablet, nausea in 4 subjects and vomiting and headache in 2 subjects each during the treatment of the powder in capsule, and headache in 1 subject each during the treatment of the formulated capsule (under fasting conditions) and during the treatment of the formulated capsule (after meal) was rated as moderate in severity, while other events were rated as mild.

There were no serious adverse events in any of the treatment periods.

The adverse event leading to crizotinib discontinuation was hepatic enzyme increased observed in 1 of 35 subjects (2.9%) during the treatment of the immediate release tablets. A causal relationship to crizotinib was not ruled out for this adverse event.

4.(iv).(7) Foreign phase I study (Study A8081009)

Adverse events were observed in 6 of 6 subjects (100%) and a causal relationship to crizotinib was not ruled out for any of these adverse events.

Adverse events reported by ≥2 subjects were diarrhoea in 4 subjects (66.7%); all of them were rated as mild in severity.

There were no serious adverse events or adverse events leading to crizotinib discontinuation.

4.(iv).(8) Foreign phase I study (Study A8081015)

Adverse events were observed in 2 of 15 subjects (13.3%), 2 of 15 subjects (13.3%), and 4 of 15 subjects (26.7%), respectively, in the crizotinib alone group, the ketoconazole alone group, and the crizotinib + ketoconazole group. Adverse events for which a causal relationship to crizotinib could not be ruled out were observed in 2 of 15 subjects (13.3%), 0 of 15 subjects, and 1 of 15 subjects (6.7%), respectively.

Adverse events reported by ≥2 subjects were constipation in 2 subjects (13.3%) in the crizotinib + ketoconazole group; both events were rated as mild. In the crizotinib alone group and the ketoconazole alone group, there were no adverse events reported by ≥2 subjects.

There were no serious adverse events or adverse events leading to crizotinib discontinuation in any of the groups.

4.(iv).(9) Foreign phase I study (Study A8081016)

Adverse events were observed in 3 of 15 subjects (20.0%), 6 of 14 subjects (42.9%), and 3 of 14 subjects (21.4%), respectively, in the crizotinib alone group, the rifampicin alone group, and the crizotinib + rifampicin group. Adverse events for which a causal relationship to crizotinib could not be ruled out were observed in 2 of 15 subjects (13.3%), 0 of 14 subjects, and 1 of 14 subjects (7.1%), respectively.

Adverse events reported by ≥2 subjects were diarrhoea in 2 subjects (13.3%) in the crizotinib alone group, constipation in 3 subjects (21.4%) in the rifampicin alone group, and constipation in 2 subjects (14.3%) in the crizotinib + rifampicin group. All events were rated as mild.

There were no serious adverse events or adverse events leading to crizotinib discontinuation in any of the treatment groups.

4.(iv).(10) Global phase III study (Study A8081007)

This study is currently ongoing, and no detailed safety information in each treatment group is available at the present moment. As of the timepoint of the database snapshot preparation (October 27, 2010), serious adverse events were observed in 10 of 36 subjects (27.8%), and adverse events reported by ≥2 subjects were lung abscess and pneumonia in 2 subjects each (5.6%). Of these, a causal relationship to crizotinib could not be ruled out for pneumonia in 2 subjects.

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

A document-based inspection and data integrity assessment were conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application. As a result, there were no particular problems. Thus, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted product application documents.

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

GCP on-site inspection took place in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application (5.3.3.2.1, 5.3.5.2.1, 5.3.5.2.2). As a result, noncompliance with the procedures on the control of the study drug (failure to appropriately control the temperature of the study drug) was found at some clinical sites. Thus, although there are several items requiring improvements, PMDA has concluded that the clinical studies as a whole were conducted in compliance with GCP and that there should be no problem with conducting a regulatory review based on the submitted product application documents.

IV. Overall Evaluation

Based on the submitted data, PMDA concluded that the efficacy of crizotinib in patients with *ALK* -positive, unresectable, advanced or relapsed non-small cell lung cancer has been demonstrated and its safety is acceptable in view of its observed benefits. The product is a drug with a new active ingredient that exhibits an inhibitory effect on anaplastic lymphoma kinase (ALK) and its fusion protein, as well as on tyrosine kinase of hepatocyte growth factor receptor (c-Met) and recepteur d'origine nantais (RON), and thus has a clinical significance as an option for the treatment of *ALK*-positive, advanced or relapsed non-small cell lung cancer. As regards indications and items to be investigated after the market launch, PMDA will review them in further detail in the Expert Discussion

PMDA considers that crizotinib may be approved if it can be concluded based on comments from the Expert Discussion that there are no particular problems.

Review Report (2)

February 20, 2012

I. Product Submitted for Registration

[Brand name]	Xalkori Capsules 200 mg and 250 mg
[Non-proprietary name]	Crizotinib
[Applicant]	Pfizer Japan Inc.
[Date of application]	March 31, 2011

II. Content of the Review

The Expert Discussion and subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined below. 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) Clinical positioning and efficacy of crizotinib

As a result of the review as described in "4.(iii).B.(1) Clinical positioning of crizotinib" and "4.(iii).B.(2) Efficacy" of the Review Report (1), PMDA has reached the comprehensive conclusion that crizotinib is a drug that targets the oncogene driver of cancer cells and, judging from following findings, that it is expected to exhibit a certain level of efficacy against anaplastic lymphoma kinase (ALK)-positive non-small cell cancer (NSCLC), regardless of the history of chemotherapy, and that the product has clinical significance as an option for the treatment of the disease.

- Results of nonclinical studies [see "3.(i).B.(1) Mechanism of action of crizotinib and its efficacy on *ALK*-positive NSCLC" of the Review Report (1)]
- Results of the foreign phase I study (Study A8081001) and the global phase II study (Study A8081005) suggest that crizotinib is effective for patients with *ALK*-positive advanced or relapsed NSCLC.
- Crizotinib reduced the tumor size in patients with *ALK*-positive NSCLC regardless of the number of previous treatment regimens received.

However, PMDA has also concluded that the following information should be provided by the package insert, etc.: (i) in the application for crizotinib, the efficacy of crizotinib was evaluated mainly based on the response rate, and no information is available on the life-prolonging effect, and (ii) whether or not to administer crizotinib should be decided upon thorough consideration given to alternative treatments.

The applicant explained the tumor-shrinking effect of conventional antineoplastic agents in patients with *ALK*-positive NSCLC, as follows:
Results of a retrospective analysis on NSCLC patients (*J Clin Oncol*. 2009;27:4247-53) showed that the response rate of *ALK*-positive patients, epidermal growth factor receptor (EGFR) mutation-positive patients, and wild-type patients with neither mutation to chemotherapy containing platinum antineoplastic agent was 25% (3 of 12 patients), 50% (4 of 8 patients), and 35% (12 of 34 patients), respectively. Also, the response rate to EGFR inhibitors was 0% (0 of 10 patients), 70% (16 of 23 patients), and 13% (3 of 23 patients), respectively. These results suggest the possibility that the response rate of *ALK*-positive patients without a history of previous chemotherapy to chemotherapy containing platinum antineoplastic agent is comparable to that of wild-type patients, and that the response rate of *ALK*-positive patients to EGFR inhibitors is lower

compared with wild-type patients and EGFR-positive patients.

PMDA's conclusion that crizotinib is expected to have a certain level of efficacy in patients with *ALK*-positive NSCLC and thus has a clinical significance as an option for the treatment of the disease was supported by all expert advisors, together with the following comments:

- Usually, the response rate of NSCLC to the standard chemotherapy is approximately 40% in the primary treatment, 10% to 20% in the secondary and tertiary treatments, and ≤10% in the quaternary and subsequent treatments (e.g., *N Engl J Med*. 2006;355:2542-50, *J Clin Oncol*. 2008;26:3543-51, *N Engl J Med*. 2002;346:92-8, *J Clin Oncol*. 2004;22:785-94, *J Clin Oncol*. 2005;23:5892-9, *J Clin Oncol*. 2001;19:3210-8, *J Clin Oncol*. 2004;22:1589-97, *J Clin Oncol*. 2000;18:2354-62, *Clin Lung Cancer*. 2012;13:39-43, *Lung cancer*. 2010;69:323-9). Given the high response rate to crizotinib of patients in the tertiary and further treatment with only a limited existing treatment options available, as demonstrated in Studies A8081001 and A8081005 involving patients with *ALK*-positive NSCLC [see "4.(iii).B.(2).1) Efficacy evaluation" of the Review Report (1)], crizotinib should be approved as an option for the treatment of the disease although no information on the life-prolonging effect is available.

The following opinions were also given by expert advisors:

- Although the tumor biological finding that crizotinib targets tyrosine kinase of fusion proteins that are considered to be oncogene drivers [see "4.(iii).B.(1) Clinical positioning of crizotinib" of the Review Report (1)] is important, it is necessary to caution against overestimating this finding in the evaluation of crizotinib.
- Two global phase III studies* involving patients with *ALK*-positive NSCLC (in chemotherapy-naïve patients [Study A8081014] and in chemotherapy-treated patients [Study A8081007]) are currently ongoing. It is recommended that measures to be taken for the results of these studies be worked out in advance.
- In patients with *ALK*-positive NSCLC for whom existing standard chemotherapy is not indicated because of poor performance status (PS) or reduced major organ functions, the clinical positioning of crizotinib is determined only based on the results of a clinical study in these patients. Therefore, an appropriate caution is exercised to avoid the casual use of crizotinib in these patients.

*: The outlines of the 2 global phase III studies are as follows. Both studies are currently being conducted as comparative studies, and no evaluable data have been submitted.

- Study A8081007
  An open-label, randomized, parallel group, comparative study to compare the efficacy (primary endpoint, progression-free survival [PFS]; secondary endpoint, overall survival [OS]) and the safety between crizotinib alone and pemetrexed sodium hydrate (pemetrexed) or docetaxel hydrate alone, in patients with *ALK*-positive advanced or relapsed NSCLC who had received ≥1 chemotherapy regimen containing platinum antineoplastic agent.

- Study A8081014
  An open-label, randomized, parallel group, comparative study to compare the efficacy (primary endpoint, PFS; secondary endpoint, OS) and the safety between crizotinib alone and concomitant use of pemetrexed with cisplatin or concomitant use of pemetrexed with carboplatin, in patients with *ALK*-positive advanced or relapsed NSCLC without a history of previous treatment.

Taking account of the comments from the Expert Discussion, PMDA considers as follows:
Although there is a limit to the evaluation of crizotinib based on the results of the clinical studies, a certain level of response rate to the drug was achieved in patients with *ALK*-positive NSCLC regardless of the number of previous treatment regimens. Also, it is pointed out by expert advisors that a high response rate was observed particularly in patients in the tertiary and subsequent treatment for whom options of existing treatments are limited. Coupled with the tumor biological

findings, these results suggest that crizotinib is expected to have a certain level of efficacy in patients with *ALK*-positive NSCLC. Therefore, PMDA has concluded that crizotinib may be positioned as an option for the treatment of the disease at the moment.

However, the ultimate objective of treatment of lung cancer with antineoplastic agents is to prolong the life. Therefore, even for crizotinib with a limited indication, it is extremely important to show the usefulness of the drug in a comparative study using OS as the primary endpoint. The currently ongoing 2 global phase III studies involving patients with *ALK*-positive NSCLC will thus provide important information. Therefore, when results become available after successful completion of the studies, the relevant information should be appropriately provided without delay [see "(5) Post-marketing investigations]. Also, based on the results of these studies, the applicant should promptly re-examine, as appropriate, the details of the approval and the Precautions section of the package insert.

In addition, PMDA instructed the applicant to appropriately provide information on the PS of patients enrolled in Studies A8081001 and A8081005 to avoid casual use of crizotinib in patients with *ALK*-positive NSCLC for whom existing standard chemotherapy is not indicated because of poor performance status (PS) or reduced major organ functions, to which the applicant agreed.

(2) Safety

Based on the submitted study data, PMDA determined that the adverse events requiring caution in administering crizotinib are pneumonitis/interstitial lung disease (ILD), visual disturbance (e.g., diplopia, photopsia, vision blurred, visual field defect, visual impairment, vitreous floaters), hepatic function disorder, blood disorder, neuropathy, QT prolonged, bradycardia, thromboembolism, photosensitivity, and complicated renal cyst.

PMDA also considered as follows:

Attention should be paid to the occurrence of the above adverse events when crizotinib is administered. However crizotinib treatment is tolerable, as long as (a) the occurrence of adverse events is monitored and controlled; appropriate measures such as dose interruption, dose reduction, or treatment discontinuation are taken by physicians with adequate knowledge and experience in cancer chemotherapy; and (c) the safety of patients is ensured by the most careful attention to serious adverse events such as ILD and their control and preventive measures, including patient education.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion, with the following comments:

- In Studies A8081005 and A8081007, additional 8 cases of ILD were reported as serious adverse events from the date of the database snapshot preparation up to December 6, 2011 and 4 patients of them were Japanese. Given these results, it is mandatory to take extremely careful measures.
- Crizotinib-induced hepatic impairment developed during the early stage of treatment with crizotinib, with the median time to the onset being 22 days in Study A8081001 and 19 days in Study A8081005, and in 2 patients who died of hepatic failure, the failure occurred on Days 24 and 36, respectively, after the start of treatment with crizotinib. Therefore, liver function test should be carried out frequently during the early stage of the treatment with crizotinib.
- Since the incidence of gastrointestinal symptoms is high, vomiting (107 of 255 patients [42.0%]) in particular, it is recommended that measures to exercise caution should be considered.

Since fatal hepatic failure occurred after the regulatory submission [see "4.(iii).B.(3).4) Hepatic impairment" of the Review Report (1)], PMDA had asked the applicant, during the preparation

of Review Report (1), about the cautions to be exercised against crizotinib-induced hepatic impairment, to which the applicant explained the plan of periodically providing cautions to perform liver function tests in the package insert.

Taking account of the comments from the Expert Discussion, PMDA considers as follows:

(a) ILD

There were cases of crizotinib-induced ILD that resulted in death and, in 2 Japanese patients, ILD developed during the relatively early stage of treatment: one at 9 days and the other at 10 days after the start of administration [see "4.(iii).B.(3).2).a Incidences and its characteristic features"of the Review Report (1)], suggesting the necessity of more careful patient management during the early stage of administration. Therefore, with consideration given to the descriptions in the package inserts of related products, PMDA has concluded that the following description should be included in the Warnings section of the package insert to exercise caution.

- It has been reported that interstitial lung disease occured after administration of crizotinib, resulting in a fatal outcome in some cases. Therefore, patients should be closely monitored, such as by checking for early stage symptoms (e.g., shortness of breath, dyspnoea, cough, pyrexia) and by chest CT. If any abnormalities are observed, administration of crizotinib should be discontinued and appropriate measures should be taken. It has also been reported that interstitial lung disease occured in Japanese patients during the early stage of treatment with crizotinib, resulting in a fatal outcome in some cases. During the early stage of the treatment, patients should be closely monitored under hospitalized or equivalent conditions, and closely monitored for serious adverse drug reactions such as interstitial lung disease.

When a similar discussion was made on the caution related to hospitalization at the Expert Discussion on erlotinib hydrochloride, an oral drug in the same disease category as crizotinib, some advisors commented that patient management under hospitalized condition is appropriate for the early detection and treatment of ILD, whereas other expert advisors did not agree to the necessity of hospitalization (see "Review Report on Tarceva Tablet 25 mg, 100 mg, 150 mg, dated July 18, 2007"). With the establishment of regional core centers for cancer treatment in recent years, the system for cancer treatment in specialized medical institutions on an outpatient basis is now being put into place (e.g., deployment of physicians, nurses, and pharmacists with special knowledge and experience on cancer chemotherapy, establishment of outpatient chemotherapy room). When discussion was made on the cautions related to patient hospitalization at the Expert Discussion of bortezomib which caused ILD as an adverse event requiring caution, some expert advisors gave the opinion that, since hospitalization poses economical and psychological burdens on patients, the necessity of hospitalization should be re-considered when a certain use experience has been accumulated after the market launch (see "Review Report on Velcade Injection 3 mg, dated August 10, 2006").

PMDA considers that ensuring the check for early stage symptoms and systemic conditions is the most important for the early detection and treatment of ILD. Given the current status of cancer treatment system, management under hospitalization is not necessarily the appropriate method. For the time being, however, it is considered appropriate to exercise similar cautions as those for erlotinib hydrate, etc., because information on crizotinib-induced ILD is extremely limited. As pointed out by expert advisors at the Expert Discussion on bortezomib, it is recommended that, when a certain amount of data has been accumulated after the market launch, cautions related to hospitalized management be revised, as appropriate.

(b) Hepatic impairment

Crizotinib-induced hepatic impairment developed at a relative early stage and resulted in death in some patients, and predictive factors are unknown. Therefore, taking account of the comments

from the Expert Discussion, PMDA has concluded that the following description be included in the Warnings section of the package insert to raise caution.

- It has been reported that tepatic failure occured after administration of crizotinib, resulting in a fatal outcome in some cases. Patients should be closely monitored before and during crizotinib administration (frequently during the early phase of administration in particular) through periodic liver function tests. If any abnormalities are observed, appropriate measures, such as crizotinib discontinuation, should be taken.

(c) Gastrointestinal symptoms

Although the incidence of gastrointestinal symptoms such as vomiting and diarrhoea is high, most of them are Grade ≤2. Given that crizotinib is used by physicians with adequate knowledge and experience in cancer chemotherapy, it is appropriate to exercise caution in the Other Adverse Reactions section of the package insert, at the moment.

Based on the above, PMDA instructed the applicant to raise the above cautions in the Warnings section of the package insert and make sure to provide safety information on crizotinib using materials, as well, to which the applicant agreed.

PMDA asked the applicant to explain the most updated safety information after the preparation of Review Report (1), to which the applicant replied that no new safety information requiring changes of post-marketing safety measures were obtained.

PMDA accepted the applicant's explanation.

(3) Indications

As a result of its review included in "4.(iii).B.(1) Clinical positioning of crizotinib," "4.(iii).B.(2) Efficacy," "4.(iii).B.(3) Safety," and "4.(iii).B.(4) Indications" of the Review Report (1), PMDA considers that the indications for crizotinib should be "*ALK*-positive, unresectable, advanced or relapsed non-small cell lung cancer" for the following reasons: (i) crizotinib is expected to be effective for *ALK*-positive advanced or relapsed NSCLC and (ii) proposed indications should clearly state that because efficacy of crizotinib in adjuvant therapy has not been investigated and crizotinib is thus indicated only for patients with "unresectable" cancer.

Also, since it is currently unknown how crizotinib affects the survival period of these patients [see "(1) Clinical positioning and efficacy of crizotinib"], PMDA has concluded that this finding should be added to the following precautions proposed by the applicant.

[Precautions for Indications]

- Crizotinib should be administered to patients who are confirmed as *ALK* positive by pathologists or testing facilities with sufficient experience.
- The efficacy and safety of crizotinib in adjuvant therapy has not been established.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion, with the following comments:

- Immunohistological staining (IHC) and reverse transcription-polymerase chain reaction (RT-PCR) are reported as tests for *ALK* fusion gene but are not standardized at the moment. Consideration should be given to providing caution in the "Precautions for Indications" section that it is desirable to carry out, as appropriate, the test for *ALK* fusion gene using the fluorescence in situ hybridization method (FISH), the method used in Study A8081005, upon checking for the correlation among tests that may be clinically used.
- Cautions should be exercised, in clearly understandable terms using the package insert, regarding the fact that the life-prolonging effect of crizotinib in patients with *ALK*-positive

advanced or relapsed NSCLC is unknown.

Regarding the tests for *ALK* fusion gene, PMDA asked the applicant to explain the relationship between FISH recommended by the applicant and IHC or RT-PCR which may be used in clinical settings.

The applicant responded as follows:
Relationships between FISH (Vysis LSI ALK Break Apart Rearrangement Probes of Abbott Molecular Inc. was used) versus IHC and RT-PCR have been investigated. It is reported that the positive agreement rate and the negative agreement rate of the IHC method against the FISH method were 90.0% and 97.8%, respectively (*J Thorac Oncol.* 2011;6:459-65) and 100% and 95.8%, respectively (*J Thorac Oncol.* 2011;6:466-72), and that the rates for the RT-PCR method were 75.0% and 100%, respectively (*Cancer Genet.* 2011;204:45-52).

Taking account of the comments from the Expert Discussion, PMDA considers as follows:

(a) Test for *ALK* fusion gene

Test for *ALK* fusion gene by IHC or RT-PCR has not yet been standardized. Since the response rate observed in Studies A8081001 and A8081005 submitted in the application were obtained from patients selected by FISH. The information that FISH was used in these studies should be provided appropriately using the package insert. Also, information on the testing methods for *ALK* fusion gene should be collected continuously from published papers, academic meetings, and guidelines, and newly obtained useful information should be provided in an appropriate manner.

(b) Exercising caution about the effect of crizotinib on the overall survival, etc.

Before administering crizotinib to patients with *ALK*-positive advanced or relapsed NSCLC, the physician should thoroughly understand the efficacy and safety of the drug and give careful consideration also to the feasibility of alternative treatment. Therefore, the Clinical Studies section of the package insert should include (i) the outline of Studies A8081001 and A8081005 and response rates, and (ii) the caution statement that no study data are available on the effect of crizotinib on the overall survival, etc. In addition, caution should be provided in the Precautions for Indications section that "Phycians should select elibible patients for crizotinib treatment after careful consideration of the feasibility of alternative treatments based on full knowledge of the information provided in the Clinical Studies section as well as full understanding of the efficacy and safety of crizotinib," so that the physician clearly understands the fact that no information is currently available on the effect of crizotinib on the overall survival, etc.

- Crizotinib is designated as an orphan drug and, based on the results of the currently available results of Studies A8081001 and A8081005, PMDA has concluded that crizotinib may be approved for the treatment of patients with *ALK*-positive advanced or relapsed NSCLC [see "(1) Clinical positioning and efficacy of crizotinib"]. However, the overall survival achieved by crizotinib is now being investigated in the ongoing global phase III studies (Studies A8081014 and A8081007), and no such information is available at the moment.
- Based on the tumor biological findings, crizotinib is attracting attention in various clinical practice guidelines from the point of view of efficacy. However, crizotinib has also caused serious adverse events such as ILD and hepatic failure, and even deaths in some patients, requiring careful use for safety.

Based on the above, PMDA instructed the applicant to include the above information in the Clinical Studies section and the following statements in the Indications and Precautions for indications sections of the package insert, and the applicant accepted it.

[Indications]
ALK-positive, unresectable, advanced or relapsed NSCLC

[Precautions for Indications]
- Crizotinib should be administered to patients who are confirmed as *ALK* positive by pathologists or testing facilities with sufficient experience.
- The efficacy and safety of crizotinib in adjuvant chemotherapy has not been established.
- Physicians should select eligible patients for crizotinib treatment should be selected after careful consideration of the feasibility of alternative treatments based on adequate knowledge of the information provided in the Clinical Studies section as well as full understanding of the efficacy and safety of crizotinib.

(4) Dosage and Administration
Based on the results of review in "4.(iii).B.(5) Dosage and Administration" of the Review Report (1), PMDA has concluded that that the dosage and administration should be "The usual adult dosage is 250 mg of crizotinib administered orally twice daily every day. The dose may be adjusted according to the patient's condition," as proposed by the applicant.

PMDA has also concluded that criteria for crizotinib dose reduction, dose interruption and treatment discontinuation should be included in the Precautions for Dosage and Administration section of the package insert to raise caution. Regarding the method for dose reduction (200 mg twice daily [BID] at the first dose reduction, 250 mg once daily [QD] at the second dose reduction), since there are no patients who reduced the dose from 200 mg BID to 250 mg QD, including those in the ongoing clinical studies, the safety and efficacy of continued crizotinib administration using this dose reduction method is unknown. Therefore, information on the specific method for dose reduction, which is being investigated in clinical studies, should be provided by methods other than the package insert. Also, the fact that the withdrawal criteria had been set for "nonhaematological toxicity (as a whole)," "left ventricular contractile dysfunction," and "visual disturbance" in the clinical studies should be informed using materials, together with the detailed information.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion, with the following comments:
- The criteria for crizotinib dose reduction, dose interruption and treatment discontinuation due to hepatic impairment differ depending on the Grade of blood bilirubin level. The rationale for setting such criteria and their appropriateness should be confirmed.

PMDA asked the applicant to explain the justification for setting the criteria for crizotinib dose reduction and interruption and treatment discontinuation due to hepatic disorder in Studies A8081001 and A8081005.

The applicant responded as follows:
The criteria were set based on the US FDA guideline on drug-induced liver injury (Guidance for Industry. Drug-Induced Liver Injury: Premarketing Clinical Evaluation. July 2009). It is considered that, in patients with increased serum aminotransferase (AT) not accompanied by an increase in total bilirubin, continued drug administration rarely induces severe drug-induced liver injury, whereas patients with increases in both total bilirubin and serum AT are highly likely to develop severe drug-induced liver injury. For these reasons, 2 sets of criteria were established for dose reduction, dose interruption, and treatment discontinuation due to hepatic impairment, depending on the levels of total bilirubin and serum AT.

PMDA accepted the explanation of the applicant.

Taking account of the comments from the Expert Discussion, PMDA instructed the applicant to include the following statements in the Dosage and Administration and Precautions for Dosage and Administration sections, and the applicant accepted it. The term "every day" used in the proposed Dosage and Administration was considered unnecessary and deleted by the applicant.

[Dosage and Administration]
The usual adult dosage is 250 mg of crizotinib administered orally twice daily. The dose may be adjusted according to the patient's condition."

[Precautions for Dosage and Administration]
Crizotinib dose interruption, dose reduction, and treatment discontinuation due to adverse drug reactions should be done with consideration given to the following criteria, depending on the symptoms and severity.

<table>
<tr><th>Grade[1)]
Adverse drug reaction</th><th>1</th><th>2</th><th>3</th><th>4</th></tr>
<tr><td>Hematological[2)]</td><td colspan="2">Continue the same dose.</td><td>Withdraw crizotinib until the symptom improves to Grade ≤2. After recovery, resume the administration at the same dose as before the withdrawal.</td><td>Withdraw crizotinib until the symptom improves to Grade ≤2. After recovery, resume the administration starting from 200 mg twice daily.[3)]</td></tr>
<tr><td>ALT or AST increased with Grade ≤1 blood bilirubin increased</td><td colspan="2">Continue the same dose.</td><td colspan="2">Withdraw crizotinib until the symptom improves to Grade ≤1, or to baseline. After recovery, resume the administration starting from 200 mg twice daily.[4)]</td></tr>
<tr><td>ALT or AST increased with Grade 2 to 4 blood bilirubin increased[5)]</td><td>Continue the same dose.</td><td colspan="3">Discontinue the administration.</td></tr>
<tr><td>Interstitial lung disease</td><td colspan="4">Discontinue the administration.</td></tr>
<tr><td>QT interval prolonged</td><td colspan="2">Continue the same dose.</td><td>Withdraw crizotinib until the symptom improves to Grade ≤1. After recovery, resume the administration starting from 200 mg twice daily.[4)]</td><td>Discontinue the administration.</td></tr>
</table>

1: Grade according to NCI-CTCAE
2: Except lymphopenia not accompanied by clinical events such as opportunistic infection
3: In case of relapse, withdraw the administration until the symptom improves to Grade ≤2. After recovery, resume the administration at a further reduced dose. If a Grade 4 event relapses, discontinue the administration.
4: In case of relapse, withdraw crizotinib until the symptom improves to Grade ≤1. After recovery, resume the administration at a further reduced dose. If a Grade 3 or 4 event relapses, discontinue the administration.
5: Except patients with cholestasis or haemolysis

(5) Post-marketing investigations

The applicant plans to conduct a post-marketing all-case surveillance with a planned number of patients of 200 for analysis (52-week observation period, follow-up period up to 104 weeks). The priority surveillance items will include the following: ILD, QT prolonged, bradycardia, hepatotoxicity, visual disturbance, neutropenia/leukopenia, neuropathy, and renal cyst. [see "4.(iii).B.(6) Post-marketing investigations" of the Review Report (1)].

As a result of the review of the submitted plan for the post-marketing surveillance, PMDA has concluded as follows:

- Since the data submitted in the present application contain only a limited amount of

information on the safety of crizotinib in Japanese patients, it is necessary to promptly collect relevant information. Therefore, the post-market surveillance should be conducted involving all patients treated with crizotinib.

- Among adverse events requiring caution in administering crizotinib, ILD in particular may occur with a higher incidence in Japanese patients than in foreign patients. ILD resulted in death in some patients [see "4.(iii).B.(3).2) ILD" of the Review Report (1)]. Therefore, the number of patients analyzed should be adjusted so that predicting factors for ILD can be identified in the all-case surveillance.
- The maximum observation period may be set at 52 weeks, as planned by the applicant. The follow-up of patients treated with crizotinib for >52 weeks should be performed separately from the all-case surveillance so that the final results of the all-case surveillance can be obtained promptly. In addition, it is necessary to analyze the information obtained from the all-case surveillance at an early stage and, based on the results of the analysis, to re-design the surveillance plan.

The surveillance plan should be designed to make sure that the following information on the priority items of the all-case surveillance be collected:

- Characteristic features of ILD (e.g., patient background, imaging findings, severity, time to onset and outcome, outcome, treatment given, response to the treatment, predicting factors)
- Clinical characteristics of visual disturbance (e.g., time to onset, symptom duration, signs of aggravation)
- Safety of crizotinib in patients with hepatic impairment
- Safety of crizotinib in patients with severe renal impairment
- Clinical characteristics of neuropathy (e.g., reversibility)
- Incidence and clinical characteristics of photosensitivity (e.g., reversibility)

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion, with the following comments:

- To allow detailed investigation of ILD, the plan should be designed in such a way that the applicant can obtain the data of chest imaging in patients with ILD (i) before the start of crizotinib administration, (ii) during crizotinib administration, (iii) at the onset of ILD, and (iv) after treatment with corticoid or other drugs.
- It is recommended to collect information in the post-marketing surveillance on the safety and the method of dose reduction in patients in whom crizotinib dose is reduced, temporarily withdrawn, or discontinued.

PMDA considered it necessary to appropriately address the expert advisors' opinion on information collection from patients in whom crizotinib dose is reduced, interrupted, or discontinued as a result of chest imaging for ILD. Therefore, PMDA instructed the applicant to revise the design of the surveillance plan to allow the collection of the above information on patients with ILD, in addition to the revision to ensure information collection as described above. The applicant accepted it.

Taking also account of the comments from the Expert Discussion, PMDA instructed the applicant to re-examine the planned number of patinets analyzed to allow the analysis of predictive factors of ILD, etc.

The applicant responded as follows:
Currently, the incidence of ILD in Japanese patients in Studies A8081001, A8081005, A8081007, and A8081014 was 3.6% (4 of 111 patients*). Therefore, the incidence of crizotinib-induced ILD was assumed to be 4%. By referring to the results of surveillance on the predictive factors of ILD in other antineoplastic agents, the incidence of ILD in the low risk population is assumed to be 2.5%, and the planned number of patients is changed to 2000 to allow the detection, at a certain

statistical power by χ^2 test with a significance level of 0.05, of factors with a risk ratio of 2.0 when the range of the case composition ratio of factors studied is between 1:3 and 3:1. Assuming that 2000 patients are analyzed by χ^2 test with a significance level of 0.15, the statistical power is ≥85% when the composition ratio is between 1:3 and 3:1. The applicant considers that it is possible to detect and investigate potential predictive factors by multivariate analysis of these and other factors.

*: Studies A8081007 and A8081014 are currently ongoing randomized, parallel group, comparative study and the accurate number of patients is unknown. The calculation is based on the assumption that, a half of patients treated with the investigational product on or before December 6, 2011 received crizotinib.

PMDA further instructed the applicant to collect the follow-up information of patients treated with crizotinib for >52 weeks separately from the all-case surveillance so that the final results of the all-case surveillance can be obtained promptly, and to address the PMDA's conclusion that it is necessary to analyze the information obtained from the all-case surveillance at an early stage and, based on the results of the analysis, to re-design the surveillance plan.

The applicant responded as follows:
Re-examination of the available data showed that there were no adverse events that occurred with an increased incidence with the increase of treatment duration. Therefore, the follow-up of patients treated with crizotinib for >52 weeks will not be performed. Information obtained from the all-case surveillance will be subjected to analysis at an early stage and, based on the results of the analysis, additional safety measures will be taken and the surveillance plan will be re-designed, as necessary.

PMDA accepted the explanation of the applicant. Results of the early stage analysis of data obtained from the all-case surveillance should be provided to the medical practice, as appropriate.

Since the currently available safety and efficacy information on crizotinib is extremely limited, results of the ongoing 2 global phase III studies and other information to be obtained in future are very important. PMDA instructed the applicant that, when new information related to crizotinib, including the results of clinical studies, becomes available, it should be promptly supplied to the medical practice, to which the applicant agreed.

(6) Actions to minimize risk after the market launch
The applicant explained that they plan to carry out the following activities to minimize risks after the market launch: (i) to set the requirements for medical institutions and to control the distribution of the product, (ii) to promote confirmation and proper use of patient background at the advanced registration for the all-case surveillance, and (iii) to provide information to healthcare professionals and patients using materials.

PMDA has concluded as follows:
Taking account of the following, the applicant's planned activities to minimize risks are acceptable: (i) since the target molecule of crizotinib is different from that of existing antineoplastic agents, the safety profile of crizotinib may be different from those of the existing antineoplastic agents, and (ii) among adverse events requiring caution in administering crizotinib, ILD in particular may occur with a higher incidence in Japanese patients than in foreign patients, and ILD resulted in death in some of the patients.

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

PMDA considers as follows:
The applicant's planned individual activities for minimizing risks should be re-examined when

information on the safety profile of crizotinib in routine clinical use, particularly safety information related to predictive factors of ILD, becomes available. For this purpose, the risk-minimizing activities, (i) and (ii) above in particular, should be re-examined, including whether or not to terminate the activities, at the latest when results of the all-case surveillance are obtained.

III. Addition to Review Report (1)

Below are described matters that were being asked to the applicant during the preparation of the Review Report (1).

3. Non-clinical data

3.(ii) Summary of pharmacokinetic studies

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

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

The applicant explained the results of 2 studies on enzyme inhibition and induction by crizotinib obtained after the regulatory submission, as follows:

(a) Human liver cells obtained from 2 subjects were treated with crizotinib (0.25-7 μmol/L) or with the positive control rifampicin (10 μmol/L) for 3 days, and expression levels (mRNA) of *CYP2B6*, *2C8*, *2C9*, *2C19*, and *3A4* genes were measured. As a result, the expression levels of *CYP2B6*, *2C8*, and *3A4* genes showed statistically significant increases compared with the vehicle control in the liver cells of both subjects, with the maximum increase being 3.6-, 2.4-, and 10-fold, respectively. The expression level of *CYP2C9* gene showed a statistically significant increase in liver cells of 1 of 2 subjects, with the maximum 2.2-fold increase, whereas no statistically significant increase in the expression level was observed in the liver cells of the other subject in the presence of crizotinib or rifampicin. The expression level of *CYP2C19* gene was not changed in the liver cells of either subject. No increase in the expression level was observed even in the presence of rifampicin, suggesting that the ability of crizotinib to induce *CYP2C19* may not have appropriately evaluated in this experiment.

(b) Substrates of CYP isoforms (1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A) were incubated with human liver microsomes in the presence of crizotinib (0.1-100 μmol/L). As a result, IC_{50} against CYP2B6 and 3A (nifedipine oxidation and testosterone 6β-hydroxylation) was 19, 13, and 14 μmol/L, respectively, and >30 μmol/L for CYP1A2, 2C8, 2C9, 2C19, 2D6, and 3A (midazolam 1'-hydroxylation). The results were similar to those described in "3.(ii).A.(5).1) Enzyme inhibition" of the Review Report (1).

Crizotinib (0.1-100 μmol/L) was incubated with human liver microsomes for 30 minutes in the presence or absence of NADPH. As a result, crizotinib inhibited the enzyme activity of CYP2B6 and 3A (nifedipine oxidation, testosterone 6β-hydroxylation, midazolam 1'-hydroxylation) in a time-dependent manner in the presence of NADPH. After preincubation with crizotinib, IC_{50} decreased to 1/2, 1/21, 1/34, and 1/115, respectively. In contrast, crizotinib did not inhibit CYP2C8, 2C9, and 2C19 in a time-dependent manner, suggesting that the expression level (mRNA) of *CYP* gene can be used for evaluating the inducing effect of crizotinib on these CYP isoforms.

Thus, crizotinib increased the expression level of *CYP2B6* gene in the study (a) but inhibited the enzyme activity of CYP2B6 in a time-dependent manner in the study (b), which suggests that the actual change of CYP2B6 enzyme activity is smaller than that estimated using mRNA level. In order to clarify this point, an *in vitro* study is being conducted with human liver cells using the enzyme activity to evaluate the CYP2B6-inducing activity of crizotinib. Also, an *in vitro* study using human liver microsomes is being carried out to investigate the details (k_{inact} and Ki) of the time-dependent inhibition of CYP2B6 by crizotinib. Reports of both studies are scheduled to be

completed in April 2012. Whether or not it is necessary to exercise cautions on CYP2B6-mediated pharmacokinetic interactions of crizotinib and/or to conduct an additional study will be decided based on the results of these *in vitro* studies.

In the study (a) metioned above, although crizotinib increased the expression levels of *CYP2C8* and *2C9* genes, the extent of the increase was smaller than that caused by the positive control rifampicin (6.9- and 3.3-fold increase for CYP2C8 and 2C9, respectively), which suggested that administration of crizotinib 250 mg BID is unlikely to cause marked pharmacokinetic interactions with drugs that serve as substrates for CYP2C8 and 2C9.

PMDA largely accepted the explanation of the applicant. However, results of the study (a) failed to show rifampicin-induced increases in the expression levels of *CYP2C19* gene (2 of 2 subjects) and *CYP2C9* gene (1 of 2 subjects), suggesting that the ability of crizotinib to induce these CYP isotypes was not evaluated appropriately. Therefore, PMDA considers that it is recommended that information on the ability of crizotinib to induce these CYP isotypes should be continuously collected, by conducting additional studies as appropriate. Also, information on the findings related to the pharmacokinetic interactions of crizotinib, including those obtained from the ongoing and future studies, should be adequately provided to the medical practice.

IV. Overall Evaluation

Based on the result of the review, PMDA has concluded that the product may be approved for the indications and dosage and administration that have been modified as shown below, provided that appropriate cautions will be included in the package insert and information concerning the proper use of crizotinib will be provided appropriately after market launch, the compliance with the proper use of crizotinib will be ensured under the supervision of a physician with adequate knowledge and experience in cancer chemotherapy at medical institutions with adequate facilities for the treatment of emergencies. The re-examination period of crizotinib is 10 years, the drug substance and the drug product are both classified as powerful drugs, and the product is not classified as a biological product or a specified biological product.

[Indication]	*ALK*-positive, unresectable, advanced or relapsed non-small-cell lung cancer
[Dosage and administration]	The usual adult dosage is 250 mg of crizotinib administered orally twice daily. The dose may be adjusted according to the patient's condition.

[Conditions for approval]

1. The applicant is required to conduct a drug use-results survey involving all patients treated with the product after the market launch until data from a certain number of patients have been accumulated in order to grasp the demographic information of the treated patients, since the product has been studied in only a limited number of patients in the Japanese clinical studies. At the same time, data on the safety and efficacy of the product should be collected without delay and necessary measures should be taken to ensure proper use of the product.
2. The applicant is required to take necessary measures to ensure that the product will be administered only under the supervision of a physician who is familiar with the diagnosis and chemotherapy treatment of lung cancer and is also fully capable of managing risks etc. associated with the product, at a medical institution with facilities that allow the physician to perform those duites, along with a supervising pharmacist (at a pharmacy) who is familiar with the chemotherapy and risk managment.

[Warnings]

1. The product should be administered only to patients who are considered eligible for the therapy given under the supervision of a physician with adequate knowledge and experience in cancer chemotherapy at medical institutions with adequate facilities for the treatment of emergencies. Before the initiation of the treatment, the physician must obtain informed consent from the patient or his/her family member after providing a full explanation about the efficacy and risk of the product (e.g., particularly, initial symptoms of interstitial lung diseases, precautions during the treatment, and the information that some deaths have been reported).
2. It has been reported that interstitial lung disease occured after administration of crizotinib, resulting in a fatal outcome in some cases. Therefore, patients should be closely monitored, such as by checking for early stage symptoms (e.g., shortness of breath, dyspnoea, cough, pyrexia) and by chest CT. If any abnormalities are observed, administration of crizotinib should be discontinued and appropriate measures should be taken. It has also been reported that interstitial lung disease occured in Japanese patients during the early stage of treatment with crizotinib, resulting in a fatal outcome in some cases. During the early stage of the treatment, patients should be closely monitored in hospital or under equivalent conditions, and closely monitored for serious adverse events such as interstitial lung disease.
3. It has been reported that hepatic failure occured after administration of crizotinib, resulting in a fatal outcome in some cases. Patients should be closely monitored before and during the crizotinib treatment (frequently during the early phase of treatment in particular) through periodic liver function tests. If any abnormalities are observed, appropriate measures, such as crizotinib discontinuation, should be taken.

[Contraindications]

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

[Precautions for Indications]

1. Crizotinib should be administered to patients who are confirmed as *ALK* positive by pathologists or testing facilities with adequate experience.
2. The efficacy and safety of crizotinib in adjuvant chemotherapy has not been established.
3. Physicians should select eligible patients for crizotinib treatment after careful consideration of the feasibility of alternative treatments based on adequate knowledge of the information provided in the Clinical Studies section as well as full understanding of the efficacy and safety of crizotinib.

[Precautions for Dosage and Administration]

Dose interruption, dose reduction, or treatment discontinuation due to adverse drug reactions should be done with consideration given to the following criteria, depending on the symptoms and severity.

<table>
<tr><th>Grade[1)]
Adverse drug reaction</th><th>1</th><th>2</th><th>3</th><th>4</th></tr>
<tr><td>Hematological[2)]</td><td colspan="2">Continue the same dose.</td><td>Withdraw crizotinib until the symptom improves to Grade ≤2. After recovery, resume the administration at the same dose as before the withdrawal.</td><td>Withdraw crizotinib until the symptom improves to Grade ≤2. After recovery, resume the administration starting from 200 mg twice daily. [3)]</td></tr>
<tr><td>ALT or AST increased with Grade ≤1 blood bilirubin increased</td><td colspan="2">Continue the same dose.</td><td colspan="2">Withdraw crizotinib until the symptom improves to Grade ≤1, or to baseline. After recovery, resume the administration starting from 200 mg twice daily. [4)]</td></tr>
<tr><td>ALT or AST increased with Grade 2 to 4 blood bilirubin increased[5)]</td><td>Continue the same dose.</td><td colspan="3">Discontinue the administration.</td></tr>
<tr><td>Interstitial lung disease</td><td colspan="4">Discontinue the administration.</td></tr>
<tr><td>QT interval prolonged</td><td colspan="2">Continue the same dose.</td><td>Withdraw crizotinib until the symptom improves to Grade ≤1. After recovery, resume the administration starting from 200 mg twice daily. [4)]</td><td>Discontinue the administration.</td></tr>
</table>

1: Grade according to NCI-CTCAE
2: Except lymphopenia not accompanied by clinical events such as opportunistic infection.
3: In case of relapse, withdraw the administration until the symptom improves to Grade ≤2. After recovery, resume the administration at a further reduced dose. If a Grade 4 event relapses, discontinue the administration.
4: In case of relapse, withdraw crizotinib until the symptom improves to Grade ≤1. After recovery, resume the administration at a further reduced dose. If a Grade 3 or 4 event relapses, discontinue the administration.
5: Except patients with cholestasis or haemolysis