Report on the Deliberation Results

June 10, 2014

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

[Brand name]	Alecensa Capsules 20 mg, and Alecensa Capsules 40 mg
[Non-proprietary name]	Alectinib Hydrochloride (JAN*)
[Applicant]	Chugai Pharmaceutical Co., Ltd.
[Date of application]	October 7, 2013

[Results of deliberation]
In the meeting held on May 26, 2014, the Second Committee on New Drugs concluded that the products may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

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

[Conditions for approval]
The applicant is required to:

1. Conduct a drug use-results survey covering all patients treated with alectinib after the market launch until data have been accumulated from a certain number of patients, in order to grasp the characteristics of patients treated with alectinib, since only a limited number of patients participated in the Japanese clinical studies. At the same time, collect data on the safety and efficacy of alectinib without delay and take necessary measures to ensure proper use of alectinib.
2. Take necessary measures to ensure that alectinib is used only under the supervision of a physician experienced in the diagnosis of lung cancer and chemotherapy in a medical institution capable of controlling the risks associated with treatment, and by a supervising pharmacist with knowledge about the use of alectinib.

**Japanese Accepted Name (modified INN)*

Review Report

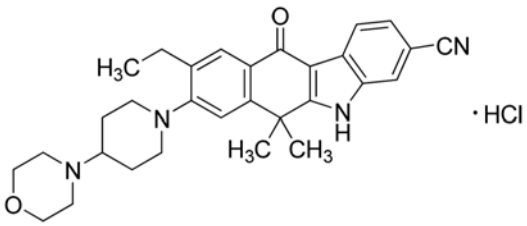
May 16, 2014

The Pharmaceuticals and Medical Devices Agency

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

[Brand name]	Alecensa Capsules 20 mg, and Alecensa Capsules 40 mg
[Non-proprietary name]	Alectinib Hydrochloride
[Applicant]	Chugai Pharmaceutical Co., Ltd.
[Date of application]	October 7, 2013
[Dosage form/Strength]	Each capsule contains 21.51 mg or 43.02 mg of Alectinib Hydrochloride (corresponding to 20 mg or 40 mg of alectinib).
[Application classification]	Prescription drugs (1) Drugs with a new active ingredient

[Chemical structure]



Molecular formula: $C_{30}H_{34}N_4O_2 \cdot HCl$

Molecular weight: 519.08

Chemical name: 9-Ethyl-6,6-dimethyl-8-[4-(morpholin-4-yl)piperidin-1-yl]-11-oxo-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carbonitrile monohydrochloride

[Items warranting special mention]

Orphan drug (Designation number [25 yaku] No. 316, Notification No. 0913-9 from the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW, dated September 13, 2013)

[Reviewing office] Office of New Drug V

Review Results

May 16, 2014

[Brand name] Alecensa Capsules 20 mg, and Alecensa Capsules 40 mg
[Non-proprietary name] Alectinib Hydrochloride
[Applicant] Chugai Pharmaceutical Co., Ltd.
[Date of application] October 7, 2013
[Results of review]
Based on the data submitted by the applicant, the Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that these products show a certain level of efficacy in the treatment of anaplastic lymphoma kinase (*ALK*) fusion gene-positive, unresectable, recurrent or advanced non-small cell lung cancer, and that the safety of these products is acceptable in view of their observed benefits. PMDA believes that the applicant should further investigate the occurrence of interstitial lung disease, hepatic function disorder, neutrophil count decreased, and white blood cell count decreased in the post-marketing surveillance of these products.

As a result of its regulatory review, PMDA has concluded that these products may be approved for the intended use and dosage regimen as shown below, with the following conditions.

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

[Dosage and administration] The usual adult dose is 300 mg of alectinib given orally twice daily.

[Conditions for approval]
The applicant is required to:

1. Conduct a drug use-results survey covering all patients treated with alectinib after the market launch until data have been accumulated from a certain number of patients, in order to grasp the characteristics of patients treated with alectinib, since only a limited number of patients participated in the Japanese clinical studies. At the same time, collect data on the safety and efficacy of alectinib without delay and take necessary measures to ensure proper use of alectinib.
2. Take necessary measures to ensure that alectinib is used only under the supervision of a physician experienced in the diagnosis of lung cancer and chemotherapy and in a medical institution capable of controlling the risks associated with treatment, and by a supervising pharmacist with knowledge about the use of alectinib.

Review Report (1)

April 7, 2014

I. Product Submitted for Registration

[Brand name] Alecensa Capsules 20 mg, and Alecensa Capsules 40 mg

[Non-proprietary name] Alectinib Hydrochloride

[Applicant] Chugai Pharmaceutical Co., Ltd.

[Date of application] October 7, 2013

[Dosage form/Strength] Each capsule contains 21.51 mg or 43.02 mg of Alectinib Hydrochloride (corresponding to 20 mg or 40 mg of alectinib).

[Proposed indication] *ALK* fusion gene-positive, unresectable, recurrent or advanced non-small cell lung cancer

[Proposed dosage and administration]

The usual adult dose is 300 mg of alectinib given orally twice daily.

II. Summary of the Submitted Data and Outline of 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) Drug overview

Studies on non-small cell lung cancer (NSCLC) have revealed that an inversion involving the anaplastic lymphoma kinase (ALK) gene locus generates ALK fusion proteins such as an echinoderm microtubule-associated protein-like 4 (EML4)-ALK fusion protein (EML4-ALK), which contributes to the growth and survival of cancer cells as well as tumorigenesis in normal cells (*Nature.* 2007;448:561-6, and others). The *ALK* fusion gene-positive NSCLC patients are reported to account for 2% to 13% of NSCLC patients (*Nature*. 2007;448:561-6, and others).

Alectinib Hydrochloride (referred to as "alectinib" hereinafter) is a tyrosine kinase inhibitor developed by the applicant, and is thought to inhibit tumor growth by inhibiting the phosphorylation of ALK.

In Japan, crizotinib, a drug that has inhibitory effect on the phosphorylation of ALK similarly to alectinib, has been approved for the treatment of *ALK* fusion gene-positive, unresectable, recurrent or advanced NSCLC.

(2) Pharmaceutical development

As of February 2014, there are no countries or regions where alectinib has been approved.

In Japan, the applicant has been conducting a phase I/II clinical study of alectinib (referred to as "Study AF-001JP" hereinafter) in patients with *ALK* fusion gene-positive NSCLC since August 2010. In November 2013, a phase III study of alectinib in patients with *ALK* fusion gene-positive NSCLC was initiated in order to investigate the efficacy and safety of alectinib as first- or second-line treatment.

In the United States, a phase I/II study of alectinib (Study AF-002JG/NP28761) in patients with *ALK* fusion gene-positive NSCLC was initiated in May 2012. This study is being conducted by F. Hoffmann-La Roche.*

In October 2013, the applicant submitted a new drug application for alectinib in Japan mainly on the basis of the results of Study AF-001JP.

* Study AF-002JG/NP28761 was originally initiated by the applicant, but has been conducted by F. Hoffmann-La Roche since December 2012.

Alectinib was designated as an orphan drug in September 2013 with the expected indication of *ALK* fusion gene-positive, unresectable, recurrent or advanced NSCLC (Designation Number [25 yaku] No. 316).

2. Data relating to quality

2.A. Summary of the submitted data

2.A.(1) Drug substance

2.A.(1).1) Characterization

The drug substance is a white lumpy powder and has been determined for descriptions, optical rotation, solubility, hygroscopicity, melting point, pH, acid dissociation constant, particle size, distribution coefficient, and polymorphism. [redacted] The chemical structure of the drug substance has been confirmed by elemental analysis, mass spectrometry, ultraviolet-visible spectrophotometry, infrared spectrophotometry (IR), and nuclear magnetic resonance spectroscopy (^{1}H-NMR, and ^{13}C-NMR).

2.A.(1).2) Manufacturing method

[redacted]

The following assessments are made using a quality by design (QbD) approach.

- Critical quality attributes (CQA) identified for the drug substance: [redacted]
- Formulation of control strategies based on the identified CQA.

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

[redacted]

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

The following stability tests were conducted for the drug substance. The photostability study revealed that the drug substance is unstable to light. The primary batches and confirmatory batches were manufactured by methods and processes representative of and simulating those to be applied on a full production scale batch.

Stability studies of the drug substance

Study	Type	Number of batches tested	Temperature	Humidity	Storage form	Duration of storage
Long-term testing	Primary batch	3 pilot scale batches	25°C	60% RH	[redacted]	[redacted] or [redacted] months
	Confirmatory batch	1 pilot scale batch 2 production batches				[redacted] months
Accelerated testing	Primary batch	3 pilot scale batches	40°C	75% RH		6 months
	Confirmatory batch	1 pilot scale batch 2 production batches				

[redacted]

2.A.(2) Drug products

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

The drug product is rapid-release capsules containing 21.51 mg or 43.02 mg of alectinib hydrochloride (corresponding to 20 mg or 40 mg of alectinib). The drug product contains lactose hydrate, microcrystalline cellulose, sodium starch glycolate, hydroxypropylcellulose, sodium lauryl sulfate, and magnesium stearate as excipients.

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

The drug product is manufactured through processes consisting of raw material mixing, granulation, wet sizing, drying, dry sizing, blending, and capsule filling.

[redacted]

The following assessments are made using a QbD approach.

- CQA specified identified for the drug product: [redacted]
- CQA for intermediate substances: [redacted]
- Estimation of critical processes and parameters and formulation of CQA control strategy

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

Specifications for the drug product have been set for appearance, identification (HPLC and ultraviolet spectra), purity tests (related substances [HPLC]), uniformity of dosage units (content uniformity [HPLC]), microbial limits, dissolution (ultraviolet-visible spectrophotometry), and assay (HPLC).

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

The following stability tests were conducted for the drug product. The photostability study revealed the drug product is photostable.

Stability tests of drug product

Contents	Study	Type	Number of batches tested	Temperature	Humidity	Storage form	Duration of storage
20 mg	Long-term testing	Primary batch	2 small-scale production batches 1 production batch	25°C	60% RH	[redacted]	Small-scale production batches: 30 or [redacted] months Production batches: [redacted] months
		Confirmatory batch	1 small-scale production batch 2 production batches				[redacted] months
	Accelerated testing	Primary batch	2 small-scale production batches 1 production batch	40°C	75% RH		6 months
		Confirmatory batch	1 small-scale production batch 2 production batches				
40 mg	Long-term testing	Primary batch	2 small-scale production batches 1 production batch	25°C	60% RH		Small-scale production batches: 30 or [redacted] months Production batches: [redacted] months
		Confirmatory batch	3 production batches				[redacted] months
	Accelerated testing	Primary batch	2 small-scale production batches 1 production batch	40°C	75% RH		6 months
		Confirmatory batch	3 production batches				

A small-scale batch is defined as a batch smaller than the pilot scale batch.

[redacted] The long-term testing of the primary and confirmatory batches is planned to be continued for up to [redacted] months.

2.B Outline of the review by PMDA

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

Shelf life for the drug product

The applicant proposed a shelf life for the drug product of 30 months according to the results of the long-term stability testing of the primary batches. However, only 1 of the batches used by the applicant was larger than the pilot scale [see "2.A.(2).4) Stability of drug product"], despite a guideline to ensure that 2 of the 3 batches used in the long-term stability testing of drug product should be at least pilot scale (PFSB/ELD Notification No. 0603001, dated June 3, 2003, referred to as the "ICH Q1A Guideline" hereinafter). [redacted]

[redacted]

PMDA requested the applicant to explain the effects of differences in manufacturing scale and packaging on the stability of drug product, and the applicant responded as follows.

The following results indicate that manufacturing scale does not affect the stability of the drug product.
[redacted]

[redacted]

PMDA considers as follows:
The shelf life of drug product should in principle be set on the basis of the results of long-term testing conducted in accordance with the ICH Q1A guideline. However, PMDA may accept the applicant's explanations that the drug product will be manufactured at a small scale and that manufacturing scale and packaging do not affect or only slightly affect the shelf life. Considering the submitted data that suggest the high clinical benefits of the drug product, PMDA concluded that it is acceptable to set a shelf life of 30 months on the basis of the above results of the long-term storage testing of the drug product.

3. Non-clinical data

In this section, the dose and concentration of alectinib are expressed in free base equivalents.

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) Inhibition of the phosphorylation of anaplastic lymphoma kinase

i) Studies using recombinant proteins (Reports PHM[redacted]-0213 and PHM[redacted]-0054)

The inhibitory effects of alectinib on phosphorylation of kinases including anaplastic lymphoma kinase (ALK) were evaluated using recombinant proteins by either a time-resolved fluorescence resonance energy transfer (TR-FRET) assay or fluorescence polarization technique. The following table summarizes IC_{50} values for enzymes tested.

Inhibitory effects of alectinib on phosphorylation of kinases (recombinant proteins)

Kinase	IC_{50} value (nmol/L)
ALK (wild type)	1.9 (+0.25, -0.22)
ALK (C1156Y)*1	0.93 (+0.15, -0.13)
ALK (F1174L)*2	1.0 (+0.14, -0.12)
ALK (L1196M)*1	2.1 (+0.44, -0.37)
ALK (R1275Q)*2	3.5 (+0.32, -0.30)
INSR	550 (+45, -42)
KDR	1,400 (+180, -160)
ABL, EGFR, FGFR2, HER2, IGF1R, JAK1, KIT, c-MET, PDGFRβ, SRC, AKT1, Aurora A, CDK1, CDK2, MEK1, PKA, PKCα, PKCβ1, PKCβ2, Raf-1	> 5,000

Geometric mean (standard deviation); n = 3; *1, Crizotinib-resistant mutations; *2, activating mutation

ii) Study using cell lines (Report PHM[redacted]-0237S [reference data])

The inhibitory effect of alectinib on the phosphorylation of ALK was assessed using the NCI-H2228 cell line derived from a patient with microtubule-associated protein-like 4 (EML4)-*ALK* fusion gene-positive, non-small cell lung cancer (NSCLC) and KARPAS-299 cell line derived from a patient with nucleophosmin (NPM)-*ALK* fusion gene-positive, anaplastic large cell lymphoma. After immunoprecipitation using anti-phosphotyrosine antibodies, the phosphorylation of ALK was determined by immunoblot technique using an anti-ALK antibody for the NCI-H2228 cell line and an anti-phosphorylated ALK antibody for the KARPAS-299 cell line. The results indicated that alectinib suppresses the phosphorylation of ALK.

3.(i).A.(1).2) Interactions of alectinib with ALK kinase domains (Report [redacted]BB00288 [reference data], Cancer Cell 2011; 19: 679-90 [reference data])

An X-ray crystal structure analysis conducted to investigate interactions between alectinib and ALK

kinase domains (recombinant proteins) revealed that alectinib interacts with M1199 of ALK via hydrogen bonding, L1196 via CH/π bonding, and K1150, E1167 and others via hydrophilic interactions. According to the applicant, the presence of these amino-acid residues in the ATP binding site of ALK suggests that alectinib binds to the ATP binding site of ALK.

An *in silico* analysis of the interaction between alectinib and L1196 using a 3D structural model of ALK (L1196M) revealed that the interaction between alectinib and L1196 via CH/π bonding is maintained. The applicant explained that the results of this study support from the aspect of structure that the inhibitory effect of alectinib on mutant ALK (L1196M) is comparable in degree to that on the wild type ALK.

3.(i).A.(1).3) Growth inhibitory effects on cell lines derived from *ALK* fusion gene-positive tumors (Reports PHM[redacted]-0105, PHM[redacted]-0067, PHM[redacted]-0057, PHM[redacted]-0058, PHM[redacted]-0242S [reference data], PHM[redacted]-0243S [reference data], and PHM[redacted]-0020S [reference data])

i) *In vitro*

(a) NSCLC cell lines

The antiproliferative effect of alectinib on the *ALK* fusion gene-positive cell line NCI-H2228 was assessed by determining intracellular ATP levels, and the IC_{50} value was 12 nmol/L. Also, the antiproliferative effect of alectinib on *ALK* fusion gene-negative NSCLC cell lines was investigated by the same method, using the PC-9 cell line harboring epithelial growth factor receptor (EGFR) exon 19 deletion, the NCI-H1993 cell line with hepatocyte growth factor receptor (c-MET) gene amplification, and the A549 cell line with an activating mutation of Kirsten Rat sarcoma viral oncogene homolog (KRAS); the IC_{50} values for these 3 lines were 400 nmol/L, ≥1000 nmol/L, and ≥1000 nmol/L, respectively.

(b) Cell lines derived from tumors other than NSCLC

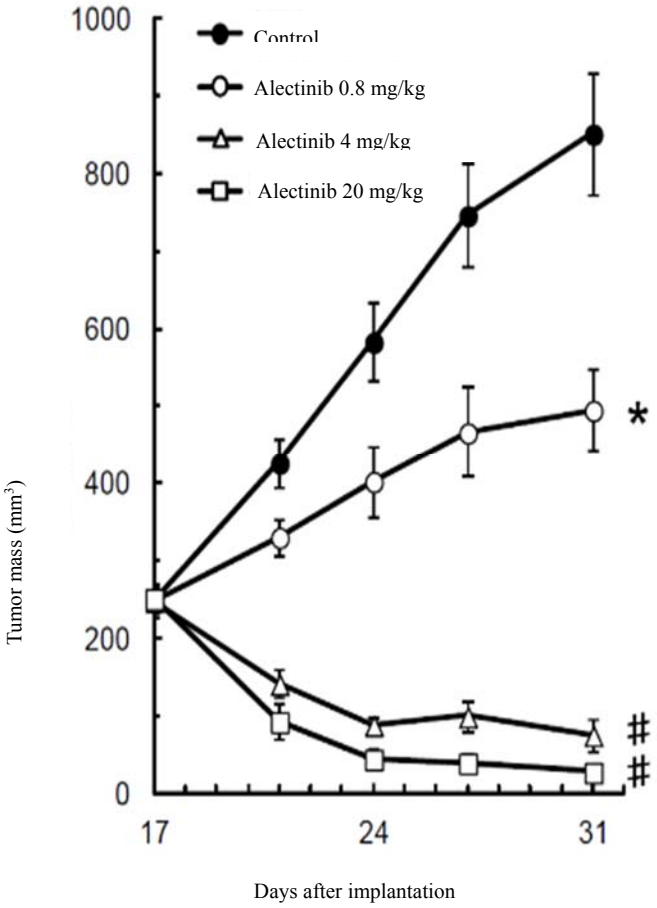
The antiproliferative effects of alectinib on the SR and KARPAS-299 cell lines derived from *ALK* fusion gene-positive human anaplastic large-cell lymphoma cells were assessed by determining intracellular ATP levels, and the IC_{50} values were 14 nmol/L for both cell lines. In a study of the antiproliferative effect of alectinib using the same method, the IC_{50} value of alectinib for the U-937 cell line derived from *ALK* fusion gene-negative human histiocytic lymphoma cells was ≥1000 nmol/L.

ii) *In vivo*

Using severe combined immunodeficiency (SCID) mice implanted subcutaneously with NCI-H2228 cells, the effects of alectinib of inhibiting tumor growth and phosphorylation of ALK were evaluated. From 17 days after implantation (with a tumor volume between 220 and 280 mm^3), animals received alectinib orally (at doses of 0.8, 4, and 20 mg/kg) once daily for 14 days, and the tumor volume was calculated [see the figure below]. In a study using immunoprecipitation with anti-phosphotyrosine antibodies followed by immunoblot analysis with an anti-ALK antibody, the phosphorylation of ALK

in NCI-H2228 cells implanted to SCID mice was inhibited 4 hours after a single administration of alectinib (20 mg/kg). Control animals received vehicle.

Alectinib did not inhibit tumor growth in SCID mice subcutaneously implanted with A549 cells.



Antiproliferative effect of alectinib

Mean ± standard deviation; n = 7; * $P = 0.0006$ vs. the vehicle control; # $P < 0.0001$ vs. the vehicle control (Dunnett's test)

In SCID mice subcutaneously implanted with KARPAS-299 cells and NB-1 cells, a cell line derived from human neuroblastoma cells with amplification of *ALK* gene, alectinib inhibited tumor growth significantly as compared with the vehicle control group.

3.(i).A.(1).4) Antiproliferative effects of alectinib on crizotinib-resistant, *ALK* fusion gene-positive cell lines (Report PHM[redacted]-0140)

Using SCID mice subcutaneously implanted with mouse pro-B-lymphoid BA/F3 cells expressing *EML4-ALK* gene with the crizotinib-resistance mutation L1196M, the antiproliferative effect of alectinib was evaluated. Control animals received vehicle or crizotinib.

Crizotinib did not exhibit a significant antiproliferative effect as compared with vehicle, while alectinib

exhibited a significant antiproliferative effect as compared with vehicle. On the basis of these results, the applicant explained that alectinib might be effective in the treatment of *ALK* fusion gene-positive tumors with crizotinib-resistant mutation (L1196M).

3.(i).A.(1).5) Pharmacological actions of metabolites (Reports PHM[redacted]-0143 and PHM[redacted]-0144)

The inhibitory effect of M-4, a major metabolite of alectinib [see "3.(ii).A.(3) Metabolism"] on phosphorylation of ALK was evaluated using the TR-FRET assay. The IC_{50} value of M-4 was 1.2 nmol/L, which was similar to that of alectinib, 1.9 nmol/L. The antiproliferative effect of M-4 on NCI-H2228 cells was assessed by determining intracellular ATP levels, and the IC_{50} value was 37 nmol/L.

3.(i).A.(2) Secondary pharmacodynamics (Reports TOX[redacted]-0007S [reference data], TOX[redacted]-0027S [reference data], and TOX[redacted]-0047S [reference data])

A study was conducted to evaluate the inhibitory effects of alectinib on binding of a total of 151 different receptors, ion channels, transporters and enzymes with their relevant ligands. An *in vitro* functional evaluation conducted on the basis of these results revealed that alectinib inhibits the uptake of serotonin, norepinephrine, and dopamine into rat synaptosomes with the IC_{50} values of 0.10, 0.33, and 0.26 μmol/L (48.3, 159.3, and 125.5 ng/mL), respectively. The applicant explained that alectinib is unlikely to cause adverse drug reactions (ADRs) by inhibiting the uptake of these neurotransmitters at the recommended clinical dose since no findings suggesting the effect of alectinib on the central nervous system were observed in a study in rats receiving alectinib up to 300 mg/kg to investigate the effect on the central nervous system [see "3.(i).A.(3).1). Effects on the central nervous system"] and repeated-dose toxicity studies in rats and cynomolgus monkeys receiving alectinib up to 60 mg/kg [see "3.(iii).A.(2).1). Four-week repeated oral dose toxicity study in rats"] in which the mean C_{max} value was 1770 ng/mL in rats and ≤2000 ng/mL in cynomolgus monkeys and since the mean C_{max} value of patients receiving alectinib at the recommended dose of 300 mg twice a day (BID) was 575 ng/mL.

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

3.(i).A.(3).1) Effects on the central nervous system (Report TOX[redacted]-0165)

Male rats (6/group) received a single oral dose of alectinib (3, 30, or 300 mg/kg) and were observed for the effects on clinical signs and behaviors. No effects of alectinib were observed.

3.(i).A.(3).2) Effects on the cardiovascular and respiratory systems

i) Effects on hERG current (Report TOX[redacted]-0150)

The human embryonic kidney cell line HEK293 integrated with the human ether-a-go-go-related gene (hERG) was used to investigate the effect of alectinib on hERG-mediated potassium current. The IC_{50} value of alectinib was 0.45 μmol/L (217 ng/mL).

The applicant explained that alectinib is unlikely to cause significant ADRs involving the cardiovascular or respiratory systems when used at the recommended clinical dose, considering the facts that in 2

studies in cynomolgus monkeys receiving alectinib at 15 and 60 mg/kg respectively [see "3.(i).A.(3).2).ii) Effects on the cardiovascular system"], no ECG abnormalities were found until the mean plasma alectinib concentration increased to 279 ng/mL in one of the two studies (at the dose of 15 mg/kg) and until the mean C_{max} value increased to 695 ng/mL in the other study (at the dose of 60 mg/kg), that the plasma protein binding rate of alectinib exceeds 99%, and that the mean C_{max} value in patients receiving alectinib 300 mg BID was 575 ng/mL.

ii) Effects on the cardiovascular system (Reports TOX[redacted]-0048S [non-GLP study, reference data] and TOX[redacted]-0151)

Cynomolgus monkeys (2/sex/group) received a single oral dose of alectinib (20 or 60 mg/kg) and were observed for the effects on blood pressure, heart rate, and electrocardiogram (ECG). Blood pressure decreased slightly in animals in both dose groups but returned to baseline about 22 hours post-dose in animals in the 20 mg/kg group. Male cynomolgus monkeys (4/group) received a single oral dose of alectinib (1.7, 5, or 15 mg/kg) and were observed for the effects on blood pressure, heart rate, ECG, and body temperature. No effects of alectinib were observed.

In order to clarify the mechanism of the decrease in blood pressure in animals receiving alectinib at 20 and 60 mg/kg, the following studies were conducted.

(a) Effects on calcium channels (Report TOX[redacted]-0060 [non-GLP study, reference data])

Using a cell line which was derived from Chinese hamster ovary (CHO) cells and forced to express voltage-dependent calcium channel (Cav1.2), the effects of alectinib (at actual concentrations of 0.189, 0.339, and 0.764 μmol/L) on Cav1.2 channels were investigated. Alectinib blocked the Cav1.2 channel current with an IC_{50} value of 0.461 μmol/L.

(b) Effects on blood vessels (Report TOX[redacted]-0055S [non-GLP study, reference data])

Isolated rat aorta strips were used to investigate the effect of alectinib (at actual concentrations of 0.0160, 0.0723, 0.247, 0.860, and 3.38 μmol/L) on potassium-induced contraction. Alectinib blocked aortic contraction in a concentration-dependent manner, and the IC_{50} value was 0.168 μmol/L. The applicant explained that alectinib decreased blood pressure by blocking calcium channels and thereby dilating blood vessels.

3.(i).A.(3).3) Effects on the respiratory system (Report TOX[redacted]-0167)

Male rats (8/group) received a single oral dose of alectinib (at 3, 30, or 300 mg/kg) and were observed for the effect on respiratory rate, tidal volume, and respiratory minute volume. No effects of alectinib were observed.

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

Based on the submitted data and the following review, PMDA concluded that alectinib is expected to be

effective in the treatment of *ALK* fusion gene-positive NSCLC.

3.(i).B.(1) Efficacy of alectinib in the treatment of *ALK* fusion gene-positive NSCLC

PMDA pointed out that although the applicant submitted the results of studies using NSCLC cell lines expressing EML4-ALK, both immunohistochemical (IHC) staining and fluorescence *in situ* hybridization (FISH), which are recommended by the applicant as assays for *ALK* fusion genes, detect not only *EML4-ALK gene* but also other *ALK* fusion genes, and requested the applicant to explain the efficacy of alectinib in the treatment of NSCLC carrying *ALK* fusion genes other than *EML4-ALK*.

The applicant responded as follows.

In addition to the *EML4* gene, *ALK* has been reported to fuse with the tropomyosin-receptor kinase fused gene (TFG) (*Cell* 2007;131:1190-203), kinesin family member 5B (KIF5B) (*Clin Cancer Res.* 2009;15:3143-9), and kinesin light chain 1 (KLC1) (*PLoS One*. 2012;7:e31323). As these *ALK* fusion genes contain a coiled-coil domain which is believed to be involved in dimer formation and constant activation of ALK (*Nature*. 2007;448;561-6, *Cancer Sci*. 2008;99:2349-55), it is considered these genes and *EML4-ALK* gene share the same mechanism of carcinogenesis. The X-ray crystal structure analysis conducted to investigate interactions revealed that alectinib binds to the ATP binding site of ALK [see "3.(i).A.(1).2) Interactions of alectinib with ALK kinase domains"], and these ALK fusion proteins maintain the ATP binding site. Therefore, alectinib is expected to be effective in the treatment of NSCLC with ALK fusion proteins other than EML4-ALK.

As alectinib may be used for patients with *ALK* fusion gene-positive NSCLC who have been treated with crizotinib, a drug with inhibitory effect on the phosphorylation of ALK like alectinib, PMDA requested the applicant to explain the efficacy of alectinib in crizotinib-resistant NSCLC.

The applicant responded as follows.

In addition to the ALK mutations described in the submitted data (L1196M and C1156Y), ALK mutations (L1152R, G1202R, S1206Y, and G1269A, as well as the amino acid insertion mutation [1151Tins]), which have been reported to be resistant to crizotinib (*Clin Cancer Res.* 2012; 18: 1472-82 and others), were used to investigate the inhibitory effects of alectinib on the phosphorylation of ALK harboring these mutations and the antiproliferative effects on cells implanted to mice. On the basis of the results that alectinib did not inhibit phosphorylation or exert an antiproliferative effect on ALK with the G1202R mutation, but did exert these effects on ALK with mutations other than G1202R (internal reference document), alectinib is expected to be effective for crizotinib-resistant NSCLC associated with *ALK* fusion genes.

PMDA considers as follows:

PMDA concluded that the applicant's explanation is generally acceptable. However, as alectinib did not exert antiproliferative effects on a part of *ALK* fusion gene mutations tested, the efficacy of alectinib

may differ among them depending on the type of mutation. Since information on the efficacy of alectinib in tumors with different *ALK* fusion gene mutations will be useful in selecting patients to be treated with alectinib, PMDA concluded that the applicant should continue to collect information and provide updates when new information becomes available.

3.(i).B.(2) Hypotensive effect of alectinib

The applicant explained the hypotensive effect observed in safety pharmacology studies as follows:

In cynomolgus monkeys, blood pressure decreased in animals receiving alectinib at 20 and 60 mg/kg. Considering the mean C_{max} values in cynomolgus monkeys (i.e., 719 and 695 ng/mL at 20 and 60 mg/kg, respectively) and the mean C_{max} value in humans receiving alectinib 300 mg BID (575 ng/mL), it cannot be ruled out that a slight decrease in blood pressure develops in patients in the clinical setting. However, considering the fact that there were no cases of adverse events related to decreased blood pressure or abnormal vital signs in clinical studies of alectinib, the hypotensive effect observed in safety pharmacology studies is not clinically relevant.

PMDA considers as follows:

Information obtained through clinical studies of alectinib is limited, and it is difficult to conclude that the hypotensive effect observed in safety pharmacology studies is not clinically relevant. Accordingly, it is also necessary to continue to collect information including published literature and appropriately provide information when new findings become available.

3**.(ii) Summary of pharmacokinetic studies**

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

Pharmacokinetics of alectinib was investigated in rats and cynomolgus monkeys. Biological samples derived from humans and animals were used to investigate plasma protein binding, drug-metabolizing enzymes, and transporters of alectinib.

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

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

Male rats received a single oral or intravenous dose of alectinib 1 mg/kg in the fasting condition, and plasma alectinib concentrations were determined [see the table below]. The clearance (CL) of alectinib after intravenous administration is equivalent to about 20% of the rat hepatic plasma flow rate (55.2 mL/min/kg) (*Pharm Res.* 1993;10:1093-5). The applicant explained that the steady-state volume of distribution (Vss) of alectinib was about 20-fold the total body water of rats (0.668 L/kg) (*Pharm Res.* 1993;10:1093-5), suggesting that alectinib distributes extensively in the body.

Pharmacokinetic parameters of alectinib (male rats, single oral or intravenous administration)

Route	T_{max} (h)	C_{max} (ng/mL)	AUC_{inf} (ng·h/mL)	V_{ss} (L/kg)	CL (mL/min/kg)	$t_{1/2}$ (h)	BA (%)

Oral	8.0 ± 0.0	60.9 ± 14.0	1400 ± 320	-	-	32.1 ± 4.9	88.6
Intravenous	-	-	1580 ± 450	13.3 ± 4.3	11.0 ± 2.8	24.4 ± 10.9	-

Mean ± standard deviation; n = 3; BA, bioavailability; - , not applicable

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

Pharmacokinetic parameters after repeated administration of alectinib were determined in rats receiving the drug for 4 and 13 weeks and cynomolgus monkeys for 2, 4, and 13 weeks. The applicant explained that the pharmacokinetics of alectinib after repeated administration was discussed using the data of the 13-week repeated dose study in which the plasma concentration of alectinib achieved steady state in all dose groups.

Male and female rats received alectinib at 3, 9, or 27 mg/kg once daily orally in the non-fasting condition for 13 weeks, and plasma alectinib concentrations were determined [see the table below]. In both male and female animals, the C_{max} and $AUC_{0\text{-}24h}$ values after the first administration were generally dose-proportional within the dose range investigated. During repeated dosing, the C_{max} and $AUC_{0\text{-}24h}$ values were generally dose-proportional for the 3 mg/kg and 9 mg/kg groups but were less than dose-proportional for the 27 mg/kg groups. The C_{max} and $AUC_{0\text{-}24h}$ values in females tended to be higher than those in males. From Day 28 on, no substantial increases in the trough plasma concentration of alectinib were observed.

Pharmacokinetic parameters of alectinib (male and female rats, 13-week repeated oral dose administration)

Dose (mg/kg)	Day of measurement	sex	T_{max} (h)	C_{max} (ng/mL)	$AUC_{0\text{-}24h}$ (ng·h/mL)
3	1	M	3.2 ± 1.2	208 ± 30	3010 ± 660
		F	4.0 ± 0.0	238 ± 26	4000 ± 490
	91	M	4.0 ± 0.0	370 ± 82	5100 ± 1410
		F	2.7 ± 1.2	524 ± 114	8450 ± 750
9	1	M	6.7 ± 2.3	649 ± 45	9770 ± 720
		F	5.3 ± 2.3	872 ± 149	15,100 ± 700
	91	M	5.3 ± 2.3	1250 ± 380	18,600 ± 5700
		F	3.3 ± 1.2	1520 ± 190	25,800 ± 1900
27	1	M	9.3 ± 2.3	1780 ± 130	30,000 ± 4000
		F	6.7 ± 4.6	1960 ± 30	35,800 ± 1800
	91	M	9.3 ± 2.3	1840 ± 160	35,300 ± 3300
		F	8.0 ± 4.0	2170 ± 90	41,100 ± 2100

Mean ± standard deviation, n = 3

Male and female cynomolgus monkeys received alectinib orally at doses of 1.3, 4, and 12 mg/kg once daily for 13 weeks, and plasma alectinib concentrations were determined [see the table below]. The C_{max} and $AUC_{0\text{-}24h}$ values after the first and repeated administration were generally dose proportional for the 1.3 mg/kg and 4 mg/kg groups but were less than dose-proportional for 12 mg/kg dose groups. Except that the C_{max} value after the first dose at 1.3 mg/kg tended be higher in female than male animals, no other gender-differences in C_{max} or $AUC_{0\text{-}24h}$ values were observed in any group. From Day 28 on, no substantial increases in the trough plasma concentrations of alectinib were observed.

Pharmacokinetic parameters of alectinib (male and female cynomolgus monkeys, 13-week repeated oral dose administration)

Dose (mg/kg)	Day of measurement	Sex	n	T_{max} (h)	C_{max} (ng/mL)	$AUC_{0\text{-}24h}$ (ng·h/mL)
1.3	1	M	3	5.3 ± 2.3	59.8 ± 26.9	792 ± 274
		F	3	3.3 ± 1.2	87.5 ± 8.2	942 ± 133
	91	M	2	2.0, 2.0*	66.7, 100*	637, 1150*
		F	3	3.3 ± 1.2	94.3 ± 26.0	1030 ± 60
4	1	M	5	6.8 ± 2.7	170 ± 42	2700 ± 530
		F	5	4.0 ± 0.0	175 ± 45	2520 ± 420
	91	M	5	2.4 ± 0.9	243 ± 33	3610 ± 580
		F	5	3.2 ± 1.1	189 ± 51	2810 ± 1040
12	1	M	5	8.0 ± 0.0	394 ± 129	6640 ± 2370
		F	5	4.0 ± 0.0	439 ± 82	6410 ± 1170
	91	M	5	4.4 ± 2.2	461 ± 134	7060 ± 2530
		F	5	4.4 ± 2.2	463 ± 60	6920 ± 1680

Mean ± standard deviation; *, showing results in individual animals

The applicant explained the reasons why the exposure to alectinib was less than dose-proportional in rats and monkeys in the highest dose groups as follows: As alectinib has low solubility in water, the concentration of alectinib in the gastrointestinal tract reached the saturation point in animals receiving higher doses, and the absorption through the gastrointestinal tract was reduced.

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

The human colon carcinoma-derived Caco-2 cell line was used to investigate the permeability of alectinib through gastrointestinal tract membranes in humans. The apparent permeation coefficient of alectinib (10 μmol/L) from the apical surface to the basolateral surface ($P_{app\ A\rightarrow B}$) was $1.88 \pm 0.23 \times 10^{-6}$ cm/sec (mean ± standard deviation; n = 3).

The applicant explained that the absorption of alectinib after oral administration was assumed to be 89% from a theoretical curve derived from the absorption after oral administration and the $P_{app\ A\rightarrow B}$ values of different commercially available drugs (*J Pharmacol Exp Ther.* 2005;314:391-9, *Int J Pharm.* 2004;274:221-32, *Int J Pharm.* 2002;241:241-51, *Pharm Res.* 2006;23:1144-56, *Pharm Res.* 2003;20:1674-80, *Int J Pharm.* 2005;297:235-41, *Drug Metab Dispos.* 2010;38:1230-7, *Pharm Res.* 2004;21:749-55, *J Pharm Sci.* 2001;90:749-84, *Drug Metab Dispos.* 2011;39:265-74) and that permeability in the gastrointestinal tract is moderate or higher.

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

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

Male albino rats received a single oral administration of ^{14}C-labeled alectinib ("^{14}C-alectinib") 1 mg/kg, and the distribution of radioactivity in tissues was investigated using quantitative whole-body autoradiography (QWBA) method. Plasma radioactivity concentration peaked at 4 hours after administration with a maximum concentration of 68.9 ng eq/g and decreased slowly with a half-life ($t_{1/2}$)

of 41.6 hours. In almost all tissues tested, radioactivity concentrations peaked 8 to 12 hours after administration, and those in tissues other than the eyes, spine, cerebellum, and cerebrum were higher than the peak plasma radioactivity concentration. Tissue radioactivity concentrations were highest in the adrenal gland (8960 ng eq/g), which was followed by those in the Harderian gland, lung, brown fat, and liver (4790, 3590, 2590, and 2100 ng eq/g, respectively). The applicant explained that as radioactivity concentrations in the cerebrum and cerebellum changed as the same level as the plasma radioactivity concentration during the first 24 hours after administration, alectinib was believed to cross the blood-brain barrier. Although residual radioactivity was still detected at 168 hours after administration in the adrenal gland, liver, Harderian gland, kidney, and brown fat, the radioactivity concentrations decreased to 1.6% to 5.7% of the peak tissue radioactivity levels. The $t_{1/2}$ values in the blood, kidney, skin, and adrenal gland (56.0, 51.1, 48.6, and 42.9 hours, respectively) were longer than that in the plasma.

Male pigmented rats received a single oral administration of ^{14}C-alectinib 10 mg/kg, and the tissue distribution of radioactivity was determined using the QWBA method. In almost all tissues except for the uvea and eyes, the elimination profile of radioactivity in pigmented rats was similar to that in albino rats. The radioactivity concentration was highest in the uvea, which contains melanin, among all tissues tested, and peaked (66,900 ng eq/g) at 24 hours after administration. The radioactivity concentration in the uvea at 504 hours after administration still was equivalent to 56.4% of the peak concentration. The radioactivity concentration in the eye peaked (699 ng eq/g) at 12 hours after administration, and the concentration at 504 hours after administration was equivalent to 20.5% of the peak concentration. The radioactive concentrations in colored skin tissues were higher at any time points than those in non-colored skin tissues, and the $t_{1/2}$ value in colored skin tissues was 1.5-fold that in non-colored skin tissues. The applicant explained that these results suggest that the unchanged drug or metabolites of alectinib have a high affinity for melanin.

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

Plasma samples from mice, rats, cynomolgus monkeys, and humans were incubated with ^{14}C-alectinib (0.1, 1, and 10 μg/mL [1 μg/mL only for mice]), and plasma protein binding of alectinib was determined using an equilibrium dialysis method. The plasma protein binding rate of alectinib was 99.4%, 99.5% to 99.6%, 99.6%, and 99.6% to 99.7% in the samples from mice, rats, monkeys, and humans, respectively, which indicates that the plasma protein binding rate of alectinib was high in all animal species tested and was constant regardless of the concentration of alectinib. The binding rate of alectinib to human serum albumin ranged between 96.9% and 97.0% at all concentrations tested, while that to alpha-1-acid glycoprotein was less than 4.9%. Thus, the applicant explained that alectinib in human plasma binds mainly to albumin.

Blood samples from mice, rats, cynomolgus monkeys, and humans were incubated with ^{14}C-alectinib (0.1, 1, and 10 μg/mL [1 μg/mL only for mice]), and the distribution of alectinib into blood cells was determined. The distribution of radioactivity in blood cells of rats, cynomolgus monkeys, and humans

were 72.8%, 86.6%, and 82.2%, respectively, at 0.1 μg/mL, 72.8%, 84.9%, and 80.3%, respectively, at 1 μg/mL, and 60.0%, 68.4%, and 59.8%, respectively, at 10 μg/mL. The distribution into blood cells tended to be smaller at 10 μg/mL than at 0.1 and 1 μg/mL. In the samples from mice, the distribution of radioactivity in blood cells was 53.4% at 1 μg/mL, which was the lowest among the animal species tested.

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

Female albino rats on gestation day 17 received a single oral dose of ^{14}C-alectinib 1 mg/kg, and the tissue distribution of radioactivity was determined using the QWBA methods. During the first 72 hours after administration, radioactivity concentrations in the mammary gland, ovary, uterus, placenta, and embryonic membrane of the dam were as high as 3.7- to 21-fold that in plasma, but radioactivity concentrations in the amniotic fluid were ≤0.8-fold that in plasma. Radioactivity concentrations in the brain, heart, lung, liver, kidney, and gastrointestinal tract of the fetus peaked at 4 or 8 hours after administration and then decreased over time. Tissue radioactivity concentrations in the fetus were as high as 1.2- to 5.8-fold that in plasma of the dam during the first 48 hours after administration.

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

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

In order to identify metabolites of alectinib, ^{14}C-alectinib (10 μmol/L) was incubated with hepatocytes of mice, rats, dogs, cynomolgus monkeys, and humans for 1 and 4 hours. After 4-hour incubation, alectinib was most stable against metabolic degradation in mice, which were followed by dogs, rats, humans, and cynomolgus monkeys in this order, and the unchanged drug accounted for 89.9%, 85.9%, 68.0%, 66.8%, and 47.5% of the radioactivity administered in the corresponding species. The variety of metabolites was similar among the animal species tested. The most common metabolite was M-4 (a metabolite resulting from morpholine ring-opening and dealkylation), and as other major metabolites, M-1 (a metabolite resulting from morpholine ring opening and hydroxylation) and M-6 (a dealkylated metabolite of M-4) were also detected.

^{14}C-alectinib (10 μmol/L) was incubated with recombinant human cytochrome P450 (CYP) isozymes (1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C18, 2C19, 2D6, 2E1, 3A4, 3A5, and 4A11) for 1 hour in order to identify CYP isozymes involved in the metabolism of alectinib. Following 1-hour incubation with cells expressing CYP3A4, the unchanged drug accounted for 46.7% of the total radioactivity, and the main metabolite was M-4 (28.1% of the total radioactivity) as observed in the study using hepatocytes. In other CYP expression systems, the unchanged compound accounted for 91.0% to 95.9% of the total radioactivity.

In a study in which ^{14}C-alectinib (10 μmol/L) was incubated with human hepatic microsomes in the presence or absence of reduced nicotinamide adenine dinucleotide phosphate (NADPH) for 15 minutes. Alectinib was metabolized only in the presence of NADPH (residual rate of the unchanged compound,

86.5%), and the major metabolite was M-4 (4.1% of total radioactivity).

^{14}C-alectinib (10 μmol/L) was incubated with human hepatic microsomes in the presence of inhibitors of CYPs (1A2, 2C9, 2C19, 2D6, or 3A4/5) for 15 minutes in order to specify CYP isozymes involved in the metabolism of alectinib. The metabolism of alectinib was inhibited by 97% in the presence of CYP3A4/5 inhibitors but was essentially unaffected in the presence of inhibitors specific to other CYPs. When ^{14}C-alectinib (10 μmol/L) was incubated with human hepatic microsomes in the presence of benzylimidazole (1000 μmol/L) or ketoconazole (1 μmol/L), which are non-specific CYP inhibitors, the metabolism of alectinib was inhibited by 93% or 78%, respectively.

When ^{14}C-alectinib (2 μmol/L) was incubated with human hepatic microsomes in the presence of benzylimidazole (1000 μmol/L) or ketoconazole (10 μmol/L), the metabolism of alectinib was inhibited by 99% or 47%, respectively.

The applicant explained that CYP3A4 is the major human CYP enzyme responsible for the metabolism of alectinib.

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

Male rats received a single oral dose of ^{14}C-alectinib 1 mg/kg, and metabolites in the plasma, urine, and feces were determined. At 2, 4, 8, 12, and 24 hours after administration, the percentage of the unchanged ^{14}C-alectinib in total radioactivity in plasma was 89.6%, 92.1%, 90.7%, 88.3%, and 72.6%, respectively, and the percentage of metabolites was 6.3%, 5.6%, 5.4%, 7.9%, and 14.0%, respectively. M-4, the major metabolite in the *in vitro* studies, was found in a trace amount (1.5%) in plasma only at 24 hours after administration. The urinary and fecal excretion rates of the unchanged drug, expressed as the percentage of the unchanged ^{14}C-alectinib in total radioactivity in the respective sample, were 8.1% and 51.8%, respectively, during the first 24 hours after administration, and 6.5% and 30.2%, respectively, during the period between 24 and 48 hours after administration. The major metabolite both in urine and in feces was M-4. The urinary and fecal excretion rates of M-4 were 48.1% and 22.1%, respectively, during the first 24 hours after administration, and 63.3% and 39.3%, respectively, during the period between 24 and 48 hours after administration.

Male rats with bile duct cannulation received a single intravenous administration of ^{14}C-alectinib 1 mg/kg, and metabolites in bile were examined. M-4 was the major metabolite in bile up to 24 hours after administration and accounted for 40.6% of the total radioactivity in bile. The unchanged ^{14}C-alectinib accounted for as low as 4.0% of the total radioactivity in bile. The results of β-glucuronidase treatment of bile samples suggested that no glucuronide conjugates of alectinib are produced as metabolites of alectinib in bile.

Male and female rats received alectinib at a dose of 27 mg/kg once daily orally for 13 weeks to determine

plasma concentrations of M-4 and M-6 [see the table below]. The C_{max} and $AUC_{0\text{-}24h}$ values of M-4 and M-6 tended to be higher in males than in females. The C_{max} and $AUC_{0\text{-}24h}$ values of M-6 were equivalent to 6.4% to 11.0% of those of M-4. Plasma trough concentrations of M-4 and M-6 did not increase substantially on Day 28 and thereafter. The C_{max} and $AUC_{0\text{-}24h}$ values on the final day of administration, Day 91, were 1.7- to 2.0-fold those after the first administration for M-4 and 1.1- to 1.7-fold those for M-6.

In rats, the exposure to alectinib in males was lower than that in females [see "3.(ii).A.(1).2) Repeated-dose studies"], and the exposure to the metabolites (M-4 and M-6) tended to be higher in males than females. The applicant explained that this may reflect the difference in CYP profile between male and female rats, in light of the followings.

- In humans, CYP3A4 is the enzyme mainly responsible for the metabolism of alectinib [see "3.(ii).A.(3).1) *in vitro* metabolism"], and it is assumed that the CYP3A subfamily is involved in the metabolism of alectinib in rats as well.

- CYP3A1/23 and CYP3A2 have been reported to have higher expression levels among the CYP3A subfamily in rats and exhibit higher activities in males than in females (*Biol Pharm Bull.* 2005;28:311-5).

Pharmacokinetic parameters of M-4 and M-6 (male and female rats, 13-week repeated oral dose administration)

Day of measurement	Sex	Metabolite	C_{max} (ng/mL)	$AUC_{0\text{-}24h}$ (ng·h/mL)
1	M	M-4	55.3 ± 13.1	934 ± 167
		M-6	6.07 ± 3.78	90.8 ± 32.0
	F	M-4	31.3 ± 5.2	593 ± 112
		M-6	3.03 ± 0.31	49.3 ± 13.8
91	M	M-4	94.9 ± 9.1	1830 ± 140
		M-6	6.45 ± 1.02	118 ± 13
	F	M-4	58.9 ± 7.4	1060 ± 180
		M-6	4.50 ± 0.73	84.9 ± 15.0

Mean ± standard deviation, n = 3

Trough plasma concentrations of M-4 and M-6 (male and female rats, 13-week repeated oral dose administration)

Sex	Metabolite	Day 2	Day 28	Day 56	Day 91
M	M-4	31.0 ± 1.6	75.7 ± 8.0	60.1 ± 7.9	59.0 ± 5.1
	M-6	4.15 ± 0.79	5.49 ± 0.91	5.18 ± 1.35	4.25 ± 1.48
F	M-4	24.8 ± 6.3	41.2 ± 12.2	47.2 ± 12.6	43.9 ± 12.9
	M-6	2.27 ± 0.97	3.23 ± 1.51	3.78 ± 1.16	3.63 ± 0.82

Mean ± standard deviation (ng/mL), n = 3

Male and female cynomolgus monkeys received alectinib orally at a dose of 12 mg/kg once daily for 13 weeks to determine plasma concentrations of M-4 and M-6 [see the table below]. The C_{max} and $AUC_{0\text{-}24h}$ values of M-4 and M-6 did not differ substantially between the sexes. The C_{max} and $AUC_{0\text{-}24h}$ values of M-6 were equivalent to 6.3% to 10.2% of those of M-4. Plasma trough concentrations of M-4 and M-6 did not increase substantially on Day 28 and thereafter. The C_{max} and $AUC_{0\text{-}24h}$ values on the final day of administration, Day 91, were 1.9- to 2.4-fold those after the first administration for M-4 and 2.1- to 3.7-fold those for M-6.

Pharmacokinetic parameters of M-4 and M-6 (male and female cynomolgus monkeys, 13-week repeated oral dose administration)

Day of measurement	Sex	Metabolite	C_{max} (ng/mL)	$AUC_{0\text{-}24h}$ (ng·h/mL)
1	M	M-4	45.8 ± 20.1	778 ± 377
		M-6	2.89 ± 1.26	51.5 ± 28.2
	F	M-4	49.1 ± 16.7	795 ± 283
		M-6	4.30 ± 0.51	59.7 ± 17.4
91	M	M-4	107 ± 22	1890 ± 680
		M-6	10.4 ± 4.2	192 ± 91
	F	M-4	98.5 ± 25.2	1530 ± 290
		M-6	9.10 ± 2.46	146 ± 39

Mean ± standard deviation, n = 5

Trough plasma concentrations of M-4 and M-6 (male and female cynomolgus monkeys, 13-week repeated oral dose administration)

Sex	Metabolite	Day 2	Day 28	Day 56	Day 91
M	M-4	27.2 ± 15.2	76.1 ± 25.1	80.4 ± 38.9	56.5 ± 25.5
	M-6	2.24 ± 1.66	7.61 ± 3.24	9.00 ± 6.35	5.61 ± 2.46
F	M-4	21.3 ± 6.9	65.9 ± 14.0	55.2 ± 10.9	45.8 ± 7.8
	M-6	1.69 ± 1.59	6.85 ± 2.76	5.23 ± 2.04	4.66 ± 0.47

Mean ± standard deviation (ng/mL), n = 5

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

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

In male rats receiving a single oral dose of ^{14}C-alectinib 1 mg/kg, 0.5% and 95.7% of the administered radioactivity were excreted in urine and feces, respectively, by 168 hours after administration.

Male rats with bile duct cannulation received a single intravenous dose of ^{14}C-alectinib 1 mg/kg, and the urinary, fecal, and biliary excretion rates (the percentage of the administered radioactivity) were determined. The urinary, fecal, and biliary excretion rates by 48 hours after administration were 2.0%, 10.3%, and 42.5%, respectively.

Taken together, the applicant explained that alectinib and its metabolites are excreted mainly in feces via bile.

3.(ii).A.(4).2) Enterohepatic circulation

Bile was obtained from male rats with bile duct cannulation after an intravenous dose of ^{14}C-alectinib 1 mg/kg and then was infused into the duodenum of another group of rats in order to determine the urinary, fecal, and biliary excretion rates (the percentage of the administered radioactivity). By 48 hours after administration, 76.3% and 3.0% of the administered radioactivity were excreted in feces and bile, respectively. The excretion rate in urine was below the lower detection limit.

Based on the above, the applicant explained that alectinib hardly undergo substantial enterohepatic circulation in rats.

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

3.(ii).A.(5).1) *In vitro* enzyme induction

Human hepatocytes were treated with alectinib (0.01, 0.1, and 1 μmol/L) for 72 hours to examine the expression of mRNA for CYPs (1A2, 2B6, and 3A4). After the treatment with 0.1 μmol/L alectinib, the mRNA expression levels for all 3 CYP isozymes were essentially identical to those after vehicle treatment. After the treatment with 1 μmol/L alectinib, the mRNA expression levels for CYP3A4 and CYP2BR were 2.5- to 3.9-fold and 1.5- to 3.1-fold, respectively, those after vehicle treatment. The mRNA expression level for CYP1A2 after exposure to alectinib at the highest concentration tested was about the same as that after vehicle exposure.

The applicant explained the above results as follows:

These findings suggest that alectinib may induce CYP3A4 and CYP2B6. However, it is unlikely that alectinib causes pharmacokinetic drug interactions by inducing CYP3A4 and CYP2B6 in the clinical setting for the following reasons:

- The concentration of free (unbound) alectinib in the medium treated with 0.1 μmol/L alectinib, at which mRNA levels did not increase for any CYP isozymes, was 18 to 19 ng/mL during the preparation of the medium, 9.4 to 10 ng/mL at 48 hours of incubation immediately after the replacement of the medium, and 0.4 ng/mL after 72 hours of incubation.

- In humans, the C_{max} value of free (unbound) alectinib in patients receiving alectinib 300 mg BID ranged from 1.7 to 2.3 ng/mL [see "3.(ii)A.(2).2) Plasma protein binding and distribution in blood cells" and "4.(ii).A.(1) Phase I/II study in Japan"].

3.(ii).A.(5).2) *In vitro* enzyme inhibition

In the presence of alectinib (0.01, 0.1, and 1 μmol/L), substrates of human CYPs (1A2, 2B6, 2C8, 2C9,

2C19, 2D6, and 3A4) were incubated with human hepatic microsomes at 37°C to evaluate the inhibitory effects of alectinib on these CYP isozymes. Alectinib competitively inhibited the metabolism of CYP2C8 substrates with an inhibition constant (Ki) of 1.98 μmol/L. The results of pre-incubation for 30 minutes indicated that alectinib inhibits the metabolism of CYP3A4 substrates in a time dependent manner with a maximum inactivation rate constant (k_{inact}) of 0.0624/min. The inhibitor concentration when the apparent inactivation rate constant reaches half of k_{inact} was calculated to be ≥60 μmol/L. Alectinib did not show substantial inhibitory effects on the other CYP isozymes even at the highest concentration tested.

The applicant explained the above results as follows:
Although alectinib inhibited the metabolism of CYP2C8 substrates, it is unlikely that the combination of alectinib and CYP2C8 substrates induces pharmacokinetic drug interactions in the clinical setting on the basis of the findings below. However, as it has been suggested that alectinib inhibits the CYP3A4 isozyme in a time dependent manner, the combination of alectinib and CYP3A4 substrates may increase the exposure to CYP3A4 substrates.

- The Ki value of alectinib was 1.98 μmol/L (956 ng/mL).

- The mean steady-state C_{max} value in patients receiving alectinib at the proposed dosage regimen was 575 ng/mL [see "4.(ii).A.(1) Phase I/II study in Japan"].

- Free alectinib accounts for <1% of the total alectinib present in plasma [see "3.(ii)A.(2).2) Plasma protein binding and distribution in blood cells"].

3.(ii).A.(5).3) Transporters
The applicant submitted the following results of studies on the substrate potential of alectinib for transporters.

- Using the Caco-2 cell line, the transport of ^{14}C-alectinib (0.3 and 1 μmol/L) via P-glycoprotein was examined. The efflux ratio of ^{14}C-alectinib, defined as the ratio of the apparent permeability coefficient of alectinib from the basolateral surface to the apical surface ($P_{app\ B\rightarrow A}$) to that from the apical surface to the basolateral surface ($P_{app\ A\rightarrow B}$), was 0.924 at 0.3 μmol/L and 1.32 at 1 μmol/L. The efflux ratio of the positive control digoxin (1 μmol/L) was 8.01.

- Using Madin-Darby canine kidney (MDCK) cells expressing breast cancer resistance protein (BCRP), the transport of ^{14}C-alectinib (0.3, 1, and 3 μmol/L) via BCRP was examined. The corrected efflux ratio, obtained by dividing the efflux ratio in BCRP-expressing MDCK cells by that in MDCK cells, was 1.20, 1.62, and 1.13 for ^{14}C-alectinib at 0.3, 1, and 3 μmol/L, respectively. The corrected efflux ratio of prazosin hydrochloride (10 μmol/L), a positive control, was 4.77.

Based on the above, the applicant explained that alectinib is not a substrate of P-glycoprotein or BCRP.

The applicant also submitted the results of the following studies on the inhibitory effects of alectinib on transporters.

- Using the Caco-2 cell line, the inhibitory effect of alectinib (0.03 to 3 μmol/L) on the transport of ^{3}H-digoxin (1 μmol/L) via P-glycoprotein was examined. Alectinib inhibited the transport of ^{3}H-digoxin via P-glycoprotein in a concentration-dependent manner with an IC_{50} of 1.13 μmol/L.

- Using BCRP-expressing MDCK cells, the inhibitory effect of alectinib (0.01 to 3 μmol/L) on the transport of ^{3}H-prazosin (10 nmol/L) via P-glycoprotein was examined. Alectinib inhibited the transport of ^{3}H-prazosin via P-glycoprotein in a concentration-dependent manner with an IC_{50} of 0.103 μmol/L.

- Using the HEK293 human fetal kidney cell line transfected with the human organic anion-transporting polypeptide (OATP) 1B1, organic anion transporter (OAT) 1 and OAT 3, or organic cation transporter (OCT) 2, the inhibitory effects of alectinib (3 μmol/L) on the transport of substrates via these transporters were examined (as substrates of these transporters, ^{3}H-estradiol-17β-D-glucuronide was used for OATP 1B1, ^{3}H-p-aminohippuric acid for OAT 1, ^{3}H-estrone sulfate ammonium salt for OAT 3, and ^{14}C-metformin hydrochloride for OCT 2). Alectinib did not show substantial inhibitory effects on any transporters even at the highest concentration tested.

The applicant explained that the above findings indicated the inhibitory effects of alectinib on P-glycoprotein and BCRP.

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

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

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

As both unchanged alectinib and its metabolites are suggested to have high affinity for melanin [see "3.(ii).A.(2).1) Tissue distribution"], PMDA requested the applicant to explain whether the distribution of alectinib or its metabolites in melanin-containing tissues may pose safety problems in the clinical setting. The applicant responded that the risk was low considering the followings:

- In the repeated dose toxicity studies in cynomolgus monkeys, no toxicological findings suggesting the effect of alectinib or its metabolites were observed in melanin-containing tissues such as the

eye and skin [see "3.(iii).A.(2).3) Preliminary 2-week repeated oral dose toxicity study in cynomolgus monkeys" to "3.(iii).A.(2).5) Thirteen-week repeated oral dose toxicity study in cynomolgus monkeys"].

- In light of the facts that the wavelength of light that reaches the posterior segment of the eyes of adult humans exceeds 400 nm and that alectinib absorbs light at [redacted] to [redacted] nm [see "3.(iii).A.(6).1) Photosafety study"], the photosafety risk of alectinib is considered low.

- In a phase I/II study in patients with *ALK* fusion gene-positive, unresectable, recurrent or advanced NSCLC in Japan (Study AF-001JP), the incidence of ophthalmic adverse events and that of dermal/subdermal adverse events following the treatment with alectinib at the proposed dosage regimen was 19% (11 of 58 patients) and 37.9% (22 of 58 patients), respectively. No patients discontinued treatment due to these adverse events, and all patients could restart treatment after appropriately suspending treatment.

- In an ongoing foreign phase I/II study in patients with *ALK* fusion gene-positive NSCLC who have developed resistance to crizotinib (Study AF002-JG/ Study NP28761), the incidence of ophthalmic and dermal/subdermal adverse events does not tend to be higher in non-white patients (n = 14) than in white patients (n = 33), although the number of patients is limited. Also, the adverse event profile of Japanese patients enrolled in Study AF-001JP did not differ significantly from that of foreign patients.

PMDA accepted the applicant's explanation.

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

As alectinib has been demonstrated to be metabolized mainly by CYP3A4 [see "3.(ii).A.(3).1) *In vitro* metabolism"] and inhibit CYP3A4, P-glycoprotein, and BCRP [see "3.(ii).A.(5).2) *In vitro* enzyme inhibition" and "3.(ii).A.(5).3) Transporters"], PMDA requested the applicant to explain about plans of clinical studies to examine pharmacokinetic interactions with CYP3A4 inhibitors or inducers or substrates of CYP3A4, P-glycoprotein, or BCRP.

The applicant responded as follows:

In foreign countries the applicant is conducting studies on pharmacokinetic drug interactions between alectinib and (1) a potent CYP3A4 inhibitor posaconazole (Study NP28990) and (2) a potent CYP3A4 inducer rifampicin (Study NP29042) in healthy adults, as well as a phase I/II study on pharmacokinetic drug interactions between alectinib and (3) the CYP3A4 substrate midazolam (the phase II segment of Study NP28673) in patients with *ALK* fusion gene-positive NSCLC. However, no studies on pharmacokinetic drug interactions between alectinib and P-glycoprotein or BCRP substrates are planned at the present time because no safety concerns considered attributable to pharmacokinetic drug

interactions have been suggested for the use of alectinib with P-glycoprotein or BCRP substrates as below.

- In Study AF-001JP, 1 of the 6 patients (16.7%) who received alectinib with fexofenadine hydrochloride ("fexofenadine" hereafter), a substrate of P-glycoprotein, developed grade 2 neutropenia. However, as this event was transient, and disappeared without discontinuing treatment with alectinib and fexofenadine, it is unlikely that this event was attributable to a pharmacokinetic drug interaction between alectinib and fexofenadine.

- In Study AF-001JP, 1 of the 3 patients (33.3%) who received alectinib with rosuvastatin calcium ("rosvastatin" hereafter), a substrate of BCRP, developed grade 1 pneumonia interstitial. However, considering the facts that the patient had been treated with rosuvastatin before alectinib therapy began, that pneumonia interstitial developed about 3 months after the start of alectinib therapy, and that blood cholesterol levels did not change significantly before and after alectinib therapy began, it is unlikely that the adverse event was attributable to a pharmacokinetic drug interaction between alectinib and rosuvastatin.

PMDA considers as follows:
The results of the NP28990, NP29042, and NP28673 Studies must be provided to healthcare professionals as soon as the data become available.

Regarding pharmacokinetic drug interactions between alectinib and P-glycoprotein or BCRP substrates, there have been no safety concerns attributable to interactions between alectinib and these substrates in clinical studies. However, as information on pharmacokinetic drug interactions of alectinib via transporters is important to ensure proper use of alectinib in the future, PMDA concluded that it is necessary to continue to collect information including published literature and appropriately provide information when useful information becomes available.

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 studies of alectinib have been conducted. Acute toxicity of alectinib was assessed on the basis of clinical signs of rats in the micronucleus test (where alectinib was given at doses of up to 2000 mg/kg once daily for 2 days) and monkeys in the 2-week repeated dose oral toxicity study (non-GLP study, reference data). Rats in the micronucleus test were observed until the following day of the second dose, and monkeys were observed until the following day of the first dose.

Rats showed decreased food consumption at ≥20 mg/kg, decreased weight gain or decreased body weight at ≥500 mg/kg, and decreased fecal volume at ≥1000 mg/kg, but no animals receiving alectinib

≤2000 mg/kg died. Thus, the approximate lethal dose was estimated over 2000 mg/kg.

In monkeys, no deaths or abnormal clinical signs were observed in animals receiving alectinib at ≤60 mg/kg. Therefore, the approximate lethal dose was determined to be >60 mg/kg.

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

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

WIST rats (15/sex/group) received alectinib orally at a dose of 0 (vehicle), 6, 20, or 60 mg/kg once daily for 4 weeks. Five animals in each group were allowed a 4-week recovery period after the final administration of alectinib. No deaths attributable to alectinib treatment were observed. Findings observed in the ≥6 mg/kg groups were abnormal red blood cell morphology (i.e., echinocyte and red blood cell fragmentation), increases in megathrombocyte count, alkaline phosphatase (ALP) level, bone ALP level, glucose level in the blood, and macrophage infiltration into alveoli. Findings observed in the ≥20 mg/kg groups were decreased weight gain, increased reticulocyte count, increased white blood cell count, increased hepatic ALP level, increased total cholesterol level, increased weight of the liver, spleen, adrenal gland, and heart, decreased absolute weight of the pituitary gland, increased extramedullary red blood cell production in the spleen, increased number of mature megakaryocytes in the spleen, enlarged hepatocytes, vacuolization of bile duct epithelial cells, hypertrophy of the adrenal gland, degradation of glandular stomach epithelium, inflammatory cell infiltration and expanded proliferative zone in gastrointestinal mucosa, infiltration of macrophages and multinucleated giant cells into bronchial or gastrointestinal mucosa, decreased lymphocyte count in lymphoid tissues, and mild atrophy of anterior lobe cells of the pituitary. Animals in the 60 mg/kg dose group showed increased γ-glutamyltransferase (γ-GTP), increase in activated osteoclasts in bone, trabecular bone loss, and increased number of neutrophils in the bone marrow. During the 4-week recovery period, these findings resolved or tended to resolve.

The applicant explained as follows:

Among the findings described above, the increase in blood glucose level is not of toxicological significance as the event was mild in severity and was not observed in other repeated dose toxicity studies. The atrophy of anterior lobe cells of the pituitary is also not of toxicological significance because no changes were observed in tissues of the thyroid gland, genital organs, or other organs controlled by the pituitary gland and because this finding may be a secondary change associated with a deterioration in nutritional status.

According to these findings, the NOAEL of alectinib in rats in this study was determined to be <6 mg/kg/day.

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

WIST rats (15/sex/group) received alectinib orally at a dose of 0 (vehicle), 3, 9, or 27 mg/kg once daily

for 13 weeks. Five animals in each group were allowed an 8-week recovery period after the final administration of alectinib. No deaths attributable to alectinib treatment were observed. Animals in the ≥3 mg/kg groups showed decreased weight gain, increased aspartate aminotransferase (AST), infiltration of foamy macrophages in the alveoli, single cell or focal necrosis in the liver, yellow-brown pigmentation or swollen sinusoidal cells in the liver, increase in the number of large lipid droplets in the zona fasciculata of the adrenal gland, and extramedullary hemopoiesis in the spleen. Animals in the ≥9 mg/kg groups showed decreased food consumption; abnormal red cell morphology; platelet-large cells in the blood; increased reticulocyte count; increases in ALP, hepatic ALP, and intestinal ALP; increases in neutrophil count, alpha-2 globulin, and beta-globulin, which are considered to be developed secondarily in association with inflammatory change; increased heart weight; infiltration of macrophages, multinucleated giant cells, and inflammatory cells and expansion of the proliferative zone in the gastrointestinal mucosa; epithelial hypertrophy of the glandular stomach mucosa associated with mucus secretion; degeneration of the glandular stomach epithelium; macrophages/hemophagocytosis/red blood cells in the lymph node, and decreased lymphocytes in lymphoid tissues. Findings observed in the 27 mg/kg dose group included black stools, anaemic changes, increased total white blood cell count, prolonged activated partial thromboplastin time (APTT), prolonged prothrombin time, increases in bone ALP and gamma-GTP, decreases in albumin and blood glucose, increases in blood urea nitrogen and inorganic phosphorus, extramedullary haemopoiesis, increased liver weight, increased mature megakaryocytes in the spleen, vacuolization/degeneration/necrosis of the bile duct epithelium, increased neutrophils and megakaryocytes in the bone marrow, infiltration of macrophage/multinucleated giant cells/inflammatory cells in the lamina propria of the tracheal mucosa, disarrangement/detachment of the mucosal epithelium of the small intestine, haemorrhage in ileal mucosa, multinucleated giant cells in mesenteric lymph nodes, hemosiderin deposition in mesenteric lymph nodes, decreased lipid droplets in zona fasciculata cells in the adrenal gland, an increase in activated osteoclasts, trabecular bone loss, disarrangement/degradation/necrosis of ameloblasts and capillarectasia in the papillary layer and odontoblastic layer in incisor teeth, disarrangement of odontoblasts in incisor teeth, slight atrophy of the pituitary anterior lobe, and yellow-brown pigmentation in the proximal tubule. During the 8-week recovery period, these findings resolved or tended to resolve.

The applicant explained that the effects of alectinib on teeth and bones were not relevant to adult patients whose teeth and bones are already fully formed for the following reasons:

- Bone metabolism in adult humans is different from that in rodents in which bone turnover is high and in which the bone continues to grow even after maturation.
- Unlike humans, rat incisors grow continuously throughout life.
- It has been reported that the rate of enamel formation in humans is lower than that in rats (*Scand J Dent Res*. 1986;94:394-404, and *Crit Rev Oral Biol Med.*1998;9:128-61).
- No effects on bones and teeth were observed in monkeys receiving alectinib in repeated dose toxicity studies.

According to these findings, the NOAEL of alectinib in this study was determined to be <3 mg/kg/day.

The exposure to alectinib in the 3 mg/kg group ($AUC_{0\text{-}24h}$) was 5100 ng·h/m in males and 8450 ng·h/mL in females, both of which are lower than the clinical exposure level.*

* The estimated $AUC_{0\text{-}24h}$ value calculated as 2.4-fold the mean $AUC_{0\text{-}10h}$ value in NSCLC patients receiving alectinib 300 mg BID in Study AF-001JP was 11,900 ng·h/mL.

3.(iii).A.(2).3) Preliminary 2-week repeated oral dose toxicity study in cynomolgus monkeys (Non-GLP study, reference data)

Cynomolgus monkeys (1/sex/group) received alectinib orally at a dose of 0 (vehicle), 6, 20, or 60 mg/kg once daily for 2 weeks. One of the 2 animals in the 60 mg/kg group was sacrificed moribund. This animal started to show decreased fecal volume or no feces on Day 4 of treatment, and the animal's poor condition was considered to be caused by gastrointestinal abnormalities such as stagnation of intestinal contents and gastrointestinal dilation. The most commonly observed findings in the 20 mg/kg group were abnormal red blood cell morphology; decreases in mean cell volume, haemoglobin concentration, and haematocrit; increases in mean cell haemoglobin concentration and reticulocyte count; bile duct proliferation associated with inflammatory cells; enlargement of hepatocytes; and hypertrophy of the adrenal cortex. In addition to these findings, animals showed increased platelet count, decreased haematopoietic cells in the bone marrow, irregular-shaped pancreatic islets, spleen congestion, and pituitary anterior lobe atrophy. Since these findings were not observed in the 4-week repeated dose toxicity study in cynomolgus monkeys [see "3.(iii).A.(2).4) Four-week repeated oral dose toxicity study in cynomolgus monkeys"], they were not thought to be toxicological significance. Major findings observed in survived animals in the 60 mg/kg group included decreased fecal volume or no feces, vomiting, abdominal distension, decreased food consumption, increases in ALP and total bilirubin, increased liver weight, bile pigmentation in bile capillaries, gastric erosion/ulceration and atrophy, duodenal erosion, stagnation of intestinal contents in the large intestine, and gases in the large intestine.

According to these findings, the NOAEL of alectinib in this study was determined to be 6 mg/kg/day.

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

Cynomolgus monkeys (3-5 animals/sex/group) received alectinib orally at a dose of 0 (vehicle), 1.7, 5, or 15 mg/kg once daily for 4 weeks. Two animals in each group excluding the 1.7 mg/kg group were allowed a 4-week recovery period after the final administration of alectinib. No deaths attributable to alectinib treatment were observed. Abnormal red blood cell morphology was observed in the ≥1.7 mg/kg groups, and increased hepatic ALP, expanded proliferative zone in the large intestinal mucosa, hypertrophy of the adrenal cortex, and black stools were observed in the ≥5 mg/kg groups. However, black stools were not accompanied by abnormal necropsy or histopathological findings suggestive of gastrointestinal haemorrhage and were not observed in the 13-week repeated oral dose toxicity study in cynomolgus monkeys [see "3.(iii).A.(2).5) Thirteen-week repeated oral dose toxicity study in

cynomolgus monkeys"]. Accordingly, it was concluded that black stools were not of toxicological significance. Findings in the 15 mg/kg group included decreases in red blood cells, haemoglobin concentration, and hematocrit, increased mean cell hemoglobin concentration, increased direct bilirubin, increased liver weight, enlargement of hepatocytes, infiltration of inflammatory cells in the Glisson's sheath, increased neutrophils in the bone marrow, dilatation of the large intestine, expanded proliferative zone in the small intestinal mucosa. During the 4-week recovery period, red blood cell morphology tended to return to normal, while other findings resolved.

According to these findings, the NOAEL of alectinib in this study was determined to be <1.7 mg/kg/day.

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

Cynomolgus monkeys (3-5 animals/sex/group) received alectinib orally at a dose of 0 (vehicle), 1.3, 4, or 12 mg/kg once daily for 13 weeks. Two animals in each group excluding the 1.3 mg/kg group were allowed an 8-week recovery period after the final administration of alectinib. No deaths attributable to alectinib treatment were observed. Animals in the ≥1.3 mg/kg groups showed abnormal red blood cell morphology, and those in the ≥4 mg/kg groups showed increased gamma-GTP, increased liver weight, bile duct proliferation, expanded proliferative zone in gastrointestinal tract mucosa, and decreased lipid droplets in the adrenal cortex. Findings in the 12 mg/kg dose group included decreased red blood cell count, dilatation of the large intestine, enlargement of hepatocytes, infiltration of inflammatory cells in the Glisson's sheath, hypertrophy of the adrenal cortex. A male animal in the 12 mg/kg group had pulmonary haemorrhage (brown discoloration of entire lung lobes, red spots in the lungs, multifocal haemorrhage in the alveoli, and circumvascular aggregation of hemosiderin laden macrophages). However, the applicant explained that these findings were highly likely to have developed accidentally for the following reasons:

- There were no findings of cell disorder and inflammation.
- This animal showed good general condition, and these findings did not suggest serious lung disorder.
- Haemorrhagic changes have developed in animals used in this testing facility in the past.
- Other than this animal, haemorrhagic changes did not develop in any cynomolgus monkeys used in the repeated dose toxicity studies of alectinib. Haemorrhagic changes in the lungs were not observed among rats in repeated dose toxicity studies in which the exposure to alectinib was higher than that in cynomolgus monkeys.

According to these findings, the NOAEL of alectinib in this study was determined to be <1.3 mg/kg/day.

The exposure level ($AUC_{0\text{-}24h}$) in the 1.3 mg/kg group was 894 ng・h/mL in males and 1030 ng・h/mL in females, both of which were lower than the clinical exposure level.*

* The estimated $AUC_{0\text{-}24h}$ value calculated as 2.4-fold the mean $AUC_{0\text{-}10h}$ value in NSCLC patients receiving alectinib 300 mg BID in Study AF-001JP was 11,900 ng・h/mL.

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

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

In bacterial reverse mutation assays using Salmonella typhimurium (TA100, TA1535, TA98, and TA1537) and Escherichia coli (WP2*uvrA*), alectinib did not induce gene mutations.

3.(iii).A.(3).2) Chromosomal aberration assay using Chinese hamster lung cells

In a chromosomal aberration assay using Chinese hamster lung (CHL) cells, polyploid cells increased slightly with alectinib at 10 μg/mL, the highest dose tested, in the presence of metabolic activation system, which suggests that alectinib may induce aneuploidy. However, alectinib did not increase the risk of chromosomal structural abnormality.

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

In an *in vivo* micronucleus test of alectinib in rats, a positive result was obtained. In order to clarify how alectinib induces micronuclei, the applicant additionally conducted an *in vitro* micronucleus test using human lymphoblastoid (TK6) cells (non-GLP study, reference data) and an *in vivo* micronucleus test in rats. The applicant explained that alectinib induced micronuclei by causing abnormal chromosome division rather than directly affecting chromosomes for the following reasons:

- In the above studies, fluorescence in situ hybridization (FISH) analysis revealed an increase in micronuclei-containing cells and micronuclei-containing immature erythrocytes, both of which contained centromeres.
- Negative results were obtained in the reverse mutation assays.
- The incidence of structural chromosomal damages did not increase in the chromosomal aberration assay.

As the exposure to the NOAEL in the *in vivo* micronucleus test in rats is about 3-fold the clinical exposure,* it cannot be ruled out that alectinib may cause abnormal chromosome division in the clinical setting.

* A comparison was made between the exposure to the no observed adverse effect level (NOAEL, 200 mg/kg/day) in the *in vivo* micronucleus test in rats (C_{max}, 1850 ng/mL; $AUC_{0\text{-}24h}$, 36,700 ng･h/mL) and the exposure in Japanese NSCLC patients receiving alectinib 300 mg BID in Study AF-001JP (the mean C_{max}, 575 ng/mL; the estimated $AUC_{0\text{-}24h}$, 11,900 ng･h/mL calculated by multiplying the mean $AUC_{0\text{-}10h}$ by 2.4).

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

No carcinogenicity studies have been conducted with alectinib as it will be indicated for the treatment of advanced or recurrent NSCLC.

3.(iii).A.(5) Reproduction toxicity

3.(iii).A.(5).1) Effects on fertility and early embryonic development

No studies on the effects on fertility and early embryonic development have been conducted with alectinib as it will be indicated for the treatment of advanced or recurrent NSCLC.

The applicant explained that the effects of alectinib on male and female genital organs were examined in the repeated dose toxicity studies in rats and cynomolgus monkeys [see "3.(iii).A.(2) Repeated-dose toxicity studies"], and no histopathological abnormalities attributable directly to alectinib were observed.

3.(iii).A.(5).2) Effects on embryo-fetal development

As alectinib was suggested to cause toxic effects on embryo-fetal development such as embryo-fetal death and visceral anomalies in range-finding tests for embryo-fetal developmental toxicity studies in rats and rabbits, the applicant has not conducted embryo-fetal developmental toxicity studies using the sufficient number of animals that enables meaningful interpretation of data as indicated in the "Guidelines for Toxicity Studies of Drugs" (PAB/FERD Notification No. 24 of the First Evaluation and Registration Division, Pharmaceutical Affairs Bureau dated September 11, 1989).

The applicant explained that the toxicological effect of alectinib on embryo-fetal development is attributable to the induction of micronuclei rather than the inhibition of ALK as it has been reported that *ALK* knockout mice have been found to possess no detectable gross or histological defects (*J Cell Physiol. 2004*;199:330-58). The exposures to alectinib (the $AUC_{0\text{-}24}$ values on the first and final days of administration) at the NOAEL for the embryo-fetal development (i.e., 3 mg/kg/day in rats and 9 mg/kg/day in rabbits) ranged from 6060 to 13,900 ng·h/mL in rats and from 6130 to 6650 ng·h/mL in rabbits, and were similar to or lower than the clinical exposure level.*

* The estimated $AUC_{0\text{-}24h}$ value calculated as 2.4-fold the mean $AUC_{0\text{-}10h}$ value in NSCLC patients receiving alectinib 300 mg BID in Study AF-001JP was 11,900 ng·h/mL.

i) Range-finding test for the embryo-fetal developmental toxicity study in rats

Pregnant WIST rats (6/group) received alectinib orally at a dose of 0 (vehicle control), 3, 9, or 27 mg/kg once daily between gestation days 7 and 17, and the fetuses were delivered by caesarian section on gestation day 20. No dams died during the study. Animals in the ≥9 mg/kg groups showed decreased weight gain, and those in the 27 mg/kg group showed decreased weight gain, decreased food consumption, red lesions in the glandular gastric mucosa, dark red-colored mesenteric lymph nodes, and blackish brown-colored adrenal glands. Fetuses in the 9 mg/kg group showed low body weight, delayed ossification (decreased numbers of sacral and caudal vertebrae), and increased incidence of visceral anomalies (e.g., ureteric dilatation, thymic cord, small ventricles, and thin ventricular wall). In the 27 mg/kg group, all dams showed total litter losses, which resulted in increases in fetal mortality, early embryonic mortality, and total mortality.

The applicant explained that the increased incidence of visceral anomalies in fetuses may have developed secondarily to the delay in development such as low body weight or may be attributable to the direct teratogenic effect of alectinib.

On the basis of these results, the NOAEL for reproductive function in dams was concluded to be 9

mg/kg/day, and those for general toxicity in dams and embryo-fetal toxicity were both concluded to be 3 mg/kg/day.

ii) Range-finding test for the embryo-fetal developmental toxicity study in rabbits

Pregnant NZW rabbits (6/group) received alectinib at a dose of 0 (vehicle control), 3, 9, or 27 mg/kg once daily orally between gestation days 6 and 18, and the fetuses were delivered by caesarian section on gestation day 28. No dams died during the study. Dams in the ≥9 mg/kg groups showed abnormal red blood cell morphology. In the 27 mg/kg group, abortion occurred in 1 of the 6 animals on gestation day 21, and all dams showed low body weight, decreased food consumption, decreased fecal volume/no feces. Hematology and blood chemistry on gestation day 18 revealed anemia, deteriorated nutritional condition, and changes due to inflammation or stress (e.g., decreases in hematocrit, mean cell volume, eosinophil count, and basophil count; increases in mean cell hemoglobin concentration, platelet count, and neutrophil count; decreases in total protein, triglyceride level, and calcium level; and increases in total cholesterol and blood glucose level) in the 27 mg/kg group. As for fetal development, 2 of the 6 dams in the 27 mg/kg group showed total litter losses. The 27 mg/kg group also showed an increased incidence of post-implantation losses, increased numbers of embryo-fetal deaths, a decreased number of live fetuses, decreased fetal and placental weights, and increased incidence of full supernumerary ribs in fetuses.

On the basis of these results, the NOAEL for general toxicity in dams was concluded to be 3 mg/kg/day, and those for reproductive function in dams and embryo-fetal toxicity were both concluded to be 9 mg/kg/day.

3.(iii).A.(5).3) Effects on pre- and post-natal development, including maternal function

No studies on the effects on pre- and post-natal development and maternal function have been conducted with alectinib as it will be indicated for the treatment of advanced or recurrent NSCLC.

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

3.(iii).A.(6).1) Photosafety study (Non-GLP study, reference data)

As alectinib absorbs light at wavelengths from about [redacted] to [redacted] nm, an *in vitro* photosafety study using mouse 3T3 fibroblast cells was conducted, and showed positive results. The applicant explained that as highpersensitivity reactions to light observed in clinical studies of alectinib were considered to be related to alectinib therapy, the package insert for the product would include a precaution for photosensitivity reactions.

3.(iii).A.(6).2) Toxicity studies of metabolites (Non-GLP study, reference data)

Genotoxicity of M-4, a major metabolite of alectinib in humans [see "3.(ii).A.(3).1) *In vitro* metabolism"] was assessed. M-4 was negative for genotoxicity in reverse mutation assays using Salmonella typhimurium (TA100, TA1535, TA98, and TA1537) and Escherichia coli (WP2*uvrA*), as

well as in an *in vitro* micronucleus test using human lymphoblastoid TK6 cells.

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

Based on the submitted data and the following considerations, PMDA concluded that alectinib may be used in the clinical setting. PMDA also concluded that the use of alectinib in pregnant women or women who may be pregnant is not appropriate.

Administration of alectinib to pregnant women or women who may be pregnant

PMDA requested the applicant to explain the reasons why the proposed package insert for alectinib, submitted at the time of filing, describes that "Pregnant women or women who may be pregnant should be administered this drug only if the potential benefits outweigh the risks," and the applicant responded as follows:

In the range-finding tests for embryo-fetal developmental toxicity studies, alectinib exerted embryo-fetal toxicity such as embryo-fetal deaths and visceral anomalies. The exposure to alectinib on the first day of administration at the NOAELs for embryo-fetal development found in the range-finding tests for embryo-fetal developmental toxicity studies in rats and rabbits (i.e., 3 mg/kg/day in rats and 9 mg/kg/day in rabbits) was 6060 ng·h/mL in rats and 6130 ng·h/mL in rabbits, which were lower than the clinical exposure level in patients receiving alectinib 300 mg BID in Study AF-001JP (estimated $AUC_{0\text{-}24h}$, 11,900 ng·h/mL). As *ALK* fusion gene-positive NSCLC tends to be more common in young women (Biomarker Committee of the Japan Lung Cancer Society *Guidance for ALK gene testing in lung cancer patients.* version 1.2; 2011), it is likely that pregnant women may receive alectinib or women receiving alectinib become pregnant during treatment and that fetal development may be affected by alectinib. However, patients for whom alectinib is indicated have an extremely poor prognosis, and alectinib is expected to be more effective than the conventional chemotherapy agents. As it is important for patients to make a decision on whether or not to receive alectinib treatment with understanding the risk for the fetus, the above precaution was included in the proposed package insert.

PMDA considers as follows:

As the exposure to alectinib at the NOAEL in the embryo-fetal developmental toxicity studies was lower than the clinical exposure level [see "3.(iii).A.(5).2) Effects on embryo-fetal development"], the risk for the embryos and fetuses at the clinical dose is considered high. PMDA thus concluded that alectinib should be contraindicated for pregnant women or women who may be pregnant.

4. Clinical data

4.(i) Summary of biopharmaceutical study results and associated analytical methods

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

In the clinical studies of alectinib hydrochloride (referred to as "alectinib" hereinafter), hard capsules containing 20 or 40 mg alectinib (to-be-marketed) were used to investigate the pharmacokinetics of

alectinib and its metabolites, M-4 (a metabolite resulting from morpholine ring-opening and dealkylation) and M-6 (a dealkylated metabolite of M-4). The applicant is currently developing alectinib 150 mg capsules, and a bioequivalence study between alectinib 150 mg capsules and alectinib 20 and 40 mg capsules (JP28927 Study) is currently underway.

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

In the phase I/II study in Japanese patients with anaplastic lymphoma kinase (ALK) fusion gene-positive, advanced or recurrent, non-small cell lung cancer (NSCLC) who have a history of chemotherapy (AF-001JP Study), "*ALK* fusion genes" were detected using Histofine ALK iAEP Kit, an immunohistochemical (IHC) staining kit distributed by Nichirei Biosciences Inc. This analytical kit was applied for marketing approval in Japan on November 7, 2013, as an *in vitro* diagnostic that helps determine whether alectinib is indicated for.

In Study AF-001JP, "*ALK* fusion genes" were detected using a fluorescence in situ hybridization (FISH) method established in the Cancer Institute of the Japanese Foundation for Cancer Research (referred to as the "JFCR-FISH method" hereinafter). The JFCR-FISH method has been demonstrated to be equivalent to the Vysis ALK Break Apart FISH Probe Kit, an approved *in vitro* diagnostic distributed by Abbott Japan Co., Ltd. On November 26, 2013, Abbott Japan submitted an application for partial changes for the Vysis ALK Break Apart FISH Probe Kit to include an additional indication for use in determining whether alectinib is indicated for.

4.(i).A.(2) Quantitative assays

Alectinib, M-4, and M-6 in human plasma were quantified by LC-MS/MS analysis with lower limits of quantification of 0.1, 0.0488, and 0.0482 ng/mL, respectively.

4.(i).A.(3) Phase I/II study in Japan (5.3.5.2-1: AF-001JP Study, from August 2010, ongoing, data cut-off on April 18, 2013)

On the basis of data from the 240 mg and 300 mg groups in phase I segment (steps 1a and 1b) of Study AF-001JP in patients with *ALK* fusion gene-positive, advanced, or recurrent NSCLC with a history of chemotherapy [see "4.(ii).A.(1) Phase I/II study in Japan"], the effect of food on the pharmacokinetics of alectinib was assessed.

During step 1a of Study AF-001JP, alectinib was administered as a single oral dose of 20, 40, 80, 160, 240, or 300 mg in the fasting condition (fasting from 10 hours before to 2 hours after administration). After a 2-day rest, alectinib was administered orally twice a day (BID) without meal (fasting from 2 hours before to 1 hour after administration). During step 1b of Study AF-001JP, alectinib was administered as a single oral dose immediately after meal at 240 or 300 mg. After a 2-day rest, the drug was given BID orally immediately after meal.

Pharmacokinetic parameters of alectinib after single and repeated doses are tabulated below. After single dose administration, C_{max} and AUC were higher and T_{max} was longer when alectinib was given immediately after meal than when the drug was given during fasting. After repeated doses of alectinib, T_{max} was longer when alectinib was given immediately after meal than when it was given without meal, but C_{max} and AUC did not differ substantially in relation to meal.

Pharmacokinetic parameters after single oral doses of alectinib during fasting and immediately after meal (steps 1a and 1b of Study AF-001JP)

Dose (mg)	Timing of dosing	n	$AUC_{0\text{-}72h}$ (ng·h/mL)	AUC_{inf} (ng·h/mL)	C_{max} (ng/mL)	$t_{1/2}$ (h)	T_{max} (h)
240	During fasting	3	920 ± 341	968 ± 375	58.6 ± 15.6	17.7 ± 5.14	2.69 ± 1.21
	Immediately after meal	3	2200 ± 804	2310 ± 810	118 ± 52.2	17.1 ± 2.06	4.63 ± 1.08
300	During fasting	6	1540 ± 560	1640 ± 580	84.1 ± 35.8	19.3 ± 1.95	2.38 ± 0.799
	Immediately after meal	6	2700 ± 1030	2830 ± 1080	162 ± 63.6	16.4 ± 4.14	5.89 ± 2.07

Mean ± standard deviation

Pharmacokinetic parameters after repeated oral doses of alectinib without meal and immediately after meal (steps 1a and 1b of Study AF-001JP)

Dose (mg)	Timing of dosing	n	$AUC_{0\text{-}10h}$ (ng·h/mL)	C_{max} (ng/mL)	$t_{1/2}$ (h)	T_{max} (h)
240	Without meal	3	2970 ± 937	385 ± 100	20.9 ± 15.8	3.33 ± 1.15
	Immediately after meal	3	3300 ± 838	380 ± 82.8	-*1	5.24 ± 1.13
300	Without meal	6	4970 ± 3260	575 ± 322	12.4 ± 3.17*2	3.99 ± 2.17
	Immediately after meal	6	4220 ± 1190	528 ± 138	16.5 ± 3.83*3	5.32 ± 1.58

Mean ± standard deviation; *1, Not calculated as n = 1; *2., n = 5; *3, n = 3

Pharmacokinetic parameters of the metabolites (M-4 and M-6) after a single and repeated doses of alectinib 300 mg are tabulated below. There were no substantial differences in the ratios of C_{max} and $AUC_{0\text{-}72h}$ values of the metabolites versus those of the unchanged drug in relation to meal (i.e., when the drug was given immediately after meal, in the fasting condition, or without meal). Similarly to the results of *in vitro* studies [see "3.(ii).A.(3) Metabolism"], the major metabolite of alectinib in humans was M-4.

Pharmacokinetic parameters of metabolites

Metabolite	Treatment	Timing of dosing	C_{max}(ng/mL)	$AUC_{0\text{-}72h}$(ng·h/mL)
M-4	Single dose	During fasting	35.0 ± 33.3(37.8)	743 ± 557(45.9)
		Immediately after meal	45.7 ± 17.5(29.4)	1080 ± 413(42.3)
	Repeat doses	Without meal	233 ± 66.6(46.5)	1980 ± 596(47.2)
		Immediately after meal	241 ± 71.6(46.1)	2030 ± 563(49.8)
M-6	Single dose	During fasting	1.71 ± 1.74(1.81)	46.1 ± 38.0(2.80)
		Immediately after meal	2.21 ± 0.877(1.41)	60.7 ± 20.1(2.49)
	Repeat doses	Without meal	19.2 ± 8.86(3.89)	168 ± 77.0(4.14)
		Immediately after meal	22.8 ± 9.64(4.44)	198 ± 82.7(5.03)

Mean ± standard deviation (ratio[%] of the value of the metabolite relative to that of unchanged alectinib); n = 6

The applicant explained the effect of food on the pharmacokinetics of alectinib as follows:

The applicant provided the following 2 possible mechanisms for (1) the higher C_{max} and AUC values

and (2) longer T_{max} after a single dose alectinib given immediately after meal than those given during fasting. Regarding the absence of differences in C_{max} and AUC values after repeated doses of alectinib in relation to meal, the previous meal may affect the gastrointestinal absorption of alectinib given without food as it is said that bile secretion peaks 1 to 2 hours after meal [*Kiso Eiyogaku.*, 3rd edition, Kagaku Dojin Publishing Co., Inc. 2010].

- Regarding (1), bile acid secreted after meal increased the solubility of alectinib, which is highly lipid-soluble, in the gastrointestinal fluid, and the amount of alectinib absorbed was increased.

- Regarding (2), the meal delayed gastric emptying, and time to reach to the absorptive site was prolonged, resulting in a delay of absorption.

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

4.(i).B.(1) Effects of food

Although the pharmacokinetic profile of alectinib is affected by meal [see "4.(i).A.(3) Phase I/II study in Japan"] and alectinib was determined to be administered without food in the phase II segment of Study AF-001JP, no specific precautions regarding the timing of administration are included in the proposed dosage regimen of alectinib. PMDA requested the applicant to explain whether or not precautions for the timing of administration is necessary, and the applicant responded as follows:

The C_{max} and AUC values after a single dose of alectinib were higher when the drug was given immediately after meal than when it was given during fasting, but no differences related to meal were observed in these parameters after repeated doses of alectinib. Based on the following results of efficacy and safety evaluation of alectinib, the applicant thinks that there is little need to include precautions for the timing of administration in relation to meal.

- All patients with measurable lesions, i.e., 3 and 4 patients receiving alectinib 240 and 300 mg, respectively, without meal and 3 and 5 patients receiving alectinib 240 and 300 mg, respectively, immediately after meal, achieved partial response (PR) regardless of meal.

- No substantial differences in the safety profile of alectinib were observed between patients receiving alectinib without meal (3 and 6 patients receiving 240 and 300 mg, respectively) and those who receiving the drug immediately after meal (3 and 6 patients receiving 240 and 300 mg, respectively).

PMDA considers as follows:

The C_{max} and AUC values after repeated doses of alectinib did not differ between patients receiving alectinib without meal and those who receiving the drug immediately after meal. However, as (1) the results of single-dose administration indicate that the pharmacokinetics of alectinib is affected by meal

and as (2) the number of patients evaluated for the effect of meal on the pharmacokinetics after administration of repeated doses was limited, it is appropriate at this time to recommend administering alectinib without meal as did in the phase II segment of Study AF-001JP, and the applicant should provide appropriate precautions to healthcare professionals.

4.(i).B.(2) Effects of gastric pH

PMDA requested the applicant to explain the effect of change in gastric pH level associated with low gastric acid or the use of proton-pump inhibitors (PPIs) on the pharmacokinetics of alectinib, and the applicant responded as follows:

In Study AF-001JP, no patients with low gastric acid were enrolled.

In step 1a of Study AF-001JP, 2 patients who received PPIs or H_2-blockers during the pharmacokinetic assessment did not show changes in plasma alectinib concentration due to the use of PPIs or H_2-blockers. However, as the number of patients investigated was small, no clear evidence has been obtained for the effect of gastric pH on the pharmacokinetic profile of alectinib.

PMDA considers as follows:

As the effect of gastric pH on the pharmacokinetic profile of alectinib has been uncertain, information on the effect of gastric pH on the pharmacokinetic profile of alectinib is important to ensure the proper use of alectinib. Accordingly, PMDA concluded that it is necessary to continue to collect information, including published literature, on this matter.

4.(ii) Summary of clinical pharmacology studies

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

The pharmacokinetic profile of alectinib in patients with *ALK* fusion gene-positive, advanced or recurrent NSCLC who had a history of chemotherapy was assessed after a single dose administration of alectinib.

4.(ii).A.(1) Phase I/II study in Japan (5.3.5.2-1: Study AF-001JP, conducted from August 2010 to April 2013)

An open-label non-controlled study of alectinib was conducted in 70 patients with *ALK* fusion gene-positive, advanced or recurrent NSCLC who had a history of chemotherapy, and all 70 patients were included in PK analysis. Study AF-001JP consisted of a phase I segment (steps 1a and 1b) and a phase II segment. Alectinib was administered in a cycle of 21 days at the dosage regimen as below, and plasma alectinib concentrations were determined.

- Phase I segment

  Step 1a:

- Patients are to receive a single oral dose of alectinib 20, 40, 80, 160, 240, or 300 mg in the fasting condition. After a 2-day rest, patients are to receive alectinib at the corresponding dose BID without meal.

Step 1b:

- Patients are to receive a single oral dose of alectinib 240 mg or 300 mg immediately after meal. After a 2-day rest, patients are to receive alectinib at the corresponding dose BID immediately after meal.

・ Phase II segment

- Patients are to receive alectinib 300 mg BID orally without meal.

The table below summarizes the results of step 1a in the phase I segment. The results of step 1b are described in "4.(i).A.(3) Phase I/II study in Japan."

Pharmacokinetic parameters after a single oral dose of alectinib in the fasting condition in step 1a of Study AF-001JP

Dose (mg)	n	$AUC_{0\text{-}72h}$ (ng・h/mL)	AUC_{inf} (ng・h/mL)	C_{max} (ng/mL)	$t_{1/2}$ (h)	T_{max} (h)
20	1	143	206	4.52	42.4	5.97
40	1	248	288	12.3	26.6	3.97
80	1	670	696	41.4	16.1	3.98
160	3	1030 ± 717	1120 ± 766	60.3 ± 42.2	22.3 ± 6.88	2.62 ± 1.18
240	3	920 ± 341	968 ± 375	58.6 ± 15.6	17.7 ± 5.14	2.69 ± 1.21
300	6	1540 ± 560	1640 ± 580	84.1 ± 35.8	19.3 ± 1.95	2.38 ± 0.799

Mean ± standard deviation

Pharmacokinetic parameters after a single oral dose of alectinib without meal in step 1a of Study AF-001JP

Dose (mg)	n	$AUC_{0\text{-}10h}$ (ng・h/mL)	C_{max} (ng/mL)	$t_{1/2}$ (h)	T_{max} (h)
20	1	220	25.5	39.1	4.00
40	1	479	63.9	9.37	3.83
80	1	1310	150	14.1	2.00
160	3	2310 ± 598	300 ± 104	13.7,16.6[*1]	4.61 ± 1.15
240	3	2970 ± 937	385 ± 100	20.9 ± 15.8	3.33 ± 1.15
300	6	4970 ± 3,260	575 ± 322	12.4 ± 3.17[*2]	3.99 ± 2.17

Mean ± standard deviation; *1, n = 2; *2, n = 5

The elimination of alectinib after a single oral dose in step 1a was slow (mean $t_{1/2}$, 16.1 to 42.4 hours). Within the dose range from 20 to 160 mg, the exposure to alectinib increased dose-proportionally, but in the range from 160 to 300 mg, the exposure to alectinib did not increase substantially with increasing dose. The applicant explained these non-linear pharmacokinetic parameters by saying that the concentration of alectinib may have reached the saturation point in the gastrointestinal fluid when the drug, which is low in solubility to water, was given at the high dose, resulting in the decrease in gastrointestinal absorption.

The elimination of alectinib after repeated doses in step 1a was slow (mean $t_{1/2}$, 9.37 to 39.1 hours). Throughout the dose range tested, the exposure to alectinib increased dose-proportionally.

In the phase II segment, the trough plasma concentration of alectinib after repeated oral doses of 300 mg BID was 355 ± 132 ng/mL and 386 ± 171 ng/mL on the first day of Cycles 2 and 4, respectively, which suggests that plasma alectinib concentration reached a steady state by the first day of Cycle 2.

4.(ii).A.(2) Studies on the relationship between drug exposure and QT/QTc interval changes

A total of 24 patients who enrolled in the phase I segment of Study AF-001JP were evaluated for a possible effect of alectinib on QTc intervals. Only 1 patient in the 160 mg/kg group had a corrected QT interval according to Bazett's formula (QTcB) or Fridericia's formula (QTcF) of ≥450 ms after administration of alectinib. Among the 3 patients in the 160 mg/kg group, this patient had the lowest plasma alectinib concentration at the time of ECG recording. As the prolonged QT intervals disappeared without dose reduction or discontinuation in this patient, the Independent Review Committee concluded that this event was caused by the patient's specific problem (i.e., location of lesions) or occurred accidentally.

The applicant explained that the relationship between plasma alectinib concentration and prolonged QT intervals was low.

4.(ii).A.(3) Population pharmacokinetic analysis (PPK)

On the basis of pharmacokinetic data obtained (n = 70; time points, 609) in Study AF-001JP, a population pharmacokinetic (PPK) analysis was conducted using a 2-compartment model and non-linear mixed effect modeling (NONMEM). As covariates for apparent clearance (CL/F), the analysis examined age, height, weight, body mass index (BMI), body surface area, sex, Eastern Cooperative Oncology Group Performance Status (ECOG PS), type of cancer, stage, smoking history, epithelial growth factor receptor (EGFR) mutations, alkaline phosphatase (ALP), total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyltransferase (gamma-GTP), creatinine clearance (CrCL), neutrophil count, creatinine kinase, phosphorus, red blood cell count, and magnesium. As covariates for apparent volume of distribution for the central compartment (V_2/F), the analysis examined age, height, weight, BMI, body surface area, sex, ECOG PC, and EGFR mutations. As a result, AST was selected as a significant covariate for CL/F. The applicant explained that among the patients eligible for analysis, those with the lowest (10.0 U/L), median (21.0 U/L), and highest (75.0 U/L) values of AST are assumed to have a CL/F of 147, 118, and 80.7 L/h, respectively, which suggests that CL/F of alectinib decreases with increasing AST.

4.(ii).A.(4) Effects of renal impairment on the pharmacokinetic profile of alectinib

The applicant explained that renal impairment was unlikely to affect the pharmacokinetic profile of

alectinib for the following reasons:

- In the PPK analysis, CrCL was not selected as a significant covariate for CL/F of alectinib [see "4.(ii).A.(3) Population pharmacokinetic analysis (PPK)"]
- In the phase II segment of Study AF-001JP, no clear relationship was noted between CrCL and trough plasma concentration of alectinib in 5 patients who had renal or urinary tract disorder at baseline.
- A foreign clinical study (Study NP28989) in healthy volunteers is currently underway to investigate the mass balance of alectinib after oral administration of ^{14}C-labeled alectinib. In a preliminary analysis of the study, the mean urinary and fecal excretion rates during the first 7 days after administration (n = 6) was respectively 0.476% and 97.8% of the administered radioactivity, and the contribution of renal excretion to overall drug elimination is considered small.

4.(ii).A.(5) Relationships of exposure to alectinib with efficacy and safety of treatment

On the basis of the results of Study AF-001JP, the relationship between the exposure to alectinib, expressed as the mean AUC value at steady state (from Day 8 on), and the efficacy and safety of alectinib was assessed. The AUC at steady state was calculated using CL/F of individual patients estimated in the PPK analysis.

On the basis of a regression curve obtained in the logistic regression analysis of the relationship between response rate and AUC, the response rates in quartile groups by AUC at steady state were calculated. The response rates in patients whose AUC value was in the range from the minimum to the first quartile, from the first quantity to the medium, and from the medium to higher were 82%, 88%, and 100%, which indicates the response rate increases as AUC of alectinib increases.

On the basis of a regression curve obtained in a logistic regression analysis of the relationship between the presence/absence of adverse events for which a causal relationship with alectinib could not be ruled out (i.e., grade 3 or higher adverse events, gastrointestinal disorders, hepatic function abnormal, neutrophil count decreased, rash, myalgia, and creatinine increased) and AUC, the incidence of adverse events for which a causal relationship with alectinib could not be ruled out was calculated at quartile points of AUC at steady state. The calculated incidence of hepatic function abnormal at the first quartile, median, third quartile, and forth quartile were 22.2%, 35.3%, 55.6%, 58.8%, respectively, those of rash were 22.2%, 11.8%, 33.3%, and 35.3%, respectively, and those of creatinine increased were 22.2%, 11.8%, 27.8%, and 41.2%, respectively, which indicates a tendency towards increased incidence of hepatic function abnormal in patients with higher AUC values. No clear relationships were observed between the incidence of other types of adverse events and AUC at steady state.

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

Dose adjustment for patients with hepatic function disorder

Since AST was selected as a significant covariate for CL/F in the PPK analysis, and since it was assumed

that CL/F decreases with increasing AST [see "4.(ii).A.(3) Population pharmacokinetic analysis (PPK)"], PMDA requested the applicant to explain whether or not the dose of alectinib should be modified for patients with hepatic function disorder, and the applicant responded as follows:

There is little need to adjust the dose of alectinib for patients with hepatic function disorder for the following reasons: In patients receiving alectinib 300 mg BID in Study AF-001JP, (1) the adverse drug profile did not differ substantially between 19 patients who had hepatic function disorder at baseline and 39 patients with normal hepatic function at baseline, and (2) the trough plasma concentration of alectinib did not tend to be higher in patients who had hepatic function disorder at baseline than those with normal hepatic function. The applicant plans to conduct a clinical study to investigate the effect of hepatic function disorder on the pharmacokinetics of alectinib.

PMDA considers as follows:
As no clinical studies in patients with hepatic function disorder have been conducted, and as no data have been obtained regarding the effect of hepatic function disorder on the pharmacokinetics of alectinib, PMDA largely accepted the applicant's explanation that there is little need to adjust the dose of alectinib in patients with hepatic function disorder. However, PMDA considers that the applicant should provide the results of the foreign clinical study to be conducted in patients with hepatic function disorder appropriately to healthcare professionals when new information becomes available.

4.(iii) Summary of clinical efficacy and safety

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

As data for efficacy and safety reviews, the results of a phase I/II clinical study in Japan were submitted.

List of clinical studies on the efficacy and safety of alectinib

Category of data	Site	Study	Phase	Participants	No. of registered patients	Outline of dosage regimens	Major endpoint
Evaluation data	Japan	AF-001JP	I/II	*ALK* fusion gene-positive, advanced or recurrent NSCLC with a history of chemotherapy	(1) 15 (2) 9 (3) 46	Phase I segment (1) Step 1a: Alectinib 20, 40, 80, 160, 240, or 300 mg BID orally during fasting or without meal (2) Step 1b: Alectinib 240 or 300 mg BID orally immediately after meal Phase II segment (3) Alectinib 300 mg BID orally without meal	PK Safety Efficacy

ALK, Anaplastic lymphoma kinase; NSCLC, non-small cell lung cancer; BID, twice a day; PK, pharmacokinetics

The results of the clinical studies are as follows.
Commonly observed non-fatal adverse events in the clinical study are described in "4.(iv) Adverse events observed in clinical studies," and the results of pharmacokinetic assessment are described in "4.(i) Summary of biopharmaceutical study results and associated analytical methods" and "4.(ii) Summary of clinical pharmacology studies."

Evaluation data

Phase I/II study in Japan (5.3.5.2-01: Study AF-001JP, from August 2010, ongoing, data cat off on April 18, 2013)

An open-label, non-controlled clinical study in *ALK* fusion gene-positive, advanced or recurrent, non-small cell lung cancer (NSCLC) with a history of chemotherapy*[1] was conducted in 13 medical institutions in Japan. The target sample size was 10 to 30 patients in the phase I segment and 45 patients in the phase II segment.*[2] Study AF-001JP consisted of a phase I segment (steps 1a and 1b) and a phase II segment. The phase I segment was to be conducted to investigate the safety, tolerability, and pharmacokinetics of alectinib, and the phase II segment was to be conducted to assess the efficacy and safety of alectinib at recommended doses, determined in the phase I segment.

The dosage regimens of alectinib in steps 1a and 1b of the phase I segment were as follows. As no dose-limiting toxicity (DLT) was observed even at the highest dose of 300 mg BID among the 24 patients registered in the phase I segment (15 patients in step 1a and 9 patients in step 1b), an oral dose regimen of 300 mg BID without meal was selected for the phase II segment.

- Step 1a:
  Patients are to receive a single oral dose of alectinib 20, 40, 80, 160, 240, or 300 mg in the fasting condition. After a 2-day rest, patients are to receive alectinib at the corresponding dose BID without meal.
- Step 1b:
  Patients are to receive a single oral dose of alectinib 240 mg or 300 mg immediately after meal. After a 2-day rest, patients are to receive alectinib at the corresponding dose BID immediately after meal.

A total of 46 patients registered in the phase II segment were defined as the intention-to-treat (ITT) population, and were analyzed for efficacy. A total of 58 patients, consisting of the ITT population and 12 patients receiving alectinib 300 mg BID in the phase I segment (i.e., 6 patients in step 1a and 6 patients in step 1b), were defined as the safety analysis set.

The response rate*[3] determined by the Independent Review Committee (IRC), the primary efficacy endpoint of the study, was as follows:

*1 Combination chemotherapy containing platinum-based antineoplastic agents, combination chemotherapy containing molecular targeted agents, or monotherapy with an antineoplastic agent (e.g., docetaxel hydrate, pemetrexed sodium hydrate, erlotinib hydrochloride, and gefitinib)

*2 In this study, the threshold response rate was set at 25% on the basis of the response rate of combination chemotherapy containing platinum-based antineoplastic agents in patients with *ALK* fusion gene-positive, advanced or recurrent NSCLC, and the target sample size was set at 15 patients. However, since crizotinib, a drug that inhibits ALK similarly to alectinib, was approved in the United States during Study AF-001JP, the protocol of the study was amended to examine the non-inferiority of alectinib to crizotinib in terms of the response rate in patients with *ALK* fusion gene-positive, advanced or recurrent NSCLC. The response rate of crizotinib in this patient population was assumed at least 42% on the basis of the 95% confidence intervals in clinical studies of crizotinib, and a hypothesis with a threshold response rate of 45% for alectinib was newly added. The target sample size was changed to 45 patients.

*3 In the statistical analysis in Study AF-001JP, the data of the first 15 patients who enrolled early were to be used to test the null hypothesis with a claim of a threshold response rate of 25%. Only when the null hypothesis was rejected, an

additional analysis was to be conducted in the ITT population for the null hypothesis with a claim of a threshold response rate of 45%. The response rate of alectinib in the first 15 patients who had enrolled early was 93.3% [95% confidence interval: 68.1%-99.8%], and the null hypothesis with a claim of a threshold response rate of 25% was rejected.

Best overall response and response rate (RECIST Ver. 1.1, evaluated by the IRC, ITT population, n = 46)

	No. of patients (%)
Complete response (CR)	7 (15.2)
Partial response (PR)	36 (78.3)
Stable disease (SD)	1 (2.2)
Progressive disease (PD)	0
Impossible to judge	2 (4.3)
Response (CR+PR)	43
(Response rate [95% CI], (%))	(93.5 [82.1, 98.6])

CI, confidence interval

Safety analysis revealed that no patients died during the study or within 28 days after the end of the treatment period.

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

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

PMDA concluded that alectinib is effective to a certain extent in the treatment of patients with *ALK* fusion gene-positive, advanced or recurrent NSCLC who have a history of chemotherapy, on the basis of the following considerations.

Results of efficacy evaluation

The applicant explained the results of efficacy evaluation as follows:

As patients with advanced or recurrent NSCLC often suffer from clinical symptoms associated with the disease such as dyspnea and pain, it is important to reduce tumor burden and obtain response in order to improve these symptoms. In fact, it has been reported that in clinical studies in patients with advanced or recurrent NSCLC, attendant clinical symptoms were relieved in patients responding to treatment (*JAMA.* 2003; 290:2149-58, *J Clin Oncol.* 2004;22:3238-47).

Also, the response rate of alectinib in Study AF-001JP [see "Evaluation data: Phase I/II study in Japan" in "4.(iii).A. Summary of the submitted data"] is considered to be clinically relevant for the following reasons.

- The response rate of alectinib was higher than the 25% threshold response rate specified on the basis of the response rate of combination chemotherapy containing platinum-based antineoplastic agents in patients with *ALK* fusion gene-positive, advanced or recurrent NSCLC, as well as significantly higher than the 45% threshold response rate of specified based on the response rate of crizotinib, an ALK inhibitor like alectinib, which indicates a higher response rate of alectinib than crizotinib.
- Although the median duration of response, which is defined from the day of confirmation of

complete response (CR) or partial response (PR) to the day of event onset or censoring, cannot be estimated by Kaplan-Meier method, the median duration of response was estimated to be 12.9 months by handling the results as continuous data without considering censoring, indicating a persistent response.

PMDA considers as follows:
Although the true endpoint in patients with *ALK* fusion gene-positive, advanced or recurrent NSCLC is overall survival (OS), the relationship between response rate and OS is unclear. It is difficult to assess the effect of alectinib on survival advantage in this patient population at this time. However, considering the fact that alectinib is an ALK inhibitor targeting an oncogenic driver, which can be selected based on the evidence of molecular diagnosis (see the review report of Xalkori Capsules 200 mg and Xalkori Capsules 250 mg dated February 20, 2012), PMDA concluded that data including the response rate described above demonstrate the efficacy of alectinib to a certain extent in patients with *ALK* fusion gene-positive, advanced or recurrent NSCLC who have a history of chemotherapy.

4.(iii).B.(2) Safety [see "4.(iv) Adverse events observed in clinical studies" for adverse events]
PMDA concludes that adverse events requiring special attention are interstitial lung disease (ILD), hepatic function disorder, neutrophil count decreased, and white blood cell count decreased, and the physician should observe the patient carefully for these adverse events during the treatment with alectinib.

However, PMDA considers that alectinib is tolerable by patients if physicians with sufficient knowledge and experience in cancer chemotherapy observe patients carefully for adverse events, manage adverse events if they occur, and perform appropriate measures such as suspension or discontinuation of treatment and also if safety management is ensured through strict monitoring, management, and treatment of serious adverse events such as ILD. However, as safety information on alectinib is quite limited, the applicant should continue to collect information after launch and appropriately provide information without delay when new safety information becomes available.

4.(iii).B.(2).1) Safety profile of alectinib
The applicant explained the safety profile of alectinib as follows:
The following table shows the outline of the safety profile and adverse events that developed in ≥10% of the patients in Study AF-001JP. Serious adverse events observed in the study were brain oedema, convulsion, cholangitis sclerosing, maculopathy, alveolitis allergic, radius fracture, tumour haemorrhage, and neutrophil count decreased in 1 patient each (1.7%). The causal relationship between the event and alectinib therapy could not be ruled out for the patients of maculopathy,[*1] cholangitis sclerosing,[2*] tumour haemorrhage,[*3] and neutrophil count decreased. Adverse events resulting in discontinuation of treatment were brain oedema, cholangitis sclerosing, alanine aminotransferase increased, tumour haemorrhage, and interstitial lung disease observed in 1 patient each (1.7%). The causal relationship

between the event and alectinib therapy could not be ruled out for the patients of cholangitis sclerosing, alanine aminotransferase increased, tumour haemorrhage, and interstitial lung disease.

[*1] The investigator reported this event as "worsening of right premacular membrane." The patient showed right premacular membrane, as a complication, at baseline. This event developed on Day 55, and was indicated for surgery. The patient underwent cataract surgery and vitreous surgery of the right eye. Outcome was "recovered."

[*2] The investigator reported this event as "IgG4-related autoimmune cholangitis." This event developed on Day 152, and the patient had epigastric pain and jaundice. Endoscopic retrograde cholangiopancreatography revealed diffuse lower bile duct stenosis, and endoscopic nasobiliary drainage was conducted. As biopsy findings were suggestive of IgG4-related cholangitis and a rapid improvement was observed after steroid therapy, the patient was diagnosed as having "IgG4-related autoimmune cholangitis."

[*3] This event developed on Day 74. Bleeding from a metastatic site in the sigmoid colon was observed. Endoscopic haemostasis was performed. The lesion was surgically removed thereafter.

Summary of safety findings in Study AF-001JP

	No. of patients (%) 58 patients
All adverse events	58 (100)
Grade 3 or 4 adverse events	24 (41.4)
Grade 5 adverse events	0
Serious adverse events	7 (12.1)
Adverse events resulting in discontinuation of treatment	5 (8.6)
Adverse events requiring dose reduction	1 (1.7)
Adverse events requiring suspension of treatment	29 (50.0)

Adverse events developed in ≥10% of the patients in Study AF-001JP

Systemic organ class Preferred term (MedDRA ver.13.1)	No. of patients (%) 58 patients	
	All Grades	Grade 3 or higher
All adverse events	58 (100)	24 (41.4)
Investigations		
Blood bilirubin increased	20 (34.5)	2 (3.4)
Aspartate aminotransferase increased	19 (32.8)	0
Blood creatinine increased	17 (29.3)	0
Blood creatine phosphokinase increased	16 (27.6)	5 (8.6)
Alanine aminotransferase increased	15 (25.9)	2 (3.4)
Neutrophil count decreased	15 (25.9)	4 (6.9)
Weight gain	12 (20.7)	5 (8.6)
Blood alkaline phosphatase increased	10 (17.2)	1 (1.7)
White blood cell count decreased	12 (20.7)	1 (1.7)
Infections and infestations		
Nasopharyngitis	30 (51.7)	0
Upper respiratory tract infection	7 (12.1)	0
Gastrointestinal disorders		
Constipation	21 (36.2)	0
Stomatitis	11 (19.0)	0
Nausea	10 (17.2)	0
Diarrhoea	8 (13.8)	0
Vomiting	6 (10.3)	0
Nervous system disorders		
Dysgeusia	21 (36.2)	0
Headache	8 (13.8)	0
Skin and subcutaneous tissue disorders		
Rash	19 (32.8)	0
Musculoskeletal and connective tissue disorders		
Myalgia	12 (20.7)	0
General disorders and administration site conditions		
Malaise	11 (19.0)	0

PMDA considers as follows:

As the number of patients assessed for the safety of alectinib therapy is quite limited, careful attention should be paid for the adverse events observed in Study AF-001JP. PMDA concluded that alectinib is tolerable if physicians with sufficient knowledge and experience in cancer chemotherapy perform appropriate measures such as drug suspension and if safety measures are appropriately taken after launch. In this regard, information on these events should be provided appropriately to healthcare professionals. [see "4.(iii).B.(6) Post-marketing risk minimization actions"].

In the following sections, major adverse events observed in Study AF-001JP are discussed in reference to adverse events described in the "Clinically significant adverse reactions" section in the package insert for crizotinib, a drug that inhibits ALK similarly to alectinib.

Prolonged QT intervals, bradycardia, and vision disorders, which require attention during treatment with crizotinib but are not discussed in the following sections, are considered tolerable in light of the occurrence of these events in Study AF-001JP. However, as the number of patients assessed for the safety of alectinib therapy is quite limited, the applicant should carefully collect information on these

adverse events after launch, and appropriately provide information without delay to healthcare professionals when new safety information becomes available.

4.(iii).B.(2).2) Interstitial lung disease (ILD)

The applicant explained the occurrence of ILD associated with the use of alectinib as follows:

Adverse events falling under a standardized MedDRA Query (SMQ) "interstitial lung disease" were tabulated as ILD-like events including ILD.

In Study AF-001JP, 3 of 58 patients (5.2%) developed ILD-like events, including ILD, radiation pneumonitis, and alveolitis allergic in 1 patient each. All these events were grade 1 in severity [See the table below]. One of 58 patients (1.7%), the patient who had ILD, discontinued treatment due to the adverse event.

Outline of patients with ILD-like events in Study AF-001JP

Sex	Age (yrs)	ECOG PS	Preferred term (MedDRA ver.13.1)	Grade	Onset (day of treatment)	Duration (days)	Treatment	Outcome	Causal relationship with alectinib
F	[redacted]	1	Interstitial lung disease	1	102	40	Antibiotics	Not recovered	Related
F	[redacted]	1	Irradiation pneumonitis	1	21	60	None	Not recovered	Not related
F	[redacted]	1	Pneumonitis allergic	1	145	141	Antibiotics/steroid	Recovered	Not related

In order to evaluate the incidence of ILD in Study AF-001JP, the IRC reviewed the findings of patients who presented with ground-glass opacities on computed tomography (CT) images and who developed some respiratory symptoms during the study period, in addition to patients reported by the investigator, to assess whether or not these findings come under ILD. The IRC reviewed the findings of 9 patients (including cases of the women [redacted] years of age and the woman [redacted] years of age in the above table) and concluded that the 1 patient (the woman [redacted] years of age in the above table) diagnosed as "drug-induced pneumonia (interstitial)" by the investigator developed ILD. Among 8 patients for whom the investigator did not diagnose as having ILD, 1 patient was suspected of having ILD by the IRC, and ILD was denied for the remaining 7 patients. In the patient suspected to have ILD, the IRC pointed out the presence of opacities associated with ILD at baseline, and concluded that alectinib might have contributed to the prolongation of ILD. When this event is considered as an ILD-like event, the incidence of ILD-like events in Study AF-001JP was 6.9% (4 of 58 patients).

Although all ILD-like events observed in Study AF-001JP were mild in severity, attention should be paid for ILD-like events as the events may result in a fatal outcome.

PMDA considers as follows:

The incidence of ILD-like events among Japanese patients receiving alectinib in clinical studies was not substantially higher than the incidence of the events in clinical studies of crizotinib, an ALK inhibitor

approved in Japan. However, as (1) the number of patients assessed for the safety of alectinib therapy is quite limited, and as (2) in clinical studies of crizotinib, which inhibits ALK similarly to alectinib, the incidence of ILD is higher in Japanese patients than non-Japanese patients and fatal cases of ILD have been reported (see the review report of Xalkori Capsules 200 mg and Xalkori Capsules 250 mg dated February 20, 2012), appropriate precautions should be provided in the package insert and other relevant documents to instruct physicians to check for a past or current history of ILD and select patients carefully prior to administration, observe patients continuously for occurrence of ILD throughout treatment, and treat ILD appropriately when it occurs.

4.(iii).B.(2).3) Hepatic function disorder

The applicant explained about hepatic function disorder due to alectinib therapy as follows:

Adverse events falling under a standardized MedDRA Query (SMQ) "drug related hepatic disorders" were tabulated as adverse events indicating hepatic function disorder.

The following table summarizes the profile of adverse events relating to hepatic function disorder in Study AF-001JP.

Drug-related hepatic disorders in Study AF-001JP

Preferred term (MedDRA ver.13.1)	No. of patients (%) 58 patients	
	All grades	Grade 3 or higher
All adverse events	33 (56.9)	5 (8.6)
Blood bilirubin increased	20 (34.5)	2 (3.4)
Aspartate aminotransferase increased	19 (32.8)	0
Alanine aminotransferase increased	15 (25.9)	2 (3.4)
Blood alkaline phosphatase increased	10 (17.2)	1 (1.7)
Liver disorder	1 (1.7)	0

In Study AF-001JP, no cases of serious hepatic function disorder were observed. One of 58 patients (1.7%) who were enrolled in the study discontinued alectinib therapy due to hepatic function disorder (grade 3 alanine aminotransferase increased), and a causal relationship between the event and alectinib therapy could not be ruled out. Hepatic function disorder resulting in suspension of alectinib was blood bilirubin increased in 6 patients, aspartate aminotransferase increased in 1 patient, alanine aminotransferase increased in 2 patients, and alkaline phosphatase increased in 3 patients. There were no cases of hepatic function disorder that meet the criteria of Hy's Law (defined on the basis of *Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation.* U.S. Department of Health and Human Services, Food and Drug Administration. July 2009).

PMDA considers as follows:

Since only 1 patient discontinued alectinib due to hepatic function disorder in Study AF-001JP, and since the event could be managed with suspension of alectinib, alectinib is considered tolerable when appropriate measures such as suspension are provided according to the patient's condition. However, as

(1) the number of patients assessed for the safety of alectinib therapy is quite limited, and as (2) cases of deaths from hepatic failure were observed in clinical studies of crizotinib, which inhibits ALK similarly to alectinib (see the review report of Xalkori Capsules 200 mg and Xalkori Capsules 250 mg dated February 20, 2012), appropriate precautions on the risk of hepatic function disorder due to alectinib therapy should be provided in the package insert and other relevant documents.

4.(iii).B.(2).4) Neutrophil count decreased and white blood cell count decreased

The applicant explained about decreases in neutrophil count and white blood cell count due to alectinib therapy as follows:

Adverse events falling under a standardized MedDRA Query (SMQ) "haematopoietic erythropenia" were tabulated as haematopoiesis impaired including neutrophil count decreased and white blood cell count decreased.

The following table summarizes the profile of haematopoiesis impaired, including neutrophil count decreased and white blood cell count decreased, reported as adverse events in Study AF-001JP.

Cytopenia due to haematopoiesis impaired (AF-001JP Study)

Preferred term (MedDRA ver.13.1)	No. of patients (%) 58 patients	
	All grades	Grade 3 or higher
All adverse events	17 (29.3)	5 (8.6)
Neutrophil count decreased	15 (25.9)	4 (6.9)
White blood cell count decreased	12 (20.7)	1 (1.7)
Anemia	3 (5.2)	1 (1.7)
Lymphocyte count decreased	1 (1.7)	0

In Study AF-001JP, serious haematopoiesis impaired (grade 3 neutrophil count decreased) was observed in 1 of 58 patients (1.7%), and a causal relationship between the event and alectinib therapy could not be ruled out. No patients discontinued alectinib therapy due to haematopoiesis impaired. Haematopoiesis impaired resulting in suspension of alectinib was neutrophil count decreased in 7 patients, white blood cell count decreased in 1 patient, and anaemia in 1 patient.

PMDA considers as follows:

In Study AF-001JP, no patients discontinued alectinib therapy due to haematopoiesis impaired, and these events were manageable with suspension of alectinib. PMDA thus considers that alectinib may be tolerable providing that appropriate measures such as suspension of alectinib are taken according to the patient's condition. However, as neutrophil count decreased and white blood cell count decreased have developed at a certain level of frequency, and although rare, serious adverse events have been reported, information on these adverse events should be provided appropriately in package insert and other relevant documents.

4.(iii).B.(3) Clinical positioning and indications

The proposed indication of alectinib is "*ALK* fusion gene-positive, unresectable, advanced or recurrent non-small cell lung cancer," and the "Precautions for Indications" section includes the followings:

- Alectinib should be administered to patients confirmed to be positive for the *ALK* fusion gene through testing by an experienced pathologist or in an appropriate laboratory.
- The efficacy and safety of alectinib in post-operative adjuvant chemotherapy have not been established.
- Physicians should select patients eligible for alectinib therapy after closely reading the Clinical Studies section to fully understand the efficacy and safety of alectinib and carefully considering other treatment options.

On the basis of the review of "4.(iii).B.(1) Efficacy" and "4.(iii).B.(2) Safety," as well as the following considerations described in this section, PMDA concluded that it is appropriate to indicate alectinib for "*ALK* fusion gene-positive, unresectable, advanced or recurrent non-small cell lung cancer" as proposed by the applicant. However, Study AF-001JP was conducted in patients with a history of chemotherapy, and the clinical efficacy of alectinib in chemotherapy-naive patients has not been demonstrated. Thus, PMDA concluded that by adding information to this effect, the above precautions for indications proposed by the applicant should be modified as follows:

- Alectinib should be administered to patients confirmed to be positive for the *ALK* fusion gene through testing by an experienced pathologist or in an appropriate laboratory. Testing should be performed using an approved in vitro diagnostic based on the principles of immunohistochemical staining and fluorescence in situ hybridization.
- The efficacy and safety of alectinib in chemotherapy-naive patients have not been established.
- The efficacy and safety of alectinib in post-operative adjuvant chemotherapy have not been established.
- Physicians should select patients eligible for alectinib therapy after closely reading the Clinical Studies section to fully understand the efficacy and safety of alectinib and carefully considering other treatment options.

4.(iii).B.(3).1) Intended patient population

PMDA confirmed that no descriptions on alectinib are found in various Japanese or foreign practice guidelines or international oncology textbooks such as "DeVita, Hellman, and Rosenberg's *Cancer: Principles & Practices of Oncology.* 9th ed." (PA, USA: Lippincott Williams & Wilkins; 2011).

The applicant explained the clinical positioning and intended patient population of alectinib as follows:

Considering that the response rate of alectinib in patients with *ALK* fusion gene-positive, advanced or

recurrent NSCLC enrolled in Study AF-001JP was higher than the response rate of crizotinib, which inhibits ALK similarly to alectinib, in its clinical studies and that the safety profile of alectinib was tolerable, alectinib is expected to be highly useful in the clinical setting and will be positioned as an treatment option for patients with *ALK* fusion gene-positive, unresectable, advanced or recurrent non-small cell lung cancer. The following studies are underway to clarify the clinical positioning of alectinib and crizotinib and the choice between the 2 drugs.

- Phase III clinical study in Japan (Study JO28928)

  An open-label randomized comparative study (target sample size, 200) of alectinib vs. crizotinib in patients with *ALK* fusion gene-positive, advanced or recurrent NSCLC who are chemotherapy-naïve or have received 1 regimen of chemotherapy is being conducted to compare the efficacy and safety of the 2 drugs using progression-free survival (PFS) as the primary endpoint.

In Study AF-001JP , patients receiving alectinib in the second-line or later setting showed (1) a high response rate of alectinib regardless of the number of regimens received prior to the study [see the table below], and (2) that the PFS was estimated to be at least 22 months (the median PFS could not be determined, but was estimated on the basis of the median of treatment durations described in the case report forms as of January 8, 2014), suggesting that the duration will be longer than the median PFS under combination chemotherapy regimens containing platinum-based antineoplastic agents, standard first-line therapy for patients with *ALK* fusion gene-positive, advanced or recurrent NSCLC (3.87-8.5 months). Alectinib is expected to be highly useful in the treatment of *ALK* fusion gene-positive, advanced or recurrent NSCLC in various settings, including the first-line treatment.

Response rate (RECIST Ver.1.1, evaluated by the IRC, ITT population)

		No. of patients	No. of patients with response (CR/PR)	Response rate [95% CI] (%)
Efficacy analysis set		46	43	93.5 [82.1, 98.6]
Number of regimens prior to the study	0*	1	1	100 [2.5, 100]
	1	21	18	85.7 [63.7, 97.0]
	2	9	9	100 [66.4, 100]
	≥ 3	15	15	100 [78.2, 100]

CI, confidential interval; *, Patients who developed disease recurrence within 6 months after the end of postoperative adjuvant chemotherapy could be enrolled in Study AF-001JP.

Although Study AF-001JP does not include patients who have received crizotinib, an ALK inhibitor like alectinib, for the treatment of *ALK* fusion gene-positive, advanced or recurrent NSCLC, the currently ongoing bioequivalence study (Study JP28927) [see "4.(i).A. Summary of the submitted data"] has enrolled patients with a history of crizotinib therapy, and the response rate of alectinib determined by the investigators was 70.8% (17 of 24 patients, including 3 patients with undetermined response) in patients with a history of crizotinib therapy and 65.0% (13 of 20 patients, including 3 patients with undetermined response) in patients who had not responded to crizotinib (cut-off date, January 11, 2014). Considering these facts, crizotinib is expected to be clinically useful even in patients with *ALK* fusion gene-positive, advanced or recurrent NSCLC not responding to crizotinib, which has the same

mechanism of action with alectinib.

PMDA considers as follows:
Considering the patient population and results of the AF-001JP study, PMDA may accept the applicant's explanation that alectinib may be positioned as a treatment option for patients with *ALK* fusion gene-positive, unresectable, advanced or recurrent NSCLC. However, all participants in Study AF-001JP had a history of chemotherapy, and no information on the efficacy and safety of alectinib in chemotherapy-naive patients has been obtained. PMDA concluded that it is appropriate to provide a precaution to this effect in the "Precautions for Indications" section.

In this application, the efficacy of alectinib was mainly based on response rate, and no data on the effect on survival are available. As physicians should consider treatment options other than alectinib before determining whether or not alectinib can be indicated for the patient, PMDA concluded that precautions to this effect should be provided in the package insert or other relevant materials.

4.(iii).B.(3).2) *ALK* fusion gene testing
The applicant included "Alectinib should be administered to patients confirmed to be positive for the *ALK* fusion gene in examination by an experienced pathologist or in an appropriate laboratory" in the proposed "Precautions for Indications" section since it is important to test patients for the *ALK* fusion gene before prescribing alectinib in order to ensure the efficacy expected from its mechanism of action.

The applicant explained about *ALK* fusion gene testing used in Study AF-001JP to determine the eligibility of patients [see "4.(i).A.(1) Analytical procedures"] as follows:

In Study AF-001JP, the following 2 criteria were used for the presence/absence of the *ALK* fusion gene depending on the type of samples used.

- Formalin-fixed paraffin-embedded tumor tissues: The immunohistochemical (ICH) analysis proposed by Takeuchi et al. (*PLoS One.* 2013;8;e69794) is to be used to confirm the expression of the ALK fusion protein, and patients with a negative test result are to be excluded from the study. Patients with an equivocal negative, equivocal positive or positive result of the ICH analysis are to be tested with the FISH analysis to examine the expression of the *ALK* fusion gene, and patients with a positive result are to be considered eligible for the study.

- Frozen tumor samples and non-tumor tissue samples (e.g., pleural effusion, alveolar lavage fluid, and sputum): Samples are to be tested using reverse transcription polymerase chain reaction (PR-PCR) to investigate the expression of the *ALK* fusion gene. Patients with a negative test or “impossible to judge” are to be excluded from the study, and patients with a positive test are to be enrolled in the study.

It is appropriate to choose the testing methods used in Study AF-001JP with reference to the relevant documents, such as "*Guidance for ALK gene testing in lung cancer patients version 1.2*" (edited by the Biomarker Committee, the Japan Lung Cancer Society, in 2011), and the methods proposed by Takeuchi et al. (*PLoS One.* 2013;8:e69794), to specify patients for whom alectinib is indicated in the clinical setting. The applicant plans to produce appropriate materials on *ALK* fusion gene testing and provide information to healthcare professionals to ensure appropriate selection of patients in whom alectinib is expected to be effective.

PMDA considers as follows:
It is appropriate to use both of the IHC and FISH tests to detect the *ALK* fusion gene in formalin-fixed paraffin-embedded samples and to select patients for whom alectinib is indicated by using the Histofine ALK iAEP Kit and the Vysis ALK Break Apart FISH Probe Kit as companion diagnostics. PMDA concluded that the following precautions should be included in the "Precautions for Indications" section.

- Alectinib should be administered to patients confirmed to be positive for the *ALK* fusion gene in examination by an experienced pathologist or in an appropriate laboratory. Testing should be performed using an approved in vitro diagnostic based on the principles of immunohistochemical staining and fluorescence in situ hybridization

4.(iii).B.(3).3) Efficacy and safety in postoperative adjuvant chemotherapy
On the basis of the fact that no clinical study results have been obtained in terms of the efficacy and safety of alectinib in postoperative adjuvant chemotherapy, the applicant explained that the Precautions for Indications will include a statement to this effect.

PMDA accepted the applicant's explanation.

4.(iii).B.(4) Dosage and administration
The proposed dosage regimen is that "The usual adult dose is 300 mg of alectinib given orally twice daily."

PMDA concluded that it is appropriate to define the Dosage and Administration as above, as proposed by the applicant. PMDA also concluded that the Precautions for Dosage and Administration section should describe as follows on the basis of the discussion in "4.(i).B.(1) Effects of food."

- In order to avoid the effect of food, alectinib should be taken without meal according to the protocol of clinical studies.

Dosage regimen, dose reduction, and suspension of dose

The applicant explained about the rationale for the dosage regimen of alectinib, and the necessity to provide guidance for dose reduction and suspension in the package insert.

A dosage regimen of "300 mg BID orally" was selected for the following reasons: No dose-limiting toxicity (DLT) was observed even at the highest dose of 300 mg BID in the phase I segment of Study AF-001JP, and the efficacy and safety of alectinib at the same regimen was confirmed in patients with *ALK* fusion gene-positive, advanced or recurrent NSCLC in the phase II segment of the study.
In foreign countries, alectinib is currently under development for the treatment of patients with *ALK* fusion gene-positive NSCLC who have developed resistance to crizotinib. On the basis of the findings of this patient population in the phase I segment of the foreign phase I/II study (Study AF-002JG), the recommended dose in the phase II segment was set at 600 mg BID.

It is not necessary to describe guidance for dose reduction and suspension in the package insert for alectinib for the following reasons:

- Although the criteria for dose reduction were established for Study AF-001JP, none of the patients receiving 300 mg BID met the criteria or decreased the dose.
- The criteria for suspension in Study AF-001JP state that when grade 4 haematotoxicity (platelet count decreased or neutrophil count decreased) or grade ≥3 non-haematologic toxicity develops, alectinib treatment should be held until the toxicity resolves to grade ≤1 or to the severity at baseline. However, these criteria are not special.

PMDA considers as follows:
PMDA concluded that the dosage regimen at which alectinib demonstrated the efficacy and safety to a certain extent in Study AF-001JP can be adopted as the Dosage and Administration of alectinib, as proposed by the applicant. However, further investigation should be made for the dosage regimens of alectinib since the recommended dose of alectinib is 600 mg BID in foreign countries, though the target population of patients with crizotinib-resistant *ALK*-fusion gene-positive NSCLC is not consistent with Study AF-001JP.

PMDA accepted the applicant's explanation on the needlessness of including guidance for dose reduction or suspension in the package insert.

4.(iii).B.(5) Post-marketing investigations
The applicant explained the contents of post-marketing investigations as follows:

In order to identify unexpected adverse drug reactions (ADRs) to alectinib and determine the incidence of ADRs in the clinical setting after launch, the applicant plans to conduct a post-marketing surveillance covering all patients receiving alectinib (all-case survey).

The all-case survey will investigate ILD and hepatic function disorder as priority survey items, since these events were observed in Study AF-001JP and since fatal cases have been reported in association with crizotinib, an ALK inhibitor like alectinib.

The target sample size will be set at 1000 in order to capture at least 1 case each of ADRs that develop in 0.3% of patients with a probability of ≥95%, as it is important to detect rare (< 1%) unknown ADRs to alectinib, which has been used only in a limited number of patients, and the survey should be able to detect ADRs occurring at an incidence of half the mortality due to ILD in the early post-marketing phase vigilance of crizotinib (0.77%, 4 of 520 patients), which inhibits ALK similarly to alectinib. It is expected to take 1 year and 6 months to register 1000 patients.

As the medium treatment duration in Study AF-001JP was 15.8 months, patients will be followed for 1 year and 6 months in the all-case survey in order to collect data comparable with those of Study AF-001JP.

PMDA considers as follows:
As safety information submitted for the marketing application for alectinib quite limited, the applicant should conduct the all-case survey to collect safety information promptly in an unbiased way and provide safety information to healthcare professionals without delay.

The survey on the priority survey items should be designed carefully to ensure that the following information as well is collected.

- Characteristics of ILD (e.g., patient characteristics, imaging findings, severity, time to onset and outcome assessment, outcome, treatment, response to treatment, and factors predictive of ILD)
- Clinical characteristics of hepatic function disorder (e.g., time to onset, duration of symptoms, and signs of aggravation)

PMDA accepted the applicant's explanation on the target sample size.

The observation period may be set at 1 year and 6 months as planned by the applicant, but the applicant should perform interim analyses during the all-case survey to consider amending the protocol.

4.(iii).B.(6) Post-marketing risk minimization actions
The applicant explained the contents of post-marketing risk minimization actions as follows:

Regarding ILD and hepatic function disorder selected as priority survey items for the post-marketing surveillance, no serious or fatal cases of ILD or hepatic function disorder were observed in Study AF-

001JP. However, (1) the number of patients evaluated for the safety of alectinib is quite limited, (2) serious or fatal cases of ILD or hepatic function disorder have been reported in association with a drug that inhibits ALK similarly to alectinib, and (3) a phase III study of alectinib is currently underway and no data have been obtained from confirmatory clinical studies. For these reasons, as additional risk minimization actions, the applicant plans to provide information based on the results of early post-marketing phase vigilance, materials for healthcare professionals (guidance for proper use of alectinib), and materials for patients, as well as to set conditions for use of alectinib (e.g., conditions for physicians and medical institutions, request for pharmacies to ensure proper use of alectinib, and careful baseline assessment of patients before prescribing alectinib) and provide updates on ADRs to the drug on websites during an early period after launch.

PMDA considers as follows:
PMDA considers that no specific problems are found in the contents of additional risk minimization actions planned by the applicant. Although the applicant explained that it will set conditions for use of alectinib and provide updates on ADRs to alectinib on websites during an early period after launch, the applicant should not set a time limit for these actions to an early period after launch, but consider the continuation of these actions at each juncture such as at the time of analysis of post-marketing surveillance data.

4.(iv) Adverse events observed in clinical studies

This section describes the most common non-fatal adverse events observed in the clinical studies presented in the document for safety review. Fatal adverse events are described in Section "4.(iii) Summary of clinical efficacy and safety."

Phase I/II study in Japan (Study AF-001JP)

(a) Phase I segment

Adverse events developed in 1 of the 1 patient (100%) in the 20 mg/kg group, 1 of the 1 patient (100%) in the 40 mg/kg group, 1 of the 1 patient (100%) in the 80 mg/kg group, 3 of the 3 patients (100%) in the 160 mg/kg group, 3 of the 3 patients (100%) receiving 240 mg without meal, 3 of the 3 patients (100%) receiving 240 mg immediately after meal, 6 of the 6 patients (100%) receiving 300 mg without meal, and 6 of the 6 patients (100%) receiving 300 mg immediately after meal. All patients experienced events for which a causal relationship with alectinib could not be ruled out.

In the 20, 40, and 80 mg dose groups that contained 1 patient each, the following adverse events were observed: diarrhoea, dysgeusia, headache, malaise, back pain, nausea, decreased appetite, insomnia, pyrexia, laryngitis, peripheral sensory neuropathy, photopsia, procedural pain, and rhinorrhoea in the 20 mg group; nasopharyngitis, neutrophil count decreased, white blood cell count decreased, headache, aspartate aminotransferase increased, back pain, blood bilirubin increased, convulsion, fatigue, haemoglobin decreased, rhinitis, cholelithiasis, and musculoskeletal stiffness in the 40 mg group; and

constipation, headache, malaise, back pain, stomatitis, alanine aminotransferase increased, nausea, contrast media allergy, decreased appetite, oropharyngeal pain, upper respiratory tract infection, blood glucose increased, dysphonia, fatigue, blood cholesterol increased, dysphagia, haemoptysis, neuropathy peripheral, and visual field defect in the 80 mg group. Among these, neutrophil count decreased in the patient in the 40 mg group was grade ≥3 in severity.

Adverse events that occurred in ≥2 patients in the 160 mg group were constipation, nasopharyngitis, and back pain; these events were observed in 2 patients each (33.3%) and grade ≤2 in severity.

The following table summarizes adverse events that developed in ≥2 patients in at least one of the 4 groups, 240 mg (without meal), 240 mg (immediately after meal), 300 mg (without meal), and 300 mg (immediately after meal).

Adverse events observed in 2 or more patients in at least one of the 4 groups, 240 mg (without meal), 240 mg (immediately after meal), 300 mg (without meal), and 300 mg (immediately after meal)

Adverse events	No. of patients (%)							
	240 mg without meal (n = 3)		240 mg immediately after meal (n = 3)		300 mg without meal (n = 6)		300 mg immediately after meal (n = 6)	
	All grades	Grade 3 or higher	All grades	Grade 3 or higher	All grades	Grade 3 or higher	All grades	Grade 3 or higher
All adverse events	3 (100)	1 (33.3)	3 (100)	0	6 (100)	3 (50.0)	6 (100)	2 (33.3)
Constipation	0	0	1 (33.3)	0	5 (83.3)	0	4 (66.7)	0
Nasopharyngitis	2 (66.7)	0	1 (33.3)	0	4 (66.7)	0	2 (33.3)	0
Diarrhoea	1 (33.3)	0	2 (66.7)	0	3 (50.0)	0	2 (33.3)	0
Neutrophil count decreased	1 (33.3)	0	1 (33.3)	0	3 (50.0)	1 (16.7)	3 (50.0)	1 (16.7)
Blood creatine phosphokinase increased	1 (33.3)	1 (33.3)	1 (33.3)	0	4 (66.7)	2 (33.3)	2 (33.3)	1 (16.7)
Dysgeusia	1 (33.3)	0	0	0	2 (33.3)	0	5 (83.3)	0
White blood cell count decreased	0	0	1 (33.3)	0	3 (50.0)	0	4 (66.7)	1 (16.7)
Headache	0	0	0	0	2 (33.3)	0	2 (33.3)	0
Malaise	0	0	0	0	3 (50.0)	0	2 (33.3)	0
Aspartate aminotransferase increased	0	0	0	0	4 (66.7)	0	2 (33.3)	0
Blood bilirubin increased	0	0	0	0	5 (83.3)	1 (16.7)	1 (16.7)	0
Stomatitis	1 (33.3)	0	2 (66.7)	0	2 (33.3)	0	1 (16.7)	0
Alanine aminotransferase increased	0	0	0	0	3 (50.0)	0	2 (33.3)	0
Blood creatinine increased	0	0	1 (33.3)	0	2 (33.3)	0	3 (50.0)	0
Myalgia	1 (33.3)	0	0	0	4 (66.7)	0	0	0
Nausea	0	0	1 (33.3)	0	1 (16.7)	0	2 (33.3)	0
Rash	0	0	1 (33.3)	0	3 (50.0)	0	2 (33.3)	0
Weight gain	0	0	1 (33.3)	0	2 (33.3)	1 (16.7)	2 (33.3)	1 (16.7)
Blood alkaline phosphatase increased	0	0	1 (33.3)	0	2 (33.3)	0	1 (16.7)	0
Contrast media allergy	0	0	0	0	1 (16.7)	0	2 (33.3)	0
Cough	1 (33.3)	0	0	0	2 (33.3)	0	0	0
Oropharyngeal pain	0	0	2 (66.7)	0	0	0	0	0
Arthralgia	0	0	1 (33.3)	0	2 (33.3)	0	0	0
Blood triglycerides increased	0	0	0	0	2 (33.3)	0	0	0
Dry eye	0	0	0	0	1 (16.7)	0	2 (33.3)	0
Pyrexia	0	0	0	0	2 (33.3)	0	0	0
Oedema	0	0	2 (66.7)	0	0	0	0	0
Productive cough	0	0	0	0	2 (33.3)	0	0	0
Rash maculo-papular	0	0	0	0	2 (33.3)	0	0	0

Serious adverse events were observed in 1 of the 3 patients (33.3%) in the 160 mg group, 1 of the 3 patients (33.3%) receiving 240 mg immediately after meal, and 1 of the 6 patients (16.7%) receiving 300 mg without meal. The observed serious adverse events were electrocardiogram T wave inversion in 1 patient receiving 160 mg, lung infection in 1 patient receiving 240 mg immediately after meal, and neutrophil count decreased and convulsion in 1 patient each receiving 300 mg without meal. Among these, a causal relationship with alectinib could not be ruled out for electrocardiogram T wave inversion in 1 patient receiving 160 mg and neutrophil count decreased in 1 patient receiving 300 mg without meal.

No adverse events resulted in discontinuation of treatment.

(b) Phase II segment

Adverse events developed in 46 of the 46 patient (100%). Forty-four of the 46 patients experienced adverse events for which a causal relationship with alectinib could not be ruled out. The following table summarizes adverse events observed in ≥10% of patients.

Adverse events observed in ≥10% of patients

Adverse events	No. of patients (%)	
	300 mg (without meal) (n = 46)	
	All grades	Grade 3 or higher
All adverse events	46 (100)	19 (41.3)
Nasopharyngitis	24 (52.2)	0
Dysgeusia	14 (30.4)	0
Blood bilirubin increased	14 (30.4)	1 (2.2)
Rash	14 (30.4)	0
Aspartate aminotransferase increased	13 (28.3)	0
Constipation	12 (26.1)	0
Blood creatinine increased	12 (26.1)	0
Blood creatine phosphokinase increased	10 (21.7)	2 (4.3)
Alanine aminotransferase increased	10 (21.7)	2 (4.3)
Neutrophil count decreased	9 (19.6)	2 (4.3)
Myalgia	8 (17.4)	0
Weight gain	8 (17.4)	3 (6.5)
Stomatitis	8 (17.4)	0
Blood alkaline phosphatase increased	7 (15.2)	1 (2.2)
Upper respiratory tract infection	7 (15.2)	0
Nausea	7 (15.2)	0
Malaise	6 (13.0)	0
Vomiting	5 (10.9)	0
White blood cell count decreased	5 (10.9)	0

Serious adverse events developed in 6 of the 46 patients (13.0%) in the phase II segment. Serious adverse events observed in the phase II segment were brain oedema, cholangitis sclerosing, maculopathy, alveolitis allergic, radius fracture, and tumour haemorrhage reported in 1 patient each (2.2%). Among these, a causal relationship with alectinib could not be ruled out for maculopathy, cholangitis sclerosing, and tumour haemorrhage in 1 patients each.

Adverse events resulting in discontinuation of treatment were observed in 5 of the 46 patients (10.9%). The observed adverse events resulting in discontinuation of treatment were cholangitis sclerosing, alanine aminotransferase increased, tumour haemorrhage, brain oedema, and ILD in 1 patient each (2.2%). Among these, a causal relationship with alectinib could not be ruled out for cholangitis sclerosing, alanine aminotransferase increased, tumour haemorrhage, and ILD in 1 patient each.

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

GLP/GCP inspections are currently underway. The results and PMDA's conclusion will be reported in the Review Report (2).

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

GCP on-site inspection is currently underway. The results and PMDA's conclusion will be reported in

the Review Report (2).

IV. Overall Evaluation

Based on the data submitted by the applicant, PMDA has concluded that alectinib shows a certain level of efficacy in the treatment of anaplastic lymphoma kinase (ALK) fusion gene-positive, unresectable, advanced or recurrent non-small cell lung cancer, and that the safety of alectinib is acceptable in view of their observed benefits. Alecensa is a drug product containing a new active ingredient that inhibits tumor growth by inhibiting the phosphorylation of ALK, and is expected to be a clinically significant option for the treatment of *ALK* fusion gene-positive, unresectable, advanced or recurrent non-small cell lung cancer. PMDA will call for Expert Discussions to discuss the indication of alectinib and post-marketing investigations in detail.

PMDA has concluded that Alecensa may be approved when Expert Discussions reveal no problems in this drug.

Review Report (2)

May 13, 2014

I. Product Submitted for Registration

[Brand name] Alecensa Capsules 20 mg, and Alecensa Capsules 40 mg
[Non-proprietary name] Alectinib Hydrochloride
[Name of applicant] Chugai Pharmaceutical Co., Ltd.
[Date of application] October 7, 2013

II. Content of the Review

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

(1) Efficacy

PMDA reviewed efficacy data as described in the Review Report (1) "4.(iii).B.(1) Efficacy." Alectinib hydrochloride ("alectinib" hereinafter) is an ALK inhibitor targeting an oncogenic driver and can be selected based on the evidence of molecular diagnosis. On the basis of this fact and data including the response rate shown in the Japanese phase I/II study conducted in chemotherapy-experienced patients with *ALK* fusion gene-positive, unresectable, advanced or recurrent NSCLC (Study AF-001JP), PMDA concluded that alectinib has a certain level of efficacy in chemotherapy-experienced patients with *ALK* fusion gene-positive, advanced or recurrent, non-small cell lung cancer.

At the Expert Discussions, expert advisors expressed the following opinions and supported the above conclusion by PMDA.

- Efficacy data have been obtained from only a limited number of patients enrolled in Study AF-001JP. The efficacy of alectinib should therefore be re-evaluated on the basis of the ongoing phase III study in patients with *ALK* fusion gene-positive, advanced or recurrent NSCLC (Study JO28928).

PMDA considers as follows:
Surviving longer with antineoplastic agents is important for patients with lung cancer. It is therefore essential to demonstrate the usefulness of a drug (including those targeting a small patient population, such as alectinib) by comparative clinical studies with a primary endpoint of overall survival. Since the

ongoing Study JO28928 is expected to provide important data, the applicant should complete the Study JO28928 without fail and should provide information to healthcare professionals without delay when the results have become available [see "4.(iii).B.(5) Post-marketing investigations"]. Revision of the package insert or other appropriate measures should be considered without delay as needed based on the study results.

(2) Safety

PMDA's conclusion is as follows:

On the basis of the review in the Review Report (1) "4.(iii).B.(2) Safety," patients on alectinib therapy should be observed carefully for interstitial lung disease (ILD), hepatic function disorder, neutrophil count decreased, and white blood cell count decreased; patients should be monitored for the occurrence of these adverse events in particular.

Alectinib is tolerable by Japanese patients with NSCLC if physicians with sufficient knowledge and experience in cancer chemotherapy monitor patients carefully for adverse events, manage adverse events if they occur, and perform appropriate measures such as suspension or discontinuation of treatment and also if safety management is ensured through strict monitoring, management, and treatment of serious adverse events such as ILD.

The above conclusion was supported by the expert advisers at the Expert Discussions. The expert advisers provided the following opinion as well.

- The number of patients included in this application review is quite limited. All safety information available at present should therefore be assessed.

PMDA requested the applicant to describe the latest safety information obtained after the preparation of the Review Report (1).

The applicant explained as follows:

Serious adverse events newly reported between the data cut-off date for AF-001JP (April 18, 2013) and another data cut-off date (February 14, 2014) were lung infection in 2 patients (3.4%), and pneumonia, bacterial prostatitis, and metastases to meninges in 1 patient each (1.7%). A causal relationship with alectinib could not be ruled out for the case of bacterial prostatitis.*

* Bacterial prostatitis developed on Day 771. Alectinib therapy was suspended, and antibiotics were administered. The patient recovered on Day 786.

Serious adverse events reported in the ongoing bioequivalence study of alectinib in patients with *ALK* fusion gene-positive, advanced or recurrent NSCLC (Study JP28927) were pulmonary artery thrombosis, loss of consciousness, and liver disorder in 1 patient each (2.9%). A causal relationship with alectinib therapy could not be ruled out for the case of pulmonary artery thrombosis.*

* Pulmonary artery thrombosis developed on Day 83 and was treated with anticoagulants. The patient recovered on Day 169.

Serious adverse events reported in the Study JO28928 were renal impairment and blood creatine phosphokinase increased, both occurring in a single patient.* A causal relationship with alectinib therapy could not be ruled out for both events.

* Both events developed on Day 15. Alectinib therapy was suspended and the patient was treated with lactated Ringer's solution. The outcome is "not recovered."

Serious adverse events reported in an ongoing foreign phase I/II study in patients with *ALK* fusion gene-positive, advanced or recurrent NSCLC (Study AF-002JG/NP28761) were dyspnoea, acute kidney injury, syncope, pericardial effusion, metastases to the central nervous system, convulsion, nausea, vomiting, embolic stroke, and drug-induced liver injury in 1 patient each. A causal relationship with alectinib therapy could not be ruled out for the case of drug-induced liver injury.*

* This event developed on Day 24. Treatment was suspended, and the patient improved on Day 55.

Serious adverse events reported in Study NP28673, an ongoing foreign phase I/II study in patients with *ALK* fusion gene-positive, advanced or recurrent NSCLC, were vomiting in 4 patients, dyspnoea in 3 patients, and haemoptysis, subdural haematoma, depression, constipation, intestinal perforation, asthenia, bronchospasm, pneumonia, ligament rupture, pulmonary embolism, breast cancer, and malaise in 1 patient each. For 2 cases of vomiting,*1 and 1 case each of depression,*2 constipation,*3 intestinal perforation,*4 and pneumonia,*5 a causal relationship with alectinib could not be ruled out.

*1 In 1 patient, vomiting developed on Day 7. Gastrointestinal prokinetic drugs and steroids were administered. On Day 10, the patient recovered. The other patient had vomiting on Day 109 and received antiulcer drugs. Whether alectinib therapy was continued is unknown. Outcome of the adverse event is also unknown.

*2 Depression developed on Day 10. Treatment was suspended and anxiolytics were administered. The patient recovered on Day 17.

*3 Constipation developed on Day 11. The outcome is "not recovered." No detailed information has been reported on this case.

*4 Intestinal perforation developed on Day 19. Alectinib therapy was discontinued. The patient died on Day 26. CT revealed perforation of diverticulum of the colon.

*5 Pneumonia developed on Day 28. Alectinib therapy was discontinued, and antibiotics and steroids were administered. The outcome is "improved."

As shown in the above, the latest safety information obtained after the preparation of the Review Report (1) includes no new findings requiring modification of post-marketing safety measures.

PMDA considers as follows:

PMDA generally accepts the applicant's explanation. However, since a patient enrolled in a foreign clinical study died of intestinal perforation, precaution against intestinal perforation should be included in the package insert.

(3) Clinical positioning and indications

PMDA's conclusion is as follows:

On the basis of the review in the Review Report (1) "4.(iii).B.(3) Clinical positioning and indications,"

it is appropriate to indicate alectinib for the treatment of "*ALK* fusion gene-positive, unresectable, advanced or recurrent NSCLC" as proposed by the applicant, since alectinib may be positioned as a treatment option for this patient population. However, all participants in Study AF-001JP had a history of chemotherapy; no information is available on the efficacy and safety of alectinib in chemotherapy-naive patients. Thus, it is appropriate to provide the following precautions in the Precautions for Indications section.

- Alectinib should be administered to patients confirmed to be positive for the *ALK* fusion gene through testing by an experienced pathologist or in an appropriate laboratory. Approved diagnostics based on the principle of immunohistochemistry (IHC) or a fluorescence *in situ* hybridization (FISH) should be used to test patients for the *ALK* fusion gene.
- The efficacy and safety of alectinib in chemotherapy-naive patients have not been established.
- The efficacy and safety of alectinib in postoperative adjuvant chemotherapy have not been established.
- Physicians should select patients eligible for alectinib therapy after closely reading the Clinical Studies section to fully understand the efficacy and safety of alectinib and carefully considering other treatment options.

The above conclusion was supported by the expert advisers at the Expert Discussions.

PMDA requested the applicant to modify the description of the Indications and Precautions for Indications sections as above; the applicant accepted the request.

(4) Dosage and administration

As a result of the review in the Review Report (1) "4.(iii).B.(4) Dosage and Administration," PMDA concluded that the dosage regimen may be defined as "The usual adult dose is 300 mg of alectinib given orally twice daily," as proposed by the applicant, given that the Precautions for Indications section includes the following statement.

- In order to avoid the effect of food, alectinib should be taken in the fasted state according to the protocol of clinical studies.

The above conclusion was supported by the expert advisers at the Expert Discussions.

PMDA requested the applicant to modify the Indications and Precautions for Indications sections as above; the applicant accepted the request.

(5) Draft risk management plan

The applicant has planned post-marketing surveillance with a target sample size of 1000 and an observation period of 1 year and 6 months to investigate the safety of alectinib therapy in all patients

receiving alectinib for the treatment of *ALK* fusion gene-positive, unresectable, advanced or recurrent non-small cell lung cancer in the clinical setting ("all-case survey" hereinafter). The priority survey items are to be ILD and hepatic function disorder.

PMDA's conclusion is as follows:
On the basis of the review in the Review Report (1) "4.(iii).B.(5) Post-marketing investigations," unbiased safety information should be collected promptly through the all-case survey. Safety information collected should be provided to healthcare professionals without delay.

The priority survey items should include neutrophil count decreased and white blood cell count decreased in addition to ILD and hepatic function disorder. The survey should be carefully designed to ensure the following information is collected: characteristics of ILD (e.g., patient characteristics, imaging findings, severity, time to onset and outcome assessment, outcome, treatment, response to treatment, and factors predictive of ILD); and clinical characteristics of hepatic function disorder (e.g., time to onset, duration of symptoms, and signs of aggravation). The all-case survey's target sample size and observation period proposed by the applicant are acceptable, but interim analyses of data from the all-case survey should be performed early to consider amending the protocol.

The above conclusion was supported by the expert advisers at the Expert Discussions.

PMDA requested the applicant to appropriately handle the above-mentioned matters during the all-case survey; the applicant accepted the request.

Only limited data on the efficacy and safety of alectinib are currently available. Data to be obtained, including results of the ongoing Study JO28928, will thus become of critical importance. PMDA therefore requested the applicant to inform healthcare professionals without delay when any new information on alectinib (e.g., clinical study results) has become available and to take other appropriate measures. The applicant accepted the request.

PMDA's conclusion is as follows:
In view of the above discussions on the proposed risk management plan, the items of Safety and Efficacy Specifications and planned additional pharmacovigilance activities defined as below are appropriate. On the basis of the review described in "4.(iii).B.(6) Post-marketing risk minimization actions," the following additional risk minimization activities should be conducted.

Safety and Efficacy Specifications in the Risk Management Plan

Safety Specifications		
Important identified risks	Important potential risks	Important missing information
- ILD - Hepatic function disorder - Neutrophil count decreased and	- Bradycardia - QT interval prolonged - Vision disorders	- Drug interactions with CYP3A4 inhibitors - Use in patients with hepatic function

decreased white blood cell count decreased	- Gastrointestinal perforation	disorder
Efficacy Specifications		
- Effectiveness in the clinical setting (drug use-results survey) - A comparison of the efficacy of alectinib versus crizotinib in patients with *ALK* fusion gene-positive, advanced or recurrent NSCLC (a post-marketing clinical study of the phase III Study JO28928 in Japan)		

Outline of Additional Pharmacovigilance Activities and Additional Risk Minimization Activities

Additional pharmacovigilance activities	Additional risk minimization activities
- Early post-marketing phase vigilance - Drug use-results survey (See the table below for the protocol outline) - Post-marketing clinical study (Study JO28928) - Post-marketing clinical study (Study AF-001JP)	- Providing information on early post-marketing phase vigilance - Preparing and providing materials for healthcare professionals (guidance for proper use of alectinib) - Preparing and providing materials for patients - Providing information via websites - Setting conditions for the use of alectinib - Measures to prevent overdosing and underdosing

Draft Outline of Post-marketing Surveillance

Purpose	To detect unknown adverse drug reactions to alectinib in the clinical setting, determine the incidence of ADRs such as ILD and hepatic function disorder, and investigate factors that affect the occurrence of ADRs
Methods	All-case survey using a central registration system
Participants	Patients with *ALK* fusion gene-positive, unresectable, advanced or recurrent non-small cell lung cancer
Observation period	One year and 6 months after the initiation of alectinib therapy
Target sample size	1000 patients
Major survey items	Priority survey items: ILD, hepatic function disorder, neutrophil count decreased, and white blood cell count decreased Other major survey items: Patient characteristics (e.g., history of treatment for the target disease, histological type, disease stage, primary lesion [location], metastatic sites [location], history of smoking, *ALK* fusion gene testing, history of allergy, past pulmonary disease, and presence/absence of hepatic function disorder), adverse events, and laboratory findings, and others.

(6) Others

At the Expert Discussions, expert advisors expressed the following opinions.

- In foreign countries, alectinib is under development with a recommended dosage regimen of 600 mg BID. The applicant should therefore evaluate the clinical usefulness of alectinib 600 mg BID in Japanese patients with NSCLC.
- No diagnostics using reverse transcription polymerase chain reaction (RT-PCR) have been developed. In Study AF-001JP, however, the expression of the *ALK* fusion gene was assessed with RT-PCR using frozen tumor tissue samples and non-tumor samples (e.g., pleural fluid, alveolar lavage fluid, and sputum). If alectinib is expected to be effective in patients who tested positive for the *ALK* fusion gene using the RT-PCR method, it is desirable to develop RT-PCR based diagnostics.

For Study AF-001JP, PMDA requested the applicant to explain whether alectinib is expected to be effective in patients who tested positive for the *ALK* fusion gene by the RT-PCR method using frozen tumor tissue samples and non-tumor samples (e.g., pleural fluid, alveolar lavage fluid, and sputum).

The applicant explained as follows:
All 7 patients who tested positive for the *ALK* fusion gene using the RT-PCR method during the phase II segment of Study AF-001JP (5 patients were tested only by the RT-PCR method using non-tumor samples such as pleural fluid and bronchial lavage fluid) showed partial response (PR) to alectinib. Alectinib is thus expected to be effective in patients who tested positive for the *ALK* fusion gene using the RT-PCR method.

PMDA considers as follows:
The safety and efficacy of alectinib 600 mg BID have not been investigated in Japanese patients with NSCLC, and no clear data have been obtained on possible differences in clinical usefulness of alectinib between 600 mg BID and 300 BID. The applicant should investigate this matter proactively in the future.

The applicant explained that alectinib is expected to be effective for patients who tested positive for the *ALK* fusion gene using RT-PCR. It is therefore desirable to develop diagnostics using the RT-PCR technique considering the fact that RT-PCR may be the only method available for some patients.

PMDA requested the applicant to consider the above points proactively, and the applicant accepted the request.

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 compliance 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, PMDA concluded that there should be no major problems with conducting a regulatory review based on the submitted application documents.

2) PMDA’s conclusion on the results of GCP on-site inspection

A GCP on-site inspection was conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application (5.3.5.2.1). The inspection revealed protocol deviations (i.e., deviation from the pre-defined use of study drugs, omission of some test items, and deviation from the pre-defined rules for tumor lesion assessment) and inappropriate storage of source documents (i.e., part of data about timing of blood sampling for pharmacokinetic analysis) in some institutions. PMDA concluded that, although there are some points to be improved as above, the clinical studies of alectinib were conducted according to the GCP in general, and that there should be no problem with conducting a regulatory review based on the submitted application documents.

IV. Overall Evaluation

As a result of the above review, PMDA has concluded that alectinib may be approved if the following conditions are satisfied: the Indications and the Dosage and Administration sections are modified as below; the conditions for approval presented below are satisfied; precautions are included in the package insert and information on the proper use of alectinib is provided appropriately after the market launch; and alectinib is used by physicians with sufficient knowledge and experience in cancer chemotherapy in medical institutions capable of providing emergency services. Since alectinib is designated as an orphan drug, the re-examination period is 10 years. The drug substance and drug product are classified as a powerful drug, but are not categorized as a biological product or specified biological product.

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

[Dosage and administration] The usual adult dose is 300 mg of alectinib given orally twice daily.

[Conditions for approval] The applicant is required to:

1. Conduct a drug use-results survey covering all patients treated with alectinib after the market launch until data have been accumulated from a certain number of patients, in order to grasp the characteristics of patients treated with alectinib, since only a limited number of patients participated in the Japanese clinical studies. At the same time, collect data on the safety and efficacy of alectinib without delay and take necessary measures to ensure proper use of alectinib.
2. Take necessary measures to ensure that alectinib is used only under the supervision of a physician experienced in the diagnosis of lung cancer and chemotherapy and in a medical institution capable of controlling the risks associated with treatment, and by a supervising pharmacist with knowledge about the use of alectinib.

[Warnings]

1. Alectinib should be administered to patients in whom alectinib therapy has been determined to be appropriate, under the supervision of a physician with sufficient knowledge and experience in cancer chemotherapy, in medical institutions capable of providing emergency services. Patients or their family members should be fully explained about the benefits and risks of alelctinib, and informed consent should be obtained before starting treatment.

2. The administration of alectinib may induce interstitial lung disease. Patients should therefore be monitored carefully for early symptoms of the disease (e.g., shortness of breath, dyspnoea, cough, and pyrexia) and should undergo chest CT or other examinations. If any abnormality is observed, appropriate measures, such as discontinuation of the drug, should be taken. In the initial treatment phase, patients should be hospitalized or supervised under equivalent conditions to be carefully monitored for serious adverse reactions such as interstitial lung disease

[Contraindications]

1. Patients with a history of hypersensitivities to any components of the drug product
2. Pregnant women or women who may be pregnant

[Precautions for indications]

1. Alectinib should be administered to patients confirmed to be positive for the *ALK* fusion gene through testing by an experienced pathologist or in an appropriate laboratory. Testing should be performed using an approved in vitro diagnostic based on the principles of immunohistochemical staining and fluorescence in situ hybridization
2. The efficacy and safety of alectinib in chemotherapy-naive patients have not been established.
3. The efficacy and safety of alectinib in postoperative adjuvant chemotherapy have not been established.
4. Physicians should select patients eligible for alectinib therapy after closely reading the Clinical Studies section to fully understand the efficacy and safety of alectinib and carefully considering other treatment options.

[Precautions for dosage and administration]

In order to avoid the effect of food, alectinib should be taken without meal according to the protocol of clinical studies.