**Report on the Deliberation Results**

May 10, 2017

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

| | |
|---|---|
| **Brand Name** | Xalkori Capsules 200 mg |
| | Xalkori Capsules 250 mg |
| **Non-proprietary Name** | Crizotinib (JAN*) |
| **Applicant** | Pfizer Japan Inc. |
| **Date of Application** | August 31, 2016 |

**Results of Deliberation**

In its meeting held on April 21, 2017, the Second Committee on New Drugs concluded that the partial change application for the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period is 10 years.

**Conditions of Approval**

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

**Japanese Accepted Name (modified INN)*

**Review Report**

April 7, 2017
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

| | |
|---|---|
| **Brand Name** | Xalkori Capsules 200 mg<br>Xalkori Capsules 250 mg |
| **Non-proprietary Name** | Crizotinib |
| **Applicant** | Pfizer Japan Inc. |
| **Date of Application** | August 31, 2016 |
| **Dosage Form/Strength** | A capsule containing 200 mg Crizotinib<br>A capsule containing 250 mg Crizotinib |
| **Application Classification** | Prescription drug, (4) Drug with a new indication |
| **Items Warranting Special Mention** | Orphan drug (Drug Designation No. 386 of 2016 [*28 yaku*]; PSEHB/PED Notification No. 0824-7 dated August 24, 2016, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare) |
| **Reviewing Office** | Office of New Drug V |

**Results of Review**

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of *ROS1*-positive, unresectable, advanced or relapsed non-small-cell lung cancer, and that the product has acceptable safety in view of its benefits.

As a result of its regulatory review, PMDA has concluded that the product may be approved for the indications and dosage and administration with the conditions described below. The occurrence of interstitial lung disease, QTc prolonged, bradycardia, hepatotoxicity, visual disturbance, neutropenia/leukopenia, neuropathy, complicated renal cyst, and photosensitivity need to be further investigated via post-marketing surveillance.

**Indications**

*ALK*-positive, unresectable, advanced or relapsed non-small-cell lung cancer
<u>*ROS1*-positive, unresectable, advanced or relapsed non-small-cell lung cancer</u>

(Underline denotes additions.)

**Dosage and Administration**

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

**Conditions of Approval**

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

**Attachment**

**Review Report (1)**

February 23, 2017

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency.

**Product Submitted for Approval**

| | |
|---|---|
| **Brand Name** | Xalkori Capsules 200 mg<br>Xalkori Capsules 250 mg |
| **Non-proprietary Name** | Crizotinib |
| **Applicant** | Pfizer Japan Inc. |
| **Date of Application** | August 31, 2016 |
| **Dosage Form/Strength** | A capsule containing 200 mg Crizotinib<br>A capsule containing 250 mg Crizotinib |
| **Proposed Indications** | *ALK*-positive, unresectable, advanced or relapsed non-small-cell lung cancer<br>*ROS1*-positive, unresectable, advanced or relapsed non-small-cell lung cancer |

(Underline denotes additions.)

**Proposed Dosage and Administration**

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

**Table of Contents**

**List of Abbreviations**

| | |
|---|---|
| ALK | anaplastic lymphoma kinase |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| ATP | adenosine triphosphate |
| BID | twice daily |
| BSEP | bile salt export pump |
| CHO cell line | Chinese hamster ovary cell line |
| CI | confidence interval |
| CR | complete response |
| $C_{trough, ss}$ | trough plasma concentration at steady state |
| CYP | cytochrome P450 |
| ELISA | enzyme-linked immunosorbent assay |
| ERK | extracellular signal-regulated kinase |
| EZR | ezrin |
| FIG | fused in glioblastoma |
| FISH | fluorescence in situ hybridization |
| Gab1 | GRB2 associated binding protein 1 |
| HCl | hydrochloric acid |
| ILD | interstitial lung disease |
| Japanese Clinical Practice Guidelines | EBM Guidelines for Diagnosis and Treatment of the Lung Cancer 2016 (edited by the Japan Lung Cancer Society) |
| MedDRA/J | Medical Dictionary for Regulatory Activities Japanese version |
| NCCN Guidelines | National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Non-Small Cell Lung Cancer |
| NE | not evaluable |
| NSCLC | non-small cell lung cancer |
| OS | overall survival |
| Partial change application | application for partial change approval |
| PD | progressive disease |
| PK | pharmacokinetics |
| PMDA | Pharmaceuticals and Medical Devices Agency |
| PR | partial response |
| PS | performance status |
| RECIST | response evaluation criteria in solid tumors |
| ROS1 | c-ros oncogene 1 |
| RT-PCR | reverse transcription polymerase chain reaction |
| SDC | syndecan |
| SHP2 | Src homology 2-containing protein tyrosine phosphatase |
| SLC34A2 | solute carrier family 34 member 2 |
| SPC | surfactant protein C |
| STAT3 | signal transducer and activator of transcription 3 |
| 5-HT | 5- hydroxytryptamine |

## 1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

### 1.1 Drug overview

Crizotinib, developed by Pfizer Inc. (US), is a small molecule compound that inhibits multiple tyrosine kinases, including c-ros oncogene 1 (ROS1) kinase and anaplastic lymphoma kinase (ALK). Crizotinib is believed to suppress tumor growth by inhibiting signal transduction mediated via the activities of these tyrosine kinases.

In Japan, crizotinib was approved for the indication of "*ALK*-positive, unresectable, advanced, or relapsed non-small-cell lung cancer" in March 2012.

### 1.2 Development history etc.

In non-small-cell lung cancer (NSCLC), *ROS1* rearrangements result in the generation of fusion proteins, such as CD74-ROS1, and these fusion proteins contribute to the growth and survival of cancer cells and neoplastic transformation of normal cells (*Cell.* 2007;131:1190-1203, etc.) Patients who have tumors positive for *ROS1* fusion genes account for 1% to 2% of NSCLC patients (*Oncologist.* 2013;18:865-875 and *J Clin Oncol.* 2012;30:863-870).

As part of the clinical development program of crizotinib for the treatment of *ROS1*-positive NSCLC, Pfizer Inc. (US) initiated a phase I study in patients with *ROS1*-positive NSCLC (Study A8081001) outside Japan in October 2010. Then Pfizer, etc. initiated a global phase II study in patients with *ROS1*-positive NSCLC (Study OO12-01) in September 2013.

By using the results of Study A8081001 as pivotal study data, marketing applications for crizotinib for the treatment of *ROS1*-positive NSCLC were submitted in the US and EU in October 2015 and February 2016, respectively. In March 2016, crizotinib was approved in the US for the following indication: "treatment of patients with metastatic NSCLC whose tumors are ROS1-positive," and in August 2016 it was approved in the EU for the following indication: "treatment of adults with ROS1-positive advanced non-small cell lung cancer (NSCLC)."

As of January 2017, crizotinib has been approved for the indication of *ROS1*-positive NSCLC in 34 countries or regions.

In Japan and other countries, Pfizer, etc. initiated the global phase II study (Study OO12-01) in patients with *ROS1*-positive NSCLC in September 2013.

In Japan, the applicant has filed a partial change application for approval of crizotinib for an additional indication of *ROS1*-positive NSCLC on the basis of the results of the pivotal Study OO12-01.

Crizotinib was designated as an orphan drug in August 2016, with the intended indication of "*ROS1*-positive, unresectable, advanced or relapsed non-small-cell lung cancer" (Drug Designation No. 386 of 2016 [*28 yaku*]).

## 2. Data Relating to Quality and Outline of the Review Conducted by PMDA

No data relating to quality were submitted because the present application is for approval of the additional indication.

## 3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

### 3.1 Primary pharmacodynamics

#### 3.1.1 Inhibition of ROS1 phosphorylation and other effects (CTD 4.2.1.1.1)

The inhibitory effect of crizotinib on the phosphorylation of human ROS1 (recombinant protein) was investigated by using a fluorescence electrophoretic mobility shift assay. Its Ki value (mean ± standard deviation) was 0.48 ± 0.32 nmol/L (n = 2).

The inhibitory effect of crizotinib on the phosphorylation of ROS1 fusion proteins was measured with the enzyme-linked immunosorbent assay (ELISA) method by using various cell lines expressing ROS1 fusion proteins. Its $IC_{50}$ values are shown in Table 1.

**Table 1. Inhibitory effect of crizotinib on the phosphorylation of ROS1 fusion proteins**

| ROS1 fusion protein | Cell line | Origin | $IC_{50}$ (nmol/L) | n |
|---|---|---|---|---|
| SLC34A2-ROS1[s][1] and [L][2] | HCC78 | Human NSCLC | 47 ± 23 | 12 |
| FIG-ROS1[s][3] | U138MG | Human glioblastoma | 60 | 1 |
| CD74-ROS1 | NIH-3T3 | Mouse fibroblast | 11 ± 3.6 | 6 |
| SLC34A2-ROS1[s][1] | NIH-3T3 | Mouse fibroblast | 42 ± 21 | 7 |
| SLC34A2-ROS1[L][2] | NIH-3T3 | Mouse fibroblast | 104 ± 45 | 6 |
| FIG-ROS1[s][3] | NIH-3T3 | Mouse fibroblast | 74 ± 48 | 6 |
| FIG-ROS1[L][4] | NIH-3T3 | Mouse fibroblast | 35 ± 11 | 5 |

Mean ± standard deviation

The inhibitory effect of crizotinib on the phosphorylation of ROS1 and its downstream signal molecules (i.e., Src homology 2-containing protein tyrosine phosphatase [SHP2], GRB2 associated binding protein 1 [Gab1], signal transducer and activator of transcription 3 [STAT3], AKT, and extracellular signal-regulated kinase [ERK] 1/2) were investigated with Western blotting using HCC78 cell line derived from human NSCLC expressing solute carrier family 34 member 2 (SLC34A2)-ROS1[s] and [L]. In this assay, crizotinib inhibited the phosphorylation of ROS1, SHP2, STAT3, AKT, and ERK1/2 in a concentration-dependent manner.

[1] Fusion protein product of exon 12 of *SLC34A2* and exon 34 of *ROS1*
[2] Fusion protein product of exon 12 of *SLC34A2* and exon 32 of *ROS1*
[3] Fusion protein product of exon 7 of *FIG* and exon 36 of *ROS1*
[4] Fusion protein product of exon 7 of *FIG* and exon 35 of *ROS1*

Crizotinib-induced apoptosis was evaluated with Western blotting by measuring the expression level of cleaved caspase 3 in the HCC78 cell line. In this assay, crizotinib induced concentration-dependent apoptosis.

### 3.1.2 Tumor growth inhibition in malignant tumor-derived cell lines

#### 3.1.2.1 *In vitro* (CTD 4.2.1.1.1)

The anti-tumor growth effect of crizotinib was determined by measuring the reductase activity of live cells in the HCC78 cell line and a mouse pro-B cell line Ba/F3 expressing CD74-ROS1. Its $IC_{50}$ values (mean ± standard deviation) were 46 ± 13 nmol/L for the HCC78 cell line (n = 5), and 5.8 ± 4.4 nmol/L for the mouse pro-B cell line Ba/F3 (n = 4).

#### 3.1.2.2 *In vivo* (CTD 4.2.1.1.1, 4.2.1.1.2)

The anti-tumor growth effect of crizotinib was evaluated in nude mice subcutaneously implanted with NIH 3T3 cells expressing SLC34A2-ROS1(S),[1)] SLC34A2-ROS1(L),[2)] CD74-ROS1, fused in glioblastoma (FIG)-ROS1(S),[3)] or FIG-ROS1(L)[4)] (5-10 animals/group). When the tumor volume reached 100 to 200 $mm^3$, crizotinib (75 mg/kg) was administered orally twice daily for 17 consecutive days to measure tumor volume. All of the crizotinib-treated groups showed a tumor volume reduction, compared with their corresponding control groups treated with 0.036 mol/L hydrochloric acid (HCl).

The anti-tumor growth effect of crizotinib was evaluated in nude mice subcutaneously implanted with NIH-3T3 cells expressing CD74-ROS1 (10-12 animals/group). Crizotinib (10, 20, 40, and 80 mg/kg) was administered orally twice daily to the animals from Day 11 after implantation (when the tumor volume reached approximately 200 $mm^3$). Tumor volume was calculated on Day 20 after implantation. In addition, the inhibitory effect of crizotinib on the phosphorylation of ROS1 in tumor tissue was investigated with Western blotting. In comparison with the 0.036 mol/L HCl-treated control group, all of the crizotinib-treated groups showed a statistically significant inhibition of tumor growth ($P < 0.00001$, one-way analysis of variance) and dose-dependent inhibition of the phosphorylation of ROS1. The plasma concentration of unbound crizotinib that produced 100% inhibition of tumor growth[5)] in these mice was 99 nmol/L when calculated using a nonlinear mixed effect model and an indirect response model.

The anti-tumor growth effect of crizotinib was evaluated in nude mice subcutaneously implanted with NIH-3T3 cells expressing SLC34A2-ROS1[L][2)] (10-12 animals/group). Crizotinib (10, 20, and 40 mg/kg) was administered orally twice daily to the animals from Day 14 after implantation (when the tumor volume reached approximately 200 $mm^3$). The tumor volume was calculated on Day 24 after implantation. In addition, the inhibitory effect of crizotinib on the phosphorylation of ROS1 in tumor tissue was investigated with Western blotting. In comparison with the 0.036 mol/L HCl-treated control group, the 20 and 40 mg/kg crizotinib-treated groups showed a statistically significant

[5)] Percent inhibition of tumor growth (%) = (1− ((tumor volume in the crizotinib-treated group on Day 20 after implantation) − (tumor volume in the crizotinib-treated group on Day 11 after implantation)) / ((tumor volume in the control group on Day 20 after implantation) − (tumor volume in the control group on Day 11 after implantation)) × 100

inhibition of tumor growth ($P$ < 0.00002, one-way analysis of variance) and dose-dependent inhibition of the phosphorylation of ROS1. The plasma concentration of unbound crizotinib that produced 100% inhibition of tumor growth[6] in these mice was 84 nmol/L when calculated using a nonlinear mixed effect model and an indirect response model.

### 3.2 Secondary pharmacodynamics (CTD 4.2.1.2.1)

The agonistic activity of crizotinib on 5-hydroxytryptamine 2B (5-$HT_{2B}$) receptor was investigated by measuring intracellular calcium levels in a Chinese hamster ovary (CHO) cell line expressing human 5-$HT_{2B}$ receptor. Crizotinib exerted no agonistic activity at ≤10 μmol/L.

### 3.R Outline of the review conducted by PMDA

On the basis of the submitted data and the following reviews, PMDA has concluded that crizotinib is expected to be effective against *ROS1*-positive NSCLC.

### 3.R.1 Mechanism of action of crizotinib and its efficacy for *ROS1*-positive NSCLC

The applicant's explanation about the potential action mechanism of crizotinib and its efficacy for *ROS1*-positive NSCLC:

Lung tumors developed at 2 to 4 weeks after birth in transgenic mice forced to express the *ezrin (EZR)-ROS1, CD74-ROS1,* or *syndecan 4 (SDC4)-ROS1* fusion gene in lung alveolar epithelial cells by modifying the promoter region of the *surfactant protein C (SPC)* gene (*PLoS One.* 2013;8:e56010; *Carcinogenesis.* 2016;37:452-460). This and other findings suggest that *ROS1* fusion genes are essential oncogenic drivers in the oncogenesis of (or transformation to) *ROS1*-positive NSCLC. *ROS1* genes fused with an oligomerization-facilitating domain are believed to constitutively activate the *ROS1* kinase and eventually enhance cell growth; this is the role of *ROS1* fusion genes in the oncogenesis (transformation) of *ROS1*-positive NSCLC (*J Thorac Oncol.* 2012;7:1625-1630).

Crizotinib binds to the adenosine triphosphate (ATP)-binding site of the ROS1 kinase domain (*Bioorg Med Chem.* 2014;22:3871-3878), thereby inhibiting ROS1 phosphorylation and eventually suppressing tumor growth in *ROS1*-positive NSCLC [see Sections 3.1.1 and 3.1.2]. The oncogenic mechanism of *ROS1* fusion genes and the following findings suggest that crizotinib has efficacy against *ROS1*-positive NSCLC.

- All *ROS1* fusion genes identified to date retain the ROS1 kinase domain (*Transl Lung Cancer Res.* 2015;4:156-164); therefore, regardless of partner genes fused with the *ROS1* gene, crizotinib is believed to bind to ROS1 fusion proteins, thereby inhibiting ROS1 kinase activity.
- Crizotinib inhibited tumor growth in multiple cell lines expressing different ROS1 fusion proteins [see Section 3.1.2].

[6] Percent inhibition of tumor growth (%) = (1− ((tumor volume in the crizotinib-treated group on Day 24 after implantation) − (tumor volume in the crizotinib-treated group on Day 14 after implantation))/((tumor volume in the control group on Day 24 after implantation) − (tumor volume in the control group on Day 14 after implantation))) × 100

PMDA accepted the applicant's explanation.

## 4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

The effects of crizotinib on drug-metabolizing enzymes, transporters, etc. were studied using human-derived biomaterials.

### 4.1 Pharmacokinetic drug interactions

#### 4.1.1 Enzyme induction

The application data for the initial approval of crizotinib appeared not to appropriately evaluate the ability of crizotinib to induce cytochrome P450 (CYP) isoforms (CYP2C9 and CYP2C19) (see Review Report of Xalkori Capsules 200 mg and 250 mg dated February 20, 2012).

The applicant's explanation about the ability of crizotinib to induce CYP isoforms:
Human hepatocytes were incubated with crizotinib (0.01-6 μmol/L) or rifampicin (10 μmol/L) for 24 hours to investigate the enzyme activities and mRNA expression levels of CYP isoforms (CYP2C8, CYP2C9, and CYP2C19). Unlike the vehicle control, the positive control rifampicin increased the enzyme activities of CYP2C8, CYP2C9, and CYP2C19 and the mRNA expression levels of CYP2C8 and CYP2C9, whereas crizotinib did not significantly increase the enzyme activities or mRNA expression levels of the CYP isoforms in the concentration range studied. Crizotinib is therefore unlikely to induce CYP2C8, CYP2C9, or CYP2C19.

#### 4.1.2 Transporters

The inhibitory effect of crizotinib (0.03-31.6 μmol/L) on the uptake of $^{3}$H-labeled taurocholic acid (2 μmol/L) into membrane vesicles via the bile salt export pump (BSEP) was investigated by using membrane vesicles prepared from Sf9 insect cells expressing BSEP. The $IC_{50}$ value of crizotinib for inhibition of the BSEP-mediated transport was estimated to be >31.6 μmol/L. The applicant stated that crizotinib is unlikely to cause pharmacokinetic drug interactions via BSEP inhibition in clinical use, given the results of this assay and the plasma $C_{max}$ of unbound crizotinib (0.12 μmol/L) after administration of crizotinib 250 mg twice daily in Japanese patients (see Review Report of Xalkori Capsules 200 mg and 250 mg dated February 20, 2012).

### 4.2 Others

#### 4.2.1 Enantiomerization

The R-enantiomer crizotinib (1 μmol/L) was incubated for up to 4 hours with (a) phosphate buffer (pH 7.4), (b) human plasma, or (c) human hepatocytes, to test its conversion to the S-enantiomer. Concentrations of the S-enantiomer did not increase after incubation with any of the three. On the basis of this result, the applicant considers that the conversion of the R- to the S-enantiomer is unlikely to occur in the living body.

### 4.R Outline of the review conducted by PMDA

On the basis of the submitted data, PMDA has concluded that the applicant's discussion of the pharmacokinetic interactions, etc. of crizotinib is acceptable.

## 5. Toxicity and Outline of the Review Conducted by PMDA

### 5.1 Other toxicity studies

#### 5.1.1 Safety evaluation of impurities

Of impurities present in the drug substance at levels greater than the qualification thresholds, Related Substances A and B were further evaluated as described below.

##### 5.1.1.1 Genotoxicity of impurities

The genotoxic potential of Related Substances A and B was evaluated by a bacterial reverse mutation test and a chromosomal aberration assay in human peripheral lymphocytes.

Both Related Substances A and B were negative in the reverse mutation test, and Related Substance B was negative in the chromosomal aberration assay. Chromosomal structural aberrations and polyploidy were observed after treatment with Related Substance A at concentrations of ≥25 μg/mL.

The applicant's explanation:

In the chromosomal aberration assay, the no-observed-effect level (NOEL) of Related Substance A was 12.5 μg/mL for both chromosomal structural aberration and polyploidy. This NOEL is approximately 77,000 times higher than the estimated maximum clinical exposure[7)] to Related Substance A contained in crizotinib at the upper limit concentration of the acceptance criteria. This safety margin suggests that Related Substance A is unlikely to induce chromosomal aberrations in humans treated with crizotinib.

### 5.R Outline of the review conducted by PMDA

On the basis of the non-clinical toxicity data submitted, PMDA has concluded that there are no additional issues with the clinical use of crizotinib.

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7) The estimated maximum clinical exposure is estimated $C_{max}$ of unbound Related Substance A following oral administration of crizotinib 250 mg BID to Japanese patients; the estimation is based on (a) the steady-state plasma concentrations of unbound crizotinib following oral administration of crizotinib 250 mg BID to Japanese patients and (b) the upper limit of the acceptance criteria for Related Substance A.

## 6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

### 6.1 Summary of biopharmaceutic studies and associated analytical methods

#### 6.1.1 Analytical methods

The presence or absence of *ROS1* fusion genes in tumor tissues was determined by using mainly the fluorescence *in situ* hybridization (FISH) method in the foreign phase I study (Study A8081001), and a reverse transcription polymerase chain reaction (RT-PCR) kit (Riken Genesis, Tokyo, Japan) in the global phase II study (Study OO12-01). On January 31, 2017, OncoGuide AmoyDx ROS1 fusion gene detection kit based on RT-PCR (Riken Genesis), was approved for marketing in Japan as an *in vitro* diagnostic product to help identify eligible patients for treatment with crizotinib.

### 6.2 Clinical pharmacology

The pharmacokinetics (PK) of crizotinib monotherapy were studied in patients with NSCLC.

#### 6.2.1 Foreign phase I study (CTD 5.3.3.2.1, Study A8081001 [ongoing since October 2010 (data cutoff on November 30, 2014)])

This study consists of 2 cohorts: (a) a dose-escalation cohort and (b) a recommended dose cohort. The recommended dose cohort comprised 53 patients with *ROS1*-positive advanced or relapsed NSCLC (43 of them included in PK analysis), 119 patients with *ALK*-positive advanced or relapsed NSCLC (111 of them included in PK analysis), and other patients. The PK of crizotinib was evaluated after repeated administration of crizotinib 250 mg twice daily to patients in the recommended dose cohort. As shown in Table 2, no clear differences were found in steady-state trough plasma concentrations ($C_{trough,\ ss}$) between patients with *ROS1*-positive advanced or relapsed NSCLC and those with *ALK*-positive advanced or relapsed NSCLC from any of the Asian, non-Asian, or overall population.

**Table 2. PK parameters of crizotinib**

| | $C_{trough,\ ss}$ (ng/mL) | | | | | |
|---|---|---|---|---|---|---|
| | n | Asian | n | Non-Asian | n | Overall |
| Patients with *ROS1*-positive advanced or relapsed NSCLC | 19 | 424 ± 196 | 24 | 237 ± 102 | 43 | 320 ± 176 |
| Patients with *ALK*-positive advanced or relapsed NSCLC | 23 | 381 ± 137 | 88 | 278 ± 91 | 111 | 299 ± 110 |

Arithmetic mean ± standard deviation

#### 6.2.2 Ethnic differences in PK of crizotinib

The applicant explained that the PK of crizotinib would not differ between Japanese and other Asian patients with *ROS1*-positive advanced or relapsed NSCLC, the target disease of Study OO12-01, given the following findings:

- No clear differences were found in systemic exposures ($C_{max}$ and $AUC_{\tau}$) to crizotinib between Japanese and other Asian patients with *ALK*-positive advanced or relapsed NSCLC after repeated administration of 250 mg twice daily (see Review Report of Xalkori Capsules 200 mg and 250 mg dated February 20, 2012).

- No clear differences were found in $C_{trough, ss}$ of crizotinib between patients with *ALK*-positive advanced or relapsed NSCLC and those with *ROS1*-positive advanced or relapsed NSCLC [see Section 6.2.1].

## 6.R Outline of the review conducted by PMDA

On the basis of the submitted data, PMDA has concluded that the applicant's statements on the PK of crizotinib are acceptable.

## 7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted results from 2 clinical studies, a foreign phase I study and a global phase II study, for efficacy and safety evaluation (Table 3).

**Table 3. List of clinical studies for efficacy and safety evaluation**

| Data category | Region | Study | Phase | Patient population | No. of subjects enrolled | Dosage regimen | Endpoints |
|---|---|---|---|---|---|---|---|
| Evaluation data | Global | OO12-01 | II | Patients with *ROS1*-positive advanced or relapsed NSCLC | 127 | Crizotinib 250 mg BID, oral | Efficacy<br>Safety |
| | Outside Japan | A8081001 | I | ROS1 cohort:<br>Patients with *ROS1*-positive advanced or relapsed NSCLC | 53 | Crizotinib 250 mg BID, oral | Safety<br>PK |

Each of these clinical studies is outlined below. Major adverse events other than death reported in each clinical study are described in Section "7.2 Adverse events etc. observed in clinical studies." PK data are provided in Section "6.2 Clinical pharmacology."

### 7.1 Evaluation data

#### 7.1.1 Global study

##### 7.1.1.1 Global phase II study (CTD 5.3.5.2.1, Study OO12-01 [ongoing since September 2013 (data cutoff on July 30, 2015)])

An open-label uncontrolled study was conducted to evaluate the efficacy and safety of crizotinib in patients with *ROS1*-positive[8)] advanced or relapsed NSCLC (target sample size, 110) at 37 centers in 4 countries, including Japan.

Crizotinib was orally administered at a dose of 250 mg twice daily. Treatment with crizotinib was continued until disease progression occurred or any of the criteria for treatment discontinuation was met.

The efficacy analysis population included 127 patients enrolled and treated with crizotinib. The same population also served as the safety analysis population.

Table 4 summarizes results for the primary efficacy endpoint in this study, that is, response rates assessed by central review according to the Response Evaluation Criteria in Solid Tumors (RECIST)

8) Tested at the central laboratory using a RT-PCR kit (Riken Genesis).

ver. 1.1.[9)]

**Table 4. Best overall response and response rate**
**(RECIST ver. 1.1, efficacy analysis population, central review, data cutoff on July 30, 2015)**

| Best overall response | Number of subjects (%) |
|---|---|
| | N = 127 |
| CR | 14 (11.0) |
| PR | 74 (58.3) |
| SD | 24 (18.9) |
| PD | 9 (7.1) |
| NE | 6 (4.7) |
| Response (CR + PR) (response rate [95% CI*] (%)) | 88 (69.3 [60.5, 77.2]) |

*Calculated with the Clopper-Pearson method

Safety results:
In total, 8 of 127 subjects (6.3%) died during the crizotinib treatment period or within 28 days after the last dose. The causes of death included disease progression (4 subjects), pneumonia (2 subjects), and respiratory failure (2 subjects). Causal relationships to crizotinib were ruled out for all of the deaths.

### 7.1.2 Foreign clinical study

#### 7.1.2.1 Foreign phase I study (CTD 5.3.5.2.2, Study A8081001 ROS1 cohort [ongoing since October 2010 (data cutoff on November 30, 2014)])

An open-label uncontrolled study was conducted to evaluate the safety of crizotinib in patients with *ROS1*-positive[10)] advanced or relapsed NSCLC (target sample size, 50) at 8 centers in countries outside Japan.

Crizotinib was orally administered at a dose of 250 mg twice daily. The administration was continued until disease progression occurred or any of the criteria for treatment discontinuation was met.

The safety analysis population included 53 patients enrolled and treated with crizotinib.

Safety results:
In total, 9 of 53 subjects (17.0%) died during the crizotinib treatment period or within 28 days after the last dose. All the deaths were due to disease progression, and their causal relationships to crizotinib were ruled out.

## 7.R Outline of the review conducted by PMDA

### 7.R.1 Data for review

PMDA judged that Study OO12-01 (a global phase II study to evaluate the efficacy and safety of crizotinib in patients with *ROS1*-positive advanced or relapsed NSCLC) provided important data for evaluating the efficacy and safety of crizotinib. PMDA therefore decided to conduct a review and

9) The threshold response rate was set at 30% based on response rates reported from clinical studies of platinum-based chemotherapy regimens in chemotherapy-naive patients with advanced or relapsed NSCLC (*N Engl J Med.* 2006;355:2542-2550, *J Clin Oncol*. 2008;26:3543-3551, etc.).
10) Tested mainly by FISH method at each study center.

evaluation primarily based on results from Study OO12-01.

### 7.R.2 Efficacy

PMDA has concluded that crizotinib demonstrated a certain efficacy against *ROS1*-positive advanced or relapsed NSCLC, on the basis of the discussion presented in Sections 7.R.2.1 and 7.R.2.2.

#### 7.R.2.1 Efficacy endpoints and evaluation results

The applicant explained the primary endpoint and efficacy of crizotinib in patients with *ROS1*-positive advanced or relapsed NSCLC in Study OO12-01.

The applicant's explanation:

The applicant selected response rate as the primary endpoint because published literatures (*J Clin Oncol.* 2006;24:3831-3837; *JAMA.* 2003;290:2149-2158, etc.) reported that clinical symptoms accompanying disease progression are expected to improve in responders to treatment for advanced or relapsed NSCLC, and the response rate is therefore considered clinically significant.

The applicant expects crizotinib to have efficacy in patients with *ROS1*-positive advanced or relapsed NSCLC, because the response rate to crizotinib in Study OO12-01 (69.3% [60.5%, 77.2%]) was significantly higher than the threshold response rate defined based on response rates to standard first-line therapies in patients with advanced or relapsed NSCLC [see Section 7.1.1.1], and for the following reasons:

- *ROS1* fusion genes are deemed essential oncogenic drivers of *ROS1*-positive NSCLC [see Section 3.R.1].
- The response rate to crizotinib in Study OO12-01 is clinically significant.

PMDA's view:

Overall survival (OS) is the true endpoint for patients with *ROS1*-positive advanced or relapsed NSCLC, but relationships between response rate and OS are unclear. This means that the survival benefit of crizotinib in these patients cannot be fully evaluated based on the results for the primary endpoint (i.e., response rate) in Study OO12-01. Nevertheless, PMDA has concluded that crizotinib demonstrated a certain efficacy against *ROS1*-positive advanced or relapsed NSCLC, in view of the applicant's reasonable discussion of the efficacy of crizotinib as well as the response rates and other results obtained in Study OO12-01.

### 7.R.2.2 Efficacy in Japanese patients

The Japanese population of Study OO12-01 had a response rate of 65.4% (95% confidence interval [CI]: 44.3%, 82.8%) (17 of 26 subjects), as determined by central review according to RECIST version 1.1.

PMDA's view:

Although the efficacy evaluation of crizotinib in Japanese is limited by the small Japanese study population, the results in the Japanese population were similar to those in the overall population of Study OO12-01. PMDA has therefore concluded that crizotinib is expected to be effective also in Japanese patients.

## 7.R.3 Safety [for adverse events, see Section "7.2 Adverse events etc. observed in clinical studies"]

On the basis of the discussion presented in Sections 7.R.3.1 and 7.R.3.2, PMDA has concluded that attention should be paid to the following adverse events when administering crizotinib to patients with *ROS1*-positive advanced or relapsed NSCLC:

- ✓ Interstitial lung disease (ILD), visual disturbance (diplopia, photopsia, vision blurred, visual field defect, visual impairment, vitreous floaters, etc.), hepatic dysfunction, blood disorder, neuropathy, QTc prolonged, bradycardia, thromboembolism, photosensitivity, and complicated renal cyst.
  (These events were identified as requiring attention at the regulatory reviews for the previously approved indication, *ALK*-positive advanced or relapsed NSCLC [see Review Report of Xalkori Capsules 200 mg and 250 mg dated February 20, 2012]).
- ✓ Heart failure
  (A caution regarding heart failure was added to the package insert for crizotinib in response to reports of heart failure in Japan after the market launch [see Appendix 1 to PFSB/SD Notification No. 0602-1 dated June 2, 2015, by the Safety Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare]).

PMDA has also concluded that although careful attention should be paid to the occurrence of the above adverse events, crizotinib is tolerable as long as physicians with adequate knowledge and experience in cancer chemotherapy monitor and manage adverse events, adjust doses of crizotinib, and take other appropriate measures.

### 7.R.3.1 Safety profile of crizotinib

The applicant's explanation about the safety profile of crizotinib based on safety data from Study OO12-01:

The safety data from Study OO12-01 are summarized in Table 5.

**Table 5. Summary of safety results (Study OO12-01)**

| | Number of subjects (%)<br>N = 127 |
|---|---|
| All adverse events | 126 (99.2) |
| Grade ≥3 adverse events | 52 (40.9) |
| Adverse events leading to death | 8 (6.3) |
| Serious adverse events | 30 (23.6) |
| Adverse events leading to treatment discontinuation | 9 (7.1) |
| Adverse events leading to dose reduction | 18 (14.2) |
| Adverse events leading to treatment interruption | 38 (29.9) |

In Study OO12-01, adverse events of all grades reported by ≥10% of subjects included alanine aminotransferase (ALT) increased in 65 subjects (51.2%); diarrhea in 58 subjects (45.7%); aspartate aminotransferase (AST) increased in 57 subjects (44.9%); nausea in 56 subjects (44.1%); vomiting in 47 subjects (37.0%); constipation in 44 subjects (34.6%); oedema peripheral in 24 subjects (18.9%); neutropenia in 23 subjects (18.1%); dysgeusia, decreased appetite, and vision blurred in 22 subjects (17.3%) each; visual impairment in 21 subjects (16.5%); leucopenia and fatigue in 19 subjects (15.0%) each; dizziness and cough in 18 subjects (14.2%) each; blood creatinine increased, nasopharyngitis, and pyrexia in 17 subjects (13.4%) each; rash in 15 subjects (11.8%); and headache in 14 subjects (11.0%). Adverse events of Grade ≥3 reported by ≥3% of subjects included neutropenia in 8 subjects (6.3%); ALT increased in 6 subjects (4.7%); anemia in 5 subjects (3.9%); and disease progression, pneumonia, and AST increased in 4 subjects (3.1%) each. Serious adverse events reported by ≥1% of subjects included pneumonia in 7 subjects (5.5%); disease progression in 4 subjects (3.1%); pleural effusion and respiratory failure in 3 subjects (2.4%) each; and ALT increased and renal cyst in 2 subjects (1.6%) each. Adverse events leading to treatment discontinuation reported by ≥1% of subjects were respiratory failure in 3 subjects (2.4%) and pneumonia in 2 subjects (1.6%).

The applicant explained the differences in the safety profile of crizotinib between patients with *ROS1*-positive NSCLC and those with *ALK*-positive NSCLC, the approved indication.

The applicant's explanation:
The incidences of adverse events in Study OO12-01 were compared with those in patients with *ALK*-positive NSCLC who received crizotinib in global phase III studies (Studies A8081014 and A8081007), a global phase II study (Study A8081005), or a foreign phase I study (Study A8081001) (Table 6).

**Table 6. Summary of safety results in patients with *ROS1*-positive and *ALK*-positive NSCLC**

| | Number of subjects (%) | |
|---|---|---|
| | *ROS1*-positive patients N = 127 | *ALK*-positive patients N = 1669 |
| All adverse events | 126 (99.2) | 1657 (99.3) |
| Grade ≥3 adverse events | 52 (40.9) | 1085 (65.0) |
| Adverse events leading to death | 8 (6.3) | 320 (19.2) |
| Serious adverse events | 30 (23.6) | 746 (44.7) |
| Adverse events leading to treatment discontinuation | 9 (7.1) | 342 (20.5) |
| Adverse events leading to treatment interruption | 38 (29.9) | 625 (37.4) |
| Adverse events leading to dose reduction | 18 (14.2) | 240 (14.4) |

Adverse events of all grades with a ≥10% higher incidence in patients with *ROS1*-positive NSCLC than in patients with *ALK*-positive NSCLC were ALT increased (65 patients with *ROS1*-positive NSCLC [51.2%] vs. 481 patients with *ALK*-positive NSCLC [28.8%]), AST increased (57 patients [44.9%] vs. 369 patients [22.1%]), neutropenia (23 patients [18.1%] vs. 100 patients [6.0%]), and vision blurred (22 patients [17.3%] vs. 117 patients [7.0%]). An adverse event of Grade ≥3 with a ≥3% higher incidence in the former patients was neutropenia (8 patients [6.3%] vs. 49 patients [2.9%]). There were no serious adverse events, adverse events leading to treatment discontinuation, or adverse events leading to death with a ≥3% higher incidence in the former patients.

Meanwhile, adverse events of all grades with a ≥10% higher incidence in patients with *ALK*-positive NSCLC than in patients with *ROS1*-positive NSCLC were nausea (56 patients with *ROS1*-positive NSCLC [44.1%] vs. 943 patients with *ALK*-positive NSCLC [56.5%]), vomiting (47 patients [37.0%] vs. 847 patients [50.7%]), oedema peripheral (24 patients [18.9%] vs. 671 patients [40.2%]), decreased appetite (22 patients [17.3%] vs. 498 patients [29.8%]), visual impairment (21 patients [16.5%] vs. 766 patients [45.9%]), fatigue (19 patients [15.0%] vs. 497 patients [29.8%]), and dyspnoea (7 patients [5.5%] vs. 351 patients [21.0%]). Adverse events of Grade ≥3 with a ≥3% higher incidence in patients with *ALK*-positive NSCLC were ALT increased (6 patients [4.7%] vs. 151 patients [9.0%]), neutropenia (2 patients [1.6%] vs. 162 patients [9.7%]), disease progression (4 patients [3.1%] vs. 196 patients [11.7%]), dyspnoea (1 patient [0.8%] vs. 90 patients [5.4%]), and pulmonary embolism (0 patients vs. 92 patients [5.5%]). The serious adverse event with a ≥3% higher incidence in patients with *ALK*-positive NSCLC was disease progression (4 patients [3.1%] vs. 194 patients [11.6%]). An adverse event leading to treatment discontinuation with a ≥3% higher incidence in patients with *ALK*-positive NSCLC was disease progression (0 patients vs. 148 patients [8.9%]). The adverse event leading to death with a ≥3% higher incidence in patients with *ALK*-positive NSCLC was disease progression (4 patients [3.1%] vs. 195 patients [11.7%]).

PMDA's view:

Study OO12-01 showed that some adverse events occurred at a higher incidence in patients with *ROS1*-positive NSCLC than in patients with *ALK*-positive NSCLC, the approved indication, but all of the events were known adverse events of crizotinib. PMDA has therefore concluded that crizotinib is tolerable also in patients with *ROS1*-positive NSCLC as long as physicians with adequate knowledge and experience in cancer chemotherapy monitor and manage adverse events, adjust doses of crizotinib,

and take other appropriate measures. Meanwhile, when crizotinib is administered to patients, careful attention should be paid to the common adverse events observed in Study OO12-01, and healthcare professionals should be appropriately informed of the occurrence of these adverse events by means of various materials.

### 7.R.3.2 Differences in safety profile between Japanese and non-Japanese patients

The applicant explained differences in safety profiles between Japanese and non-Japanese patients using safety data obtained in Study OO12-01.

The applicant's explanation:

Safety data from Japanese and non-Japanese patients of Study OO12-01 are summarized in Table 7.

**Table 7. Summary of safety data (Study OO12-01)**

| | Number of subjects (%) | |
|---|---|---|
| | Japanese patients N = 26 | Non-Japanese patients N = 101 |
| All adverse events | 26 (100) | 100 (99.0) |
| Grade ≥3 adverse events | 15 (57.7) | 37 (36.6) |
| Adverse events leading to death | 2 (7.7) | 6 (5.9) |
| Serious adverse events | 6 (23.1) | 24 (23.8) |
| Adverse events leading to treatment discontinuation | 1 (3.8) | 8 (7.9) |
| Adverse events leading to treatment interruption | 13 (50.0) | 25 (24.8) |
| Adverse events leading to dose reduction | 10 (38.5) | 8 (7.9) |

In Study OO12-01, adverse events of all grades with a ≥20% higher incidence in Japanese patients than in non-Japanese patients were nausea (17 Japanese patients [65.4%] vs. 39 non-Japanese patients [38.6%]), vomiting (15 patients [57.7%] vs. 32 patients [31.7%]), dysgeusia (11 patients [42.3%] vs. 11 patients [10.9%]), nasopharyngitis (9 patients [34.6%] vs. 8 patients [7.9%]), headache (8 patients [30.8%] vs. 6 patients [5.9%]), and stomatitis (6 patients [23.1%] vs. 2 patients [2.0%]). Adverse events of Grade ≥3 with a ≥5% higher incidence in Japanese patients than in non-Japanese patients were nausea (2 patients [7.7%] vs. 1 patient [1.0%]) and decreased appetite (2 patients [7.7%] vs. 0 patients). The serious adverse event with a ≥5% higher incidence in Japanese patients than in non-Japanese patients was renal cyst (2 patients [7.7%] vs. 0 patients). There were no adverse events leading to treatment discontinuation with a ≥5% higher incidence in Japanese patients than in non-Japanese patients.

PMDA's view:

Comparative safety evaluation of crizotinib between Japanese and non-Japanese patients with *ROS1*-positive NSCLC is limited by the small number of Japanese patients with the disease treated with crizotinib. However, crizotinib is tolerable also in Japanese patients with *ROS1*-positive NSCLC, because all the events occurring more frequently in Japanese patients than in non-Japanese patients were known adverse events of crizotinib, and because crizotinib is intended to be used by physicians with adequate knowledge and experience in cancer chemotherapy. Meanwhile, healthcare

professionals should be appropriately informed of adverse events that occurred more frequently in Japanese patients than in non-Japanese patients by means of various materials.

### 7.R.4 Clinical positioning and indications

The proposed indication for crizotinib is "*ROS1*-positive, unresectable, advanced or relapsed non-small-cell lung cancer," and the following statements are included in the Precautions for Indications section of the proposed package insert.

- Crizotinib should be administered to patients who are confirmed as *ROS1*-positive by pathologists or testing facilities with adequate experience. Approved *in vitro* diagnostics should be used for ALK and ROS1 testing.
- The efficacy and safety of crizotinib in adjuvant chemotherapy has not been established.
- Physicians should select eligible patients for crizotinib treatment after careful consideration of the feasibility of alternative treatments based on adequate knowledge of the information provided in the Clinical Studies section as well as full understanding of the efficacy and safety of crizotinib.

Using the results of the review in Sections "7.R.2 Efficacy" and "7.R.3 Safety" as well as the discussion presented in Sections 7.R.4.1 and 7.R.4.2, PMDA has concluded that the proposed indication for crizotinib, "*ROS1*-positive, unresectable, advanced or relapsed non-small-cell lung cancer" is acceptable if the following precautionary statements are included in the Precautions for Indications section:

- Crizotinib should be administered to patients who are confirmed as *ROS1*-positive by pathologists or testing facilities with adequate experience. Approved *in vitro* diagnostics should be used for ALK and ROS1 testing.
- The efficacy and safety of crizotinib in adjuvant chemotherapy has not been established.

#### 7.R.4.1 Clinical positioning and indications of crizotinib

The following are descriptions about crizotinib for the treatment of patients with *ROS1*-positive, unresectable, advanced or relapsed NSCLC in clinical practice guidelines in Japan and other countries and a representative Japanese textbook of clinical oncology:

**Clinical Practice Guidelines**

- National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology, Non-Small Cell Lung Cancer Guidelines (v. 4.2017)
  - Crizotinib is recommended as a first-line therapy in patients with *ROS1*-positive, unresectable, advanced or relapsed NSCLC.
- Japanese clinical practice guideline (EBM Guidelines for Diagnosis and Treatment of the Lung Cancer 2016 [edited by the Japan Lung Cancer Society]):

- Crizotinib is strongly recommended as a first-line therapy in patients (performance status [PS], 0-2) with *ROS1*-positive, unresectable, advanced or relapsed NSCLC.

**Textbook**

- New Clinical Oncology, fourth revised edition (Nankodo Co., Ltd., 2015):
  Study A8081001 suggests that crizotinib is effective in patients with *ROS1*-positive, unresectable, advanced or relapsed NSCLC.

The applicant's explanation about the target population and indication of crizotinib:
The results of Study OO12-01 and other data suggest that crizotinib is a treatment option for patients with *ROS1*-positive, unresectable, advanced or relapsed NSCLC.

Table 8 shows response rates to first- to fourth-line treatment with crizotinib in Study OO12-01. Since the response rates did not clearly differ between the treatment lines, crizotinib is expected to be effective regardless of treatment line.

**Table 8. Best overall responses and response rates**
**(RECIST ver. 1.1, efficacy analysis population, central review, data cutoff on July 30, 2015)**

| Treatment line | N | Number of responders (CR + PR) | Response rate [95% CI] (%) |
|---|---|---|---|
| First | 24 | 18 | 75.0 [53.3, 90.2] |
| Second | 53 | 35 | 66.0 [51.7, 78.5] |
| Third | 30 | 19 | 63.3 [43.9, 80.1] |
| Fourth | 20 | 16 | 80.0 [56.3, 94.3] |

The applicant's explanation about the proposed indication and proposed precautionary statements (see below) included in the Precautions for Indications section:
The applicant proposed the first precautionary statement because there are no clinical efficacy or safety data on crizotinib in adjuvant chemotherapy. The applicant also proposed the second statement, because proper patient selection would be ensured by including the results of the exploratory Study OO12-01 in the Clinical Studies section in the package insert and thereby properly informing healthcare professionals of the results.

- The efficacy or safety of crizotinib in adjuvant chemotherapy has not been established.
- Physicians should select eligible patients for crizotinib treatment after careful consideration of the feasibility of alternative treatments based on adequate knowledge of the information provided in the Clinical Studies section as well as full understanding of the efficacy and safety of crizotinib.

Under the above condition, the applicant proposed "*ROS1*-positive, unresectable, advanced or relapsed non-small-cell lung cancer" as an additional indication of crizotinib.

PMDA's view:
PMDA generally accepted the above explanation of the applicant and the additional indication for crizotinib, "*ROS1*-positive, unresectable, advanced or relapsed non-small-cell lung cancer," as proposed by the applicant, on the condition that the following precautionary statement is added in the Precautions for Indications section: the efficacy and safety of crizotinib in adjuvant chemotherapy has not been established.

PMDA has also concluded that the proposed statement below need not be included in the Precautions for Indications section, because clinical practice guidelines in Japan and other countries recommend crizotinib for treatment of *ROS1*-positive, unresectable, advanced or relapsed NSCLC more than other anti-tumor agents, and because crizotinib is intended to be used by physicians with adequate knowledge and experience in cancer chemotherapy.

- Physicians should select eligible patients for crizotinib treatment after careful consideration of the feasibility of alternative treatments based on adequate knowledge of the information provided in the Clinical Studies section as well as full understanding of the efficacy and safety of crizotinib.

#### 7.R.4.2 *ROS1* fusion gene test

Study OO12-01 enrolled patients who were found to be positive for *ROS1* fusion genes by RT-PCR-based assay using OncoGuide AmoyDx ROS1 fusion gene detection kit (Riken Genesis) [see Section 6.1.1].

The applicant stated that since crizotinib demonstrated a certain efficacy in Study OO12-01, the kit should be used to identify eligible patients for crizotinib treatment in clinical practice, and that this information will be included in the Precautions for Indications section of the package insert.

PMDA accepted the applicant's explanation.

### 7.R.5 Dosage and administration

The proposed dosage and administration is as follows: "The usual adult dosage is 250 mg of crizotinib administered orally twice daily. The dose may be adjusted according to the patient's condition." Criteria for dose interruption, dose reduction, and treatment discontinuation in case of adverse drug reactions are included in the Precautions for Dosage and Administration section of the proposed package insert.

On the basis of the review results described in Section 7.R.5.1 and discussions in Sections "7.R.2 Efficacy" and "7.R.3 Safety," PMDA has concluded that the proposed dosage and administration and the proposed Precautions for Dosage and Administration section, are appropriate.

### 7.R.5.1 Dosage and administration of crizotinib

The applicant's rationale for the proposed dosage and administration of crizotinib in patients with *ROS1*-positive advanced or relapsed NSCLC:

In consideration of the results from the dose escalation cohort in Study A8081001 (see Review Report of Xalkori Capsules 200 mg and 250 mg dated February 20, 2012), the dosage regimen of crizotinib in Study OO12-01 was determined to be 250 mg administered orally BID. Study OO12-01 demonstrated the clinical usefulness of crizotinib with this dosage in patients with *ROS1*-positive advanced or relapsed NSCLC. The proposed dosage was thus determined based on Study OO12-01.

In addition, Study OO12-01 used the same criteria for dose interruption, dose reduction, and treatment discontinuation of crizotinib as those described in the proposed package insert, and the efficacy and safety of crizotinib were demonstrated by employing the criteria. The proposed criteria (included in the Precautions for Dosage and Administration section) were thus established based on those used in Study OO12-01.

PMDA accepted the applicant's explanation.

### 7.R.6 Post-marketing investigations

The applicant's explanation about their post-marketing surveillance plan:

The applicant plans to conduct post-marketing surveillance in patients with *ROS1*-positive, unresectable, advanced or relapsed NSCLC treated with crizotinib, to investigate the safety of crizotinib in post-marketing clinical use.

No clear differences were found in the safety profiles of crizotinib between patients with *ROS1*-positive, unresectable, advanced or relapsed NSCLC and those with *ALK*-positive, unresectable, advanced or relapsed NSCLC [see Section 7.R.3.1]. This surveillance therefore includes the same key survey items as those in the surveillance of patients with *ALK*-positive, unresectable, advanced or relapsed NSCLC (i.e., ILD, QTc prolonged, bradycardia, hepatotoxicity, visual disturbance, neutropenia/leukopenia, neuropathy, complicated renal cyst, and photosensitivity).

The planned sample size was determined to be 100 patients based on the incidences of the above adverse events in Study OO12-01.

The observation period was determined to be 52 weeks because in Study A8081001 and Study OO12-01 most of the above adverse events occurred within 1 year after the start of crizotinib treatment.

PMDA's view:

The limited safety information on crizotinib in Japanese patients with *ROS1*-positive, unresectable, advanced or relapsed NSCLC warrants post-marketing surveillance to collect safety information on

crizotinib in post-marketing clinical use and to appropriately provide the information to healthcare professionals.

The proposed key survey items, sample size, and observation period are appropriate.

The conditions for use of crizotinib for the approved indication, should be applied also to the indication proposed in the present partial change application, in the form of additional risk minimization activities.

### 7.2 Adverse events etc. observed in clinical studies

Of clinical study data submitted for safety evaluation, death data are presented in Section "7.1 Evaluation data." Major non-fatal adverse events are descried below.

#### 7.2.1 Global phase II study (Study OO12-01)

Adverse events were observed in 126 of 127 subjects (99.2%). Adverse events for which a causal relationship to crizotinib could not be ruled out were observed in 121 of 127 subjects (95.3%). Adverse events reported by ≥20% of subjects are shown in Table 9.

**Table 9. Adverse events reported by ≥20% of subjects**

| System organ class<br>Preferred term<br>(MedDRA/J ver. 18.1) | Number of subjects (%)<br>N = 127 | |
|---|---|---|
| | All Grades | Grade ≥3 |
| All adverse events | 126 (99.2) | 52 (40.9) |
| Investigations | | |
| ALT increased | 65 (51.2) | 6 (4.7) |
| AST increased | 57 (44.9) | 4 (3.1) |
| Gastrointestinal disorders | | |
| Diarrhea | 58 (45.7) | 1 (0.8) |
| Nausea | 56 (44.1) | 3 (2.4) |
| Vomiting | 47 (37.0) | 0 |
| Constipation | 44 (34.6) | 0 |

Serious adverse events were observed in 30 of 127 subjects (23.6%), including pneumonia in 7 subjects (5.5%); disease progression in 4 subjects (3.1%); pleural effusion and respiratory failure in 3 subjects (2.4%) each; ALT increased and renal cyst in 2 subjects (1.6%) each; and acute myocardial infarction, abdominal pain, pyrexia, hepatic cyst, hepatic function abnormal, bronchiolitis, appendicitis, bronchopulmonary aspergillosis, cellulitis, empyema, lung infection, oesophageal infection, urinary tract infection, AST increased, hepatic enzyme increased, decreased appetite, malnutrition, spinal osteoarthritis, headache, ruptured cerebral aneurysm, seizure, pneumothorax, deep vein thrombosis, and embolism in 1 subject (0.8%) each. Among these adverse events, a causal relationship to crizotinib could not be ruled out for ALT increased and renal cyst in 2 subjects each; and hepatic cyst, hepatic function abnormal, pneumonia, urinary tract infection, and AST increased in 1 subject each.

Adverse events leading to treatment discontinuation were observed in 9 of 127 subjects (7.1%), including respiratory failure in 3 subjects (2.4%), pneumonia in 2 subjects (1.6%); and diarrhea,

stomatitis, hepatic enzyme increased, and headache in 1 subject (0.8%) each. Among these adverse events, a causal relationship to crizotinib could not be ruled out for diarrhea in 1 subject.

### 7.2.2 Foreign phase I study (Study A8081001)

Adverse events were observed in all subjects. Adverse events for which a causal relationship to crizotinib could not be ruled out were observed in 52 of 53 subjects (98.1%). Adverse events reported by ≥20% of subjects are shown in Table 10.

**Table 10. Adverse events reported by ≥20% of subjects**

| System organ class<br>Preferred term<br>(MedDRA/J ver. 18.1) | Number of subjects (%)<br>N = 53 | |
|---|---|---|
| | All Grades | Grade ≥3 |
| All adverse events | 53 (100) | 30 (56.6) |
| Eye disorders | | |
| Visual impairment | 43 (81.1) | 0 |
| Gastrointestinal disorders | | |
| Nausea | 31 (58.5) | 1 (1.9) |
| Vomiting | 27 (50.9) | 3 (5.7) |
| Diarrhea | 24 (45.3) | 1 (1.9) |
| Constipation | 23 (43.4) | 0 |
| General disorders and administration site conditions | | |
| Oedema peripheral | 26 (49.1) | 0 |
| Fatigue | 17 (32.1) | 0 |
| Infections and infestations | | |
| Upper respiratory tract infection | 14 (26.4) | 0 |
| Nasopharyngitis | 13 (24.5) | 0 |
| Investigations | | |
| ALT increased | 14 (26.4) | 2 (3.8) |
| AST increased | 14 (26.4) | 1 (1.9) |
| Metabolism and nutrition disorders | | |
| Decreased appetite | 13 (24.5) | 1 (1.9) |
| Nervous system disorders | | |
| Dizziness | 18 (34.0) | 0 |
| Headache | 13 (24.5) | 4 (7.5) |
| Dysgeusia | 12 (22.6) | 0 |
| Skin and subcutaneous tissue disorders | | |
| Rash | 14 (26.4) | 0 |

Serious adverse events were observed in 22 of 53 subjects (41.5%), including disease progression in 9 subjects (17.0%); pneumonia in 3 subjects (5.7%); nausea and headache in 2 subjects (3.8%) each; and bradycardia, pericardial effusion, adrenal insufficiency, gastrointestinal amyloidosis, large intestine perforation, vomiting, chest discomfort, bronchitis, viral gastroenteritis, influenza, oesophageal candidiasis, pneumocystis jirovecii pneumonia, scrub typhus, back pain, aphasia, mental status changes, urinary retention, dyspnoea, hypoxia, pulmonary embolism, and deep vein thrombosis in 1 subject (1.9%) each. Among these adverse events, a causal relationship to crizotinib could not be ruled out for bradycardia and gastrointestinal amyloidosis in 1 subject each.

Adverse events leading to treatment discontinuation were observed in 4 of 53 subjects (7.5%), including disease progression in 2 subjects (3.8%), and nausea and pericardial effusion in 1 subject

(1.9%) each. Among these adverse events, a causal relationship to crizotinib could not be ruled out for nausea in 1 subject.

## 8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

### 8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

### 8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.2.1) were subjected to an on-site GCP inspection in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

## 9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that crizotinib has a certain efficacy against *ROS1*-positive, unresectable, advanced or relapsed NSCLC, and that crizotinib has acceptable safety in view of its benefits. Crizotinib is clinically meaningful because it offers a treatment option for *ROS1*-positive, unresectable, advanced or relapsed NSCLC, although its efficacy should be further investigated.

PMDA has concluded that crizotinib may be approved if crizotinib is not considered to have any particular problems based on comments from the Expert Discussion.

**Review Report (2)**

April 7, 2017

**Product Submitted for Approval**

| | |
|---|---|
| **Brand Name** | Xalkori Capsules 200 mg |
| | Xalkori Capsules 250 mg |
| **Non-proprietary Name** | Crizotinib |
| **Applicant** | Pfizer Japan Inc. |
| **Date of Application** | August 31, 2016 |

## 1. Content of the Review

Comments made during the Expert Discussion and subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized in the following. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, 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).

### 1.1 Efficacy

As a result of the review described in Section "7.R.2 Efficacy" in the Review Report (1), PMDA has reached the following comprehensive conclusion:

> Crizotinib is an inhibitor of an oncogenic driver, c-ros oncogene 1 (ROS1), and will be administered to patients with theoretical evidence of the disease based on molecular diagnosis. In view of this, PMDA judges that crizotinib has a certain efficacy for the proposed indication as demonstrated by the response rate, the primary endpoint, in the global phase II study (Study OO12-01) in patients with *ROS1*-positive advanced or relapsed non-small-cell lung cancer (NSCLC).

At the Expert Discussion, the expert advisors supported the above conclusion of PMDA.

### 1.2 Safety

On the basis of the review results described in Section "7.R.3 Safety" in the Review Report (1), PMDA has concluded that special attention should be paid to the following adverse events when administering crizotinib to patients with *ROS1*-positive NSCLC:

> Interstitial lung disease (ILD), visual disturbance (diplopia, photopsia, vision blurred, visual field defect, visual impairment, vitreous floaters, etc.), hepatic dysfunction, blood disorder, neuropathy, QTc prolonged, bradycardia, thromboembolism, photosensitivity, complicated renal cyst, and heart failure. (These events were identified as requiring attention at the regulatory reviews for the previously approved indication, anaplastic lymphoma kinase (ALK)-positive

advanced or relapsed NSCLC.)

PMDA has also concluded that although cautions must be used against the occurrence of the above adverse events, crizotinib may be tolerable as long as physicians with adequate knowledge and experience in cancer chemotherapy monitor and manage adverse events, adjust doses of crizotinib, or take other appropriate measures.

At the Expert Discussion, the expert advisors supported the above conclusion of PMDA.

### 1.3 Clinical positioning and indications

As a result of the review described in Section "7.R.4 Clinical positioning and indication" in the Review Report (1), crizotinib can be positioned as a treatment option for *ROS1*-positive, unresectable, advanced or relapsed NSCLC on the basis of the results of Study OO12-01. PMDA has therefore concluded that the additional indication of crizotinib should be "*ROS1*-positive, unresectable, advanced or relapsed non-small-cell lung cancer," as proposed by the applicant, under the condition that the following precautionary statements are added to the Precautions for Indications section:

- Crizotinib should be administered to patients who are confirmed as *ROS1*-positive by pathologists or testing facilities with adequate experience. Approved *in vitro* diagnostics should be used for ALK and ROS1 testing.
- The efficacy and safety of crizotinib in adjuvant chemotherapy has not been established.

At the Expert Discussion, the expert advisors supported the above conclusion of PMDA.

In response to this, PMDA instructed the applicant to use the above indication and precautionary statements for Precautions for Indications section. The applicant agreed.

### 1.4 Dosage and administration

As a result of the review described in Section "7.R.5 Dosage and administration" in the Review Report (1), PMDA has concluded that the dosage and administration of crizotinib should be "The usual adult dosage is 250 mg of crizotinib administered orally twice daily. The dose may be adjusted according to the patient's condition," and that the following information should be included in the Precautions for Dosage and Administration section:

**Precautions for Dosage and Administration**

- Criteria for dose interruption, dose reduction, and treatment discontinuation in case of adverse drug reactions

At the Expert Discussion, the expert advisors supported the above conclusion of PMDA.

In response to this, PMDA instructed the applicant to use the above wording for the dosage and administration, and to include the above information in the Precautions for Dosage and Administration section. The applicant agreed.

### 1.5 Risk management plan (draft)

The applicant plans to conduct post-marketing surveillance in patients with *ROS1*-positive, unresectable, advanced or relapsed NSCLC who receive crizotinib, to investigate the safety etc. of crizotinib in post-marketing clinical use. The target sample size is 100 patients. The observation period is 52 weeks.

As a result of the review described in Section "7.R.6 Post-marketing investigations" in the Review Report (1), PMDA has concluded that the proposed post-marketing surveillance should be conducted to appropriately provide safety information to healthcare professionals. In addition, the proposed key survey items, sample size, and observation period are appropriate. The conditions for use of crizotinib for the approved indication, should be applied also to the indication proposed in the present partial change application, in the form of additional risk minimization activities.

At the Expert Discussion, the expert advisors supported the above conclusion of PMDA.

In view of the discussion above, PMDA has concluded that the draft risk management plan for crizotinib should include the safety and efficacy specifications presented in Table 11, and that the applicant should conduct the additional pharmacovigilance activities and risk minimization activities presented in Table 12.

**Table 11. Safety and efficacy specifications in the draft risk management plan**

| Safety specification | | |
|---|---|---|
| Important identified risks | Important potential risks | Important missing information |
| • Hepatotoxicity<br>• ILD<br>• QTc prolonged<br>• Bradycardia<br>• Visual disturbance<br>• Renal cyst<br>• Haematotoxicity<br>• Neuropathy<br>• Heart failure | • Photosensitivity<br>• Reproductive toxicity<br>• Thromboembolism | • Safety in patients with hepatic impairment<br>• Drug interactions with cytochrome P450 (CYP) 3A inhibitors |
| Efficacy specification (matters related to the present partial change application) | | |
| • Efficacy in patients with *ROS1*-positive, unresectable, advanced or relapsed NSCLC in clinical use | | |

**Table 12. Summary of additional pharmacovigilance activities and risk minimization activities included under the draft risk management plan**

| Additional pharmacovigilance activities | Additional risk minimization activities |
|---|---|
| • Specified drug use-results survey of patients with *ALK*-positive, unresectable, advanced or relapsed NSCLC (all-case surveillance)<br>• Specified drug use-results survey of patients with *ROS1*-positive, unresectable, advanced or relapsed NSCLC | • Preparation and provision of materials for healthcare providers<br>• Preparation and provision of materials for patients<br>• Establishment of conditions of use of crizotinib<br>• Provision of information on websites |

Underlines denote activities to be performed for the new indication proposed in the present application.

**Table 13. Outline of the draft post-marketing surveillance plan**

| | |
|---|---|
| Objective | To evaluate the safety etc. of crizotinib in post-marketing clinical use |
| Survey method | Central registration system |
| Population | Patients with *ROS1*-positive, unresectable, advanced or relapsed NSCLC |
| Observation period | For 52 weeks after the start of crizotinib treatment |
| Planned sample size | 100 |
| Main survey items | Key survey items: ILD, QTc prolonged, bradycardia, hepatotoxicity, visual disturbance, neutropenia/leukopenia, neuropathy, complicated renal cyst, and photosensitivity<br>Other main survey items: patient characteristics (age, sex, medical history, complications, previous treatments, etc.), treatment status with crizotinib, other adverse events, etc. |

## 2. Overall evaluation

PMDA reviewed the submitted application data and concluded that the product may be approved for the indication and dosage and administration shown below, with the conditions of approval shown below, provided that appropriate cautions are included in the package insert, information on the proper use of crizotinib is properly disseminated after the market launch, and provided that the product is used properly under the supervision of a physician with adequate knowledge and experience in cancer chemotherapy at medical institutions that can adequately respond to emergencies. Since the product is designated as an orphan drug, the re-examination period should be 10 years.

**Indications** (Underline denotes additions.)

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

*ROS1*-positive, unresectable, advanced or relapsed non-small-cell lung cancer

**Dosage and Administration** (no change)

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

**Conditions of Approval**

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

**Warnings** (no change)

1. The product should be administered only to patients who are considered eligible for the therapy given under the supervision of a physician with adequate knowledge and experience in cancer chemotherapy at medical institutions with adequate facilities for the treatment of emergencies. Before the initiation of the treatment, the physician must obtain informed consent from the patient or his/her family member after providing a full explanation about the efficacy and risk of the product (e.g., particularly, initial symptoms of interstitial lung diseases, precautions during the treatment, and the information that some deaths have been reported).
2. It has been reported that interstitial lung disease occurred after administration of crizotinib, resulting in a fatal outcome in some cases. Therefore, patients should be closely monitored, such as by checking for early stage symptoms (e.g., shortness of breath, dyspnoea, cough, pyrexia) and by chest CT. If any abnormalities are observed, administration of crizotinib should be discontinued and appropriate measures should be taken. It has also been reported that interstitial lung disease occurred in Japanese patients during the early stage of treatment with crizotinib, resulting in a fatal outcome in some cases. During the early stage of the treatment, patients should be closely monitored in hospital or under equivalent conditions, and closely monitored for serious adverse events such as interstitial lung disease.
3. It has been reported that hepatic failure occurred after administration of crizotinib, resulting in a fatal outcome in some cases. Patients should be closely monitored before and during the crizotinib treatment (frequently during the early phase of treatment in particular) through periodic liver function tests. If any abnormalities are observed, appropriate measures, such as crizotinib discontinuation, should be taken.

**Contraindications** (no change)

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

**Precautions for Indications** (Underlined texts denote additions. Crossed-out text is to be deleted.)

1. Crizotinib should be administered to patients who are confirmed as *ALK*-positive or *ROS1*-positive by pathologists or testing facilities with adequate experience. Approved *in vitro* diagnostics should be used for ALK and ROS1 testing.
2. The efficacy and safety of crizotinib in adjuvant chemotherapy has not been established.
3. ~~Physicians should select eligible patients for crizotinib treatment after careful consideration of the feasibility of alternative treatments based on adequate knowledge of the information provided in the Clinical Studies section as well as full understanding of the efficacy and safety of crizotinib.~~

**Precautions for Dosage and Administration** (no change)

Dose interruption, dose reduction, or treatment discontinuation due to adverse drug reactions should be done with consideration given to the following criteria, depending on symptoms and severity.

<table>
<tr><th>Grade[1)]<br>Adverse drug reaction</th><th>1</th><th>2</th><th>3</th><th>4</th></tr>
<tr><td>Hematological[2)]</td><td colspan="2">Continue the same dose.</td><td>Withdraw crizotinib until the symptom improves to Grade ≤2. After recovery, resume the administration at the same dose as before the withdrawal.</td><td>Withdraw crizotinib until the symptom improves to Grade ≤2. After recovery, resume the administration starting from 200 mg twice daily.[3)]</td></tr>
<tr><td>ALT or AST increased with Grade ≤1 blood bilirubin increased</td><td colspan="2">Continue the same dose.</td><td colspan="2">Withdraw crizotinib until the symptom improves to Grade ≤1, or to baseline. After recovery, resume the administration starting from 200 mg twice daily.[4)]</td></tr>
<tr><td>ALT or AST increased with Grade 2-4 blood bilirubin increased[5)]</td><td>Continue the same dose.</td><td colspan="3">Discontinue the administration.</td></tr>
<tr><td>Interstitial lung disease</td><td colspan="4">Discontinue the administration.</td></tr>
<tr><td>QT interval prolonged</td><td colspan="2">Continue the same dose.</td><td>Withdraw crizotinib until the symptom improves to Grade ≤1. After recovery, resume the administration starting from 200 mg twice daily.[4)]</td><td>Discontinue the administration.</td></tr>
</table>

Note 1) Grade according to NCI-CTCAE

Note 2) Except lymphopenia not accompanied by clinical events such as opportunistic infection.

Note 3) In case of relapse, withdraw the administration until the symptom improves to Grade ≤2. After recovery, resume the administration at a further reduced dose of 250 mg once daily. If a Grade 4 event relapses, discontinue the administration.

Note 4) In case of relapse, withdraw crizotinib until the symptom improves to Grade ≤1. After recovery, resume the administration at a further reduced dose of 250 mg once daily. If a Grade 3 or 4 event relapses, discontinue the administration.

Note 5) Except patients with cholestasis or haemolysis.