ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

XALKORI 200 mg hard capsules
XALKORI 250 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

XALKORI 200 mg hard capsules
Each hard capsule contains 200 mg of crizotinib.

XALKORI 250 mg hard capsules
Each hard capsule contains 250 mg of crizotinib.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

XALKORI 200 mg hard capsules
White opaque and pink opaque hard capsule, with “Pfizer” imprinted on the cap and “CRZ 200” on the body.

XALKORI 250 mg hard capsules
Pink opaque hard capsule, with “Pfizer” imprinted on the cap and “CRZ 250” on the body.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

XALKORI as monotherapy is indicated for:

- The first-line treatment of adults with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC)
- The treatment of adults with previously treated anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC)
- The treatment of adults with ROS1-positive advanced non-small cell lung cancer (NSCLC)

4.2 Posology and method of administration

Treatment with XALKORI should be initiated and supervised by a physician experienced in the use of anticancer medicinal products.

ALK and ROS1 testing

An accurate and validated assay for either ALK or ROS1 is necessary for the selection of patients for treatment with XALKORI (see section 5.1 for information on assays used in the clinical studies).

Either ALK-positive or ROS1-positive NSCLC status should be established prior to initiation of crizotinib therapy. Assessment should be performed by laboratories with demonstrated proficiency in the specific technology being utilised (see section 4.4).

Posology

The recommended dose schedule of XALKORI is 250 mg twice daily (500 mg daily) taken continuously.

If a dose is missed, then it should be taken as soon as the patient remembers unless it is less than 6 hours until the next dose, in which case the patient should not take the missed dose. Patients should not take 2 doses at the same time to make up for a missed dose.

Dose adjustments
Dosing interruption and/or dose reduction may be required based on individual safety and tolerability. In 1722 patients treated with crizotinib with either ALK-positive or ROS1-positive NSCLC across clinical studies, the most frequent adverse reactions (≥ 3%) associated with dosing interruptions were neutropenia, elevated transaminases, vomiting, and nausea. The most frequent adverse reactions (≥ 3%) associated with dose reductions were elevated transaminases and neutropenia. If dose reduction is necessary for patients treated with crizotinib 250 mg orally twice daily, then the dose of crizotinib should be reduced as below.

- First dose reduction: XALKORI 200 mg taken orally twice daily
- Second dose reduction: XALKORI 250 mg taken orally once daily
- Permanently discontinue if unable to tolerate XALKORI 250 mg taken orally once daily

Dose reduction guidelines for haematological and non-haematological toxicities are provided in Tables 1 and 2. For patients treated with a lower dose of crizotinib than 250 mg twice daily, then follow the dose reduction guidelines provided in Tables 1 and 2 accordingly.

Table 1. XALKORI dose modification – haematological toxicities[a,b]

CTCAE[c] Grade	XALKORI treatment
Grade 3	Withhold until recovery to Grade ≤ 2, then resume at the same dose schedule
Grade 4	Withhold until recovery to Grade ≤ 2, then resume at the next lower dose[d,e]

a. Except lymphopenia (unless associated with clinical events, e.g., opportunistic infections).
b. For patients who develop neutropenia and leukopenia, see also sections 4.4 and 4.8.
c. National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events
d. In case of recurrence, dosing should be withheld until recovery to Grade ≤ 2, then dosing should be resumed at 250 mg once daily. XALKORI must be permanently discontinued in case of further Grade 4 recurrence.
e. For patients treated with 250 mg once daily or whose dose was reduced to 250 mg once daily, discontinue during evaluation.

Table 2. XALKORI dose modification – non-haematological toxicities

CTCAE[a] Grade	XALKORI treatment
Grade 3 or 4 alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevation with Grade ≤ 1 total bilirubin	Withhold until recovery to Grade ≤ 1 or baseline, then resume at 250 mg once daily and escalate to 200 mg twice daily if clinically tolerated[b,c]
Grade 2, 3 or 4 ALT or AST elevation with concurrent Grade 2, 3 or 4 total bilirubin elevation (in the absence of cholestasis or haemolysis)	Permanently discontinue
Any Grade interstitial lung disease (ILD)/pneumonitis	Withhold if ILD/pneumonitis is suspected, and permanently discontinue if treatment-related ILD/pneumonitis is diagnosed[d]
Grade 3 QTc prolongation	Withhold until recovery to Grade ≤ 1, check and if necessary correct electrolytes, then resume at the next lower dose[b,c]
Grade 4 QTc prolongation	Permanently discontinue

CTCAE[a] Grade	XALKORI treatment
Grade 2, 3 bradycardia[d,e] Symptomatic, may be severe and medically significant, medical intervention indicated	Withhold until recovery to Grade ≤ 1 or to heart rate 60 or above Evaluate concomitant medicinal products known to cause bradycardia, as well as anti-hypertensive medicinal products If contributing concomitant medicinal product is identified and discontinued, or its dose is adjusted, resume at previous dose upon recovery to Grade ≤ 1 or to heart rate 60 or above If no contributing concomitant medicinal product is identified, or if contributing concomitant medicinal products are not discontinued or dose modified, resume at reduced dose[c] upon recovery to Grade ≤ 1 or to heart rate 60 or above
Grade 4 bradycardia[d,e,f] Life-threatening consequences, urgent intervention indicated	Permanently discontinue if no contributing concomitant medicinal product is identified If contributing concomitant medicinal product is identified and discontinued, or its dose is adjusted, resume at 250 mg once daily[c] upon recovery to Grade ≤ 1 or to heart rate 60 or above, with frequent monitoring
Grade 4 ocular disorder (visual loss)	Discontinue during evaluation of severe vision loss

a. National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events
b. XALKORI must be permanently discontinued in case of further Grade ≥ 3 recurrence. See sections 4.4 and 4.8.
c. For patients treated with 250 mg once daily or whose dose was reduced to 250 mg once daily, discontinue during evaluation.
d. See sections 4.4 and 4.8.
e. Heart rate less than 60 beats per minute (bpm).
f. Permanently discontinue for recurrence.

Hepatic impairment
Crizotinib is extensively metabolised in the liver. Treatment with crizotinib should be used with caution in patients with hepatic impairment (see Table 2 and sections 4.4, 4.8 and 5.2).

Based on the National Cancer Institute (NCI) classification, no starting dose adjustment of crizotinib is recommended for patients with mild hepatic impairment (either AST > Upper Limit of Normal (ULN) and total bilirubin ≤ ULN or any AST and total bilirubin > ULN but ≤ 1.5 × ULN). The starting crizotinib dose for patients with moderate hepatic impairment (any AST and total bilirubin > 1.5 × ULN and ≤ 3 × ULN) is recommended to be 200 mg twice daily. The starting crizotinib dose for patients with severe hepatic impairment (any AST and total bilirubin > 3 × ULN) is recommended to be 250 mg once daily (see section 5.2). Crizotinib dose adjustment according to Child-Pugh classification has not been studied in patients with hepatic impairment.

Renal impairment
No starting dose adjustment is recommended for patients with mild ($60 \leq$ creatinine clearance [CL_{cr}] < 90 mL/min) or moderate ($30 \leq CL_{cr} < 60$ mL/min) renal impairment, since the population pharmacokinetic analysis indicated no clinically meaningful changes in steady-state crizotinib exposure in these patients. Crizotinib plasma concentrations may be increased in patients with severe renal impairment ($CL_{cr} < 30$ mL/min). The crizotinib starting dose should be adjusted to 250 mg taken orally once daily in patients with severe renal impairment not requiring peritoneal dialysis or haemodialysis. The dose may be increased to 200 mg twice daily based on individual safety and tolerability after at least 4 weeks of treatment (see sections 4.4 and 5.2).

Elderly
No starting dose adjustment is required (see sections 5.1 and 5.2).

Paediatric population
The safety and efficacy of crizotinib in paediatric patients has not been established. No data are available.

Method of administration

The capsules should be swallowed whole preferably with water, and should not be crushed, dissolved, or opened. They may be taken with or without food. Grapefruit or grapefruit juice should be avoided since it may increase crizotinib plasma concentration; St. John's wort should be avoided since it may decrease crizotinib plasma concentration (see section 4.5).

4.3 Contraindications

Hypersensitivity to crizotinib or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Assessment of ALK and ROS1 status

When assessing either ALK or ROS1 status of a patient, it is important that a well-validated and robust methodology is chosen to avoid false negative or false positive determinations.

Hepatotoxicity

Drug-induced hepatotoxicity (including cases with fatal outcome) has been reported in patients treated with crizotinib across clinical studies (see section 4.8). Liver function tests including ALT, AST, and total bilirubin should be monitored once a week during the first 2 months of treatment, then once a month and as clinically indicated, with more frequent repeat testing for Grades 2, 3 or 4 elevations. For patients who develop transaminase elevations, see section 4.2.

Interstitial lung disease/pneumonitis

Severe, life-threatening, or fatal interstitial lung disease (ILD)/pneumonitis can occur in patients treated with crizotinib. Patients with pulmonary symptoms indicative of ILD/pneumonitis should be monitored. Crizotinib treatment should be withheld if ILD/pneumonitis is suspected. Drug-induced ILD/pneumonitis should be considered in the differential diagnosis of patients with ILD-like conditions such as: pneumonitis, radiation pneumonitis, hypersensitivity pneumonitis, interstitial pneumonitis, pulmonary fibrosis, acute respiratory distress syndrome (ARDS), alveolitis, lung infiltration, pneumonia, pulmonary oedema, chronic obstructive pulmonary disease, pleural effusion, aspiration pneumonia, bronchitis, obliterative bronchiolitis, and bronchiectasis. Other potential causes of ILD/pneumonitis should be excluded, and crizotinib should be permanently discontinued in patients diagnosed with treatment-related ILD/pneumonitis (see sections 4.2 and 4.8).

QT interval prolongation

QTc prolongation has been observed in clinical studies in patients treated with crizotinib (see sections 4.8 and 5.2) which may lead to an increased risk for ventricular tachyarrhythmias (e.g., *Torsade de Pointes*) or sudden death. The benefits and potential risks of crizotinib should be considered before beginning therapy in patients with pre-existing bradycardia, who have a history of or predisposition for QTc prolongation, who are taking antiarrhythmics or other medicinal products that are known to prolong QT interval and in patients with relevant pre-existing cardiac disease and/or electrolyte disturbances. Crizotinib should be administered with caution in these patients and periodic monitoring of electrocardiograms (ECG), electrolytes and renal function is required. When using crizotinib, ECG and electrolytes (e.g., calcium, magnesium, potassium) should be obtained as close as

possible prior to the first dose and periodic monitoring with ECGs and electrolytes is recommended, especially at the beginning of treatment in case of vomiting, diarrhoea, dehydration or impaired renal function. Correct electrolytes as necessary. If QTc increases by greater than or equal to 60 msec from baseline but QTc is < 500 msec, crizotinib should be withheld and cardiologist advice should be sought. If QTc increases to greater than or equal to 500 msec, cardiologist advice must be immediately sought. For patients who develop QTc prolongation, see sections 4.2, 4.8 and 5.2.

Bradycardia

All-causality bradycardia was reported in clinical studies in 13% of patients treated with crizotinib. Symptomatic bradycardia (e.g., syncope, dizziness, hypotension) can occur in patients receiving crizotinib. The full effect of crizotinib on reduction of heart rate may not develop until several weeks after start of treatment. Avoid using crizotinib in combination with other bradycardic agents (e.g., beta-blockers, non-dihydropyridine calcium channel blockers such as verapamil and diltiazem, clonidine, digoxin) to the extent possible, due to the increased risk of symptomatic bradycardia. Monitor heart rate and blood pressure regularly. Dose modification is not required in cases of asymptomatic bradycardia. For management of patients who develop symptomatic bradycardia, see Dose Modification and Undesirable Effects sections (see sections 4.2 and 4.8).

Cardiac failure

In clinical studies with crizotinib and during post marketing surveillance, severe, life-threatening, or fatal adverse reactions of cardiac failure were reported (see section 4.8).

Patients with or without pre-existing cardiac disorders, receiving crizotinib, should be monitored for signs and symptoms of heart failure (dyspnoea, oedema, rapid weight gain from fluid retention). Dosing interruption, dose reduction, or discontinuation should be considered as appropriate if such symptoms are observed.

Neutropenia and leukopenia

In clinical studies with crizotinib in patients with either ALK-positive or ROS1-positive NSCLC, Grade 3 or 4 neutropenia has been very commonly (12%) reported. Grade 3 or 4 leukopenia has been commonly (3%) reported (see section 4.8). Less than 0.5% of patients experienced febrile neutropenia in clinical studies with crizotinib. Complete blood counts including differential white blood cell counts should be monitored as clinically indicated, with more frequent repeat testing if Grade 3 or 4 abnormalities are observed, or if fever or infection occurs (see section 4.2).

Gastrointestinal perforation

In clinical studies with crizotinib, events of gastrointestinal perforations were reported. There were reports of fatal cases of gastrointestinal perforation during post-marketing use of crizotinib (see section 4.8).

Crizotinib should be used with caution in patients at risk for gastrointestinal perforation (e.g., history of diverticulitis, metastases to the gastrointestinal tract, concomitant use of medicinal products with a recognised risk of gastrointestinal perforation).

Crizotinib should be discontinued in patients who develop gastrointestinal perforation. Patients should be informed of the first signs of gastrointestinal perforations and be advised to consult rapidly in case of occurrence.

Renal effects

Blood creatinine increase and creatinine clearance decreased were observed in patients in clinical studies with crizotinib. Renal failure and acute renal failure were reported in patients treated with crizotinib in clinical studies and during post marketing. Cases with fatal outcome, cases requiring

haemodialysis and cases of Grade 4 hyperkalaemia were also observed. Monitoring of patients for renal function at baseline and during therapy with crizotinib is recommended, with particular attention to those who have risk factors or previous history of renal impairment (see section 4.8).

Renal impairment

If patients have severe renal impairment not requiring peritoneal dialysis or haemodialysis, the dose of crizotinib should be adjusted (see sections 4.2 and 5.2).

Visual effects

In clinical studies with crizotinib in patients with either ALK-positive or ROS1-positive NSCLC (N=1722), Grade 4 visual field defect with vision loss has been reported in 4 (0.2%) patients. Optic atrophy and optic nerve disorder have been reported as potential causes of vision loss.

In patients with new onset of severe visual loss (best corrected visual acuity less than 6/60 in one or both eyes), crizotinib treatment should be discontinued (see section 4.2). Ophthalmological evaluation consisting of best corrected visual acuity, retinal photographs, visual fields, optical coherence tomography (OCT) and other evaluations as appropriate for new onset of severe visual loss, should be performed. There is insufficient information to characterise the risks of resumption of crizotinib in patients with a severe visual loss. A decision to resume crizotinib should consider the potential benefit to the patient.

Ophthalmological evaluation is recommended if vision disorder persists or worsens in severity (see section 4.8).

Drug-drug interactions

The concomitant use of crizotinib with strong CYP3A4 inhibitors or with strong and moderate CYP3A4 inducers should be avoided (see section 4.5).

The concomitant use of crizotinib with CYP3A4 substrates with narrow therapeutic indices should be avoided (see section 4.5). Avoid using crizotinib in combination with other bradycardic agents, medicinal products that are known to prolong QT interval and/or antiarrhythmics (see section 4.4 QT interval prolongation, Bradycardia, and section 4.5).

Drug-food interaction

Grapefruit or grapefruit juice should be avoided during treatment with crizotinib (see sections 4.2 and 4.5).

Non-adenocarcinoma histology

Limited information is available in patients with ALK-positive and ROS1-positive NSCLC with non-adenocarcinoma histology, including squamous cell carcinoma (SCC) (see section 5.1).

Dietary sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per 200 mg or 250 mg capsule, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions

Agents that may increase crizotinib plasma concentrations
Coadministration of crizotinib with strong CYP3A inhibitors is expected to increase crizotinib plasma concentrations. Coadministration of a single 150 mg oral dose of crizotinib in the presence of ketoconazole (200 mg twice daily), a strong CYP3A inhibitor, resulted in increases in crizotinib systemic exposure, with crizotinib area-under-the-plasma-concentration versus time curve from time zero to infinity (AUC_{inf}) and maximum observed plasma concentration (C_{max}) values that were approximately 3.2-fold and 1.4-fold, respectively, those seen when crizotinib was administered alone.

Coadministration of repeated doses of crizotinib (250 mg once daily) with repeated doses of itraconazole (200 mg once daily), a strong CYP3A inhibitor, resulted in increases in crizotinib steady-state AUC_{tau} and C_{max}, that were approximately 1.6-fold and 1.3-fold, respectively, those seen when crizotinib was administered alone.

Therefore, the concomitant use of strong CYP3A inhibitors (including but not limited to atazanavir, ritonavir, cobicistat, itraconazole, ketoconazole, posaconazole, voriconazole, clarithromycin, telithromycin, and erythromycin) should be avoided. Unless the potential benefit to the patient outweighs the risk, in which case patients should be closely monitored for crizotinib adverse events (see section 4.4).

Physiologically-based pharmacokinetic (PBPK) simulations predicted a 17% increase in crizotinib steady-state AUC after treatment with the moderate CYP3A inhibitors, diltiazem or verapamil. Caution is therefore recommended in case of coadministration of crizotinib with moderate CYP3A inhibitors.

Grapefruit or grapefruit juice may also increase plasma concentrations of crizotinib and should be avoided (see sections 4.2 and 4.4).

Agents that may decrease crizotinib plasma concentrations
Coadministration of repeated doses of crizotinib (250 mg twice daily) with repeated doses of rifampicin (600 mg once daily), a strong CYP3A4 inducer, resulted in 84% and 79% decreases in crizotinib steady-state AUC_{tau} and C_{max}, respectively, compared to when crizotinib was given alone. The concurrent use of strong CYP3A inducers, including but not limited to carbamazepine, phenobarbital, phenytoin, rifampicin, and St. John's wort, should be avoided (see section 4.4).

The effect of a moderate inducer including but not limited to efavirenz or rifabutin is not clearly established; therefore, their combination with crizotinib should be also avoided (see section 4.4).

Coadministration with medicinal products that increase gastric pH
The aqueous solubility of crizotinib is pH dependent, with low (acidic) pH resulting in higher solubility. Administration of a single 250 mg crizotinib dose following treatment with esomeprazole 40 mg once daily for 5 days resulted in an approximately 10% decrease in crizotinib total exposure (AUC_{inf}) and no change in peak exposure (C_{max}); the extent of the change in total exposure was not clinically meaningful. Therefore, starting dose adjustment is not required when crizotinib is coadministered with agents that increase gastric pH (such as proton-pump inhibitors, H2 blockers, or antacids).

Agents whose plasma concentrations may be altered by crizotinib
Following 28 days of crizotinib dosing at 250 mg taken twice daily in cancer patients, the oral midazolam AUC_{inf} was 3.7-fold of those seen when midazolam was administered alone, suggesting that crizotinib is a moderate inhibitor of CYP3A. Therefore, coadministration of crizotinib with CYP3A substrates with narrow therapeutic indices, including but not limited to alfentanil, cisapride, cyclosporine, ergot derivatives, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus should be

avoided (see section 4.4). If the combination is needed, then close clinical monitoring should be exercised.

In vitro studies indicated that crizotinib is an inhibitor of CYP2B6. Therefore, crizotinib may have the potential to increase plasma concentrations of coadministered medicinal products that are metabolised by CYP2B6 (e.g., bupropion, efavirenz).

In vitro studies in human hepatocytes indicated that crizotinib may induce pregnane X receptor (PXR)- and constitutive androstane receptor (CAR)-regulated enzymes (e.g., CYP3A4, CYP2B6, CYP2C8, CYP2C9, UGT1A1). However, there was no observed induction *in vivo* when crizotinib was coadministered with the CYP3A probe substrate midazolam. Caution should be exercised in administering crizotinib in combination with medicinal products that are predominantly metabolised by these enzymes. Of note, the effectiveness of concomitant administration of oral contraceptives may be reduced.

In vitro studies indicated that crizotinib is a weak inhibitor of uridine diphosphate glucuronosyltransferase (UGT)1A1 and UGT2B7. Therefore, crizotinib may have the potential to increase plasma concentrations of coadministered medicinal products that are metabolised predominantly by UGT1A1 (e.g., raltegravir, irinotecan) or UGT2B7 (e.g., morphine, naloxone).

Based on an *in vitro* study, crizotinib is predicted to inhibit intestinal P-gp. Therefore, administration of crizotinib with medicinal products that are substrates of P-gp (e.g., digoxin, dabigatran, colchicine, pravastatin) may increase their therapeutic effect and adverse reactions. Close clinical surveillance is recommended when crizotinib is administered with these medicinal products.

Crizotinib is an inhibitor of OCT1 and OCT2 *in vitro*. Therefore, crizotinib may have the potential to increase plasma concentrations of coadministered medicinal products that are substrates of OCT1 or OCT2 (e.g., metformin, procainamide).

Pharmacodynamic interactions

In clinical studies, prolonged QT interval was observed with crizotinib. Therefore, the concomitant use of crizotinib with medicinal products known to prolong QT interval or medicinal products able to induce *Torsades de pointes* (e.g., class IA [quinidine, disopyramide] or class III [e.g., amiodarone, sotalol, dofetilide, ibutilide], methadone, cisapride, moxifloxacine, antipsychotics, etc.) should be carefully considered. A monitoring of the QT interval should be made in case of combinations of such medicinal products (see sections 4.2 and 4.4).

Bradycardia has been reported during clinical studies; therefore, use crizotinib with caution due to the risk of excessive bradycardia when used in combination with other bradycardic agents (e.g., non-dihydropyridine calcium channel blockers such as verapamil and diltiazem, beta-blockers, clonidine, guanfacine, digoxin, mefloquine, anticholinesterases, pilocarpine) (see sections 4.2 and 4.4).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should be advised to avoid becoming pregnant while receiving XALKORI.

Contraception in males and females

Adequate contraceptive methods should be used during therapy, and for at least 90 days after completing therapy (see section 4.5).

Pregnancy

XALKORI may cause foetal harm when administered to a pregnant woman. Studies in animals have shown reproductive toxicity (see section 5.3).

There are no data in pregnant women using crizotinib. This medicinal product should not be used during pregnancy unless the clinical condition of the mother requires treatment. Pregnant women, or patients becoming pregnant while receiving crizotinib, or treated male patients as partners of pregnant women, should be apprised of the potential hazard to the foetus.

Breast-feeding

It is not known whether crizotinib and its metabolites are excreted in human milk. Because of the potential harm to the infant, mothers should be advised to avoid breast-feeding while receiving XALKORI (see section 5.3).

Fertility

Based on non-clinical safety findings, male and female fertility may be compromised by treatment with XALKORI (see section 5.3). Both men and women should seek advice on fertility preservation before treatment.

4.7 Effects on ability to drive and use machines

XALKORI has minor influence on the ability to drive and use machines. Caution should be exercised when driving or operating machines as patients may experience symptomatic bradycardia (e.g., syncope, dizziness, hypotension), vision disorder, or fatigue while taking XALKORI (see sections 4.2, 4.4 and 4.8).

4.8 Undesirable effects

Summary of the safety profile

The data described below reflect exposure to XALKORI in 1669 patients with ALK-positive advanced NSCLC who participated in 2 randomised Phase 3 studies (Studies 1007 and 1014) and in 2 single-arm studies (Studies 1001 and 1005), and in 53 patients with ROS1-positive advanced NSCLC who participated in single-arm Study 1001, for a total of 1722 patients (see section 5.1). These patients received a starting oral dose of 250 mg taken twice daily continuously. In Study 1014, the median duration of study treatment was 47 weeks for patients in the crizotinib arm (N=171); the median duration of treatment was 23 weeks for patients who crossed over from the chemotherapy arm to receive crizotinib treatment (N=109). In Study 1007, the median duration of study treatment was 48 weeks for patients in the crizotinib arm (N=172). For ALK-positive NSCLC patients in Studies 1001 (N=154) and 1005 (N=1063), the median duration of treatment was 57 and 45 weeks, respectively. For ROS1-positive NSCLC patients in Study 1001 (N=53), the median duration of treatment was 101 weeks.

The most serious adverse reactions in 1722 patients with either ALK-positive or ROS1-positive advanced NSCLC were hepatotoxicity, ILD/pneumonitis, neutropenia, and QT interval prolongation (see section 4.4). The most common adverse reactions (≥ 25%) in patients with either ALK-positive or ROS1-positive NSCLC were vision disorder, nausea, diarrhoea, vomiting, oedema, constipation, elevated transaminases, fatigue, decreased appetite, dizziness, and neuropathy.

The most frequent adverse reactions (≥ 3%, all-causality frequency) associated with dosing interruptions were neutropaenia (11%), elevated transaminases (7%), vomiting (5%), and nausea (4%). The most frequent adverse reactions (≥ 3%, all-causality frequency) associated with dose reductions were elevated transaminases (4%) and neutropaenia (3%). All-causality adverse events associated with

permanent treatment discontinuation occurred in 302 (18%) patients of which the most frequent (≥ 1%) were ILD (1%) and elevated transaminases (1%).

Tabulated list of adverse reactions

Table 3 presents adverse reactions reported in 1722 patients with either ALK-positive or ROS1-positive advanced NSCLC who received crizotinib across 2 randomised Phase 3 studies (1007 and 1014) and 2 single-arm clinical studies (1001 and 1005) (see section 5.1).

The adverse reactions listed in Table 3 are presented by system organ class and frequency categories, defined using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 3. Adverse reactions reported in crizotinib clinical studies (N=1722)

System organ class	Very common	Common	Uncommon
Blood and lymphatic system disorders	Neutropaenia[a] (22%) Anaemia[b] (15%) Leukopenia[c] (15%)		
Metabolism and nutrition disorders	Decreased appetite (30%)	Hypophosphataemia (6%)	
Nervous system disorders	Neuropathy[d] (25%) Dysgeusia (21%)		
Eye disorders	Vision disorder[e] (63%)		
Cardiac disorders	Dizziness[f] (26%) Bradycardia[g] (13%)	Cardiac failure[h] (1%) Electrocardiogram QT prolonged (4%) Syncope (3%)	
Respiratory, thoracic and mediastinal disorders		Interstitial lung disease[i] (3%)	
Gastrointestinal disorders	Vomiting (51%) Diarrhoea (54%) Nausea (57%) Constipation (43%) Abdominal pain[j] (21%)	Oesophagitis[k] (2%) Dyspepsia (8%)	Gastrointestinal perforation[l] (< 1%)
Hepatobiliary disorders	Elevated transaminases[m] (32%)	Blood alkaline phosphatase increased (7%)	Hepatic failure (< 1%)
Skin and subcutaneous tissue disorders	Rash (13%)		
Renal and urinary disorders		Renal cyst[n] (3%) Blood creatinine increased[o] (8%)	Acute renal failure (< 1%) Renal failure (< 1%)
General disorders and administration site conditions	Oedema[p] (47%) Fatigue (30%)		
Investigations		Blood testosterone decreased[q] (2%)	

Event terms that represent the same medical concept or condition were grouped together and reported as a single adverse drug reaction in Table 3. Terms actually reported in the study up to the data cutoff date and contributing to the relevant adverse drug reaction are indicated in parentheses, as listed below.

a. Neutropaenia (Febrile neutropaenia, Neutropaenia, Neutrophil count decreased).

b. Anaemia (Anaemia, Haemoglobin decreased, Hypochromic anaemia).

c. Leukopenia (Leukopenia, White blood cell count decreased).

d. Neuropathy (Burning sensation, Dysaesthesia, Formication, Gait disturbance, Hyperaesthesia, Hypoaesthesia, Hypotonia, Motor dysfunction, Muscle atrophy, Muscular weakness, Neuralgia, Neuritis, Neuropathy peripheral, Neurotoxicity, Paraesthesia, Peripheral motor neuropathy, Peripheral sensorimotor neuropathy, Peripheral sensory neuropathy, Peroneal nerve palsy, Polyneuropathy, Sensory disturbance, Skin burning sensation).
e. Vision disorder (Diplopia, Halo vision, Photophobia, Photopsia, Vision blurred, Visual acuity reduced, Visual brightness, Visual impairment, Visual perseveration, Vitreous floaters).
f. Dizziness (Balance disorder, Dizziness, Dizziness postural, Presyncope).
g. Bradycardia (Bradycardia, Heart rate decreased, Sinus bradycardia).
h. Cardiac failure (Cardiac failure, Cardiac failure congestive, Ejection fraction decreased, Left ventricular failure, Pulmonary oedema). Across clinical studies (n=1722), 19 (1.1%) patients treated with crizotinib had any grade cardiac failure, 8 (0.5%) patients had Grade 3 or 4, and 3 (0.2%) patients had fatal outcome.
i. Interstitial lung disease (Acute respiratory distress syndrome, Alveolitis, Interstitial lung disease, Pneumonitis).
j. Abdominal pain (Abdominal discomfort, Abdominal pain, Abdominal pain lower, Abdominal pain upper, Abdominal tenderness).
k. Oesophagitis (Oesophagitis, Oesophageal ulcer).
l. Gastrointestinal perforation (Gastrointestinal perforation, Intestinal perforation, Large intestine perforation).
m. Elevated transaminases (Alanine aminotransferase increased, Aspartate aminotransferase increased, Gamma-glutamyltransferase increased, Hepatic enzyme increased, Hepatic function abnormal, Liver function test abnormal, Transaminases increased).
n. Renal cyst (Renal abscess, Renal cyst, Renal cyst haemorrhage, Renal cyst infection).
o. Blood creatinine increased (blood creatinine increased, creatinine renal clearance decreased).
p. Oedema (Face oedema, Generalised oedema, Local swelling, Localised oedema, Oedema, Oedema peripheral, Periorbital oedema).
q. Blood testosterone decreased (Blood testosterone decreased, Hypogonadism, Secondary hypogonadism).

Description of selected adverse reactions

Hepatotoxicity
Medicinal product-induced hepatotoxicity with fatal outcome occurred in 0.1% of 1722 patients treated with crizotinib across clinical studies. Concurrent elevations in ALT and/or AST ≥ 3 × ULN and total bilirubin ≥ 2 × ULN without significant elevations of alkaline phosphatase (≤ 2 × ULN) have been observed in less than 1% patients treated with crizotinib.

Increases to Grade 3 or 4 ALT or AST elevations were observed in 187 (11%) and 95 (6%) of patients, respectively. Seventeen (1%) patients required permanent discontinuation from treatment associated with elevated transaminases, suggesting that these events were generally manageable by dosing modifications as defined in Table 2 (see section 4.2). In randomised Phase 3 Study 1014, increases to Grade 3 or 4 ALT or AST elevations were observed in 15% and 8% of patients receiving crizotinib versus 2% and 1% of patients receiving chemotherapy. In randomised Phase 3 Study 1007, increases to Grade 3 or 4 ALT or AST elevations were observed in 18% and 9% of patients receiving crizotinib and 5% and < 1% of patients receiving chemotherapy.

Transaminase elevations generally occurred within the first 2 months of treatment. Across studies with crizotinib in patients with either ALK-positive or ROS1-positive NSCLC, median time to onset of increased Grade 1 or 2 transaminases was 23 days. Median time to onset of increased Grade 3 or 4 transaminases was 43 days.

Grade 3 and 4 transaminase elevations were generally reversible upon dosing interruption. Across studies with crizotinib in patients with either ALK-positive or ROS1-positive NSCLC (N=1722), dose reductions associated with transaminase elevations occurred in 76 (4%) patients.
Seventeen (1%) patients required permanent discontinuation from treatment.

Patients should be monitored for hepatotoxicity and managed as recommended in sections 4.2 and 4.4.

Gastrointestinal effects
Nausea (57%), diarrhoea (54%), vomiting (51%), and constipation (43%) were the most commonly reported all-causality gastrointestinal events. Most events were mild to moderate in severity. Median

times to onset for nausea and vomiting were 3 days, and these events declined in frequency after 3 weeks of treatment. Supportive care should include the use of antiemetic medicinal products. Median times to onset for diarrhoea and constipation were 13 and 17 days, respectively. Supportive care for diarrhoea and constipation should include the use of standard antidiarrhoeal and laxative medicinal products, respectively.

In clinical studies with crizotinib, events of gastrointestinal perforations were reported. There were reports of fatal cases of gastrointestinal perforation during post-marketing use of crizotinib (see section 4.4).

QT interval prolongation
Across studies in patients with either ALK-positive or ROS1-positive advanced NSCLC, QTcF (corrected QT by the Fridericia method) ≥ 500 msec was recorded in 34 (2.1%) of 1619 patients with at least 1 postbaseline ECG assessment and a maximum increase from baseline in QTcF ≥ 60 msec was observed in 79 (5.0%) of 1585 patients with a baseline and at least 1 postbaseline ECG assessment. All-causality Grade 3 or 4 Electrocardiogram QT prolonged was reported in 27 (1.6%) out of 1722 patients (see sections 4.2, 4.4, 4.5 and 5.2).

In a single-arm ECG substudy (see section 5.2) using blinded manual ECG measurements 11 (21%) patients had an increase from Baseline in QTcF value ≥ 30 to < 60 msec and 1 (2%) patient had an increase from Baseline in QTcF value of ≥ 60 msec. No patients had a maximum QTcF ≥ 480 msec. The central tendency analysis indicated that the largest mean change from baseline in QTcF was 12.3 msec (95% CI 5.1-19.5 msec, least squares mean [LS] from Analysis of Variance [ANOVA]) and occurred at 6 hours post-dose on Cycle 2 Day 1. All upper limits of the 90% CI for the LS mean change from Baseline in QTcF at all Cycle 2 Day 1 time points were < 20 msec.

QT prolongation can result in arrhythmias and is a risk factor for sudden death. QT prolongation may clinically manifest as bradycardia, dizziness, and syncope. Electrolyte disturbances, dehydration and bradycardia may further increase the risk of QTc prolongation and thus, periodic monitoring of ECG and electrolyte levels is recommended in patients with GI toxicity (see section 4.4).

Bradycardia
In studies with crizotinib in patients with either ALK-positive or ROS1-positive advanced NSCLC, all-causality bradycardia was experienced by 219 (13%) of 1722 patients treated with crizotinib. Most events were mild in severity. A total of 259 (16%) of 1666 patients with at least 1 postbaseline vital sign assessment had a pulse rate < 50 bpm.

The use of concomitant medicinal products associated with bradycardia should be carefully evaluated. Patients who develop symptomatic bradycardia should be managed as recommended in the Dose Modification and Warnings and Precautions sections (see sections 4.2, 4.4 and 4.5).

Interstitial lung disease/pneumonitis
Severe, life-threatening, or fatal ILD/pneumonitis can occur in patients treated with crizotinib. Across studies in patients with either ALK-positive or ROS1-positive NSCLC (N=1722), 50 (3%) patients treated with crizotinib had any grade all-causality ILD, including 18 (1%) patients with Grade 3 or 4, and 8 (< 1%) patients with fatal cases. According to an independent review committee (IRC) assessment of patients with ALK-positive NSCLC (N=1669), 20 (1.2%) patients had ILD/pneumonitis, including 10 (< 1%) patients with fatal cases. These cases generally occurred within 3 months after the initiation of treatment. Patients with pulmonary symptoms indicative of ILD/pneumonitis should be monitored. Other potential causes of ILD/pneumonitis should be excluded (see sections 4.2 and 4.4).

Visual effects
In clinical studies with crizotinib in patients with either ALK-positive or ROS1-positive advanced NSCLC (N=1722), Grade 4 visual field defect with vision loss has been reported in 4 (0.2%) patients. Optic atrophy and optic nerve disorder have been reported as potential causes of vision loss (see section 4.4).

All-causality, all grade, vision disorder, most commonly visual impairment, photopsia, vision blurred, and vitreous floaters, was experienced by 1084 (63%) of 1722 patients treated with crizotinib. Of the 1084 patients who experienced vision disorder, 95% had events that were mild in severity. Seven (0.4%) patients had temporary treatment discontinuation and 2 (0.1%) patients had a dose reduction associated with vision disorder. There were no permanent discontinuations associated with vision disorder for any of the 1722 patients treated with crizotinib.

Based on the Visual Symptom Assessment Questionnaire (VSAQ-ALK), patients treated with crizotinib in Study 1007 and Study 1014 reported a higher incidence of visual disturbances compared to patients treated with chemotherapy. The onset of vision disorders generally started within the first week of medicinal product administration. The majority of patients on the crizotinib arm in randomised Phase 3 Studies 1007 and 1014 (> 50%) reported visual disturbances; which occurred at a frequency of 4 to 7 days each week, lasted up to 1 minute, and had mild or no impact (scores 0 to 3 out of a maximum score of 10) on daily activities as captured by the VSAQ-ALK questionnaire.

An ophthalmology substudy using specific ophthalmic assessments at specified time points was conducted in 54 patients with NSCLC who received crizotinib 250 mg twice daily.
Thirty-eight (70.4%) of the 54 patients experienced an Eye Disorders System Organ Class treatment-emergent all-causality adverse event of which 30 patients had ophthalmic examinations. Of the 30 patients, an ophthalmic abnormality of any type was reported in 14 (36.8%) patients and no ophthalmic finding was seen in 16 (42.1%) patients. The most common findings concerned slit lamp biomicroscopy (21.1%), fundoscopy (15.8%) and visual acuity (13.2%). Pre-existing ophthalmic abnormalities and concomitant medical conditions which could be contributory to ocular findings were noted in many patients, and no conclusive causal relationship to crizotinib could be determined. There were no findings related to aqueous cell count and anterior chamber aqueous flare assessment. No visual disturbances associated with crizotinib appeared to be related to changes in best corrected visual acuity, the vitreous, the retina, or the optic nerve.

In patients with new onset of Grade 4 visual loss, crizotinib treatment should be discontinued and ophthalmological evaluation should be performed. Ophthalmological evaluation is recommended if vision disorder persists or worsens in severity (see sections 4.2 and 4.4).

Nervous system effects
All-causality neuropathy, as defined in Table 3, was experienced by 435 (25%) out of 1722 patients treated with crizotinib. Dysgeusia was also very commonly reported in these studies and was primarily Grade 1 in severity.

Renal cyst
All-causality complex renal cysts were experienced by 52 (3%) of 1722 patients treated with crizotinib. Local cystic invasion beyond the kidney was observed in some patients. Periodic monitoring with imaging and urinalysis should be considered in patients who develop renal cysts.

Neutropenia and leukopenia
Across studies in patients with either ALK-positive or ROS1-positive advanced NSCLC (N=1722), Grade 3 or 4 neutropenia was observed in 212 (12%) patients treated with crizotinib. Median time to onset of any grade neutropenia was 89 days. Neutropenia was associated with dose reduction or permanent treatment discontinuation for 3% and < 1% of patients, respectively. Less than 0.5% of patients experienced febrile neutropenia in clinical studies with crizotinib.

Across studies in patients with either ALK-positive or ROS1-positive advanced NSCLC (N=1722), Grade 3 or Grade 4 leukopenia was observed in 48 (3%) patients treated with crizotinib. Median time to onset of any grade leukopenia was 85 days.

Leukopenia was associated with a dose reduction for < 0.5% of patients, and no patients permanently discontinued crizotinib treatment associated with leukopenia.

In clinical studies of crizotinib in patients with either ALK-positive or ROS1-positive advanced NSCLC, shifts to Grade 3 or 4 decreases in leukocytes and neutrophils were observed at frequencies of 4% and 13%, respectively.

Complete blood counts including differential white blood cell counts should be monitored as clinically indicated, with more frequent repeat testing if Grade 3 or 4 abnormalities are observed, or if fever or infection occurs. For patients who develop haematologic laboratory abnormalities, see section 4.2.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Treatment of overdose with the medicinal product consists of general supportive measures. There is no antidote for XALKORI.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-neoplastic agents, protein kinase inhibitors; ATC code: L01XE16.

Mechanism of action

Crizotinib is a selective small-molecule inhibitor of the ALK receptor tyrosine kinase (RTK) and its oncogenic variants (i.e. ALK fusion events and selected ALK mutations). Crizotinib is also an inhibitor of the Hepatocyte Growth Factor Receptor (HGFR, c-Met) RTK, ROS1 (c-ros) and Recepteur d'Origine Nantais (RON) RTK. Crizotinib demonstrated concentration-dependent inhibition of the kinase activity of ALK, ROS1, and c-Met in biochemical assays and inhibited phosphorylation and modulated kinase-dependent phenotypes in cell-based assays. Crizotinib demonstrated potent and selective growth inhibitory activity and induced apoptosis in tumour cell lines exhibiting ALK fusion events (including echinoderm microtubule-associated protein-like 4 [EML4]-ALK and nucleophosmin [NPM]-ALK), ROS1 fusion events, or exhibiting amplification of the *ALK* or *MET* gene locus. Crizotinib demonstrated antitumour efficacy, including marked cytoreductive antitumour activity, in mice bearing tumour xenografts that expressed ALK fusion proteins. The antitumour efficacy of crizotinib was dose-dependent and correlated to pharmacodynamic inhibition of phosphorylation of ALK fusion proteins (including EML4-ALK and NPM-ALK) in tumours *in vivo*. Crizotinib also demonstrated marked antitumour activity in mouse xenograft studies, where tumours were generated using a panel of NIH-3T3 cell lines engineered to express key ROS1 fusions identified in human tumours. The antitumour efficacy of crizotinib was dose-dependent and demonstrated a correlation with inhibition of ROS1 phosphorylation *in vivo*.

Clinical studies

Previously untreated ALK-positive advanced NSCLC – randomised Phase 3 Study 1014
The efficacy and safety of crizotinib for the treatment of patients with ALK-positive metastatic NSCLC, who had not received previous systemic treatment for advanced disease, were demonstrated in a global, randomised, open-label Study 1014.

The full analysis population included 343 patients with ALK-positive advanced NSCLC as identified by Fluorescence In Situ Hybridisation (FISH) prior to randomisation: 172 patients were randomised to crizotinib and 171 patients were randomised to chemotherapy (pemetrexed + carboplatin or cisplatin; up to 6 cycles of treatment). The demographic and disease characteristics of the overall study

population were 62% female, median age of 53 years, baseline Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 (95%), 51% White and 46% Asian, 4% current smokers, 32% past smokers and 64% never smokers. The disease characteristics of the overall study population were metastatic disease in 98% of patients, 92% of patients' tumours were classified as adenocarcinoma histology, and 27% of patients had brain metastases.

Patients could continue crizotinib treatment beyond the time of Response Evaluation Criteria in Solid Tumours (RECIST)-defined disease progression at the discretion of the investigator if the patient was still experiencing clinical benefit. Sixty-five of 89 (73%) patients treated with crizotinib and 11 of 132 (8.3%) patients treated with chemotherapy continued treatment for at least 3 weeks after objective disease progression. Patients randomised to chemotherapy could cross over to receive crizotinib upon RECIST-defined disease progression confirmed by independent radiology review (IRR).
One hundred forty-four (84%) patients in the chemotherapy arm received subsequent crizotinib treatment.

Crizotinib significantly prolonged progression-free survival (PFS), the primary objective of the study, compared to chemotherapy as assessed by IRR. The PFS benefit of crizotinib was consistent across subgroups of baseline patient characteristics such as age, gender, race, smoking class, time since diagnosis, ECOG performance status, and presence of brain metastases. There was a numerical improvement in overall survival (OS) in the patients treated with crizotinib, although this improvement was not statistically significant. Efficacy data from randomised Phase 3 Study 1014 are summarised in Table 4, and the Kaplan-Meier curves for PFS and OS are shown in Figure 1 and 2, respectively.

Table 4. Efficacy results from randomised Phase 3 Study 1014 (full analysis population) in patients with previously untreated ALK-positive advanced NSCLC*

Response parameter	**Crizotinib N=172**	**Chemotherapy N=171**
Progression-free survival (based on IRR)		
Number with event, n (%)	100 (58%)	137 (80%)
Median PFS in months (95% CI)	10.9 (8.3, 13.9)	7.0[a] (6.8, 8.2)
HR (95% CI)[b]	0.45 (0.35, 0.60)	
p-value[c]	< 0.0001	
Overall survival[d]		
Number of deaths, n (%)	71 (41%)	81 (47%)
Median OS in months (95% CI)	NR (45.8, NR)	47.5 (32.2, NR)
HR (95% CI)[b]	0.76 (0.55, 1.05)	
p-value[c]	0.0489	
12-Month survival probability,[d] % (95% CI)	83.5 (77.0, 88.3)	78.4 (71.3, 83.9)
18-Month survival probability,[d] % (95% CI)	71.5 (64.0, 77.7)	66.6 (58.8, 73.2)
48-Month survival probability,[d] % (95% CI)	56.6 (48.3, 64.1)	49.1 (40.5, 57.1)
Objective response rate (based on IRR)		
Objective response rate % (95% CI)	74% (67, 81)	45%[e] (37, 53)
p-value[f]	< 0.0001	
Duration of response		
Months[g] (95% CI)	11.3 (8.1, 13.8)	5.3 (4.1, 5.8)

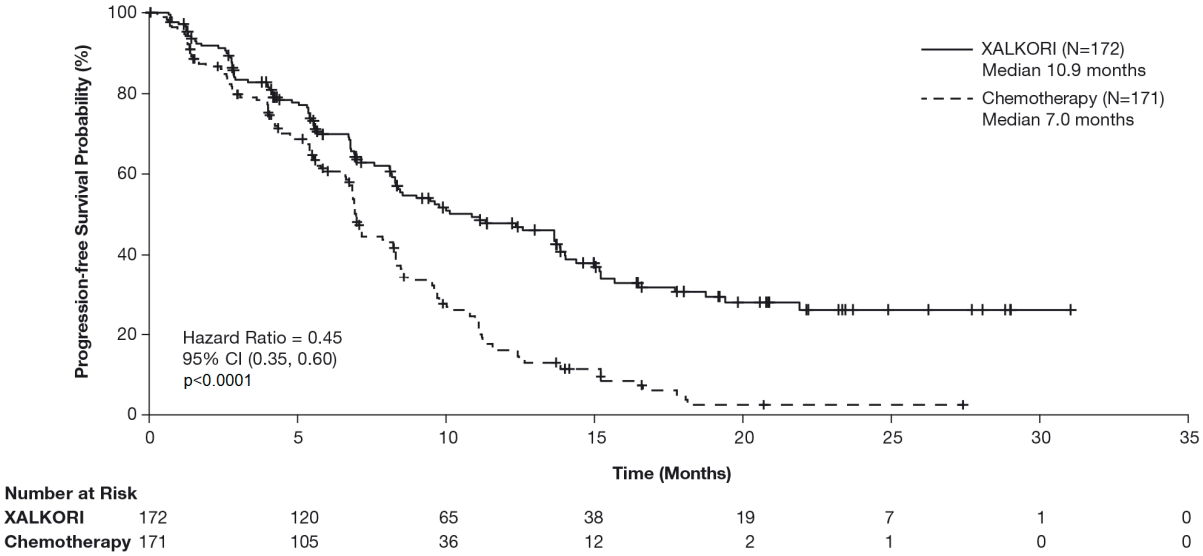
Abbreviations: CI=confidence interval; HR=hazard ratio; IRR=independent radiology review; N/n=number of patients; NR=not reached; PFS=progression-free survival; ORR=objective response rate; OS=overall survival.

* PFS, objective response rate and duration of response are based on the data cutoff date of 30 November 2013; OS is based on the last patient last visit date of 30 November 2016, and is based on a median follow up of approximately 46 months.

a. Median PFS times were 6.9 months (95% CI: 6.6, 8.3) for pemetrexed/cisplatin (HR=0.49; p-value < 0.0001 for crizotinib compared with pemetrexed/cisplatin) and 7.0 months (95% CI: 5.9, 8.3) for pemetrexed/carboplatin (HR=0.45; p-value < 0.0001 for crizotinib compared with pemetrexed/carboplatin).
b. Based on the Cox proportional hazards stratified analysis.
c. Based on the stratified log-rank test (1-sided).
d. Updated based on final OS analysis. OS analysis was not adjusted for the potentially confounding effects of cross over (144 [84%] patients in the chemotherapy arm received subsequent crizotinib treatment).

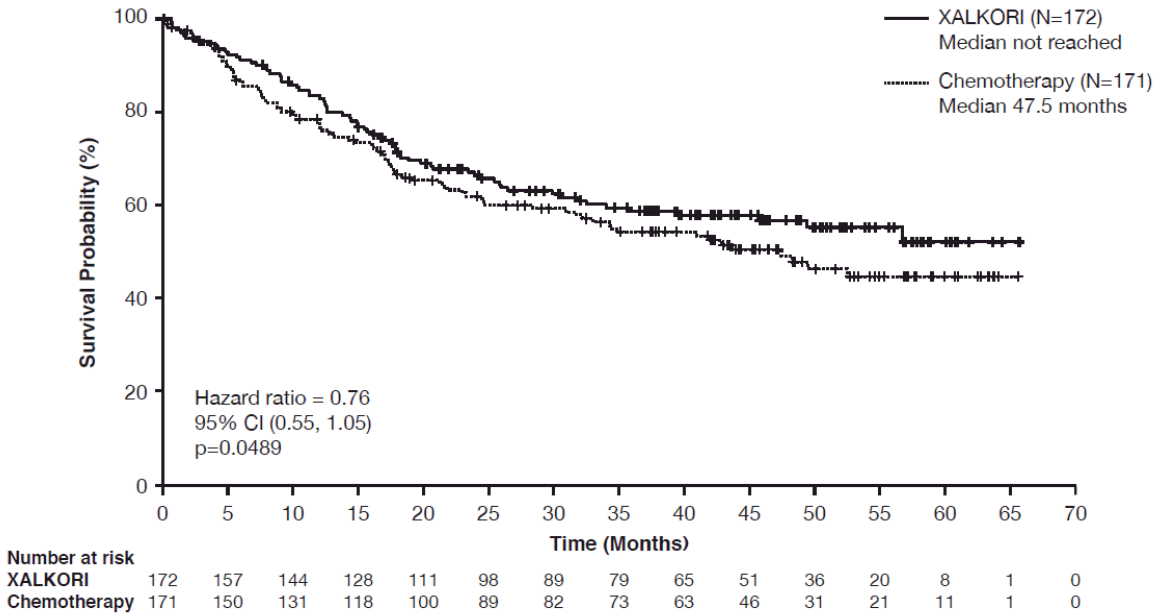
e. ORRs were 47% (95% CI: 37, 58) for pemetrexed/cisplatin (p-value < 0.0001 compared with crizotinib) and 44% (95% CI: 32, 55) for pemetrexed/carboplatin (p-value < 0.0001 compared with crizotinib).
f. Based on the stratified Cochran-Mantel-Haenszel test (2-sided).
g. Estimated using the Kaplan-Meier method.

Figure 1. Kaplan-Meier curves for progression-free survival (based on IRR) by treatment arm in randomised Phase 3 Study 1014 (full analysis population) in patients with previously untreated ALK-positive advanced NSCLC



Abbreviations: CI=confidence interval; N=number of patients; p=p-value.

Figure 2. Kaplan-Meier curves for overall survival by treatment arm in randomised Phase 3 Study 1014 (full analysis population) in patients with previously untreated ALK-positive advanced NSCLC



Abbreviations: CI=confidence interval; N=number of patients; p=p-value.

For patients with previously treated baseline brain metastases, the median intracranial time to progression (IC-TTP) was 15.7 months in the crizotinib arm (N=39) and 12.5 months in the chemotherapy arm (N=40) (HR=0.45 [95% CI: 0.19, 1.07]; 1-sided p-value=0.0315). For patients

without baseline brain metastases, the median IC-TTP was not reached in either the crizotinib (N=132) or the chemotherapy arms (N=131) (HR=0.69 [95% CI: 0.33, 1.45]; 1-sided p-value=0.1617).

Patient-reported symptoms and global QOL were collected using the EORTC QLQ-C30 and its lung cancer module (EORTC QLQ-LC13). A total of 166 patients in the crizotinib arm and 163 patients in the chemotherapy arm had completed the EORTC QLQ-C30 and LC13 questionnaires at baseline and at least 1 postbaseline visit. Significantly greater improvement in global QOL was observed in the crizotinib arm compared to the chemotherapy arm (overall difference in change from baseline scores 13.8; p-value < 0.0001).

Time to Deterioration (TTD) was prespecified as the first occurrence of a ≥ 10-point increase in scores from baseline in symptoms of pain in chest, cough, or dyspnoea as assessed by EORTC QLQ-LC13.

Crizotinib resulted in symptom benefits by significantly prolonging TTD compared to chemotherapy (median 2.1 months versus 0.5 months; HR=0.59; 95% CI: 0.45, 0.77; Hochberg-adjusted log-rank 2-sided p-value =0.0005).

Previously treated ALK-positive advanced NSCLC – randomised Phase 3 Study 1007
The efficacy and safety of crizotinib for the treatment of patients with ALK-positive metastatic NSCLC, who had received previous systemic treatment for advanced disease, were demonstrated in a global, randomised, open-label Study 1007.

The full analysis population included 347 patients with ALK-positive advanced NSCLC as identified by FISH prior to randomisation. One hundred seventy-three (173) patients were randomised to crizotinib and 174 patients were randomised to chemotherapy (either pemetrexed or docetaxel). The demographic and disease characteristics of the overall study population were 56% female, median age of 50 years, baseline ECOG performance status 0 (39%) or 1 (52%), 52% White and 45% Asian, 4% current smokers, 33% past smokers, and 63% never smokers, 93% metastatic, and 93% of patients' tumours were classified as adenocarcinoma histology.

Patients could continue treatment as assigned beyond the time of RECIST-defined disease progression at the discretion of the investigator if the patient was perceived to be experiencing clinical benefit. Fifty-eight of 84 (69%) patients treated with crizotinib and 17 of 119 (14%) patients treated with chemotherapy continued treatment for at least 3 weeks after objective disease progression. Patients randomised to chemotherapy could crossover to receive crizotinib upon RECIST-defined disease progression confirmed by IRR.

Crizotinib significantly prolonged PFS, the primary objective of the study, compared to chemotherapy as assessed by IRR. The PFS benefit of crizotinib was consistent across subgroups of baseline patient characteristics such as age, gender, race, smoking class, time since diagnosis, ECOG performance status, presence of brain metastases and prior EGFR TKI therapy.

Efficacy data from Study 1007 are summarised in Table 5, and the Kaplan-Meier curves for PFS and OS are shown in Figure 3 and 4, respectively.

Table 5. Efficacy results from randomised Phase 3 Study 1007 (full analysis population) in patients with previously treated ALK-positive advanced NSCLC*

Response parameter	**Crizotinib N=173**	**Chemotherapy N=174**
Progression-free survival (based on IRR)		
Number with event, n (%)	100 (58%)	127 (73%)
Type of event, n (%)		
Progressive disease	84 (49%)	119 (68%)
Death without objective progression	16 (9%)	8 (5%)
Median PFS in months (95% CI)	7.7 (6.0, 8.8)	3.0[a] (2.6, 4.3)
HR (95% CI)[b]	0.49 (0.37, 0.64)	
p-value[c]	< 0.0001	

Response parameter	Crizotinib N=173	Chemotherapy N=174
Overall survival[d]		
Number of deaths, n (%)	116 (67%)	126 (72%)
Median OS in months (95% CI)	21.7 (18.9, 30.5)	21.9 (16.8, 26.0)
HR (95% CI)[b]	0.85 (0.66, 1.10)	
p-value[c]	0.1145	
6-Month survival probability,[e] % (95% CI)	86.6 (80.5, 90.9)	83.8 (77.4, 88.5)
1-Year survival probability,[e] % (95% CI)	70.4 (62.9, 76.7)	66.7 (59.1, 73.2)
Objective response rate (based on IRR)		
Objective response rate % (95% CI)	65% (58, 72)	20%[f] (14, 26)
p-value[g]	< 0.0001	
Duration of response		
Median[e], months (95% CI)	7.4 (6.1, 9.7)	5.6 (3.4, 8.3)

Abbreviations: CI=confidence interval; HR=hazard ratio; IRR=independent radiology review; N/n=number of patients; PFS=progression-free survival; ORR=objective response rate; OS=overall survival.

* PFS, objective response rate and duration of response are based on the data cutoff date of 30 March 2012; OS is based on the data cutoff date of 31 August 2015.

a. The median PFS times were 4.2 months (95% CI: 2.8, 5.7) for pemetrexed (HR=0.59; p-value=0.0004 for crizotinib compared with pemetrexed) and 2.6 months (95% CI: 1.6, 4.0) for docetaxel (HR=0.30; p-value < 0.0001 for crizotinib compared with docetaxel).

b. Based on the Cox proportional hazards stratified analysis.

c. Based on the stratified log-rank test (1-sided).

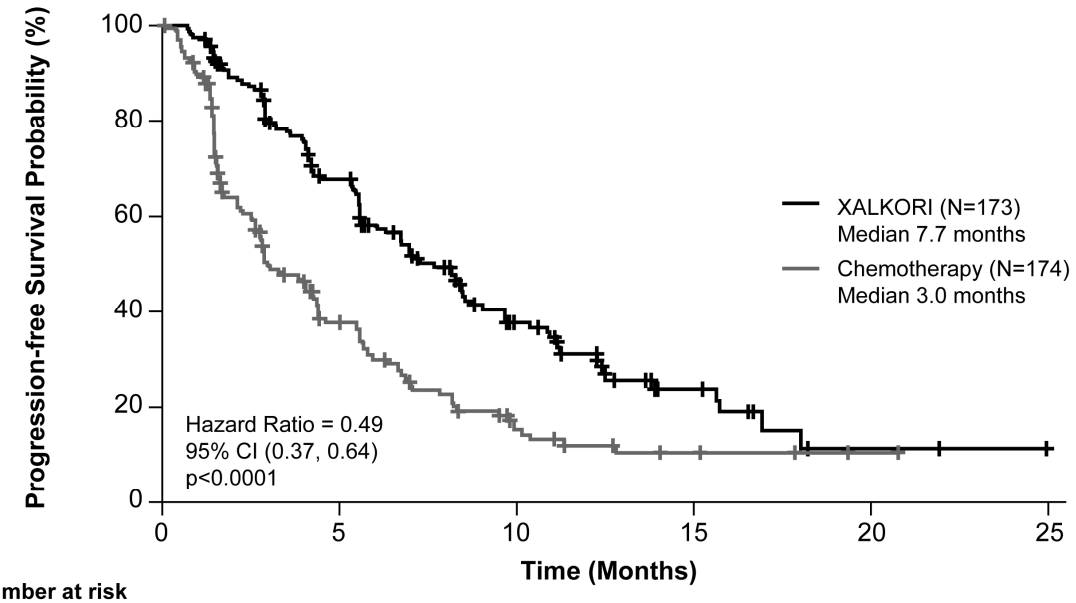
d. Updated based on final OS analysis. Final OS analysis was not adjusted for the potentially confounding effects of crossover (154 [89%] patients received subsequent crizotinib treatment).

e. Estimated using the Kaplan-Meier method.

f. ORRs were 29% (95% CI: 21, 39) for pemetrexed (p-value < 0.0001 compared with crizotinib) and 7% (95% CI: 2, 16) for docetaxel (p-value < 0.0001 compared with crizotinib).

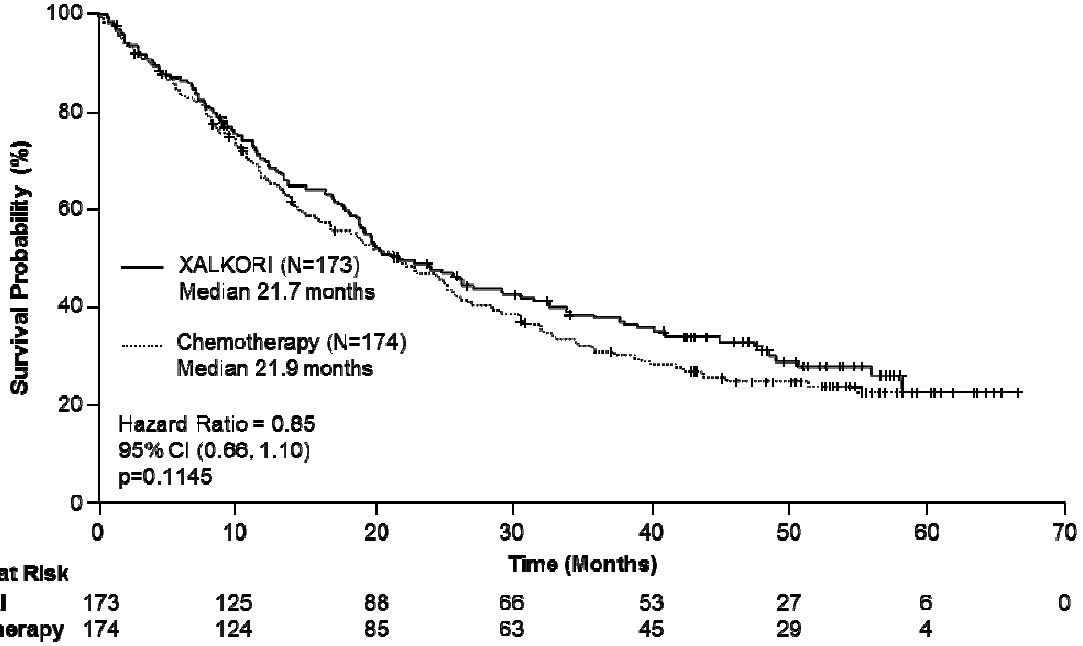
g. Based on the stratified Cochran-Mantel-Haenszel test (2-sided).

Figure 3. Kaplan-Meier curves for progression-free survival (based on IRR) by treatment arm in randomised Phase 3 Study 1007 (full analysis population) in patients with previously treated ALK-positive advanced NSCLC



Abbreviations: CI=confidence interval; N=number of patients; p=p-value.

Figure 4. Kaplan-Meier curves for overall survival by treatment arm in randomised Phase 3 Study 1007 (full analysis population) in patients with previously treated ALK-positive advanced NSCLC



Abbreviations: CI=confidence interval; N=number of patients; p=p-value.

Fifty-two (52) patients treated with crizotinib and 57 chemotherapy-treated patients with previously treated or untreated asymptomatic brain metastases were enrolled in randomised Phase 3 Study 1007. Intracranial Disease Control Rate (IC-DCR) at 12 weeks was 65% and 46% for crizotinib and chemotherapy-treated patients, respectively.

Patient-reported symptoms and global QOL were collected using the EORTC QLQ-C30 and its lung cancer module (EORTC QLQ-LC13) at baseline (Day 1 Cycle 1) and Day 1 of each subsequent treatment cycle. A total of 162 patients in the crizotinib arm and 151 patients in the chemotherapy arm had completed the EORTC QLQ-C30 and LC13 questionnaires at baseline and at least 1 postbaseline visit.

Crizotinib resulted in symptoms benefit by significantly prolonging time to deterioration (median 4.5 months versus 1.4 months) in patients who reported symptoms of pain in chest, dyspnoea, or cough, compared to chemotherapy (HR 0.50; 95% CI: 0.37, 0.66; Hochberg-adjusted log-rank $p < 0.0001$).

Crizotinib showed a significantly greater improvement from baseline compared to chemotherapy in alopecia (Cycles 2 to 15; p-value < 0.05), cough (Cycles 2 to 20; p-value < 0.0001), dyspnoea (Cycles 2 to 20; p-value < 0.0001), haemoptysis (Cycles 2 to 20; p-value < 0.05), pain in arm or shoulder (Cycles 2 to 20; p-value < 0.0001), pain in chest (Cycles 2 to 20; p-value < 0.0001), and pain in other parts (Cycles 2 to 20; p-value < 0.05). Crizotinib resulted in a significantly lower deterioration from baseline in peripheral neuropathy (Cycles 6 to 20; p-value < 0.05), dysphagia (Cycles 5 to 11; p-value < 0.05) and sore mouth (Cycle 2 to 20; p-value < 0.05) compared to chemotherapy.

Crizotinib resulted in overall global quality of life benefits with a significantly greater improvement from baseline observed in the crizotinib arm compared to the chemotherapy arm (Cycles 2 to 20; p-value < 0.05).

Single-arm studies in ALK-positive advanced NSCLC
The use of single-agent crizotinib in the treatment of ALK-positive advanced NSCLC was investigated in 2 multinational, single-arm studies (Studies 1001 and 1005). Of the patients enrolled in these studies, the patients described below had received prior systemic therapy for locally advanced or

metastatic disease. The primary efficacy endpoint in both studies was objective response rate (ORR) according to RECIST.

A total of 149 ALK-positive advanced NSCLC patients, including 125 patients with previously treated ALK-positive advanced NSCLC, were enrolled into Study 1001 at the time of data cutoff for PFS and ORR analysis. The demographic and disease characteristics were 50% female, median age of 51 years, baseline ECOG performance status of 0 (32%) or 1 (55%), 61% White and 30% Asian, less than 1% were current smokers, 27% former smokers, 72% never smokers, 94% metastatic, and 98% of the cancers were classified as adenocarcinoma histology. The median duration of treatment was 42 weeks.

A total of 934 patients with ALK-positive advanced NSCLC were treated with crizotinib in Study 1005 at the time of data cutoff for PFS and ORR analysis. The demographic and disease characteristics were 57% female, median age of 53 years, baseline ECOG performance status of 0/1 (82%) or 2/3 (18%), 52% White and 44% Asian, 4% current smokers, 30% former smokers, 66% never smokers, 92% metastatic, and 94% of the cancers were classified as adenocarcinoma histology. The median duration of treatment for these patients was 23 weeks. Patients could continue treatment beyond the time of RECIST-defined disease progression at the discretion of the investigator. Seventy-seven of 106 patients (73%) continued crizotinib treatment for at least 3 weeks after objective disease progression.

Efficacy data from Studies 1001 and 1005 are provided in Table 6.

Table 6: ALK-positive advanced NSCLC efficacy results from Studies 1001 and 1005

Efficacy parameter	**Study 1001**	**Study 1005**
	N=125[a]	**N=765[a]**
Objective response rate[b] [% (95% CI)]	60 (51, 69)	48 (44, 51)
Time to tumour response [median (range)] weeks	7.9 (2.1, 39.6)	6.1 (3, 49)
Duration of response[c] [median (95% CI)] weeks	48.1 (35.7, 64.1)	47.3 (36, 54)
Progression-free survival[c] [median (95% CI)] months	9.2 (7.3, 12.7)	7.8 (6.9, 9.5)[d]
	N=154[e]	**N=905[e]**
Number of deaths, n (%)	83 (54%)	504 (56%)
Overall survival[c] [median (95% CI)] months	28.9 (21.1, 40.1)	21.5 (19.3, 23.6)

Abbreviations: CI=confidence interval; N/n=number of patients; PFS=progression-free survival.

a. Per data cutoff dates 01 June 2011 (Study 1001) and 15 February 2012 (Study 1005).

b. Three patients were not evaluable for response in Study 1001, and 42 patients were not evaluable for response in Study 1005.

c. Estimated using the Kaplan-Meier method.

d. PFS data from Study 1005 included 807 patients in the safety analysis population who were identified by the FISH assay (data cutoff date 15 February 2012).

e. Per data cutoff date 30 November 2013.

ROS1-positive advanced NSCLC

The use of single-agent crizotinib in the treatment of ROS1-positive advanced NSCLC was investigated in multicenter, multinational, single-arm Study 1001. A total of 53 ROS1-positive advanced NSCLC patients were enrolled in the study at the time of data cutoff, including 46 patients with previously treated ROS1-positive advanced NSCLC and a limited number of patients (N=7) who had no prior systemic treatment. The primary efficacy endpoint was ORR according to RECIST. Secondary endpoints included time to tumour response (TTR), duration of response (DR), PFS, and OS. Patients received crizotinib 250 mg orally twice daily.

The demographic characteristics were 57% female; median age 55 years; baseline ECOG performance status of 0 or 1 (98%) or 2 (2%), 57% White and 40% Asian; 25% former smokers, and 75% never smokers. The disease characteristics were 94% metastatic, 96% adenocarcinoma histology, and 13% with no prior systemic therapy for metastatic disease.

In Study 1001, patients were required to have advanced ROS1-positive advanced NSCLC prior to entering the clinical study. For most patients, ROS1-positive NSCLC was identified by FISH. The

median duration of treatment was 22.4 months (95% CI: 15.0, 35.9). There were 6 complete responses and 32 partial responses for an ORR of 72% (95% CI: 58%, 83%). The median DR was 24.7 months (95% CI: 15.2, 45.3). Fifty percent of objective tumour responses were achieved during the first 8 weeks of treatment. The median PFS at the time of data cutoff was 19.3 months (95% CI: 15.2, 39.1). The median OS at the time of data cutoff was 51.4 months (95% CI: 29.3, NR).

Efficacy data from ROS1-positive advanced NSCLC patients from Study 1001 are provided in Table 7.

Table 7. ROS1-positive advanced NSCLC efficacy results from Study 1001

Efficacy parameter	**Study 1001 N=53[a]**
Objective response rate [% (95% CI)]	72 (58, 83)
Time to tumour response [median (range)] weeks	8 (4, 104)
Duration of response[b] [median (95% CI)] months	24.7 (15.2, 45.3)
Progression-free survival[b] [median (95% CI)] months	19.3 (15.2, 39.1)
OS[b] [median (95% CI)] months	51.4 (29.3, NR)

Abbreviations: CI=confidence interval; N=number of patients; NR=not reached; OS=overall survival.
OS is based on a median follow up of approximately 63 months.
a. Per data cutoff date30 June 2018.
b. Estimated using the Kaplan-Meier method.

Non-adenocarcinoma histology

Twenty-one patients with previously untreated and 12 patients with previously treated advanced ALK-positive non-adenocarcinoma histology NSCLC were enrolled in randomised Phase 3 Studies 1014 and 1007, respectively. The subgroups in these studies were too small to draw reliable conclusions. Of note, no patients with SCC histology were randomised in the crizotinib arm in Study 1007 and no patients with SCC were enrolled in Study 1014 due to pemetrexed-based regimen being used as a comparator.

Information is available from 45 response-evaluable patients with previously treated non-adenocarcinoma NSCLC (including 22 patients with SCC) in Study 1005. Partial responses were observed in 20 of 45 patients with non-adenocarcinoma NSCLC for an ORR of 44%, and 9 of 22 patients with SCC NSCLC for an ORR of 41%, both of which were less than the ORR reported in Study 1005 (54%) for all patients.

Re-treatment with crizotinib

No safety and efficacy data are available on re-treatment with crizotinib of patients who received crizotinib in previous lines of therapy.

Elderly

Of 171 ALK-positive NSCLC patients treated with crizotinib in randomised Phase 3 Study 1014, 22 (13%) were 65 years or older, and of 109 ALK-positive patients treated with crizotinib who crossed over from chemotherapy arm, 26 (24%) were 65 years or older. Of 172 ALK-positive patients treated with crizotinib in randomised Phase 3 Study 1007, 27 (16%) were 65 years or older. Of 154 and 1063 ALK-positive NSCLC patients in single arm Studies 1001 and 1005, 22 (14%) and 173 (16%) were 65 years or older, respectively. In ALK-positive NSCLC patients, the frequency of adverse reactions was generally similar for patients < 65 years of age and patients ≥ 65 years of age with the exception of oedema and constipation, which were reported with greater frequency (≥ 15% difference) in Study 1014 among patients treated with crizotinib ≥ 65 years of age. No patients in the crizotinib arm of randomised Phase 3 Studies 1007 and 1014, and single-arm Study 1005 were > 85 years. There was one ALK-positive patient > 85 years old out of 154 patients in single-arm Study 1001 (see also section 4.2 and 5.2). Of the 53 ROS1-positive NSCLC patients in single-arm Study 1001, 15 (28%) were 65 years or older. There were no ROS1-positive patients > 85 years old in Study 1001.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with XALKORI in all subsets of the paediatric population in NSCLC (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Following oral single dose administration in the fasted state, crizotinib is absorbed with median time to achieve peak concentrations of 4 to 6 hours. With twice daily dosing, steady-state was achieved within 15 days. The absolute bioavailability of crizotinib was determined to be 43% following the administration of a single 250 mg oral dose.

A high-fat meal reduced crizotinib AUC_{inf} and C_{max} by approximately 14% when a 250 mg single dose was given to healthy volunteers. Crizotinib can be administered with or without food (see section 4.2).

Distribution

The geometric mean volume of distribution (V_{ss}) of crizotinib was 1772 L following intravenous administration of a 50 mg dose, indicating extensive distribution into tissues from the plasma.

Binding of crizotinib to human plasma proteins *in vitro* is 91% and is independent of medicinal product concentration. *In vitro* studies suggest that crizotinib is a substrate for P-glycoprotein (P-gp).

Biotransformation

In vitro studies demonstrated that CYP3A4/5 were the major enzymes involved in the metabolic clearance of crizotinib. The primary metabolic pathways in humans were oxidation of the piperidine ring to crizotinib lactam and *O*-dealkylation, with subsequent Phase 2 conjugation of *O*-dealkylated metabolites.

In vitro studies in human liver microsomes demonstrated that crizotinib is a time-dependent inhibitor of CYP2B6 and CYP3A (see section 4.5). *In vitro* studies indicated that clinical drug-drug interactions are unlikely to occur as a result of crizotinib-mediated inhibition of the metabolism of medicinal products that are substrates for CYP1A2, CYP2C8, CYP2C9, CYP2C19 or CYP2D6.

In vitro studies showed that crizotinib is a weak inhibitor of UGT1A1 and UGT2B7 (see section 4.5). However, *in vitro* studies indicated that clinical drug-drug interactions are unlikely to occur as a result of crizotinib-mediated inhibition of the metabolism of medicinal products that are substrates for UGT1A4, UGT1A6, or UGT1A9.

In vitro studies in human hepatocytes indicated that clinical drug-drug interactions are unlikely to occur as a result of crizotinib-mediated induction of the metabolism of medicinal products that are substrates for CYP1A2.

Elimination

Following single doses of crizotinib, the apparent plasma terminal half-life of crizotinib was 42 hours in patients.

Following the administration of a single 250 mg radiolabelled crizotinib dose to healthy subjects, 63% and 22% of the administered dose was recovered in faeces and urine, respectively. Unchanged crizotinib represented approximately 53% and 2.3% of the administered dose in faeces and urine, respectively.

Coadministration with medicinal products that are substrates of transporters

Crizotinib is an inhibitor of P-glycoprotein (P-gp) *in vitro*. Therefore, crizotinib may have the potential to increase plasma concentrations of coadministered medicinal products that are substrates of P-gp (see section 4.5).

Crizotinib is an inhibitor of OCT1 and OCT2 *in vitro*. Therefore, crizotinib may have the potential to increase plasma concentrations of coadministered medicinal products that are substrates of OCT1 or OCT2 (see section 4.5).

In vitro, crizotinib did not inhibit the human hepatic uptake transport proteins organic anion transporting polypeptide (OATP)1B1 or OATP1B3 or the renal uptake transport proteins organic anion transporter (OAT)1 or OAT3 at clinically relevant concentrations. Therefore, clinical drug-drug interactions are unlikely to occur as a result of crizotinib-mediated inhibition of the hepatic or renal uptake of medicinal products that are substrates for these transporters.

Effect on other transport proteins

In vitro, crizotinib is not an inhibitor of BSEP at clinically relevant concentrations.

Pharmacokinetics in special patient groups

Hepatic impairment
Crizotinib is extensively metabolised in the liver. Patients with mild (either AST > ULN and total bilirubin ≤ ULN or any AST and total bilirubin > ULN but ≤1.5 × ULN), moderate (any AST and total bilirubin > 1.5 × ULN and ≤ 3 × ULN), or severe (any AST and total bilirubin > 3 × ULN) hepatic impairment or normal (AST and total bilirubin ≤ ULN) hepatic function, who were matched controls for mild or moderate hepatic impairment, were enrolled in an open-label, non-randomised clinical study (Study 1012), based on NCI classification.

Following crizotinib 250 mg twice daily dosing, patients with mild hepatic impairment (N=10) showed similar systemic crizotinib exposure at steady state compared to patients with normal hepatic function (N=8), with geometric mean ratios for area under the plasma concentration-time curve as daily exposure at steady state (AUC_{daily}) and C_{max} of 91.1% and 91.2%, respectively. No starting dose adjustment is recommended for patients with mild hepatic impairment.

Following crizotinib 200 mg twice daily dosing, patients with moderate hepatic impairment (N=8) showed higher systemic crizotinib exposure compared to patients with normal hepatic function (N=9) at the same dose level, with geometric mean ratios for AUC_{daily} and C_{max} of 150% and 144%, respectively. However, the systemic crizotinib exposure in patients with moderate hepatic impairment at the dose of 200 mg twice daily was comparable to that observed from patients with normal hepatic function at a dose of 250 mg twice daily, with geometric mean ratios for AUC_{daily} and C_{max} of 114% and 109%, respectively.

The systemic crizotinib exposure parameters AUC_{daily} and C_{max} in patients with severe hepatic impairment (N=6) receiving a crizotinib dose of 250 mg once daily were approximately 64.7% and 72.6%, respectively, of those from patients with normal hepatic function receiving a dose of 250 mg twice daily.

An adjustment of the dose of crizotinib is recommended when administering crizotinib to patients with moderate or severe hepatic impairment (see sections 4.2 and 4.4).

Renal impairment
Patients with mild ($60 \leq CL_{cr} < 90$ mL/min) and moderate ($30 \leq CL_{cr} < 60$ mL/min) renal impairment were enrolled in single-arm Studies 1001 and 1005. The effect of renal function as measured by baseline CL_{cr} on observed crizotinib steady-state trough concentrations ($C_{trough, ss}$) was evaluated. In

Study 1001, the adjusted geometric mean of plasma $C_{trough, ss}$ in mild (N=35) and moderate (N=8) renal impairment patients were 5.1% and 11% higher, respectively, than those in patients with normal renal function. In Study 1005, the adjusted geometric mean $C_{trough, ss}$ of crizotinib in mild (N=191) and moderate (N=65) renal impairment groups were 9.1% and 15% higher, respectively, than those in patients with normal renal function. In addition, the population pharmacokinetic analysis using data from Studies 1001, 1005 and 1007 indicated CL_{cr} did not have a clinically meaningful effect on the pharmacokinetics of crizotinib. Due to the small size of the increases in crizotinib exposure (5%-15%), no starting dose adjustment is recommended for patients with mild or moderate renal impairment.

After a single 250 mg dose in subjects with severe renal impairment (CL_{cr} < 30 mL/min) not requiring peritoneal dialysis or haemodialysis, crizotinib AUC_{inf} and C_{max} increased by 79% and 34%, respectively, compared to those with normal renal function. An adjustment of the dose of crizotinib is recommended when administering crizotinib to patients with severe renal impairment not requiring peritoneal dialysis or haemodialysis (see sections 4.2 and 4.4).

Age
Based on the population pharmacokinetic analysis of data from Studies 1001, 1005, and 1007, age has no effect on crizotinib pharmacokinetics (see sections 4.2 and 5.1).

Body weight and gender
Based on the population pharmacokinetic analysis of data from Studies 1001, 1005 and 1007, there was no clinically meaningful effect of body weight or gender on crizotinib pharmacokinetics.

Ethnicity
Based on the population pharmacokinetic analysis of data from Studies 1001, 1005 and 1007, the predicted area under the plasma concentration-time curve at steady-state (AUC_{ss}) (95% CI) was 23%-37% higher in Asian patients (N=523) than in non-Asian patients (N=691).

In studies in patients with ALK-positive advanced NSCLC (N=1669), the following adverse reactions were reported with an absolute difference of ≥ 10% in Asian patients (N=753) than in non-Asian patients (N=916): elevated transaminases, decreased appetite, neutropenia, and leukopenia. No adverse drug reactions were reported with an absolute difference of ≥ 15%.

Geriatric
Limited data are available in this subgroup of patients (see sections 4.2 and 5.1). Based on the population pharmacokinetic analysis of data in Studies 1001, 1005 and 1007, age has no effect on crizotinib pharmacokinetics.

Cardiac electrophysiology

The QT interval prolongation potential of crizotinib was assessed in patients with either ALK-positive or ROS1-positive NSCLC who received crizotinib 250 mg twice daily. Serial ECGs in triplicate were collected following a single dose and at steady state to evaluate the effect of crizotinib on QT intervals. Thirty-four of 1619 patients (2.1%) with at least 1 postbaseline ECG assessment were found to have QTcF ≥ 500 msec, and 79 of 1585 patients (5.0%) with a baseline and at least 1 postbaseline ECG assessment had an increase from baseline QTcF ≥ 60 msec by automated machine-read evaluation of ECG (see section 4.4).

An ECG substudy using blinded manual ECG measurements was conducted in 52 ALK-positive NSCLC patients who received crizotinib 250 mg twice daily. Eleven (21%) patients had an increase from Baseline in QTcF value ≥ 30 to < 60 msec and 1 (2%) patient had an increase from Baseline in QTcF value of ≥ 60 msec. No patients had a maximum QTcF ≥ 480 msec. The central tendency analysis indicated that all upper limits of the 90% CI for the LS mean change from Baseline in QTcF at all Cycle 2 Day 1 time points were < 20 msec. A pharmacokinetic/pharmacodynamic analysis suggested a relationship between crizotinib plasma concentration and QTc. In addition, a decrease in heart rate was found to be associated with increasing crizotinib plasma concentration (see section 4.4), with a maximum mean reduction of 17.8 beats per minute (bpm) after 8 hours on Cycle 2 Day 1.

5.3 Preclinical safety data

In rat and dog repeat-dose toxicity studies up to 3-month duration, the primary target organ effects were related to the gastrointestinal (emesis, faecal changes, congestion), haematopoietic (bone marrow hypocellularity), cardiovascular (mixed ion channel blocker, decreased heart rate and blood pressure, increased LVEDP, QRS and PR intervals, and decreased myocardial contractility), or reproductive (testicular pachytene spermatocyte degeneration, single-cell necrosis of ovarian follicles) systems. The No Observed Adverse Effect Levels (NOAEL) for these findings were either subtherapeutic or up to 2.6-fold human clinical exposure based on AUC. Other findings included an effect on the liver (elevation of liver transaminases) and retinal function, and potential for phospholipidosis in multiple organs without correlative toxicities.

Crizotinib was not mutagenic *in vitro* in the bacterial reverse mutation (Ames) assay. Crizotinib was aneugenic in an *in vitro* micronucleus assay in Chinese Hamster Ovary cells and in an *in vitro* human lymphocyte chromosome aberration assay. Small increases of structural chromosomal aberrations at cytotoxic concentrations were seen in human lymphocytes. The NOAEL for aneugenicity was approximately 1.8-fold human clinical exposure based on AUC.

Carcinogenicity studies with crizotinib have not been performed.

No specific studies with crizotinib have been conducted in animals to evaluate the effect on fertility; however, crizotinib is considered to have the potential to impair reproductive function and fertility in humans based on findings in repeat-dose toxicity studies in the rat. Findings observed in the male reproductive tract included testicular pachytene spermatocyte degeneration in rats given ≥ 50 mg/kg/day for 28 days (approximately 1.1-fold human clinical exposure based on AUC). Findings observed in the female reproductive tract included single-cell necrosis of ovarian follicles of a rat given 500 mg/kg/day for 3 days.

Crizotinib was not shown to be teratogenic in pregnant rats or rabbits. Post-implantation loss was increased at doses ≥ 50 mg/kg/day (approximately 0.4 times the AUC at the recommended human dose) in rats, and reduced foetal body weights were considered adverse effects in the rat and rabbit at 200 and 60 mg/kg/day, respectively (approximately 1.2-fold human clinical exposure based on AUC).

Decreased bone formation in growing long bones was observed in immature rats at 150 mg/kg/day following once daily dosing for 28 days (approximately 3.3 times human clinical exposure based on AUC). Other toxicities of potential concern to paediatric patients have not been evaluated in juvenile animals.

The results of an *in vitro* phototoxicity study demonstrated that crizotinib may have phototoxic potential.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content
Colloidal anhydrous silica
Microcrystalline cellulose
Anhydrous calcium hydrogen phosphate
Sodium starch glycolate (Type A)
Magnesium stearate

Capsule shell
Gelatin
Titanium dioxide (E171)
Red iron oxide (E172)

Printing ink
Shellac
Propylene glycol
Potassium hydroxide
Black iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

HDPE bottles with a polypropylene closure containing 60 hard capsules.
PVC-foil blisters containing 10 hard capsules.

Each carton contains 60 hard capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

XALKORI 200 mg hard capsules
EU/1/12/793/001
EU/1/12/793/002

XALKORI 250 mg hard capsules
EU/1/12/793/003
EU/1/12/793/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 October 2012
Date of latest renewal: 29 July 2016

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Pfizer Manufacturing Deutschland GmbH
Betriebsstätte Freiburg
Mooswaldallee 1
79090 Freiburg
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicine Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The MAH shall agree the content and format of the educational material with the National Competent Authority. The final wording used on the educational material should be in line with the approved product information.

The MAH should ensure that, at launch and thereafter, all Healthcare Professionals who are expected to use and/or prescribe XALKORI are provided with an educational pack.

The educational pack should contain the following:

1. Summary of Product Characteristics and Package Leaflet.
2. Patient brochure including a Patient Alert Card (text as agreed by the CHMP).

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

XALKORI 200 mg hard capsules
crizotinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 200 mg crizotinib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

60 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/793/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

XALKORI 200 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR BLISTER

1. NAME OF THE MEDICINAL PRODUCT

XALKORI 200 mg hard capsules
crizotinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 200 mg crizotinib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

60 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/793/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

XALKORI 200 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

XALKORI 200 mg hard capsules
crizotinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG (as MAH logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

XALKORI 250 mg hard capsules
crizotinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 250 mg crizotinib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

60 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/793/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

XALKORI 250 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR BLISTER

1. NAME OF THE MEDICINAL PRODUCT

XALKORI 250 mg hard capsules
crizotinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 250 mg crizotinib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

60 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/793/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

XALKORI 250 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

XALKORI 250 mg hard capsules
crizotinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG (as MAH logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

XALKORI 200 mg hard capsules
XALKORI 250 mg hard capsules
crizotinib

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist, or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What XALKORI is and what it is used for

XALKORI is an anticancer medicine containing the active substance crizotinib used to treat adults with a type of lung cancer called non-small cell lung cancer, that presents with a specific rearrangement or defect in either a gene called anaplastic lymphoma kinase (ALK) or a gene called ROS1.

XALKORI can be prescribed to you for the initial treatment if your disease is at an advanced stage of lung cancer.

XALKORI can be prescribed to you if your disease is at an advanced stage and previous treatment has not helped to stop your disease.

XALKORI may slow or stop the growth of lung cancer. It may help shrink tumours.

If you have any questions about how XALKORI works or why this medicine has been prescribed for you, ask your doctor.

2. What you need to know before you take XALKORI

Do not take XALKORI
- If you are allergic to crizotinib or any of the other ingredients of this medicine (listed in Section 6, “What XALKORI contains”).

Warnings and precautions
Talk to your doctor before taking XALKORI:

- If you have moderate or severe liver disease.
- If you have ever had any other lung problems. Some lung problems may get worse during treatment with XALKORI, as XALKORI may cause inflammation of the lungs during treatment. Symptoms may be similar to those from lung cancer. Tell your doctor right away if

you have any new or worsening symptoms including difficulty in breathing, shortness of breath, or cough with or without mucous, or fever.
- If you have been told that you have an abnormality of your heart tracing after an electrocardiogram (ECG) known as prolonged QT interval.
- If you have reduced heart rate.
- If you have ever had stomach or intestine problems such as holes (perforation), or if you have conditions causing inflammation inside the abdomen (diverticulitis), or if you have spread of cancer inside the abdomen (metastasis).
- If you have vision disorders (seeing flashes of light, blurred vision, and double vision).
- If you have severe kidney disease.
- If you are currently treated with any of the medicines listed in section "Other medicines and XALKORI".

Talk to your doctor right away after having taken XALKORI:
- If you are experiencing severe stomach or abdominal pain, fever, chills, shortness of breath, fast heartbeat, partial or complete loss of vision (in one or both eyes) or changes in bowel habits.

Most of the available information is available in patients with some specific histology type of ALK-positive NSCLC (adenocarcinoma) and limited information is available in the other histologies.

Children and adolescents
Treatment of children and adolescents with this medicine is not recommended. The indication does not cover children and adolescents.

Other medicines and XALKORI
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including herbal medicines and medicine obtained over the counter.

In particular, the following medicines may increase the risk of side effects with XALKORI:
- Clarithromycin, telithromycin, erythromycin, antibiotics used to treat bacterial infections.
- Ketoconazole, itraconazole, posaconazole, voriconazole, used to treat fungal infections.
- Atazanavir, ritonavir, cobicistat, used to treat HIV infections/AIDS.

The following medicines may reduce the effectiveness of XALKORI:
- Phenytoin, carbamazepine or phenobarbital, anti-epileptics used to treat seizures or fits.
- Rifabutin, rifampicin, used to treat tuberculosis.
- St. John's wort (*Hypericum perforatum*), a herbal product used to treat depression.

XALKORI may increase side effects associated with the following medicines:
- Alfentanil and other short acting opiates such as fentanyl (painkillers used for surgical procedures).
- Quinidine, digoxin, disopyramide, amiodarone, sotalol, dofetilide, ibutilide, verapamil, diltiazem used to treat heart problems.
- Medicines for high blood pressure called beta-blockers such as atenolol, propranolol, labetolol.
- Pimozide, used to treat mental illness.
- Metformin, used to treat diabetes.
- Procainamide, used to treat cardiac arrhythmia.
- Cisapride, used to treat stomach problems.
- Ciclosporin, sirolimus and tacrolimus used in transplant patients.
- Ergot alkaloids (e.g., ergotamine, dihydroergotamine), used to treat migraine.
- Dabigatran, anticoagulant used to slow down clotting of the blood.
- Colchicine, used to treat gout.
- Pravastatin, used to reduce cholesterol levels.
- Clonidine, guanfacine, used to treat hypertension.

- Mefloquine, used for the prevention of malaria.
- Pilocarpine, used to treat glaucoma (a severe eye disease).
- Anticholinesterases, used to restore muscle function.
- Antipsychotics, used to treat mental illness.
- Moxifloxacine, used to treat bacterial infections.
- Methadone, used to treat pain and for the treatment of opioid dependence.
- Bupropion, used to treat depression and smoking cessation.
- Efavirenz, raltegravir, used to treat HIV infection.
- Irinotecan, a chemotherapy medicine used to treat cancer of the colon and rectum.
- Morphine, used to treat acute and cancer pain.
- Naloxone, used to treat opiate medicine addiction and withdrawal.

These medicines *should be avoided* during your treatment with XALKORI.

Oral contraceptives
If you take XALKORI whilst using oral contraceptives, the oral contraceptives may be ineffective.

XALKORI with food and drink
You can take XALKORI with or without food; however, you should avoid drinking grapefruit juice or eating grapefruit while on treatment with XALKORI as they may change the amount of XALKORI in your body.

Pregnancy and breast-feeding
Talk to your doctor or pharmacist before taking this medicine if you are pregnant, may become pregnant or are breast-feeding.

It is recommended that women avoid becoming pregnant and that men do not father children during treatment with XALKORI because this medicine could harm the baby. If there is any possibility that the person taking this medicine may become pregnant or father a child, they must use adequate contraception during treatment, and for at least 90 days after completing therapy as oral contraceptives may be ineffective while taking XALKORI.

Do not breast-feed during treatment with XALKORI. XALKORI could harm a breast-fed baby.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines
You should take special care when driving and using machines as patients taking XALKORI may experience visual disturbances, dizziness, and tiredness.

XALKORI contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per 200 mg or 250 mg capsule, that is to say essentially ‘sodium-free’.

3. How to take XALKORI

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

- The recommended dose is one capsule of 250 mg taken orally twice daily (total amount 500 mg).
- Take the capsule once in the morning and once in the evening.
- Take the capsules at about the same time each day.

- You can take the capsules with or without food always avoiding grapefruit.
- Swallow the capsules whole and do not crush, dissolve or open the capsules.

If necessary, your doctor may decide to reduce the dose to 200 mg to be taken orally twice daily (total amount 400 mg) and if further dose reduction is necessary, to reduce it to 250 mg to be taken orally once daily. Your doctor may decide to permanently discontinue your treatment if you are unable to tolerate XALKORI 250 mg taken orally once daily.

If you take more XALKORI than you should
If you accidentally take too many capsules, tell your doctor or pharmacist right away. You may require medical attention.

If you forget to take XALKORI
What to do if you forget to take a capsule depends on how long it is until your next dose.
- If your next dose is in **6 hours or more**, take the missed capsule as soon as you remember. Then take the next capsule at the usual time.
- If your next dose is in **less than 6 hours**, skip the missed capsule. Then take the next capsule at the usual time.

Tell your doctor about the missed dose at your next visit.

Do not take a double dose (two capsules at the same time) to make up for a forgotten capsule.

If you vomit after taking a dose of XALKORI, do not take an extra dose; just take your next dose at your regular time.

If you stop taking XALKORI
It is important to take XALKORI every day, as long as your doctor prescribes it to you. If you are not able to take the medicine as your doctor prescribed, or you feel you do not need it anymore, contact your doctor right away.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If you experience any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet.

Some side effects could be serious. You should immediately contact your doctor if you experience any of the following serious side effects (see also section 2 “What you need to know before you take XALKORI ”):

- **Liver failure**
  Tell your doctor right away if you feel more tired than usual, your skin and whites of your eyes turn yellow, your urine turns dark or brown (tea colour), you have nausea, vomiting, or decreased appetite, you have pain on the right side of your stomach, you have itching, or if you bruise more easily than usual. Your doctor may do blood tests to check your liver function, and if the results are abnormal, your doctor may decide to reduce the dose of XALKORI or stop your treatment.

- **Lung inflammation**
  Tell your doctor right away if you experience difficulty in breathing, especially if associated with cough or fever.

- **Reduction in the number of white blood cells (including neutrophils)**
  Tell your doctor right away if you experience fever or infection. Your doctor may do blood tests and if the results are abnormal, your doctor may decide to reduce the dose of XALKORI.

- **Light-headedness, fainting, or chest discomfort**
  Tell your doctor right away if you experience these symptoms which could be signs of changes in the electrical activity (seen on electrocardiogram) or abnormal rhythm of the heart. Your doctor may perform electrocardiograms to check there are no problems with your heart during treatment with XALKORI.

- **Partial or complete loss of vision in one or both eyes**
  Tell your doctor right away if you experience any loss of vision or any change in vision such as difficulty seeing out of one or both eyes. Your doctor may stop XALKORI treatment and refer you to an ophthalmologist.

Other side effects of XALKORI may include:

Very common side effects (may affect more than 1 in 10 people)
- Visual effects (seeing flashes of light, blurred vision, or double vision, often beginning soon after starting treatment with XALKORI).
- Stomach upset, including vomiting, diarrhoea, nausea.
- Oedema (excess fluid in body tissue, causing swelling of the hands and feet).
- Constipation.
- Abnormalities in liver blood tests.
- Decreased appetite.
- Tiredness.
- Dizziness.
- Neuropathy (feeling of numbness or pins and needles in the joints or extremities).
- Alteration in sense of taste.
- Pain in the abdomen.
- Reduction in the number of red blood cells (anaemia).
- Skin rash.
- Reduced heart rate.

*Common side effect*s (may affect up to 1 in 10 people)
- Indigestion.
- Increased blood levels of creatinine (may indicate that kidneys are not functioning properly).
- Increased levels of the enzyme alkaline phosphatase in the blood (an indicator of organ malfunction or injury, particularly liver, pancreas, bone, thyroid gland, or gall bladder).
- Hypophosphataemia (low blood phosphate levels that can cause confusion or muscle weakness).
- Closed pouches of fluid within the kidneys (kidney cysts).
- Fainting.
- Inflammation of the oesophagus (swallowing tube).
- Decreased levels of testosterone, a male sex hormone.
- Heart failure.

*Uncommon side effect*s (may affect up to 1 in 100 people)
- Hole (perforation) in stomach or intestine.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store XALKORI

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the bottle or blister foil and carton after "EXP". The expiry date refers to the last day of that month.
- This medicine does not require any special storage conditions.
- Do not use any pack that is damaged or shows signs of tampering.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What XALKORI contains

– The active substance in XALKORI is crizotinib.
XALKORI 200 mg: each capsule contains 200 mg crizotinib
XALKORI 250 mg: each capsule contains 250 mg crizotinib

– The other ingredients are (see also section 2 "XALKORI contains sodium"):
Capsule content: colloidal anhydrous silica, microcrystalline cellulose, anhydrous calcium hydrogen phosphate, sodium starch glycolate (Type A), magnesium stearate.
Capsule shell: gelatin, titanium dioxide (E171), and red iron oxide (E172).
Printing ink: shellac, propylene glycol, potassium hydroxide, and black iron oxide (E172).

What XALKORI looks like and contents of the pack

XALKORI 200 mg is supplied as hard gelatin capsules with pink cap and white body, printed with black ink "Pfizer" on the cap, "CRZ 200" on the body.

XALKORI 250 mg is supplied as hard gelatin capsules with pink cap and body, printed with black ink "Pfizer" on the cap, "CRZ 250" on the body.

It is available in blister packs of 60 hard capsules and in plastic bottles of 60 hard capsules.

Not all pack sizes may be marketed.

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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/.