SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

XALKORI 20 mg granules in capsules for opening

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 20 mg crizotinib.

Excipient with known effect

Each capsule for opening contains 6 mg sucrose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

The granules are white to off-white and contained in an opaque hard capsule.

Light blue cap printed with “Pfizer” in black ink and a white body printed with “CRZ 20” in black ink.

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)
- The treatment of paediatric patients (age ≥1 to <18 years) with relapsed or refractory systemic anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma (ALCL)

- The treatment of paediatric patients (age ≥1 to <18 years) with recurrent or refractory anaplastic lymphoma kinase (ALK)-positive unresectable inflammatory myofibroblastic tumour (IMT)

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).

ALK-positive NSCLC, ROS1-positive NSCLC, ALK-positive ALCL or ALK-positive IMT 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

Adult patients with ALK-positive or ROS1-positive advanced NSCLC

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

Paediatric patients with ALK-positive ALCL or ALK-positive IMT

The recommended starting dose schedule of crizotinib in paediatric patients is based on body surface area (BSA). The recommended dosage of crizotinib for paediatric patients with ALCL or IMT is 280 mg/m^2 orally twice daily until disease progression or unacceptable toxicity.

The recommended dosage for paediatric patients with BSA ≥1.34 m^2 is provided in Table 1. If needed, attain the desired dose by combining different strengths of crizotinib capsules.

Table 1. Paediatric patients with body surface area (BSA) ≥1.34 m^2: Recommended crizotinib capsules[*] starting dosage

Body Surface Area (BSA)[**]	**Dose (Twice Daily)**	**Total Daily Dose**
1.34 – 1.51 m^2	400 mg (2×200 mg capsule)	800 mg
1.52 – 1.69 m^2	450 mg	900 mg

	(1×200 mg capsule + 1×250 mg capsule)	
≥1.70 m^2	500 mg (2×250 mg capsule)	1000 mg

* Refers to the XALKORI 200 mg and 250 mg hard capsules.
** For paediatric patients with BSA <1.34 m^2, refer to Table 2.

For paediatric patients with BSA <1.34 m^2, the granules in capsules for opening formulation of XALKORI should be used. The recommended dosage for paediatric patients with BSA <1.34 m^2 is provided in Table 2.

The granules are encapsulated into 3 dosage strengths: 20 mg, 50 mg and 150 mg crizotinib. If needed, attain the desired dose by combining different strengths of crizotinib granules in capsules for opening. No more than 4 capsules will be required for a single dose (see Table 2).

Table 2. Paediatric patients with body surface area (BSA) of 0.38 m^2 to 1.33 m^2: Recommended crizotinib granules* starting dosage

Body Surface Area (BSA)**	**Dose (Twice Daily)**	**Total Daily Dose**
0.38 to 0.46 m^2	120 mg (1 × 20 mg + 2 × 50 mg)	240 mg
0.47 to 0.51 m^2	140 mg (2× 20 mg + 2 × 50 mg)	280 mg
0.52 to 0.61 m^2	150 mg (1 × 150 mg)	300 mg
0.62 to 0.80 m^2	200 mg (1 × 50 mg + 1 × 150 mg)	400 mg
0.81 to 0.97 m^2	250 mg (2 × 50 mg + 1 × 150 mg)	500 mg
0.98 to 1.16 m^2	300 mg (2 × 150 mg)	600 mg
1.17 to 1.33 m^2	350 mg (1 × 50 mg + 2 × 150 mg)	700 mg

* Refers to the 20 mg, 50 mg and 150 mg crizotinib granules in capsules for opening.
** The recommended dosage for patients with a BSA less than 0.38 m^2 has not been established. For paediatric patients with BSA ≥1.34 m^2, refer to Table 1.

Administer crizotinib to paediatric patients under adult supervision.

Dose adjustments

Dosing interruption and/or dose reduction may be required based on individual safety and tolerability.

Adult patients with ALK-positive or ROS1-positive advanced NSCLC

In 1722 adult 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 3 and 4. For patients treated with a lower dose of crizotinib than 250 mg twice daily, then follow the dose reduction guidelines provided in Tables 3 and 4 accordingly.

Table 3. Adult patients: 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 4. Adult patients: 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.

Paediatric patients with ALK-positive ALCL or ALK-positive IMT

If a dose reduction is necessary for paediatric patients treated at the recommended starting dose, then the dose of XALKORI for paediatric patients with BSA ≥1.34 m^2 should be reduced as shown in Table 5.

Table 5. Paediatric patients with body surface area (BSA) ≥1.34 m2: Recommended XALKORI capsules*dose reductions

Body Surface Area (BSA)**	First Dose Reduction		Second Dose Reduction***	
	Dose (Twice daily*)	**Total Daily Dose**	**Dose** (Twice daily*)	**Total Daily Dose**
1.34 – 1.69 m^2	250 mg	500 mg	200 mg	400 mg

≥1.70 m^2	400 mg	800 mg	250 mg	500 mg

Refers to the XALKORI 200 mg and 250 mg hard capsules.
** For paediatric patients with BSA <1.34 m^2, refer to Table 6.
*** Permanently discontinue in patients who are unable to tolerate crizotinib after 2 dose reductions.

If a dose reduction is necessary for paediatric patients treated at the recommended starting dose, then the dose of XALKORI for paediatric patients with BSA <1.34 m^2 should be reduced as shown in Table 6.

Table 6. Paediatric patients with body surface area (BSA) of 0.38 m2 to 1.33 m^2: Recommended XALKORI granules* dose reductions

Body Surface Area (BSA)**	First Dose Reduction		Second Dose Reduction***	
	Dose (Twice Daily)	Total Daily Dose	Dose (Twice Daily)	Total Daily Dose
0.38 to 0.46 m^2	90 mg (2 × 20 mg + 1 × 50 mg)	180 mg	70 mg (1 × 20 mg + 1 × 50 mg)	140 mg
0.47 to 0.51 m^2	100 mg (2 × 50 mg)	200 mg	80 mg (4 × 20 mg)	160 mg
0.52 to 0.61 m^2	120 mg (1 × 20 mg + 2 × 50 mg)	240 mg	90 mg (2 × 20 mg + 1 × 50 mg)	180 mg
0.62 to 0.80 m^2	150 mg (1 × 150 mg)	300 mg	120 mg (1 × 20 mg + 2 × 50 mg)	240 mg
0.81 to 0.97 m^2	200 mg (1 × 50 mg + 1 × 150 mg)	400 mg	150 mg (1 × 150 mg)	300 mg
0.98 to 1.16 m^2	220 mg (1 × 20 mg + 1 × 50 mg + 1 × 150 mg)	440 mg	170 mg (1 × 20 mg + 1 × 150 mg)	340 mg
1.17 to 1.33 m^2	250 mg (2 × 50 mg + 1 × 150 mg)	500 mg	200 mg (1 × 50 mg + 1 × 150 mg)	400 mg

* Refers to the 20 mg, 50 mg, and 150 mg crizotinib as granules in capsules for opening.
** For paediatric patients with BSA ≥1.34 m2, refer to Table 5.
*** Permanently discontinue in patients who are unable to tolerate crizotinib after 2 dose reductions.

Recommended dosage modifications for haematologic and non-haematologic adverse reactions for paediatric patients with ALK-positive ALCL or ALK-positive IMT are provided in Tables 7 and 8, respectively.

Table 7. Paediatric patients: XALKORI dosage modification for haematologic adverse reactions

CTCAE[a] Grade	XALKORI Dosing
Absolute Neutrophil Count (ANC)	
Grade 4 Neutrophil count decreased	First occurrence: Withhold until recovery to Grade ≤2, then resume at the next lower dosage. Second occurrence: • Permanently discontinue for recurrence complicated by febrile neutropenia or infection. • For uncomplicated Grade 4 neutropenia, either permanently discontinue, or withhold until recovery to Grade ≤2, then resume at the next lower dosage.[b]
Platelet Count	
Grade 3 platelet count decreased (with concurrent bleeding)	Withhold until recovery to Grade ≤2, then resume at the same dosage.
Grade 4 platelet count decreased	Withhold until recovery to Grade ≤2, then resume at the next lower dosage. Permanently discontinue for recurrence.
Anaemia	
Grade 3	Withhold until recovery to Grade ≤2, then resume at the same dosage.
Grade 4	Withhold until recovery to Grade ≤2, then resume at the next lower dosage. Permanently discontinue for recurrence.

a. Grade based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.
b. Permanently discontinue in patients who are unable to tolerate XALKORI after 2 dose reductions, unless otherwise indicated in Tables 5 and 6.

It is recommended to monitor complete blood counts, including differential counts, weekly for the first month of therapy and then at least monthly, with more frequent monitoring if Grade 3 or 4 abnormalities, fever, or infection occur.

Table 8. Paediatric patients: XALKORI dosage modification for non-haematologic adverse reactions

CTCAE[a] Grade	XALKORI Dosing
Grade 3 or 4 ALT or AST elevation with Grade ≤1 total bilirubin	Withhold until recovery to Grade ≤1, then resume at next lower dose.
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 drug-related Interstitial lung disease/pneumonitis	Permanently discontinue.
Grade 3 QTc prolongation	Withhold until recovery to baseline or to a QTc less than 481 ms, then resume at next lower dosage.
Grade 4 QTc prolongation	Permanently discontinue.

CTCAE[a] Grade	**XALKORI Dosing**
Grade 2, 3 Bradycardia[b] Symptomatic, may be severe and medically significant, medical intervention indicated	Withhold until recovery to a resting heart rate according to the patient's age (based on the 2.5th percentile per age-specific norms) as follows: 1 to <2 years: 91 bpm or above 2 to 3 years: 82 bpm or above 4 to 5 years: 72 bpm or above 6 to 8 years: 64 bpm or above >8 years: 60 bpm or above
Grade 4 Bradycardia[b,c] Life-threatening consequences, urgent intervention indicated	Permanently discontinue if no contributing concomitant medication is identified. If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume at the second dose reduction level in Table 5[c] upon recovery to Grade ≤1 or to the heart rate criteria listed for management of symptomatic or severe, medically significant bradycardia, with frequent monitoring.
Grade 3 Nausea Inadequate oral intake for more than 3 days, medical intervention required	Grade 3 (despite maximum medical therapy): Withhold until resolved, and then resume at the next lower dose level.[d]
Grade 3, 4 Vomiting More than 6 episodes in 24 hours for more than 3 days, medical intervention required, i.e., tube feeding or hospitalisation; life-threatening consequences, urgent intervention indicated	Grade 3 or 4 (despite maximum medical therapy): Withhold until resolved, and then resume at the next lower dose level.[d]
Grade 3, 4 Diarrhoea Increase of 7 or more stools per day over baseline, incontinence, hospitalisation indicated; life-threatening consequences, urgent intervention indicated	Grade 3 or 4 (despite maximum medical therapy): Withhold until resolved, and then resume at the next lower dose level.[d]
Grade 1 (mild symptoms), 2 (moderate symptoms affecting ability to perform age-appropriate activities of daily living) Ocular disorder	Grade 1 or 2: Monitor symptoms and report any symptoms to an eye specialist. Consider dose reduction for Grade 2 visual disorders.
Grade 3, 4 Ocular disorder (visual loss, marked decrease in vision)	Grade 3 or 4: Withhold pending evaluation of severe visual loss. Permanently discontinue, if no other cause found on evaluation.

a. Grade based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.
b. Resting heart rate less than the 2.5th percentile per age-specific norms.
c. Permanently discontinue for recurrence.
d. Permanently discontinue in patients who are unable to tolerate crizotinib after 2 dose reductions, unless otherwise indicated in Tables 5 and 6.

Hepatic impairment

Crizotinib is extensively metabolised in the liver. Treatment with crizotinib should be used with caution in patients with hepatic impairment (see Tables 4 and 8, and sections 4.4, 4.8 and 5.2).

Adjustments for adult patients with ALK-positive or ROS1-positive advanced NSCLC

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.

Adjustments for paediatric patients with ALK-positive ALCL or ALK-positive IMT

Adjustments for paediatric patients are based on the clinical study conducted in adult patients (see section 5.2). No starting dose adjustment of crizotinib is recommended for patients with mild hepatic impairment (either AST >ULN and total bilirubin ≤ULN or any AST and total bilirubin >ULN but ≤1.5 × ULN). The recommended starting dose of crizotinib in patients with moderate hepatic impairment (any AST and total bilirubin >1.5 × ULN and ≤3 × ULN) is the first dose reduction based on BSA as shown in Tables 5 and 6. The recommended starting dose of crizotinib in patients with severe hepatic impairment (any AST and total bilirubin >3 × ULN) is the second dose reduction based on BSA as shown in Tables 5 and 6.

Renal impairment

Adjustments for adult patients with ALK-positive or ROS1-positive advanced NSCLC

No starting dose adjustment is recommended for patients with mild (60 ≤creatinine clearance [CL_{cr}] <90 mL/min) or moderate (30 ≤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).

Adjustments for paediatric patients with ALK-positive ALCL or ALK-positive IMT

Adjustments for paediatric patients are based on information in adult patients (see section 5.2). No starting dose adjustment is needed for patients with mild (60 ≤creatinine clearance [CL_{cr}] <90 mL/min) or moderate (30 ≤CL_{cr} <60 mL/min) renal impairment calculated using the Schwartz equation. The recommended starting dose of crizotinib in patients with severe renal impairment (CL_{cr} <30 mL/min) not

requiring dialysis is the second dose reduction based on BSA as shown in Tables 5 and 6. The dose may be increased to the first dose reduction based on BSA as shown in Tables 5 and 6 and on individual safety and tolerability after at least 4 weeks of treatment.

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 with ALK-positive or ROS1-positive NSCLC have not been established. No data are available.

The safety and efficacy of crizotinib have been established in paediatric patients with relapsed or refractory systemic ALK-positive ALCL from 3 to <18 years of age or with unresectable, recurrent, or refractory ALK-positive IMT from 2 to <18 years of age (see sections 4.8 and 5.1). No safety or efficacy data are available for crizotinib treatment in ALK-positive ALCL paediatric patients below 3 years of age or ALK-positive IMT paediatric patients below 2 years of age.

Method of administration

For oral use.

XALKORI may be taken either after a meal or while fasted. The Xalkori granules should not be sprinkled on 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).

If a dose is missed, then it should be taken as soon as the patient or caregiver remembers unless it is less than 6 hours until the next scheduled 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.

XALKORI 200 mg and 250 mg hard capsules

The XALKORI 200 mg and 250 mg hard capsules should be swallowed whole preferably with water, and should not be crushed, dissolved, or opened.

XALKORI granules in capsules for opening

The granules in capsules for opening should not be chewed, crushed or sprinkled on food. The capsule shell must not be swallowed but carefully be opened as follows:

- The capsule is held so that the printed "Pfizer" is at the top and tapped to ensure all the granules are in the lower half of the capsule.

- The bottom of the capsule is gently squeezed.
- The top and bottom of the capsule are twisted in opposite directions and pulled apart to open the capsule.
- The granules can be administered by 2 options after opening the capsule(s):
  1. Emptying the contents directly into the patient's mouth; OR
  2. Emptying the contents into a consumer supplied dry oral dosing aid (e.g., spoon, medicine cup). The granules are then administered to the patient's mouth via the dosing aid.
- Whichever option is used, the capsule is tapped to ensure all the granules are administered.

If the entire prescribed dose of granules in capsules for opening cannot be taken at one time, then the granules in capsules for opening are to be administered in portions until the entire prescribed dose is given. Immediately after administration of each portion, a sufficient amount of water should be given to ensure that all medication is swallowed. After the medication has been swallowed, other liquids or foods can be ingested (except as noted in section 4.5, *Agents that may increase crizotinib plasma concentrations*).

Detailed pictograms on how to administer the granules in capsules for opening are provided in the Package Leaflet.

Paediatric patients with ALK-positive ALCL or ALK-positive IMT

The use of antiemetics prior to and during treatment with crizotinib is recommended to prevent nausea and vomiting for paediatric patients with ALK-positive ALCL or ALK-positive IMT. Standard antiemetic and antidiarrhoeal agents are recommended to manage gastrointestinal toxicities. Supportive care such as intravenous or oral hydration, electrolyte supplementation and nutritional support are recommended as clinically indicated (see section 4.4).

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 in adult patients) 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 adult patients with ALK-positive or ROS1-positive NSCLC and in 17% of paediatric patients with ALK-positive ALCL or ALK-positive IMT 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 in adult patients, 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 adult patients with either ALK-positive or ROS1-positive NSCLC, Grade 3 or 4 neutropenia has been very commonly reported (12%). In clinical studies with crizotinib in paediatric patients with ALK-positive ALCL or ALK-positive IMT, Grade 3 or 4 neutropenia has been very commonly reported (68%). Grade 3 or 4 leukopenia has been commonly reported (3%) in patients with ALK-positive or ROS1-positive NSCLC and very commonly (24%) in paediatric patients ALK-positive ALCL or ALK-positive IMT (see section 4.8). Less than 0.5% of adult patients with either ALK-positive or ROS1-positive NSCLC experienced febrile neutropenia in clinical studies with crizotinib. In paediatric patients with either ALK-positive ALCL or ALK-positive IMT, febrile neutropenia was commonly reported in one patient (2.4%). 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 in adult patients. 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 adult patients with either ALK-positive or ROS1-positive NSCLC (N=1722), Grade 4 visual field defect with visual loss has been reported in 4 (0.2%) patients. Optic atrophy and optic nerve disorder have been reported as potential causes of visual loss.

In clinical studies with crizotinib in paediatric patients with either in ALK-positive ALCL or ALK-positive IMT, visual disorders occurred in 25 of 41 (61%) paediatric patients (see section 4.8).

For paediatric patients with ALCL or IMT, baseline ophthalmologic examination should be obtained prior to starting crizotinib. Follow-up ophthalmologic examination including retinal examination is recommended within 1 month of starting crizotinib, every 3 months thereafter, and upon any new visual symptoms. Healthcare professionals should inform patients and caregivers of the symptoms of ocular toxicity and potential risk of visual loss. For Grade 2 vision disorders, symptoms should be monitored and reported to an eye specialist with consideration of a dose reduction. Crizotinib should be withheld pending evaluation for any Grade 3 or 4 ocular disorder, and crizotinib should be permanently discontinued for Grade 3 or 4 severe visual loss unless another cause is identified (see section 4.2 Table 8).

In any patient 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 visual loss and for other visual symptoms as clinically warranted, should be performed (see sections 4.2 and 4.8). There is insufficient information to characterise the risks of resumption of crizotinib in patients who develop visual symptoms or visual loss. A decision to resume crizotinib should consider the potential benefit versus risks to the patient.

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

Photosensitivity

Photosensitivity has been reported in patients treated with XALKORI (see section 4.8). Patients should be advised to avoid prolonged sun exposure while taking XALKORI and, when outdoors, to take protective measures (e.g., use of protective clothing and/or sunscreen).

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 (NSCLC)

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).

XALKORI 200 mg and 250 mg hard capsules

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'.

XALKORI granules in capsules for opening

Dietary sucrose

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicinal product.

Paediatric population

Gastrointestinal toxicity

Crizotinib can cause severe gastrointestinal toxicities in paediatric patients with ALK-positive ALCL or ALK-positive IMT. In paediatric patients with either ALK-positive ALCL or ALK-positive IMT, vomiting and diarrhoea occurred in 95% and 85%, respectively.

The use of antiemetics prior to and during treatment with crizotinib is recommended to prevent nausea and vomiting. Standard antiemetic and antidiarrhoeal agents are recommended to manage gastrointestinal toxicities. If paediatric patients develop Grade 3 nausea lasting 3 days or Grade 3 or 4 diarrhoea or vomiting despite maximum medical therapy, it is recommended to withhold crizotinib until resolved, and then resuming crizotinib at the next lower dose level. Supportive care such as hydration, electrolyte supplementation and nutritional support are recommended as clinically indicated (see section 4.2).

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies with other medicinal products have been performed in adults.

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.

XALKORI 200 mg and 250 mg hard capsules

Administration of a single 250 mg crizotinib dose of capsules 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 considered clinically meaningful.

XALKORI granules in capsules for opening

Administration of a single 250 mg crizotinib dose of oral granules in capsules for opening following treatment with esomeprazole 40 mg once daily for 5 days resulted in an approximately 19% decrease in crizotinib AUC_{inf} and 23% decrease in C_{max}. The extent of the change in total exposure was not considered clinically meaningful.

A 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 in adult patients with ALK-positive or ROS1-positive advanced NSCLC

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 neutropenia (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 neutropenia (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 9 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 9 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 9. Adverse reactions reported in crizotinib clinical studies of NSCLC (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%)

System organ class	Very common	Common	Uncommon
Skin and subcutaneous tissue disorders	Rash (13%)		Photosensitivity (<1%)
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%)	Blood creatine phosphokinase increased (<1%)[*]

Event terms that represent the same medical concept or condition were grouped together and reported as a single adverse drug reaction in Table 9. 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.

* Creatine phosphokinase was not a standard laboratory test in the crizotinib clinical trials.

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).

Summary of the safety profile in paediatric patients

The safety analysis population for 110 paediatric patients with all tumour types (ages 1 to <18 years), which included 41 patients with relapsed or refractory systemic ALK-positive ALCL or with unresectable, recurrent, or refractory ALK-positive IMT is based on patients who received crizotinib from 2 single-arm studies, Study 0912 (n=36) and Study 1013 (n=5). In Study 0912, patients received crizotinib at a starting dose of 100 mg/m^2, 130 mg/m^2, 165 mg/m^2, 215 mg/m^2, 280 mg/m^2, or 365 mg/m^2 twice daily. In Study 1013, crizotinib was administered at a starting dose of 250 mg twice daily. There was a total population of 25 paediatric patients with ALK-positive ALCL from 3 to <18 years of age and 16 paediatric patients with ALK-positive IMT from 2 to <18 years of age. Experience on the use of crizotinib in paediatric patients in the different subgroups (age, gender and race) is limited and does not allow for definitive conclusions to be made. The safety profiles were consistent across the subgroups of age, gender and race, although there were slight differences in adverse reactions frequencies within each subgroup. The most frequent adverse reactions (≥80%) reported in all subgroups (age, gender and race) were elevated transaminases, vomiting, neutropenia, nausea, diarrhoea and leukopenia. The most frequent serious adverse reaction (90%) was neutropenia.

The median duration of treatment for paediatric patients with all tumour types was 2.8 months. Permanent discontinuation from treatment due to an adverse event occurred in 11 (10%) patients. Dosing interruptions and dose reductions occurred in 47 (43%) and 15 (14%), respectively. The most frequent adverse reactions (>60%) were elevated transaminases, vomiting, neutropenia, nausea, diarrhoea and leukopenia. The most frequent Grade 3 or 4 adverse reactions (≥40%) was neutropenia.

The median duration of treatment for paediatric patients with ALK-positive ALCL was 5.1 months. Permanent discontinuation from treatment due to an adverse event occurred in 1 patient (4%). Eleven of 25 (44%) patients with ALK-positive ALCL permanently discontinued crizotinib treatment due to subsequently having a haematopoietic stem cell transplant (HSCT). Dosing interruptions and dose reductions occurred in 17 (68%) and 4 (16%) patients, respectively. The most frequent adverse reactions (≥80%) were diarrhoea, vomiting, elevated transaminases, neutropenia, leukopenia and nausea. The most frequent Grade 3 or 4 adverse reactions (≥40%) were neutropenia, leukopenia and lymphopenia.

The median duration of treatment for paediatric patients with ALK-positive IMT was 21.8 months. Permanent discontinuation from treatment due to an adverse event occurred in 4 (25%) patients. Dosing interruptions and dose reductions occurred in 12 (75%) and 4 (25%) patients, respectively. The most frequent adverse reactions (≥80%) were neutropenia, nausea and vomiting. The most frequent Grade 3 or 4 adverse reaction (≥40%) was neutropenia.

The safety profile of crizotinib in paediatric patients with ALK-positive ALCL or with ALK-positive IMT was generally consistent with that previously established in adults with ALK-positive or ROS1-positive advanced NSCLC, with some variations in frequencies. Grade 3 or 4 adverse reactions of neutropenia, leukopenia and diarrhoea were reported with higher frequency (difference of ≥10%) in paediatric patients with either ALK-positive ALCL or ALK-positive IMT than in adult patients

with ALK-positive or ROS1-positive NSCLC. The age, comorbidities and underlying conditions are different in these 2 populations, which could explain the differences in the frequencies.

The adverse reactions for paediatric patients of all tumour types listed in Table 10 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 10. Adverse reactions reported in paediatric patients (N=110)

	All Tumour Types (N=110)	
System organ class	**Very common**	**Common**
Blood and lymphatic system disorders	Neutropenia[a] (71%) Leukopenia[b] (63%) Anaemia[c] (52%) Thrombocytopenia[d] (21%)	
Metabolism and nutrition disorders	Hypophosphataemia (30%) Decreased appetite (39%)	
Nervous system disorders	Neuropathy[e] (26%) Dysgeusia (10%)	
Eye disorders	Vision disorder[f] (44%)	
Cardiac disorders	Bradycardia[g] (14%) Dizziness (16%)	Electrocardiogram QT prolonged (4%)
Gastrointestinal disorders	Vomiting (77%) Diarrhoea (69%) Nausea (71%) Constipation (31%) Dyspepsia (10%) Abdominal pain[h] (43%)	Oesophagitis (4%)
Hepatobiliary disorders	Elevated transaminases[i] (87%) Blood alkaline phosphatase increased (19%)	
Skin and subcutaneous tissue disorders		Rash (3%)
Renal and urinary disorders	Blood creatinine increased (45%)	
General disorders and administration site conditions	Oedema[j] (20%) Fatigue (46%)	

Date of Data Cutoff: 03 Sep 2019.
Event terms that represent the same medical concept or condition were grouped together and reported as a single adverse drug reaction in Table 10. 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. Neutropenia (Febrile neutropenia, Neutropenia, Neutrophil count decreased)
b. Leukopenia (Leukopenia, White blood cell count decreased)
c. Anaemia (Anaemia, Anaemia macrocytic, Anaemia megaloblastic, Haemoglobin, Haemoglobin decreased, Hyperchromic anaemia, Hypochromic anaemia, Hypoplastic anaemia, Microcytic anaemia, Normochromic normocytic anaemia)
d. Thrombocytopenia (Platelet count decreased, Thrombocytopenia)
e. Neuropathy (Burning sensation, Gait disturbance, Muscular weakness, Paraesthesia, Peripheral motor neuropathy, Peripheral sensory neuropathy)
f. Vision disorder (Photophobia, Photopsia, Vision blurred, Visual acuity reduced, Visual impairment, Vitreous floaters)
g. Bradycardia (Bradycardia, Sinus bradycardia)
h. Abdominal pain (Abdominal discomfort, Abdominal pain, Abdominal pain lower, Abdominal pain upper, Abdominal tenderness)
i. Elevated transaminases (Alanine aminotransferase increased, Aspartate aminotransferase increased, Gamma-glutamyltransferase increased)
j. Oedema (Face oedema, Localised oedema, Oedema peripheral, Periorbital oedema)

Although not all adverse reactions identified in the adult population have been observed in clinical trials of paediatric patients, the same adverse reactions for adult patients should be considered for paediatric patients. The same warnings and precautions for adult patients should also be considered for paediatric patients.

Description of selected adverse reactions

Hepatotoxicity

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

Adult patients with NSCLC

Drug-induced hepatotoxicity with fatal outcome occurred in 0.1% of 1722 adult patients with NSCLC 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% of patients treated with crizotinib.

Increases to Grade 3 or 4 ALT or AST elevations were observed in 187 (11%) and 95 (6%) of adult 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 4 (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 adult 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 adult 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.

Paediatric patients

In clinical studies of 110 paediatric patients with various tumour types treated with crizotinib, 70% and 75% of patients had increases of AST and ALT, respectively, with Grade 3 and 4 increases in 7% and 6% of patients, respectively.

Gastrointestinal effects

Supportive care should include the use of antiemetic medicinal products. For additional supportive care for paediatric patients, see section 4.4.

Adult patients with NSCLC

Nausea (57%), diarrhoea (54%), vomiting (51%) and constipation (43%) were the most commonly reported all-causality gastrointestinal events in adult patients with either ALK-positive or ROS1-positive NSCLC. 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. 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 of adult patients with NSCLC treated 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).

Paediatric patients

In clinical trials, vomiting (77%), diarrhoea (69%), nausea (71%), abdominal pain (43%) and constipation (31%) were the most frequently reported all-causality gastrointestinal events in 110 paediatric patients with a variety of tumour types treated with crizotinib. For those patients with either ALK-positive ALCL or ALK-positive IMT treated with crizotinib, vomiting (95%), diarrhoea (85%), nausea (83%), abdominal pain (54%) and constipation (34%) were the most frequently reported all-causality gastrointestinal events (see section 4.4). Crizotinib can cause severe gastrointestinal toxicities in paediatric patients with ALCL or IMT (see section 4.4).

QT interval prolongation

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).

Adult patients with NSCLC

Across studies in adult 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 in adult patients (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.

Paediatric patients

In clinical studies with crizotinib in 110 paediatric patients with a variety of tumour types, electrocardiogram QT prolonged was reported in 4% of patients.

Bradycardia

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).

Adult patients with NSCLC

In studies with crizotinib in adult 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.

Paediatric patients

In clinical studies with crizotinib in 110 paediatric patients with a variety of tumour types, all-causality bradycardia was reported in 14% of patients, including Grade 3 bradycardia in 1% of patients.

Interstitial lung disease/pneumonitis

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).

Adult patients with NSCLC

Severe, life-threatening, or fatal ILD/pneumonitis can occur in patients treated with crizotinib. Across studies in adult 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.

Paediatric patients

ILD/pneumonitis was reported in clinical studies with crizotinib in paediatric patients with a variety of tumour types in 1 patient (1%), which was Grade 1 pneumonitis.

Visual effects

Ophthalmological evaluation is recommended if vision disorder persists or worsens in severity. Baseline and follow-up ophthalmologic examinations should be obtained for paediatric patients (see sections 4.2 and 4.4).

Adult patients with NSCLC

In clinical studies with crizotinib in adult 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 adult 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), adult 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 adult 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 adult patients with new onset of Grade 4 visual loss, crizotinib treatment should be discontinued and ophthalmological evaluation should be performed.

Paediatric patients

In clinical studies with crizotinib in 110 paediatric patients with a variety of tumour types, vision disorder has been reported in 48 (44%) patients. The most common visual symptoms were blurred vision (20%) and visual impairment (11%).

In clinical studies with crizotinib, 41 patients with ALK-positive ALCL or ALK-positive IMT, vision disorder has been reported in 25 (61%) patients. Of these paediatric patients who experienced visual disorders, one patient with IMT experienced Grade 3 myopic optic nerve disorder, which was present as Grade 1 at baseline. The most common visual symptoms were blurred vision (24%), visual impairment (20%), photopsia (17%) and vitreous floaters (15%). All were Grade 1 or 2.

Nervous system effects

Adult patients with NSCLC

All-causality neuropathy, as defined in Table 9, was experienced by 435 (25%) out of 1722 adult patients with either ALK-positive or ROS1-positive advanced NSCLC treated with crizotinib. Dysgeusia was also very commonly reported in these studies and was primarily Grade 1 in severity.

Paediatric patients

In clinical studies with crizotinib in 110 paediatric patients with a variety of tumour types, neuropathy and dysgeusia were reported in 26% and 9% of patients, respectively.

Renal cyst

Periodic monitoring with imaging and urinalysis should be considered in patients who develop renal cysts.

Adult patients with NSCLC

All-causality complex renal cysts were experienced by 52 (3%) of 1722 adult patients with either ALK-positive or ROS1-positive advanced NSCLC treated with crizotinib. Local cystic invasion beyond the kidney was observed in some patients.

Paediatric patients

In clinical studies with crizotinib in 110 paediatric patients with a variety of tumour types, renal cyst was not reported.

Neutropenia and leukopenia

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.

Adult patients with NSCLC

Across studies in adult 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 adult patients with either ALK-positive or ROS1-positive advanced NSCLC (N=1722), Grade 3 or 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 adult 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.

Paediatric patients

In clinical studies with crizotinib in 110 paediatric patients with a variety of tumour types, neutropenia was reported in 71% of patients, including Grade 3 or 4 neutropenia observed in 58 patients (53%). Febrile neutropenia was experienced by 4 patients (3.6%). Leukopenia was reported in 63% of patients, including Grade 3 or 4 leukopenia observed in 18 patients (16%).

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 yellow card scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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: L01ED01.

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*. *In vitro* studies in 2 ALCL-derived cell lines (SU-DHL-1 and Karpas-299, both containing NPM-ALK) showed that crizotinib was able to induce apoptosis, and in Karpas-299 cells, crizotinib inhibited proliferation and ALK-mediated signaling at clinically achievable doses. *In vivo* data obtained in a

Karpas-299 model showed complete regression of the tumour at a dose of 100 mg/kg once daily.

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 11, and the Kaplan-Meier curves for PFS and OS are shown in Figure 1 and 2, respectively.

Table 11. 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).

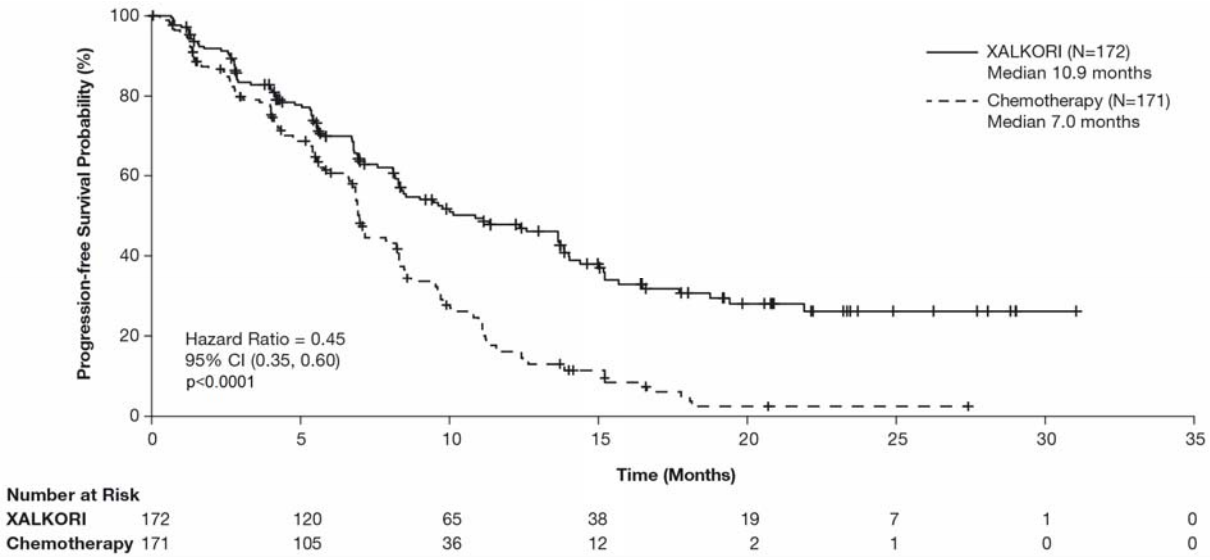
d. Updated based on final OS analysis. OS analysis was not adjusted for the potentially confounding effects of cross over (144 [84%] patients in the chemotherapy arm received subsequent crizotinib treatment).

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).

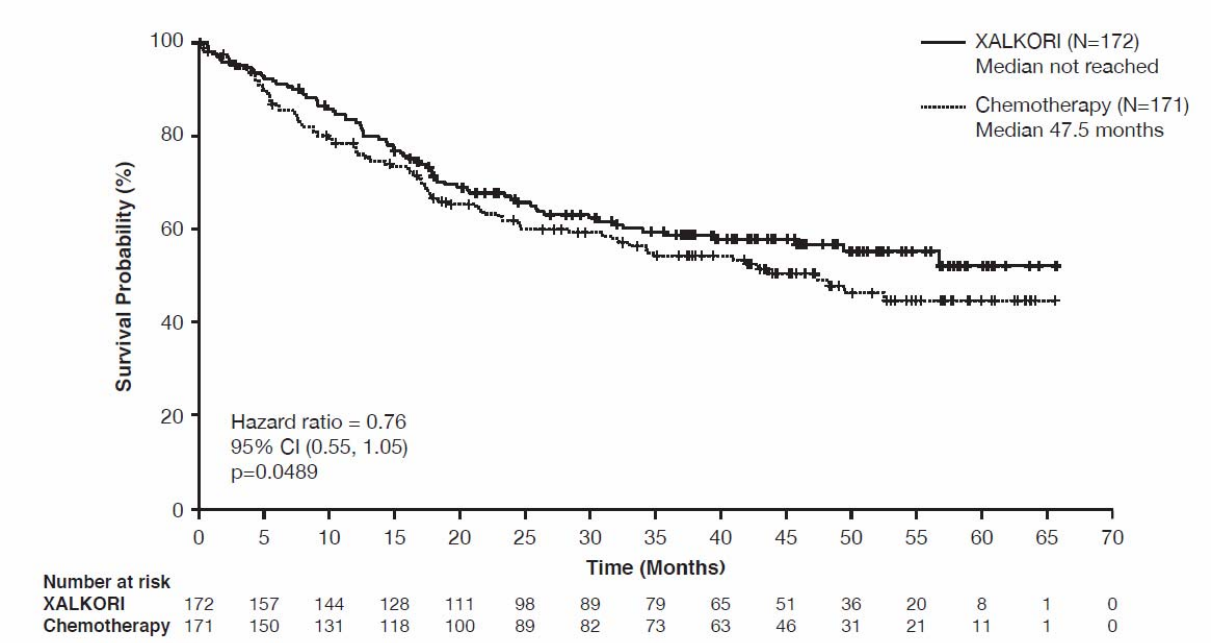
g. Estimated using the Kaplan-Meier method.

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 12, and the Kaplan-Meier curves for PFS and OS are shown in Figures 3 and 4, respectively.

Table 12. 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	
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).

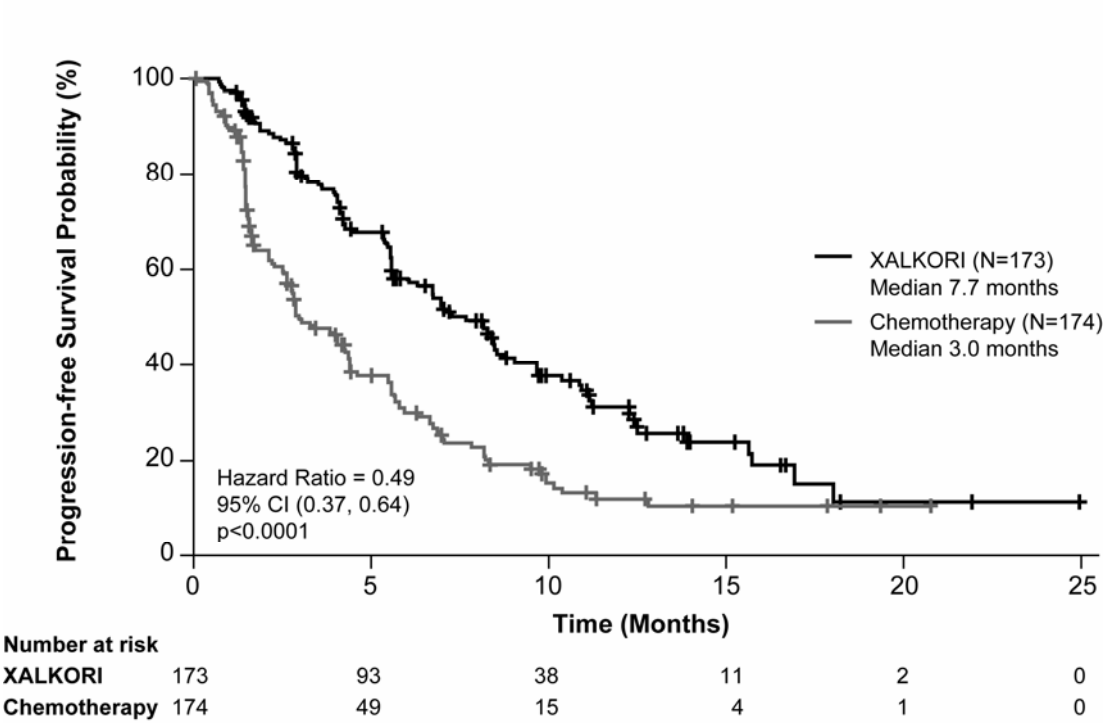
d. Updated based on final OS analysis. Final OS analysis was not adjusted for the potentially confounding effects of crossover (154 [89%] patients received subsequent crizotinib treatment).

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).

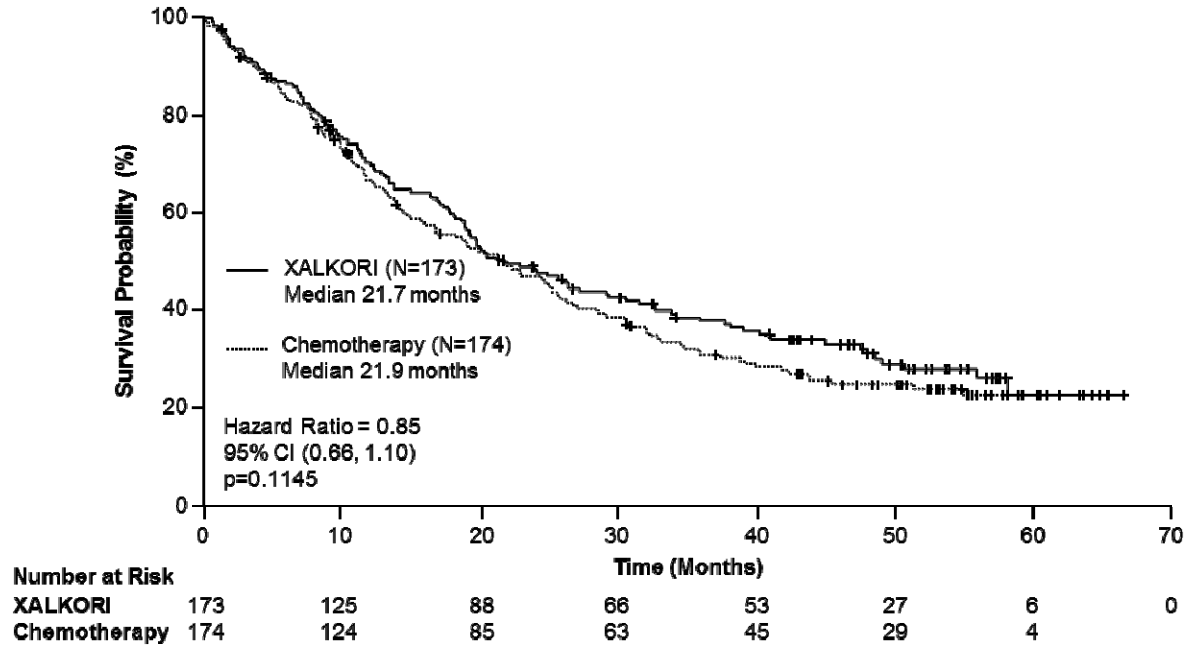
g. Based on the stratified Cochran-Mantel-Haenszel test (2-sided).

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 13.

Table 13. 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 (DoR), 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 DoR 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 14.

Table 14. 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 sections 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 safety and efficacy of crizotinib have been established in paediatric patients with relapsed or refractory systemic ALK-positive ALCL from 3 to <18 years of age or with unresectable, recurrent, or refractory ALK-positive IMT from 2 to <18 years of age (see sections 4.2 and 4.8). There are no safety or efficacy data of crizotinib treatment in ALK-positive ALCL paediatric patients below 3 years of age or ALK-positive IMT paediatric patients below 2 years of age.

Paediatric patients with ALK-Positive ALCL (see sections 4.2 and 5.2)

The use of single-agent crizotinib in the treatment of paediatric patients with relapsed or refractory systemic ALK-positive ALCL was investigated in Study 0912 (n=22). All patients enrolled had received prior systemic treatment for their disease: 14 had 1 prior line of systemic treatment, 6 had 2 prior lines of systemic treatment and 2 had more than 2 prior lines of systemic treatment. Of the 22 patients enrolled in Study 0912, 2 had received a prior bone marrow transplant. No clinical data are currently available on paediatric patients who undergo hematopoietic stem cell transplant (HSCT) following treatment with crizotinib. Patients with primary or metastatic central nervous system (CNS) tumours were excluded from the study. The 22 patients enrolled in Study 0912 received a starting dose of crizotinib at 280 mg/m^2 (16 patients) or 165 mg/m^2 (6 patients) twice daily. Efficacy endpoints from Study 0912 included ORR, TTR and DoR per independent review. The median follow-up time was 5.5 months.

The demographic characteristics were 23% female; median age 11 years; 50% White and 9% Asian. Baseline performance status as measured by Lansky Play Score (patients ≤16 years) or Karnofsky Performance Score (patients >16 years) was

100 (50% of patients) or 90 (27% of patients). Patient enrollment by age was 4 patients from 3 to <6 years, 11 patients from 6 to <12 years and 7 patients from 12 to <18 years. No patients below 3 years of age were enrolled in the study.

Efficacy data as assessed by independent review are provided in Table 15.

Table 15. Systemic ALK-positive ALCL efficacy results from Study 0912

Efficacy Parameter[a]	**N=22**[b]
ORR, [% (95% CI)][c]	86 (67, 95)
Complete response, n (%)	17 (77)
Partial response, n (%)	2 (9)
TTR[d]	
Median (range) months	0.9 (0.8, 2.1)
DoR[d,e]	
Median (range) months	3.6 (0.0, 15.0)

Abbreviations: CI=confidence interval; DoR=duration of response; N/n=number of patients; ORR=objective response rate; TTR=time to tumour response.

a. As assessed by Independent Review Committee using Lugano Classification response criteria.
b. Per data cutoff date 19 Jan 2018.
c. 95% CI based on Wilson score method.
d. Estimated using descriptive statistics.
e. Ten of the 19 (53%) patients proceeded to hematopoietic stem cell transplant after occurrence of an objective response. DoR for patients who underwent transplant was censored at the time of their last tumour assessment prior to transplant.

Paediatric patients with ALK-Positive IMT (see sections 4.2 and 5.2)

The use of single-agent crizotinib in the treatment of paediatric patients with unresectable, recurrent, or refractory ALK-positive IMT was investigated in Study 0912 (n=14). Most patients (12 out of 14) enrolled had received surgery (8 patients) or prior systemic treatment (7 patients: 5 had 1 prior line of systemic treatment, 1 had 2 prior lines of systemic treatment and 1 had more than 2 prior lines of systemic treatment) for their disease. Patients with primary or metastatic CNS tumours were excluded from the study. The 14 patients enrolled in Study 0912 received a starting dose of crizotinib at 280 mg/m^2 (12 patients), 165 mg/m^2 (1 patient) or 100 mg/m^2 (1 patient) twice daily. Efficacy endpoints for Study 0912 included ORR, TTR and DoR per independent review. The median follow-up time was 17.6 months.

The demographic characteristics were 64% female; median age 6.5 years; 71% White. Baseline performance status as measured by Lansky Play Score (patients ≤16 years) or Karnofsky Performance Score (patients >16 years) was 100 (71% of patients), 90 (14% of patients) or 80 (14% of patients). Patient enrollment by age was 4 patients from 2 to <6 years, 8 patients from 6 to <12 years and 2 patients from 12 to <18 years. No patients below 2 years of age were enrolled in the study.

Efficacy data as assessed by independent review are provided in Table 16.

Table 16. ALK-positive IMT efficacy results from Study 0912

Efficacy Parameter[a]	**N=14**[b]
ORR, [% (95% CI)][c]	86 (60, 96)
Complete response, n (%)	5 (36)
Partial response, n (%)	7 (50)
TTR[d]	
Median (range) months	1.0 (0.8, 4.6)
DoR[d,e]	
Median (range) months	14.8 (2.8, 48.9)

Abbreviations: CI=confidence interval; DoR=duration of response; N/n=number of patients; ORR=objective response rate; TTR=time to tumour response.

a. As assessed by Independent Review Committee.
b. Per data cutoff date 19 Jan 2018.
c. 95% CI based on Wilson score method.
d. Estimated using descriptive statistics.
e. None of the 12 patients with objective tumour response had follow-up disease progression, and their DoR was censored at the time of the last tumour assessment.

Paediatric patients with ALK-positive or ROS1-positive NSCLC

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

Pharmacokinetic properties of crizotinib were characterised in adults unless otherwise specifically indicated in paediatric patients.

Absorption

XALKORI 200 mg and 250 mg hard capsules

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).

XALKORI granules in capsules for opening

Following oral single-dose administration in the fasted state, the crizotinib granules in capsules for opening are bioequivalent to crizotinib capsules.

The crizotinib oral granules in capsules for opening administered with a high-fat/high-calorie meal reduced crizotinib AUC_{inf} and C_{max} by approximately 15% and 23%, respectively, compared to the same formulation administered under fasted conditions. Crizotinib granules in capsules for opening 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 Bile Salt Export Pump (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).

Paediatric population for cancer patients

At a dosing regimen of 280 mg/m^2 twice daily (approximately 2 times the recommended adult dose), observed crizotinib predose concentration (C_{trough}) at steady state is similar regardless of body weight quartiles. The observed mean C_{trough} at steady state in paediatric patients at 280 mg/m^2 twice daily is 482 ng/mL, while observed mean C_{trough} at steady state in adult cancer patients at 250 mg twice daily across different clinical studies ranged from 263 to 316 ng/mL.

In paediatric patients, body weight has a significant effect on the pharmacokinetics of crizotinib with lower crizotinib exposures observed in patients with higher body weight.

Age

Based on the population pharmacokinetic analysis of adult 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 adult 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 1.3-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 No Observed Effect Levels (NOEL) for aneugenicity was approximately 1.8- to 2.1-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- to 1.3-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 to 0.5 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- to 2.0-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 to 3.9 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

Granules content

Stearyl alcohol

Poloxamer

Sucrose

Talc (E553b)

Hypromellose (E464)

Macrogol (E1521)

Glyceryl monostearate (E471)

Medium chain triglycerides

Capsule shell

Gelatin

Titanium dioxide (E171)

Brilliant blue (E133) or Black iron oxide (E172)

Printing ink

Shellac (E904)

Propylene glycol (E1520)

Potassium hydroxide (E525)

Black iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store below 25 ^{o}C.

6.5 Nature and contents of container

XALKORI granules are supplied in high density polyethylene (HDPE) bottles with a polypropylene child-resistant (CR) closure and an aluminum foil/polyethylene heat induction seal containing 60 capsules for opening.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused product or waste material, e.g., capsule shell from granules in capsule for opening formulation, should be disposed of in accordance with local requirements. The empty XALKORI granules capsule shell(s) should be discarded in the household waste.

7 MARKETING AUTHORISATION HOLDER

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CT13 9NJ

United Kingdom

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