ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Zykadia 150 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 150 mg ceritinib.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

Capsule with white opaque body and blue opaque cap, size 00 (approximate length: 23.3 mm), with "LDK 150MG" imprinted on the cap and "NVR" on the body, containing white to almost white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Zykadia as monotherapy is indicated for the first-line treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC).

Zykadia as monotherapy is indicated for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously treated with crizotinib.

4.2 Posology and method of administration

Treatment with ceritinib should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products.

ALK testing

An accurate and validated ALK assay is necessary for the selection of ALK-positive NSCLC patients (see section 5.1).

ALK-positive NSCLC status should be established prior to initiation of ceritinib therapy. Assessment for ALK-positive NSCLC should be performed by laboratories with demonstrated proficiency in the specific technology being utilised.

Posology

The recommended dose of ceritinib is 450 mg taken orally once daily with food at the same time each day.

The maximum recommended dose with food is 450 mg taken orally once daily. Treatment should continue as long as clinical benefit is observed.

If a dose is missed, the patient should make up that dose, unless the next dose is due within 12 hours.

If vomiting occurs during the course of treatment, the patient should not take an additional dose, but should continue with the next scheduled dose.

Ceritinib should be discontinued in patients unable to tolerate 150 mg daily taken with food.

Dose adjustment due to adverse reactions
Temporary dose interruption and/or dose reduction of ceritinib may be required based on individual safety and tolerability. If dose reduction is required due to an adverse drug reaction (ADR) not listed in Table 1, then this should be achieved by decrements of 150 mg daily. Early identification and management of ADRs with standard supportive care measures should be considered.

In patients treated with ceritinib 450 mg with food, 24.1% of patients had an adverse event that required at least one dose reduction and 55.6% of patients had an adverse event that required at least one dose interruption. The median time to first dose reduction due to any reason was 9.7 weeks.

Table 1 summarises recommendations for dose interruption, reduction or discontinuation of ceritinib in the management of selected ADRs.

Table 1 Ceritinib dose adjustment and management recommendations for ADRs

Criteria	**Ceritinib dosing**
Severe or intolerable nausea, vomiting or diarrhoea despite optimal anti-emetic or anti-diarrhoeal therapy	Withhold ceritinib until improved, then reinitiate ceritinib with dose reduced by 150 mg.
Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevation >5 times upper limit of normal (ULN) with concurrent total bilirubin ≤2 times ULN	Withhold ceritinib until recovery to baseline ALT/AST levels or to ≤3 times ULN, then reinitiate with dose reduced by 150 mg.
ALT or AST elevation >3 times ULN with concurrent total bilirubin elevation >2 times ULN (in the absence of cholestasis or haemolysis)	Permanently discontinue ceritinib.
Any grade treatment-related interstitial lung disease (ILD)/pneumonitis	Permanently discontinue ceritinib.
QT corrected for heart rate (QTc) >500 msec on at least 2 separate electrocardiograms (ECGs)	Withhold ceritinib until recovery to baseline or to a QTc ≤480 msec, check and if necessary correct electrolytes, then reinitiate with dose reduced by 150 mg.
QTc >500 msec or >60 msec change from baseline and torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia	Permanently discontinue ceritinib.

Bradycardia[a] (symptomatic, may be severe and medically significant, medical intervention indicated)	Withhold ceritinib until recovery to asymptomatic (grade ≤1) bradycardia or to a heart rate of 60 beats per minute (bpm) or above. Evaluate concomitant medicinal products known to cause bradycardia, as well as anti-hypertensive medicinal products. If a contributing concomitant medicinal product is identified and discontinued, or its dose is adjusted, reinitiate ceritinib at the previous dose upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above. If no contributing concomitant medicinal product is identified, or if contributing concomitant medicinal products are not discontinued or dose modified, reinitiate ceritinib with dose reduced by 150 mg upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above.
Bradycardia[a] (life-threatening consequences, urgent intervention indicated)	Permanently discontinue ceritinib if no contributing concomitant medicinal product is identified. If a contributing concomitant medicinal product is identified and discontinued, or its dose is adjusted, reinitiate ceritinib with dose reduced by 150 mg upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, with frequent monitoring[b].
Persistent hyperglycaemia greater than 250 mg/dl despite optimal anti-hyperglycaemic therapy	Withhold ceritinib until hyperglycaemia is adequately controlled, then reinitiate ceritinib with dose reduced by 150 mg. If adequate glucose control cannot be achieved with optimal medical management, permanently discontinue ceritinib.
Lipase or amylase elevation grade ≥3	Withhold ceritinib until lipase or amylase returns to grade ≤1, then reinitiate with dose reduced by 150 mg.
[a] Heart rate less than 60 beats per minutes (bpm) [b] Permanently discontinue in the event of recurrence	

Strong CYP3A inhibitors
Concomitant use of strong CYP3A inhibitors should be avoided (see section 4.5). If concomitant use of a strong CYP3A inhibitor is unavoidable, the dose of ceritinib should be reduced by approximately one third (dose not clinically verified), rounded to the nearest multiple of the 150 mg dose strength. Patients should be carefully monitored for safety.

If long-term concomitant treatment with a strong CYP3A inhibitor is necessary and the patient tolerates the reduced dose well, the dose may be increased again with careful monitoring for safety, to avoid potential under-treatment.

After discontinuation of a strong CYP3A inhibitor, resume at the dose that was taken prior to initiating the strong CYP3A inhibitor.

CYP3A substrates
When ceritinib is co-administered with other medicinal products, the Summary of Product Characteristics (SmPC) for the other product must be consulted for the recommendations regarding co-administration with CYP3A4 inhibitors.

Co-administration of ceritinib with substrates primarily metabolised by CYP3A or CYP3A substrates known to have narrow therapeutic indices (e.g. alfuzosin, amiodarone, cisapride, ciclosporin, dihydroergotamine, ergotamine, fentanyl, pimozide, quetiapine, quinidine, lovastatin, simvastatin, sildenafil, midazolam, triazolam, tacrolimus, alfentanil and sirolimus) should be avoided and alternative medicinal products that are less sensitive to CYP3A4 inhibition should be used if possible. If unavoidable, dose reduction for co-administered medicinal products that are CYP3A substrates with narrow therapeutic indices should be considered.

Special populations

Renal impairment
A dedicated pharmacokinetic study in patients with renal impairment has not been conducted. However, based on available data, ceritinib elimination via the kidney is negligible. Therefore, no dose adjustment is necessary in patients with mild to moderate renal impairment. Caution should be used in patients with severe renal impairment, as there is no experience with ceritinib in this population (see section 5.2).

Hepatic impairment
Based on available data, ceritinib is eliminated primarily via the liver. Particular caution should be exercised when treating patients with severe hepatic impairment and the dose should be reduced by approximately one third, rounded to the nearest multiple of the 150 mg dose strength (see sections 4.4 and 5.2). No dose adjustment is necessary in patients with mild or moderate hepatic impairment.

Elderly (≥65 years)
The limited data on the safety and efficacy of ceritinib in patients aged 65 years and older do not suggest that a dose adjustment is required in elderly patients (see section 5.2). There are no available data on patients over 85 years of age.

Paediatric population
The safety and efficacy of ceritinib in children and adolescents aged up to 18 years have not been established. No data are available.

Method of administration

Ceritinib is for oral use. The capsules should be administered orally once daily with food at the same time every day. It is important that ceritinib is taken with food to reach the appropriate exposure. Food can range from a light to a full meal (see section 5.2). The capsules should be swallowed whole with water and should not be chewed or crushed.

For patients who develop a concurrent medical condition and are unable to take ceritinib with food please refer to section 4.5.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Hepatotoxicity

Cases of hepatotoxicity occurred in 1.1% of patients receiving ceritinib in clinical studies. Increases to grade 3 or 4 ALT elevations were observed in 25% of patients. The majority of cases were manageable with dose interruption and/or dose reduction. Few events required discontinuation of treatment.

Patients should be monitored with liver laboratory tests (including ALT, AST and total bilirubin) prior to the start of treatment, every 2 weeks during the first three months of treatment and monthly thereafter. In patients who develop transaminase elevations, more frequent monitoring of liver transaminases and total bilirubin should be carried out as clinically indicated (see sections 4.2 and 4.8). Particular caution should be exercised when treating patients with severe hepatic impairment, and the dose should be adjusted (see section 4.2). Limited experience in these patients showed a worsening of the underlying condition (hepatic encephalopathy) in 2 out of 10 patients exposed to 750 mg single doses of ceritinib under fasted conditions (see sections 4.2, 4.8 and 5.2). Other factors apart from study treatment could have impacted on observed events of hepatic encephalopathy, however, the relation between study treatment and events cannot be fully ruled out. No dose adjustment is necessary in patients with mild or moderate hepatic impairment (see section 4.2).

Interstitial lung disease/Pneumonitis

Severe, life-threatening or fatal ILD/pneumonitis have been observed in patients treated with ceritinib in clinical studies. Most of these severe/life-threatening cases improved or resolved with interruption of treatment.

Patients should be monitored for pulmonary symptoms indicative of ILD/pneumonitis. Other potential causes of ILD/pneumonitis should be excluded, and ceritinib should be permanently discontinued in patients diagnosed with any grade 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 ceritinib (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.

Use of ceritinib in patients with congenital long QT syndrome should be avoided. The benefits and potential risks of ceritinib should be considered before beginning therapy in patients who have pre-existing bradycardia (heart rate less than 60 beats per minute [bpm]), patients who have a history of or predisposition for QTc prolongation, patients who are taking anti-arrhythmics or other medicinal products that are known to prolong the QT interval and patients with relevant pre-existing cardiac disease and/or electrolyte disturbances. Periodic monitoring with ECGs and periodic monitoring of electrolytes (e.g. potassium) is recommended in these patients. In the event of vomiting, diarrhoea, dehydration or impaired renal function, correct electrolytes as clinically indicated. Ceritinib should be permanently discontinued in patients who develop QTc >500 msec or >60 msec change from baseline and torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia. Ceritinib should be withheld in patients who develop QTc >500 msec on at least two separate ECGs until recovery to baseline or a QTc ≤480 msec, then reinitiated with dose reduced by 150 mg (see sections 4.2, 4.8 and 5.2).

Bradycardia

Asymptomatic cases of bradycardia (heart rate less than 60 bpm) have been observed in 21 out of 925 (2.3%) patients treated with ceritinib in clinical studies.

Use of ceritinib in combination with other agents known to cause bradycardia (e.g. beta blockers, non-dihydropyridine calcium channel blockers, clonidine and digoxin) should be avoided as far as possible. Heart rate and blood pressure should be monitored regularly. In cases of symptomatic bradycardia that is not life-threatening, ceritinib should be withheld until recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, the use of concomitant medicinal products should be evaluated and the ceritinib dose adjusted if necessary. In the event of life-threatening bradycardia ceritinib should be permanently discontinued if no contributing concomitant medicinal product is identified; however, if associated with a concomitant medicinal product known to cause bradycardia or hypotension, ceritinib should be withheld until recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above. If the concomitant medicinal product can be adjusted or discontinued, ceritinib should be reinitiated with dose reduced by 150 mg on recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, with frequent monitoring (see sections 4.2 and 4.8).

Gastrointestinal adverse reactions

Diarrhoea, nausea, or vomiting occurred in 76.9% of 108 patients treated with ceritinib at the recommended dose of 450 mg taken with food in a dose optimisation study and were mainly grade 1 (52.8%) and grade 2 (22.2%) events. Two patients (1.9%) experienced one grade 3 event each (diarrhoea and vomiting respectively). Nine patients (8.3%) required study drug interruption due to diarrhoea, nausea or vomiting. One patient (0.9%) required dose adjustment due to vomiting. In the same study, the incidence and severity of gastrointestinal adverse drug reactions were higher for patients treated with ceritinib 750 mg fasted (diarrhoea 80.0%, nausea 60.0%, vomiting 65.5%; 17.3% reported a grade 3 event) compared to 450 mg with food (diarrhoea 59.3%, nausea 42.6%, vomiting 38.0%; 1.9% reported a grade 3 event).

In the 450 mg with food and 750 mg fasted arms of this dose optimisation study, no patients required discontinuation of ceritinib due to diarrhoea, nausea or vomiting (see section 4.8).

Patients should be monitored and managed using standards of care, including anti-diarrhoeals, anti-emetics or fluid replacement, as clinically indicated. Dose interruption and dose reduction should be employed as necessary (see sections 4.2 and 4.8). If vomiting occurs during the course of treatment, the patient should not take an additional dose, but should continue with the next scheduled dose.

Hyperglycaemia

Cases of hyperglycaemia (all grades) have been reported in less than 10% of patients treated with ceritinib in clinical studies; grade 3-4 hyperglycaemia was reported in 5.4% of patients. The risk of hyperglycaemia was higher in patients with diabetes mellitus and/or concurrent steroid use.

Patients should be monitored for fasting plasma glucose prior to the start of ceritinib treatment and periodically thereafter as clinically indicated. Anti-hyperglycaemic medicinal products should be initiated or optimised as indicated (see sections 4.2 and 4.8).

Lipase and/or amylase elevations

Elevations of lipase and/or amylase have occurred in patients treated with ceritinib in clinical studies. Patients should be monitored for lipase and amylase elevations prior to the start of ceritinib treatment and periodically thereafter as clinically indicated (see sections 4.2 and 4.8). Cases of pancreatitis have been reported in patients treated with ceritinib (see section 4.8).

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially “sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

Agents that may increase ceritinib plasma concentrations

Strong CYP3A inhibitors
In healthy subjects, co-administration of a single 450 mg fasted ceritinib dose with ketoconazole (200 mg twice daily for 14 days), a strong CYP3A/P-gp inhibitor, resulted in 2.9-fold and 1.2-fold increase in ceritinib AUC_{inf} and C_{max}, respectively, compared to when ceritinib was given alone. The steady-state AUC of ceritinib at reduced doses after co-administration with ketoconazole 200 mg twice daily for 14 days was predicted by simulations to be similar to the steady-state AUC of ceritinib alone. Concomitant use of strong CYP3A inhibitors should be avoided during treatment with ceritinib. If it is not possible to avoid concomitant use with strong CYP3A inhibitors (including, but not limited to, ritonavir, saquinavir, telithromycin, ketoconazole, itraconazole, voriconazole, posaconazole and nefazodone), the dose of ceritinib should be reduced by approximately one third, rounded to the nearest multiple of the 150 mg dose strength. After discontinuation of a strong CYP3A inhibitor, ceritinib should be resumed at the dose that was taken prior to initiating the strong CYP3A inhibitor.

P-gp inhibitors
Based on *in vitro* data, ceritinib is a substrate of the efflux transporter P-glycoprotein (P-gp). If ceritinib is administered with medicinal products that inhibit P-gp, an increase in ceritinib concentration is likely. Caution should be exercised with concomitant use of P-gp inhibitors and ADRs carefully monitored.

Agents that may decrease ceritinib plasma concentrations

Strong CYP3A and P-gp inducers
In healthy subjects, co-administration of a single 750 mg fasted ceritinib dose with rifampicin (600 mg daily for 14 days), a strong CYP3A/P-gp inducer, resulted in 70% and 44% decreases in ceritinib AUC_{inf} and C_{max}, respectively, compared to when ceritinib was given alone. Co-administration of ceritinib with strong CYP3A/P-gp inducers decreases ceritinib plasma concentrations. Concomitant use of strong CYP3A inducers should be avoided; this includes, but is not limited to, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampicin and St. John's Wort (*Hypericum perforatum*). Caution should be exercised with concomitant use of P-gp inducers.

Agents that affect gastric pH
Ceritinib demonstrates pH-dependent solubility and becomes poorly soluble as pH increases *in vitro*. Acid reducing agents (e.g., proton pump inhibitors, H_2-receptor antagonists, antacids) can alter the solubility of ceritinib and reduce its bioavailability. Co-administration of a single 750 mg fasted ceritinib dose with a proton pump inhibitor (esomeprazole) 40 mg daily for 6 days in healthy, fasting subjects decreased ceritinib AUC by 76% and C_{max} by 79%. The drug-drug interaction study was designed to observe the impact of proton pump inhibitor in the worst scenario, but in clinical use the impact of proton pump inhibitor on ceritinib exposure appears to be less pronounced. A dedicated study to evaluate the effect of gastric acid-reducing agents on the bioavailability of ceritinib under steady state has not been conducted. Caution is advised with concomitant use of proton pump inhibitors, as exposure of ceritinib may be reduced. There is no data with concomitant use of H_2 blockers or antacids. However, the risk for a clinically relevant decrease in bioavailability of ceritinib is possibly lower with concomitant use of H_2 blockers if they are administered 10 hours before or 2 hours after the ceritinib dose, and with antacids if they are administered 2 hours before or 2 hours after the ceritinib dose.

Agents whose plasma concentration may be altered by ceritinib

CYP3A and CYP2C9 substrates
Based on *in vitro* data, ceritinib competitively inhibits the metabolism of a CYP3A substrate, midazolam, and a CYP2C9 substrate, diclofenac. Time-dependent inhibition of CYP3A was also observed.

Ceritinib has been classified *in vivo* as a strong CYP3A4 inhibitor and has the potential to interact with medicinal products that are metabolised by CYP3A, which may lead to increased serum concentrations of the other product. Co-administration of a single dose of midazolam (a sensitive CYP3A substrate) following 3 weeks of ceritinib dosing in patients (750 mg daily fasted) increased the midazolam AUC_{inf} (90% CI) by 5.4-fold (4.6, 6.3) compared to midazolam alone.
Co-administration of ceritinib with substrates primarily metabolised by CYP3A or CYP3A substrates known to have narrow therapeutic indices (e.g. alfuzosin, amiodarone, cisapride, ciclosporin, dihydroergotamine, ergotamine, fentanyl, pimozide, quetiapine, quinidine, lovastatin, simvastatin, sildenafil, midazolam, triazolam, tacrolimus, alfentanil and sirolimus) should be avoided and alternative medicinal products that are less sensitive to CYP3A4 inhibition should be used if possible. If unavoidable, dose reduction for co-administered medicinal products that are CYP3A substrates with narrow therapeutic indices should be considered.

Ceritinib has been classified *in vivo* as a weak CYP2C9 inhibitor. Co-administration of a single dose of warfarin (a CYP2C9 substrate) following 3 weeks of ceritinib dosing in patients (750 mg daily fasted) increased the S-warfarin AUC_{inf} (90% CI) by 54% (36%, 75%) compared to warfarin alone. Co-administration of ceritinib with substrates primarily metabolised by CYP2C9 or CYP2C9 substrates known to have narrow therapeutic indices (e.g. phenytoin and warfarin) should be avoided. If unavoidable, dose reduction for co-administered medicinal products that are CYP2C9 substrates with narrow therapeutic indices should be considered. Increasing the frequency of international normalised ratio (INR) monitoring may be considered if co-administration with warfarin is unavoidable.

CYP2A6 and CYP2E1 substrates
Based on *in vitro* data, ceritinib also inhibits CYP2A6 and CYP2E1 at clinically relevant concentrations. Therefore, ceritinib may have the potential to increase plasma concentrations of co-administered medicinal products that are predominantly metabolised by these enzymes. Caution should be exercised with concomitant use of CYP2A6 and CYP2E1 substrates and ADRs carefully monitored.

A risk for induction of other PXR regulated enzymes apart from CYP3A4 cannot be completely excluded. The effectiveness of concomitant administration of oral contraceptives may be reduced.

Agents that are substrates of transporters

Based on *in vitro* data, ceritinib does not inhibit apical efflux transporter MRP2, hepatic uptake transporters OATP1B1 or OATP1B3, renal organic anion uptake transporters OAT1 and OAT3, or the organic cation uptake transporters OCT1 or OCT2 at clinically relevant concentrations. Therefore, clinical drug-drug interactions as a result of ceritinib-mediated inhibition of substrates for these transporters are unlikely to occur. Based on *in vitro* data, ceritinib is predicted to inhibit intestinal P-gp and BCRP at clinically relevant concentrations. Therefore, ceritinib may have the potential to increase plasma concentrations of co-administered medicinal products transported by these proteins. Caution should be exercised with concomitant use of BCRP substrates (e.g. rosuvastatin, topotecan, sulfasalazine) and P-gp substrates (digoxin, dabigatran, colchicine, pravastatin) and ADRs carefully monitored.

Pharmacodynamic interactions

In clinical studies, QT prolongation was observed with ceritinib. Therefore, ceritinib should be used with caution in patients who have or may develop prolongation of the QT interval, including those patients taking anti-arrhythmic medicinal products such as class I (e.g. quinidine, procainamide, disopyramide) or class III (e.g. amiodarone, sotalol, dofetilide, ibutilide) anti-arrhythmics or other medicinal products that may lead to QT prolongation such as domperidone, droperidol, chloroquine, halofantrine, clarithromycin, haloperidol, methadone, cisapride and moxifloxacin. Monitoring of the QT interval is indicated in the event of combinations of such medicinal products (see sections 4.2 and 4.4).

Food/drink interactions

Ceritinib should be taken with food. The bioavailability of ceritinib is increased in the presence of food.

For patients who develop a concurrent medical condition and are unable to take ceritinib with food, ceritinib can be taken on an empty stomach as the alternate continued treatment regimen, in which no food should be eaten for at least two hours before and one hour after the dose. Patients should not alternate between fasted and fed dosing. Dose must be adjusted properly, i.e for patients treated with 450 mg or 300 mg with food, the dose should be increased to 750 mg or 450 mg taken on an empty stomach, respectively (see section 5.2) and for patients treated with 150 mg with food treatment should be discontinued. For subsequent dose adjustment and management recommendations for ADRs, please follow table 1 (see section 4.2). The maximum allowable dose under fasted condition is 750 mg (see section 5.2).

Patients should be instructed to avoid grapefruit and grapefruit juice as they may inhibit CYP3A in the gut wall and may increase the bioavailability of ceritinib.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception

Women of childbearing potential should be advised to use a highly effective method of contraception while taking ceritinib and for up to 3 months after discontinuing treatment (see section 4.5).

Pregnancy

There are no or limited amount of data from the use of ceritinib in pregnant women.

Animal studies are insufficient with respect to reproductive toxicity (see section 5.3).

Ceritinib should not be used during pregnancy unless the clinical condition of the woman requires treatment with ceritinib.

Breast-feeding

It is unknown whether ceritinib/metabolites are excreted in human milk. A risk to the newborn/infant cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from ceritinib therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman (see section 5.3).

Fertility

The potential for ceritinib to cause infertility in male and female patients is unknown (see section 5.3).

4.7 Effects on ability to drive and use machines

Zykadia has minor influence on the ability to drive or use machines. Caution should be exercised when driving or using machines during treatment as patients may experience fatigue or vision disorders.

4.8 Undesirable effects

Summary of the safety profile

Adverse drug reactions (ADRs) described below reflect exposure to ceritinib 750 mg once daily fasted in 925 patients with ALK-positive advanced NSCLC across a pool of seven clinical studies including two randomised, active-controlled, phase 3 studies (studies A2301 and A2303).

The median duration of exposure to ceritinib 750 mg fasted was 44.9 weeks (range: 0.1 to 200.1 weeks).

ADRs with an incidence of ≥10% in patients treated with ceritinib 750 mg fasted were diarrhoea, nausea, vomiting, fatigue, liver laboratory test abnormalities, abdominal pain, decreased appetite, weight decreased, constipation, blood creatinine increased, rash, anaemia and oesophageal disorder.

Grade 3-4 ADRs with an incidence of ≥5% in patients treated with ceritinib 750 mg fasted were liver laboratory test abnormalities, fatigue, vomiting, hyperglycaemia, nausea and diarrhoea.

In the dose optimisation study A2112 (ASCEND-8) in both previously treated and untreated patients with ALK-positive advanced NSCLC, the overall safety profile of ceritinib at the recommended dose of 450 mg with food (N=108) was consistent with ceritinib 750 mg fasted (N=110), except for a reduction in gastrointestinal adverse drug reactions, while achieving comparable steady-state exposure (see section 5.1 and subsection 'Gastrointestinal adverse reactions' below).

Tabulated list of ADRs

Table 2 shows the frequency category of ADRs reported for ceritinib in patients treated at a dose of 750 mg fasted (N=925) in seven clinical studies. The frequency of selected gastrointestinal ADRs (diarrhoea, nausea and vomiting) are based on patients treated with a dose of 450 mg once-daily with food (N=108).

ADRs are listed according to MedDRA system organ class. Within each system organ class, the ADRs are ranked by frequency, with the most frequent reactions first. In addition, the corresponding frequency category using the following convention (CIOMS III) is also provided for each ADR: 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); and not known (cannot be estimated from the available data). Within each frequency grouping, ADRs are presented in the order of decreasing seriousness.

Table 2 ADRs in patients treated with ceritinib

System organ class	Ceritinib N=925 %	Frequency category
Blood and lymphatic system disorders		
Anaemia	15.2	Very common
Metabolism and nutrition disorders		
Decreased appetite	39.5	Very common
Hyperglycaemia	9.4	Common
Hypophosphataemia	5.3	Common
Eye disorders		
Vision disorder[a]	7.0	Common
Cardiac disorders		
Pericarditis[b]	5.8	Common
Bradycardia[c]	2.3	Common
Respiratory, thoracic and mediastinal disorders		
Pneumonitis[d]	2.1	Common

Gastrointestinal disorders		
Diarrhoea[e]	59.3	Very common
Nausea[e]	42.6	Very common
Vomiting[e]	38.0	Very common
Abdominal pain[f]	46.1	Very common
Constipation	24.0	Very common
Oesophageal disorder[g]	14.1	Very common
Pancreatitis	0.5	Uncommon
Hepatobiliary disorders		
Abnormal liver function tests[h]	2.2	Common
Hepatotoxicity[i]	1.1	Common
Skin and subcutaneous tissue disorders		
Rash[j]	19.6	Very common
Renal and urinary disorders		
Renal failure[k]	1.8	Common
Renal impairment[l]	1.0	Common
General disorders and administration site conditions		
Fatigue[m]	48.4	Very common
Investigations		
Liver laboratory test abnormalities[n]	60.5	Very common
Weight decreased	27.6	Very common
Blood creatinine increased	22.1	Very common
Electrocardiogram QT prolonged	9.7	Common
Lipase increased	4.8	Common
Amylase increased	7.0	Common

Includes cases reported within the clustered terms:

[a] Vision disorder (vision impairment, vision blurred, photopsia, vitreous floaters, visual acuity reduced, accommodation disorder, presbyopia)

[b] Pericarditis (pericardial effusion, pericarditis)

[c] Bradycardia (bradycardia, sinus bradycardia)

[d] Pneumonitis (interstitial lung disease, pneumonitis)

[e] The frequency of these selected gastrointestinal ADRs (diarrhoea, nausea and vomiting) is based on patients treated with the recommended dose of ceritinib 450 mg with food (N=108) in the study A2112 (ASCEND-8) (see subsection 'Gastrointestinal adverse reactions' below)

[f] Abdominal pain (abdominal pain, abdominal pain upper, abdominal discomfort, epigastric discomfort)

[g] Oesophageal disorder (dyspepsia, gastro-oesophageal reflux disease, dysphagia)

[h] Abnormal liver function test (hepatic function abnormal, hyperbilirubinaemia)

[i] Hepatotoxicity (drug-induced liver injury, hepatitis cholestatic, hepatocellular injury, hepatotoxicity)

[j] Rash (rash, dermatitis acneiform, rash maculopapular)

[k] Renal failure (acute renal injury, renal failure)

[l] Renal impairment (azotaemia, renal impairment)

[m] Fatigue (fatigue, asthenia)

[n] Liver laboratory test abnormalities (alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased, blood bilirubin increased, transaminases increased, hepatic enzyme increased, liver function test abnormal, liver function test increased, blood alkaline phosphatase increased)

Elderly (≥65 years)

Across seven clinical studies, 168 out of 925 patients (18.2%) treated with ceritinib were aged 65 years or older. The safety profile in patients aged 65 years or older was similar to that in patients less than 65 years of age (see section 4.2). There are no safety data in patients older than 85 years of age.

Hepatotoxicity

Concurrent elevations of ALT or AST greater than 3× ULN and total bilirubin greater than 2× ULN without elevated alkaline phosphatase have been observed in less than 1% of patients in clinical studies with ceritinib. Increases to grade 3 or 4 ALT elevations were observed in 25% of patients receiving ceritinib. Hepatotoxicity events were managed with dose interruptions or reductions in 40.6% of patients. 1% of patients required permanent discontinuation of treatment in clinical studies with ceritinib (see sections 4.2 and 4.4).

Liver laboratory tests including ALT, AST and total bilirubin should be performed prior to the start of treatment, every 2 weeks during the first three months of treatment and monthly thereafter, with more frequent testing for grade 2, 3 or 4 elevations. Patients should be monitored for liver laboratory test abnormalities and managed as recommended in sections 4.2 and 4.4.

Gastrointestinal adverse reactions

Nausea, diarrhoea and vomiting were among the most commonly reported gastrointestinal events. In the dose optimisation study A2112 (ASCEND-8) in both previously treated and untreated patients with ALK-positive advanced NSCLC at the recommended dose of ceritinib 450 mg taken with food (N=108), adverse events of diarrhoea, nausea and vomiting were mainly grade 1 (52.8%) and grade 2 (22.2%). Grade 3 events of diarrhoea and vomiting were each reported in two different patients (1.9%). Gastrointestinal events were managed primarily with concomitant medicinal products including anti-emetic/anti-diarrhoeal medicinal products. Nine patients (8.3%) required study drug interruption due to diarrhoea, nausea or vomiting. One patient (0.9%) required dose adjustment. In the 450 mg with food and 750 mg fasted arms, no patients had diarrhoea, nausea, or vomiting that required discontinuation of study drug. In the same study the incidence and severity of gastrointestinal adverse drug reactions were reduced for patients treated with ceritinib 450 mg with food (diarrhoea 59.3%, nausea 42.6%, vomiting 38.0%; 1.9% reported a grade 3 event) compared to 750 mg fasted (diarrhoea 80.0%, nausea 60.0%, vomiting 65.5%; 17.3% reported a grade 3 event). Patients should be managed as recommended in sections 4.2 and 4.4.

QT interval prolongation

QTc prolongation has been observed in patients treated with ceritinib. Across the seven clinical studies, 9.7% of patients treated with ceritinib had events of QT prolongation (any grade), including grade 3 or 4 events in 2.1% of patients. These events required dose reduction or interruption in 2.1% of patients and led to discontinuation in 0.2% of patients.

Treatment with ceritinib is not recommended in patients who have congenital long QT syndrome or who are taking medicinal products known to prolong the QTc interval (see sections 4.4 and 4.5). Particular care should be exercised when administering ceritinib to patients with an increased risk of experiencing torsade de pointes during treatment with a QTc-prolonging medicinal product.

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

Bradycardia

Across the seven clinical studies, bradycardia and/or sinus bradycardia (heart rate less than 60 bpm) events (all grade 1) were reported in 2.3% of patients. These events required dose reduction or interruption in 0.2% of patients. None of these events led to discontinuation of ceritinib treatment. The use of concomitant medicinal products associated with bradycardia should be carefully evaluated. Patients who develop symptomatic bradycardia should be managed as recommended in sections 4.2 and 4.4.

Interstitial lung disease/Pneumonitis

Severe, life-threatening, or fatal interstitial lung disease (ILD)/pneumonitis have been observed in patients treated with ceritinib. Across the seven clinical studies, any grade ILD/pneumonitis has been reported in 2.1% of patients treated with ceritinib, and grade 3 or 4 events have been reported in 1.2% of patients. These events required dose reduction or interruption in 1.1% of patients and led to discontinuation in 0.9% of patients. 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).

Hyperglycaemia

Hyperglycaemia (all grades) was reported in 9.4% of patients treated with ceritinib across the seven clinical studies; grade 3 or 4 events were reported in 5.4% of patients. These events required dose reduction or interruption in 1.4% of patients and led to discontinuation in 0.1% of patients. The risk of hyperglycaemia was higher in patients with diabetes mellitus and/or concurrent steroid use. Monitoring of fasting serum glucose is required prior to the start of ceritinib treatment and periodically thereafter as clinically indicated. Administration of anti-hyperglycaemic medicinal products should be initiated or optimised as indicated (see sections 4.2 and 4.4).

Reporting of suspected adverse reactions

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

4.9 Overdose

There is no reported experience with overdose in humans. General supportive measures should be initiated in all cases of overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, anaplastic lymphoma kinase (ALK) inhibitors, ATC code: L01ED02.

Mechanism of action

Ceritinib is an orally highly selective and potent ALK inhibitor. Ceritinib inhibits autophosphorylation of ALK, ALK-mediated phosphorylation of downstream signalling proteins and proliferation of ALK-dependent cancer cells both *in vitro* and *in vivo*.

ALK translocation determines expression of the resulting fusion protein and consequent aberrant ALK signaling in NSCLC. In the majority of NSCLC cases, EML4 is the translocation partner for ALK; this generates an EML4-ALK fusion protein containing the protein kinase domain of ALK fused to the N-terminal part of EML4. Ceritinib was demonstrated to be effective against EML4-ALK activity in a NSCLC cell line (H2228), resulting in inhibition of cell proliferation *in vitro* and regression of tumours in H2228-derived xenografts in mouse and rat.

Clinical efficacy and safety

Previously untreated ALK-positive advanced NSCLC - randomised phase 3 Study A2301 (ASCEND-4)
The efficacy and safety of ceritinib for the treatment of advanced ALK-positive NSCLC patients who have not received previous systemic treatment anti-cancer therapy (including ALK inhibitor) with the exception of neo-adjuvant or adjuvant therapy, was demonstrated in a global multicentre, randomised, open-label phase 3 Study A2301.

A total of 376 patients were randomised in a 1:1 ratio (stratified by WHO performance status, prior adjuvant/neoadjuvant chemotherapy and presence/absence of brain metastasis at screening) to receive either ceritinib (750 mg daily, fasted) or chemotherapy (based on investigator's choice - pemetrexed [500 mg/m^2] plus cisplatin [75 mg/m^2] or carboplatin [AUC 5-6], administered every 21 days). Patients who completed 4 cycles of chemotherapy (induction) without progressive disease subsequently received pemetrexed (500 mg/m^2) as single-agent maintenance therapy every 21 days. One hundred and eighty-nine (189) patients were randomised to ceritinib and one hundred eighty-seven (187) were randomised to chemotherapy.

The median age was 54 years (range: 22 to 81 years); 78.5% of patients were younger than 65 years. A total of 57.4% of patients were female. 53.7% of the study population was Caucasian, 42.0% Asian, 1.6% Black and 2.6% other races The majority of patients had adenocarcinoma (96.5%) and had either never smoked or were former smokers (92.0%). The Eastern Cooperative Oncology Group (ECOG) performance status was 0/1/2 in 37.0%/56.4%/6.4% of patients, and 32.2% had brain metastasis at baseline. 59.5% of patients with brain metastasis at baseline received no prior radiotherapy to the brain. Patients with symptomatic CNS (central nervous system) metastases who were neurologically unstable or had required increasing doses of steroids within the 2 weeks prior to screening to manage CNS symptoms, were excluded from the study.

Patients were allowed to continue the assigned study treatment beyond initial progression in case of continued clinical benefit as per the investigator's opinion. Patients randomised to the chemotherapy arm could cross-over to receive ceritinib upon RECIST-defined disease progression confirmed by blinded independent review committee (BIRC). One hundred and five (105) patients out of the 145 patients (72.4%) that discontinued treatment in the chemotherapy arm received subsequent ALK inhibitor as first antineoplastic therapy. Of these patients 81 received ceritinib.

The median duration of follow-up was 19.7 months (from randomisation to cut-off date) at the primary analysis.

The study met its primary objective demonstrating a statistically significant improvement in progression free survival (PFS) by BIRC (see Table 3 and Figure 1). The PFS benefit of ceritinib was consistent by investigator assessment and across various subgroups including age, gender, race, smoking class, ECOG performance status and disease burden.

At the time of the primary analysis, the overall survival (OS) data was not mature with 107 deaths representing approximately 42.3% of the required events for the final OS analysis.

Efficacy data from Study A2301 are summarised in Table 3, and the Kaplan-Meier curves for PFS and OS are shown in Figure 1 and Figure 2, respectively.

Table 3 ASCEND-4 (Study A2301) - Efficacy results in patients with previously untreated ALK-positive advanced NSCLC (primary analysis)

	Ceritinib (N=189)	Chemotherapy (N=187)
Progression-free survival (based on BIRC)		
Number of events, n (%)	89 (47.1)	113 (60.4)
Median, months[d] (95% CI)	16.6 (12.6, 27.2)	8.1 (5.8, 11.1)
HR (95% CI)[a]	0.55 (0.42, 0.73)	
p-value[b]	<0.001	
Overall survival[c]		
Number of events, n (%)	48 (25.4)	59 (31.6)
Median, months[d] (95% CI)	NE (29.3, NE)	26.2 (22.8, NE)
OS rate at 24 months[d], % (95% CI)	70.6 (62.2, 77.5)	58.2 (47.6, 67.5)
HR (95% CI)[a]	0.73 (0.50,1.08)	
p-value[b]	0.056	
Tumour response (based on BIRC)		
Overall response rate (95% CI)	72.5% (65.5, 78.7)	26.7% (20.5, 33.7)
Duration of response (based on BIRC)		
Number of responders	137	50
Median, months[d] (95% CI)	23.9 (16.6, NE)	11.1 (7.8, 16.4)
Event-free rate at 18 months[d], % (95% CI)	59.0 (49.3, 67.4)	30.4 (14.1, 48.6)

HR=hazard ratio; CI=confidence interval; BIRC=Blinded Independent Review Committee; NE=not estimable

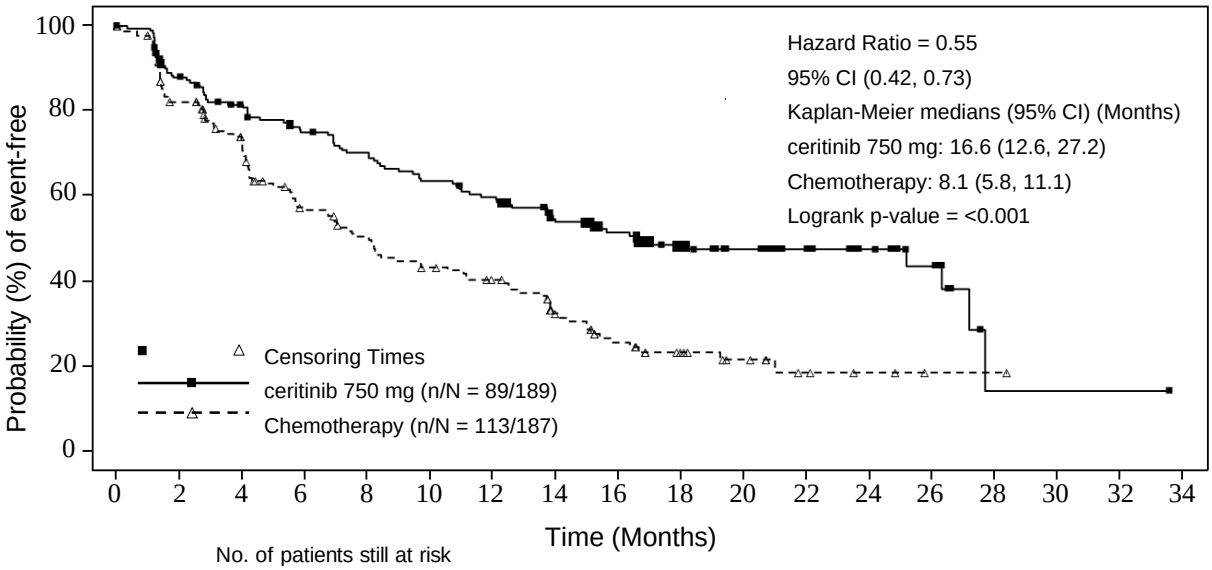
[a] Based on the Cox proportional hazards stratified analysis.

[b] Based on the stratified log-rank test.

[c] OS analysis was not adjusted for the effects of cross-over.

[d] Estimated using the Kaplan-Meier method.

Figure 1 ASCEND-4 (Study A2301) - Kaplan-Meier curves of progression-free survival as assessed by BIRC (primary analysis)

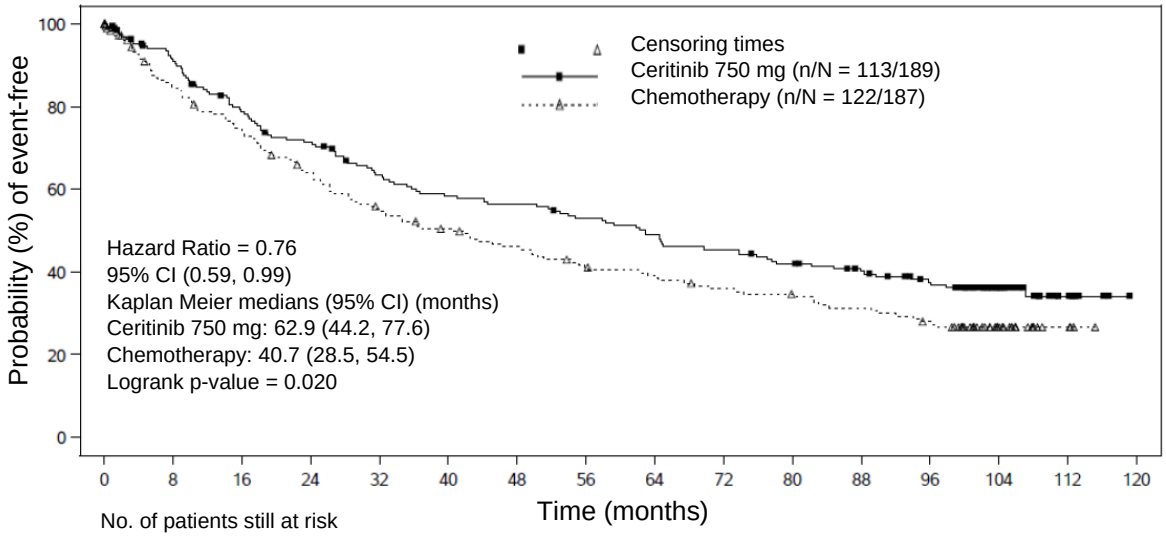


No. of patients still at risk

Time (Months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34
ceritinib 750 mg	189	155	139	125	116	105	98	76	59	43	32	23	16	11	1	1	1	0
Chemotherapy	187	136	114	82	71	60	53	35	24	16	11	5	3	1	1	0	0	0

At the final OS analysis, 113 (59.8%) patients had died in the ceritinib arm and 122 (65.2%) in the chemotherapy arm. The median OS was 62.9 months (95% CI: 44.2, 77.6) and 40.7 months (95% CI: 28.5, 54.5) for the ceritinib arm and the chemotherapy arm, respectively. There was a statistically significant 24% reduction in the risk of death in the ceritinib arm compared to the chemotherapy arm (HR 0.76; 95% CI: 0.59, 0.99; p=0.020). There was a high rate of crossover, with 61.5% of patients in the chemotherapy arm switching to receive ceritinib. Additionally, patients in both arms received next-line antineoplastic therapies, including other ALK inhibitors, which influenced the OS outcome.

Figure 2 ASCEND-4 (Study A2301)- Kaplan-Meier plot of overall survival by treatment arm (final OS analysis)



No. of patients still at risk

Time (months)	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	76	80	84	88	92	96	100	104	108	112	116	120
Ceritinib 750 mg	189	176	166	151	141	129	127	117	110	104	101	100	98	95	91	88	84	79	78	74	71	68	64	60	55	51	30	17	9	3	0
Chemotherapy	187	161	146	135	128	115	108	99	91	87	82	76	74	69	65	63	61	58	55	53	52	48	47	44	41	32	19	7	4	0	0

In Study A2301, 44 patients with measurable brain metastasis at baseline and at least one post-baseline brain radiological assessment (22 patients in the ceritinib arm and 22 patients in the chemotherapy arm) were assessed for intracranial response by BIRC neuro-radiologist per modified RECIST 1.1 (i.e. up to 5 lesions in the brain). The overall intracranial response rate (OIRR) was higher with ceritinib (72.7%, 95% CI: 49.8, 89.3) as compared to the chemotherapy arm (27.3%, 95% CI: 10.7, 50.2).

The median PFS by BIRC using RECIST 1.1 was longer in the ceritinib arm compared to the chemotherapy arm in both subgroups of patients with brain metastases and without brain metastases. The median PFS in patients with brain metastases was 10.7 months (95% CI: 8.1, 16.4) versus 6.7 months (95% CI: 4.1, 10.6) in the ceritinib and chemotherapy arms, respectively, with HR 0.70 (95% CI: 0.44, 1.12). The median PFS in patients without brain metastases was 26.3 months (95% CI: 15.4, 27.7) versus 8.3 months (95% CI: 6.0, 13.7) in the ceritinib and chemotherapy arms, respectively, with HR 0.48 (95% CI: 0.33, 0.69).

Previously treated ALK-positive advanced NSCLC - randomised phase 3 Study A2303 (ASCEND-5)
The efficacy and safety of ceritinib for the treatment of ALK-positive advanced NSCLC patients who have received previous treatment with crizotinib, was demonstrated in a global multicentre, randomised, open-label phase 3 Study A2303.

A total of 231 patients with advanced ALK positive NSCLC who have received prior treatment with crizotinib and chemotherapy (one or two regimen including a platinum-based doublet) were included in the analysis. One hundred fifteen (115) patients were randomised to ceritinib and one hundred sixteen (116) were randomised to chemotherapy (either pemetrexed or docetaxel). Seventy-three (73) patients received docetaxel and 40 received pemetrexed. In the ceritinib arm, 115 patients were treated with 750 mg once daily fasted. The median age was 54.0 years (range: 28 to 84 years); 77.1% of patients were younger than 65 years. A total of 55.8% of patients were female. 64.5% of the study population were Caucasian, 29.4% Asian, 0.4% Black and 2.6% other races. The majority of patients had adenocarcinoma (97.0%) and had either never smoked or were former smokers (96.1%). The ECOG performance status was 0/1/2 in 46.3%/47.6%/6.1% of patients respectively, and 58.0% had brain metastasis at baseline. All patients were treated with prior crizotinib. All except one patient received prior chemotherapy (including a platinum doublet) for advanced disease; 11.3% of the patients in the ceritinib arm and 12.1% of the patients in the chemotherapy arm were treated with two prior chemotherapy regimen for advanced disease.

Patients were allowed to continue the assigned study treatment beyond initial progression in case of continued clinical benefit as per the investigator's opinion. Patients randomised to the chemotherapy arm could further crossover to receive ceritinib upon RECIST-defined disease progression confirmed by BIRC.

The median duration of follow-up was 16.5 months (from randomisation to data cut-off date) at the primary analysis.

The study met its primary objective demonstrating a statistically significant improvement in PFS by BIRC with an estimated 51% risk reduction in the ceritinib arm compared to chemotherapy arm (see Table 4 and Figure 3). The PFS benefit of ceritinib was consistent across various subgroups including age, gender, race, smoking class, ECOG performance status, and presence of brain metastases or prior response to crizotinib. The PFS benefit was further supported by local investigator assessment, and analysis of overall response rate (ORR) and disease control rate (DCR).

At the primary analysis OS data was immature with 48 (41.7%) events in the ceritinib arm and 50 (43.1%) events in the chemotherapy arm, corresponding to approximately 50% of the required events for the final OS analysis. In addition, 81 patients (69.8%) in the chemotherapy arm received subsequent ceritinib as first antineoplastic therapy after study treatment discontinuation.

Efficacy data from Study A2303 are summarised in Table 4, and the Kaplan-Meier curves for PFS and OS are shown in Figure 3 and 4, respectively.

Table 4 ASCEND-5 (Study A2303) – Efficacy results in patients with previously treated ALK-positive metastatic/advanced NSCLC (primary analysis)

	Ceritinib (N=115)	Chemotherapy (N=116)
Duration of follow-up Median (months) (min – max)	16.5 (2.8 – 30.9)	
Progression-free survival (based on BIRC)		
Number of events, n (%)	83 (72.2%)	89 (76.7%)
Median, months (95% CI)	5.4 (4.1, 6.9)	1.6 (1.4, 2.8)
HR (95% CI)[a]	0.49 (0.36, 0.67)	
p-value[b]	<0.001	
Overall survival[c]		
Number of events, n (%)	48 (41.7%)	50 (43.1%)
Median, months (95% CI)	18.1 (13.4, 23.9)	20.1 (11.9, 25.1)
HR (95% CI)[a]	1.00 (0.67,1.49)	
p-value[b]	0.496	
Tumour responses (based on BIRC)		
Objective response rate (95% CI)	39.1% (30.2, 48.7)	6.9% (3.0, 13.1)
Duration of response		
Number of responders	45	8
Median, months[d] (95% CI)	6.9 (5.4, 8.9)	8.3 (3.5, NE)
Event-free probability estimate at 9 months[d] (95% CI)	31.5% (16.7%, 47.3%)	45.7% (6.9%, 79.5%)

HR=hazard ratio; CI=confidence interval; BIRC=Blinded Independent Review Committee; NE=not estimable

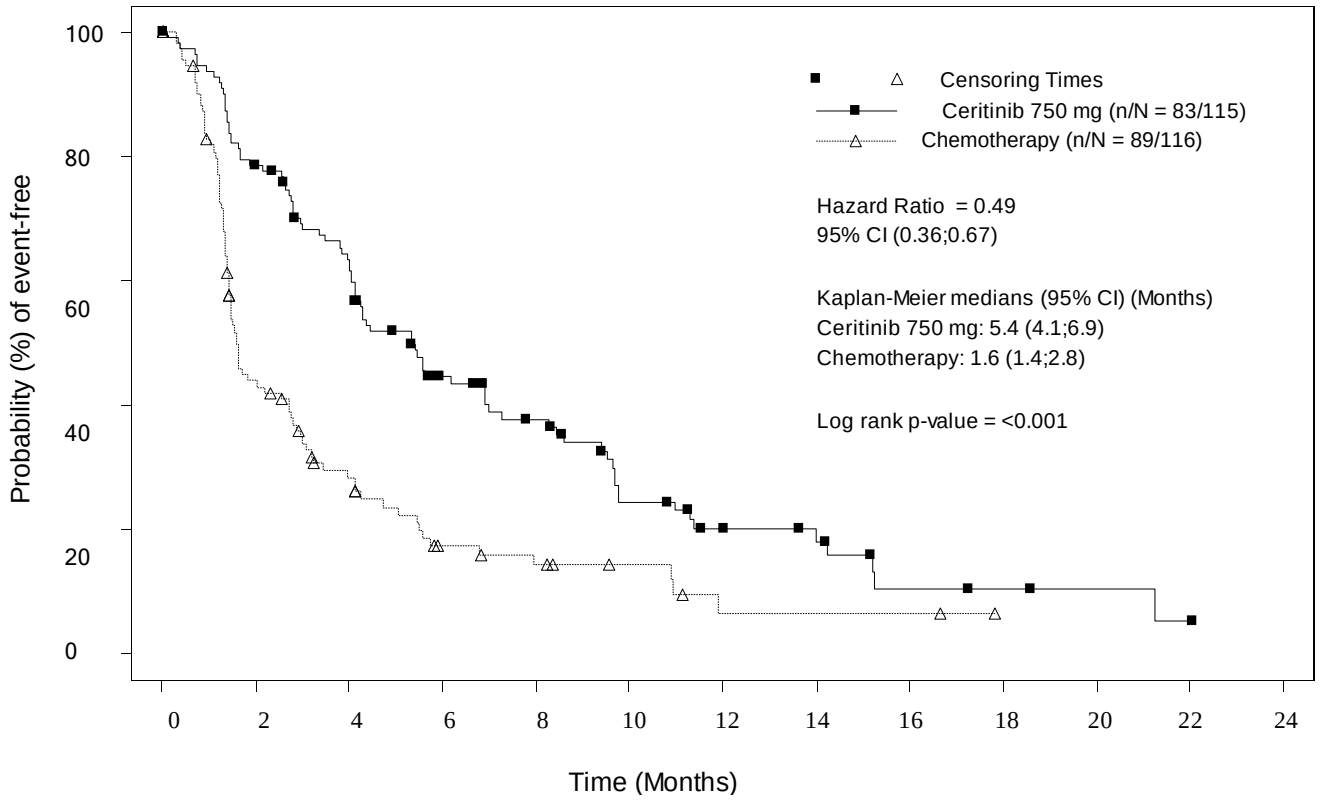
[a] Based on the stratified Cox proportional hazards analysis.

[b] Based on the stratified log-rank test.

[c] OS analysis was not adjusted for the potentially confounding effects of cross over.

[d] Estimated using the Kaplan-Meier method.

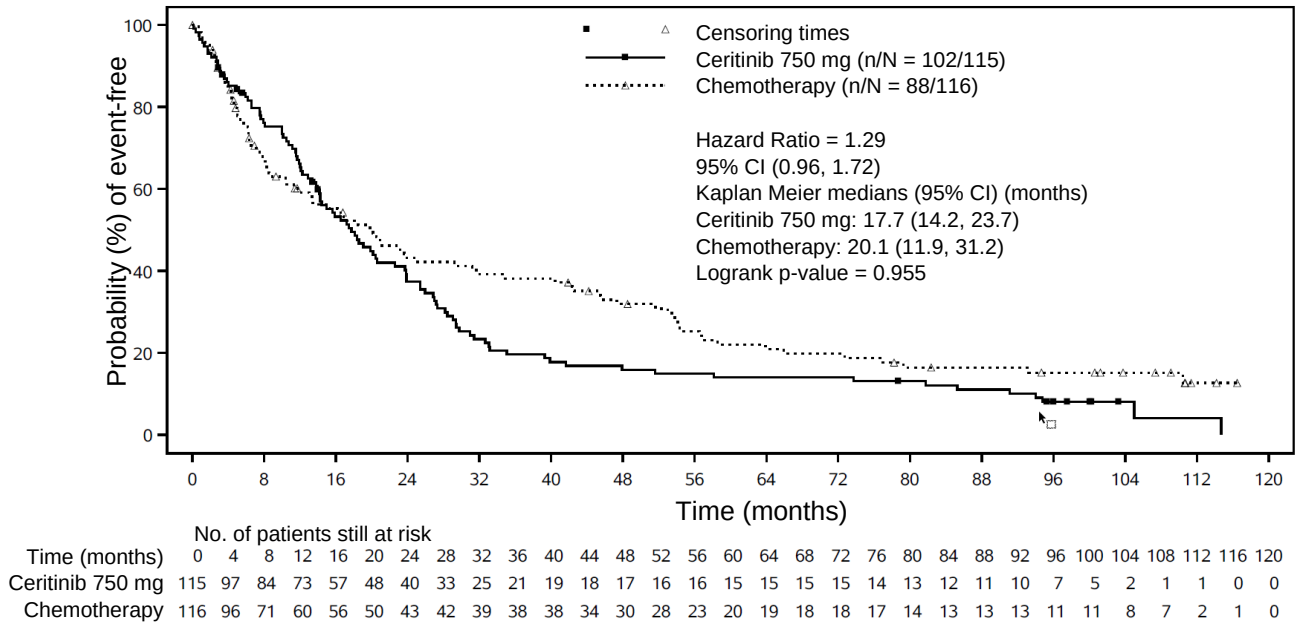
Figure 3 ASCEND-5 (Study A2303) – Kaplan-Meier plot of progression-free survival as assessed by BIRC (primary analysis)



	No. of patients still at risk												
Time (Months)	0	2	4	6	8	10	12	14	16	18	20	22	24
Ceritinib 750 mg	115	87	68	40	31	18	12	9	4	3	2	1	0
Chemotherapy	116	45	26	12	9	6	2	2	2	0	0	0	0

At the final OS analysis, with a median duration of follow-up of 110 months, 102 (88.7%) patients had died in the ceritinib arm and 88 (75.9%) in the chemotherapy arm. The median OS was 17.7 months (95% CI: 14.2, 23.7) and 20.1 months (95% CI: 11.9, 31.2) for the ceritinib arm and the chemotherapy arm, respectively. There was no statistically significant difference in OS between the two treatment arms (HR 1.29; 95% CI: 0.96, 1.72; p=0.955). There was a high rate of early crossover, with 88 (76%) of patients in the chemotherapy arm switching to receive ceritinib. Additionally, patients in both arms received next-line antineoplastic therapies, including other ALK inhibitors. Overall, crossover and next-line therapies were a major confounding factor that may have diluted any potential difference in OS between the treatment arms.

Figure 4 ASCEND-5 (Study A2303) – Kaplan-Meier plot of overall survival by treatment arm (final OS analysis)



No. of patients still at risk

Time (months)	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	76	80	84	88	92	96	100	104	108	112	116	120
Ceritinib 750 mg	115	97	84	73	57	48	40	33	25	21	19	18	17	16	16	15	15	15	15	14	13	12	11	10	7	5	2	1	1	0	0
Chemotherapy	116	96	71	60	56	50	43	42	39	38	38	34	30	28	23	20	19	18	18	17	14	13	13	13	11	11	8	7	2	1	0

In Study A2303, 133 patients with baseline brain metastasis (66 patients in the ceritinib arm and 67 patients in the chemotherapy arm) were assessed for intracranial response by BIRC neuro-radiologist (per modified RECIST 1.1 (i.e. up to 5 lesions in the brain). The OIRR in patients with measurable disease in the brain at baseline and at least one post-baseline assessment was higher in the ceritinib arm (35.3%, 95% CI: 14.2, 61.7) compared to the chemotherapy arm (5.0%, 95% CI: 0.1, 24.9). The median PFS by BIRC using RECIST 1.1 was longer in the ceritinib arm compared to the chemotherapy arm in both subgroups of patients with brain metastases and without brain metastases. The median PFS in patients with brain metastases was 4.4 months (95% CI: 3.4, 6.2) versus 1.5 months (95% CI: 1.3, 1.8) in the ceritinib and chemotherapy arms, respectively with HR 0.54 (95% CI: 0.36, 0.80). The median PFS in patients without brain metastases was 8.3 months (95% CI: 4.1, 14.0) versus 2.8 months (95% CI: 1.4, 4.1) in the ceritinib and chemotherapy arms, respectively with HR 0.41 (95% CI: 0.24, 0.69).

Dose optimisation Study A2112 (ASCEND-8)

The efficacy of ceritinib 450 mg with food was evaluated in a multicentre, open-label dose optimisation study A2112 (ASCEND-8). A total of 147 previously untreated patients with ALK-positive locally advanced or metastatic NSCLC were randomised to receive ceritinib 450 mg once daily with food (N=73) or ceritinib 750 mg once daily under fasted conditions (N=74). A key secondary efficacy endpoint was ORR according to RECIST 1.1 as evaluated by BIRC.

The population characteristics of the previously untreated patients with ALK-positive locally advanced or metastatic NSCLC across the two arms, 450 mg with food (N=73) and 750 mg fasted (N=74), were: mean age 54.3 and 51.3 years, age less than 65 (78.1% and 83.8%), female (56.2% and 47.3%), Caucasian (49.3% and 54.1%), Asian (39.7% and 35.1%), never or former smoker (90.4% and 95.9%), WHO PS 0 or 1 (91.7% and 91.9%), adenocarcinoma histology (98.6% and 93.2%), and metastases to the brain (32.9% and 28.4%), respectively.

Efficacy results from ASCEND-8 are summarised in Table 5 below.

Table 5 ASCEND-8 (Study A2112) - Efficacy results in patients with previously untreated ALK-positive locally advanced or metastatic NSCLC by BIRC

Efficacy Parameter	Ceritinib 450 mg with food (N=73)	Ceritinib 750 mg fasted (N=74)
Overall Response Rate (ORR: CR+PR), n (%) (95% CI)[a]	57 (78.1) (66.9, 86.9)	56 (75.7) (64.3, 84.9)

CI: Confidence Interval
Complete Response (CR), Partial Response (PR) confirmed by repeat assessments performed not less than 4 weeks after response criteria were first met
Overall response rate determined based on BIRC assessment per RECIST 1.1
[a]Exact binomial 95% confidence interval

Single arm studies X2101 and A2201
The use of ceritinib in the treatment of ALK-positive NSCLC patients previously treated with an ALK inhibitor was investigated in two global, multicentre, open-label, single-arm phase 1/2 studies (Study X2101 and Study A2201).

In study X2101 a total of 246 ALK-positive NSCLC patients were treated at a ceritinib dose of 750 mg once daily fasted: 163 who had received prior treatment with an ALK inhibitor and 83 who were ALK inhibitor naïve. Of the 163 ALK-positive NSCLC patients who had received prior treatment with an ALK inhibitor, the median age was 52 years (range: 24-80 years); 86.5% were younger than 65 years and 54% were female. The majority of patients were Caucasian (66.3%) or Asian (28.8%). 93.3% had adenocarcinoma and 96.9% had either never been or were former smokers. All of the patients were treated with at least one regimen prior to enrolment into the study and 84.0% with two or more regimens.

Study A2201 involved 140 patients who had been previously treated with 1-3 lines of cytotoxic chemotherapy followed by treatment with crizotinib, and who had then progressed on crizotinib. The median age was 51 years (range: 29-80 years); 87.1% of patients were younger than 65 years and 50.0% were female. The majority of patients were Caucasian (60.0%) or Asian (37.9%). 92.1% of patients had adenocarcinoma.

The main efficacy data for both studies are summarised in Table 6. Final overall survival (OS) data are presented for Study A2201. For Study X2101, OS data were not yet mature at the time of the analysis.

Table 6 ALK-positive advanced NSCLC - overview of efficacy results from Studies X2101 and A2201

	Study X2101 ceritinib 750 mg N=163	Study A2201 ceritinib 750 mg N=140
Duration of follow-up Median (months) (min – max)	10.2 (0.1 – 24.1)	14.1 (0.1 – 35.5)
Overall response rate		
Investigator (95% CI)	56.4% (48.5, 64.2)	40.7% (32.5, 49.3)
BIRC (95% CI)	46.0% (38.2, 54.0)	35.7% (27.8, 44.2)
Duration of response*		
Investigator (months, 95% CI)	8.3 (6.8, 9.7)	10.6 (7.4, 14.7)
BIRC (months, 95% CI)	8.8 (6.0, 13.1)	12.9 (9.3, 18.4)
Progression-free survival		
Investigator (months, 95% CI)	6.9 (5.6, 8.7)	5.8 (5.4, 7.6)
BIRC (months, 95% CI)	7.0 (5.7, 8.7)	7.4 (5.6, 10.9)
Overall survival (months, 95% CI)	16.7 (14.8, NE)	15.6 (13.6, 24.2)

NE = not estimable
Study X2101: Responses assessed using RECIST 1.0
Study A2201: Responses assessed using RECIST 1.1
*Includes only patients with confirmed CR, PR

In Studies X2101 and A2201, brain metastases were seen in 60.1% and 71.4% of patients, respectively. The ORR, DOR and PFS (by BIRC assessment) for patients with brain metastases at baseline were in line with those reported for the overall population of these studies.

Non-adenocarcinoma histology

Limited information is available in ALK-positive NSCLC patients with non-adenocarcinoma histology.

Elderly

Limited efficacy data are available in elderly patients. No efficacy data are available in patients over 85 years of age.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with ceritinib in all subsets of the paediatric population in lung carcinoma (small cell and non-small cell carcinoma) (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Peak plasma levels (C_{max}) of ceritinib are achieved approximately 4 to 6 hours after a single oral administration in patients. Oral absorption was estimated to be ≥25% based on metabolite percentages in the faeces. The absolute bioavailability of ceritinib has not been determined.

Systemic exposure of ceritinib was increased when administered with food. Ceritinib AUC_{inf} values were approximately 58% and 73% higher (C_{max} approximately 43% and 41% higher) in healthy subjects when a single 500 mg ceritinib dose was administered with a low fat meal (containing approximately 330 kcalories and 9 grams of fat) and a high fat meal (containing approximately 1000 kcalories and 58 grams of fat), respectively, as compared with the fasted state.

In a dose optimisation study A2112 (ASCEND-8) in patients comparing ceritinib 450 mg or 600 mg daily with food (approximately 100 to 500 kcalories and 1.5 to 15 grams of fat) to 750 mg daily under fasted conditions (dose and food condition of administration initially authorised), there was no clinically meaningful difference in the systemic steady-state exposure of ceritinib for the 450 mg with food arm (N=36) compared to the 750 mg fasted arm (N=31), with only small increases in steady-state AUC (90% CI) by 4% (-13%, 24%) and C_{max} (90% CI) by 3% (-14%, 22%). In contrast, the steady-state AUC (90% CI) and C_{max} (90% CI) for the 600 mg with food arm (N=30) increased by 24% (3%, 49%) and 25% (4%, 49%), respectively, compared to the 750 mg fasted arm. The maximum recommended dose of ceritinib is 450 mg taken orally once daily with food (see section 4.2).

After single oral administration of ceritinib in patients, plasma exposure to ceritinib, as represented by C_{max} and AUC_{last}, increased dose-proportionally over the 50 to 750 mg dose range under fasted conditions. In contrast with single-dose data, pre-dose concentration (C_{min}) after repeated daily dosing appeared to increase in a greater than dose-proportional manner.

Distribution

Binding of ceritinib to human plasma proteins *in vitro* is approximately 97% in a concentration independent manner, from 50 ng/ml to 10,000 ng/ml. Ceritinib also has a slight preferential distribution to red blood cells, relative to plasma, with a mean *in vitro* blood-to-plasma ratio of 1.35. *In vitro* studies suggest that ceritinib is a substrate for P-glycoprotein (P-gp), but not of breast cancer resistance protein (BCRP) or multi-resistance protein 2 (MRP2). The *in vitro* apparent passive permeability of ceritinib was determined to be low.

In rats, ceritinib crosses the intact blood brain barrier with a brain-to-blood exposure (AUC_{inf}) ratio of about 15%. There are no data related to brain-to-blood exposure ratio in humans.

Biotransformation

In vitro studies demonstrated that CYP3A was the major enzyme involved in the metabolic clearance of ceritinib.

Following a single oral administration of radioactive ceritinib dose at 750 mg fasted, ceritinib was the main circulating component in human plasma. A total of 11 metabolites were found circulating in plasma at low levels with mean contribution to the radioactivity AUC of ≤2.3% for each metabolite. Main biotransformation pathways identified in healthy subjects included mono-oxygenation, O-dealkylation, and N-formylation. Secondary biotransformation pathways involving the primary biotransformation products included glucuronidation and dehydrogenation. Addition of a thiol group to O-dealkylated ceritinib was also observed.

Elimination

Following single oral doses of ceritinib under fasted conditions, the geometric mean apparent plasma terminal half-life ($T_{½}$) of ceritinib ranged from 31 to 41 hours in patients over the 400 to 750 mg dose range. Daily oral dosing of ceritinib results in achievement of steady-state by approximately 15 days and remains stable afterwards, with a geometric mean accumulation ratio of 6.2 after 3 weeks of daily dosing. The geometric mean apparent clearance (CL/F) of ceritinib was lower at steady-state (33.2 litres/hour) after 750 mg daily oral dosing than after a single 750 mg oral dose (88.5 litres/hour), suggesting that ceritinib demonstrates non-linear pharmacokinetics over time.

The primary route of excretion of ceritinib and its metabolites is in the faeces. Recovery of unchanged ceritinib in the faeces accounts for a mean 68% of an oral dose. Only 1.3% of the administered oral dose is recovered in the urine.

Special populations

Hepatic impairment
The effect of hepatic impairment on the single-dose pharmacokinetics of ceritinib (750 mg under fasted conditions) was evaluated in subjects with mild (Child-Pugh class A; N=8), moderate (Child-Pugh class B; N=7), or severe (Child-Pugh class C; N=7) hepatic impairment and in 8 healthy subjects with normal hepatic function. The geometric mean AUC_{inf} (unbound AUC_{inf}) of ceritinib was increased by 18% (35%) and 2% (22%) in subjects with mild and moderate hepatic impairment, respectively, compared to subjects with normal hepatic function.

The geometric mean AUC_{inf} (unbound AUC_{inf}) of ceritinib was increased by 66% (108%) in subjects with severe hepatic impairment compared to subjects with normal hepatic function (see section 4.2). A dedicated pharmacokinetic study under steady-state in patients with hepatic impairment has not been conducted.

Renal impairment
A dedicated pharmacokinetic study in patients with renal impairment has not been conducted. Based on available data, ceritinib elimination via the kidney is negligible (1.3% of a single oral administered dose).

Based on a population pharmacokinetic analysis of 345 patients with mild renal impairment (CLcr 60 to <90 ml/min), 82 patients with moderate renal impairment (CLcr 30 to <60 ml/min) and 546 patients with normal renal function (≥90 ml/min), ceritinib exposures were similar in patients with mild and moderate renal impairment and normal renal function, suggesting that no dose adjustment is necessary in patients with mild to moderate renal impairment. Patients with severe renal impairment (CLcr <30 ml/min) were not included in the clinical studies of ceritinib (see section 4.2).

Effects of age, gender, and race
Population pharmacokinetic analyses showed that age, gender and race had no clinically meaningful influence on ceritinib exposure.

Cardiac electrophysiology
The potential for QT interval prolongation of ceritinib was assessed in seven clinical studies with ceritinib. Serial ECGs were collected following a single dose and at steady-state to evaluate the effect of ceritinib on the QT interval in 925 patients treated with ceritinib 750 mg once daily fasted. A categorical outlier analysis of ECG data demonstrated new QTc >500 msec in 12 patients (1.3%). There were 58 patients (6.3%) with a QTc increase from baseline >60 msec. A central tendency analysis of the QTc data at average steady-state concentration from Study A2301 demonstrated that the upper bound of the 2-sided 90% CI for QTc increase from baseline was 15.3 msec at ceritinib 750 mg fasted. A pharmacokinetic analysis suggested that ceritinib causes concentration-dependent increases in QTc (see section 4.4).

5.3 Preclinical safety data

Safety pharmacology studies indicate that ceritinib is unlikely to interfere with vital functions of the respiratory and central nervous systems. *In vitro* data show that the IC50 for the inhibitory effect of ceritinib on the hERG potassium channel was 0.4 micromolar. An *in vivo* telemetry study in monkeys showed a modest QT prolongation in 1 of 4 animals after receiving the highest dose of ceritinib. ECG studies in monkeys after 4- or 13-weeks of dosing with ceritinib have not shown QT prolongation or abnormal ECGs.

The micronucleus test in TK6 cells was positive. No signs of mutagenicity or clastogenicity were observed in other *in vitro* and *in vivo* genotoxicity studies with ceritinib. Therefore, genotoxic risk is not expected in humans.

Carcinogenicity studies have not been performed with ceritinib.

Reproductive toxicology studies (i.e. embryo-foetal development studies) in pregnant rats and rabbits indicated no foetotoxicity or teratogenicity after dosing with ceritinib during organogenesis; however, maternal plasma exposure was less than that observed at the recommended human dose. Formal non-clinical studies on the potential effects of ceritinib on fertility have not been conducted.

The principal toxicity related to ceritinib administration in rats and monkeys was inflammation of the extra-hepatic bile ducts accompanied by increased neutrophil counts in the peripheral blood. Mixed cell/neutrophilic inflammation of the extra-hepatic ducts extended to the pancreas and/or duodenum at higher doses. Gastrointestinal toxicity was observed in both species characterised by body weight loss, decreased food consumption, emesis (monkey), diarrhoea and, at high doses, by histopathological lesions including erosion, mucosal inflammation and foamy macrophages in the duodenal crypts and submucosa. The liver was also affected in both species, at exposures that approximate clinical exposures at the recommended human dose, and included minimal increases in liver transaminases in a few animals and vacuolation of the intra-hepatic bile duct epithelium. Alveolar foamy macrophages (confirmed phospholipidosis) were seen in the lungs of rats, but not in monkeys, and the lymph nodes of rats and monkeys had macrophage aggregates. Target organ effects showed partial to complete recovery.

Effects on the thyroid were observed in both rat (mild increases in thyroid stimulating hormone and triiodothyronine/thyroxine T3/T4 concentrations with no microscopic correlate) and monkey (depletion of colloid in males in 4-week study, and one monkey at high dose with diffuse follicular cell hyperplasia and increased thyroid stimulating hormone in 13-week study). As these non-clinical effects were mild, variable and inconsistent, the relationship between ceritinib and thyroid gland changes in animals is unclear.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content

Cellulose, microcrystalline
Hydroxypropylcellulose, low-substituted
Sodium starch glycolate (type A)
Magnesium stearate
Silica, colloidal anhydrous

Capsule shell

Gelatin
Indigotine (E132)
Titanium dioxide (E171)

Printing ink

Shellac (bleached, de-waxed) glaze 45%
Iron oxide black (E172)
Propylene glycol
Ammonium hydroxide 28%

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PCTFE (polyvinylchloride/polychlorotrifluoroethylene) – Aluminium blisters containing 10 hard capsules.

Packs containing 40, 90 or 150 (3 packs of 50) hard capsules.

PVC/PE/PVDC (polyvinylchloride/polyethylene/polyvinylidene chloride) – Aluminium blisters containing 10 hard capsules.

Packs containing 90 or 150 (3 packs of 50) hard capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

8. MARKETING AUTHORISATION NUMBERS

EU/1/15/999/001-003
EU/1/15/999/005-006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 06 May 2015
Date of latest renewal: 16 February 2022

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Zykadia 150 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 150 mg ceritinib.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)

Light blue, round, biconvex film-coated tablet with bevelled edges, without score, debossed with "NVR" on one side and "ZY1" on the other side. Approximate diameter: 9.1 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Zykadia as monotherapy is indicated for the first-line treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC).

Zykadia as monotherapy is indicated for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously treated with crizotinib.

4.2 Posology and method of administration

Treatment with ceritinib should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products.

ALK testing

An accurate and validated ALK assay is necessary for the selection of ALK-positive NSCLC patients (see section 5.1).

ALK-positive NSCLC status should be established prior to initiation of ceritinib therapy. Assessment for ALK-positive NSCLC should be performed by laboratories with demonstrated proficiency in the specific technology being utilised.

Posology

The recommended dose of ceritinib is 450 mg taken orally once daily with food at the same time each day.

The maximum recommended dose with food is 450 mg taken orally once daily. Treatment should continue as long as clinical benefit is observed.

If a dose is missed, the patient should make up that dose, unless the next dose is due within 12 hours.

If vomiting occurs during the course of treatment, the patient should not take an additional dose, but should continue with the next scheduled dose.

Ceritinib should be discontinued in patients unable to tolerate 150 mg daily taken with food.

Dose adjustment due to adverse reactions
Temporary dose interruption and/or dose reduction of ceritinib may be required based on individual safety and tolerability. If dose reduction is required due to an adverse drug reaction (ADR) not listed in Table 1, then this should be achieved by decrements of 150 mg daily. Early identification and management of ADRs with standard supportive care measures should be considered.

In patients treated with ceritinib 450 mg with food, 24.1% of patients had an adverse event that required at least one dose reduction and 55.6% of patients had an adverse event that required at least one dose interruption. The median time to first dose reduction due to any reason was 9.7 weeks.

Table 1 summarises recommendations for dose interruption, reduction or discontinuation of ceritinib in the management of selected ADRs.

Table 2 Ceritinib dose adjustment and management recommendations for ADRs

Criteria	**Ceritinib dosing**
Severe or intolerable nausea, vomiting or diarrhoea despite optimal anti-emetic or anti-diarrhoeal therapy	Withhold ceritinib until improved, then reinitiate ceritinib with dose reduced by 150 mg.
Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevation >5 times upper limit of normal (ULN) with concurrent total bilirubin ≤2 times ULN	Withhold ceritinib until recovery to baseline ALT/AST levels or to ≤3 times ULN, then reinitiate with dose reduced by 150 mg.
ALT or AST elevation >3 times ULN with concurrent total bilirubin elevation >2 times ULN (in the absence of cholestasis or haemolysis)	Permanently discontinue ceritinib.
Any grade treatment-related interstitial lung disease (ILD)/pneumonitis	Permanently discontinue ceritinib.
QT corrected for heart rate (QTc) >500 msec on at least 2 separate electrocardiograms (ECGs)	Withhold ceritinib until recovery to baseline or to a QTc ≤480 msec, check and if necessary correct electrolytes, then reinitiate with dose reduced by 150 mg.
QTc >500 msec or >60 msec change from baseline and torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia	Permanently discontinue ceritinib.

Bradycardia[a] (symptomatic, may be severe and medically significant, medical intervention indicated)	Withhold ceritinib until recovery to asymptomatic (grade ≤1) bradycardia or to a heart rate of 60 beats per minute (bpm) or above. Evaluate concomitant medicinal products known to cause bradycardia, as well as anti-hypertensive medicinal products. If a contributing concomitant medicinal product is identified and discontinued, or its dose is adjusted, reinitiate ceritinib at the previous dose upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above. If no contributing concomitant medicinal product is identified, or if contributing concomitant medicinal products are not discontinued or dose modified, reinitiate ceritinib with dose reduced by 150 mg upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above.
Bradycardia[a] (life-threatening consequences, urgent intervention indicated)	Permanently discontinue ceritinib if no contributing concomitant medicinal product is identified. If a contributing concomitant medicinal product is identified and discontinued, or its dose is adjusted, reinitiate ceritinib with dose reduced by 150 mg upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, with frequent monitoring[b].
Persistent hyperglycaemia greater than 250 mg/dl despite optimal anti-hyperglycaemic therapy	Withhold ceritinib until hyperglycaemia is adequately controlled, then reinitiate ceritinib with dose reduced by 150 mg. If adequate glucose control cannot be achieved with optimal medical management, permanently discontinue ceritinib.
Lipase or amylase elevation grade ≥3	Withhold ceritinib until lipase or amylase returns to grade ≤1, then reinitiate with dose reduced by 150 mg.
[a] Heart rate less than 60 beats per minutes (bpm) [b] Permanently discontinue in the event of recurrence	

Strong CYP3A inhibitors
Concomitant use of strong CYP3A inhibitors should be avoided (see section 4.5). If concomitant use of a strong CYP3A inhibitor is unavoidable, the dose of ceritinib should be reduced by approximately one third (dose not clinically verified), rounded to the nearest multiple of the 150 mg dose strength. Patients should be carefully monitored for safety.

If long-term concomitant treatment with a strong CYP3A inhibitor is necessary and the patient tolerates the reduced dose well, the dose may be increased again with careful monitoring for safety, to avoid potential under-treatment.

After discontinuation of a strong CYP3A inhibitor, resume at the dose that was taken prior to initiating the strong CYP3A inhibitor.

CYP3A substrates
When ceritinib is co-administered with other medicinal products, the Summary of Product Characteristics (SmPC) for the other product must be consulted for the recommendations regarding co-administration with CYP3A4 inhibitors.

Co-administration of ceritinib with substrates primarily metabolised by CYP3A or CYP3A substrates known to have narrow therapeutic indices (e.g. alfuzosin, amiodarone, cisapride, ciclosporin, dihydroergotamine, ergotamine, fentanyl, pimozide, quetiapine, quinidine, lovastatin, simvastatin, sildenafil, midazolam, triazolam, tacrolimus, alfentanil and sirolimus) should be avoided and alternative medicinal products that are less sensitive to CYP3A4 inhibition should be used if possible. If unavoidable, dose reduction for co-administered medicinal products that are CYP3A substrates with narrow therapeutic indices should be considered.

Special populations

Renal impairment
A dedicated pharmacokinetic study in patients with renal impairment has not been conducted. However, based on available data, ceritinib elimination via the kidney is negligible. Therefore, no dose adjustment is necessary in patients with mild to moderate renal impairment. Caution should be used in patients with severe renal impairment, as there is no experience with ceritinib in this population (see section 5.2).

Hepatic impairment
Based on available data, ceritinib is eliminated primarily via the liver. Particular caution should be exercised when treating patients with severe hepatic impairment and the dose should be reduced by approximately one third, rounded to the nearest multiple of the 150 mg dose strength (see sections 4.4 and 5.2). No dose adjustment is necessary in patients with mild or moderate hepatic impairment.

Elderly (≥65 years)
The limited data on the safety and efficacy of ceritinib in patients aged 65 years and older do not suggest that a dose adjustment is required in elderly patients (see section 5.2). There are no available data on patients over 85 years of age.

Paediatric population
The safety and efficacy of ceritinib in children and adolescents aged up to 18 years have not been established. No data are available.

Method of administration

Ceritinib is for oral use. The tablets should be administered orally once daily with food at the same time every day. It is important that ceritinib is taken with food to reach the appropriate exposure. Food can range from a light to a full meal (see section 5.2). The tablets should be swallowed whole with water and should not be chewed or crushed.

For patients who develop a concurrent medical condition and are unable to take ceritinib with food please refer to section 4.5.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Hepatotoxicity

Cases of hepatotoxicity occurred in 1.1% of patients receiving ceritinib in clinical studies. Increases to grade 3 or 4 ALT elevations were observed in 25% of patients. The majority of cases were manageable with dose interruption and/or dose reduction. Few events required discontinuation of treatment.

Patients should be monitored with liver laboratory tests (including ALT, AST and total bilirubin) prior to the start of treatment, every 2 weeks during the first three months of treatment and monthly thereafter. In patients who develop transaminase elevations, more frequent monitoring of liver transaminases and total bilirubin should be carried out as clinically indicated (see sections 4.2 and 4.8). Particular caution should be exercised when treating patients with severe hepatic impairment, and the dose should be adjusted (see section 4.2). Limited experience in these patients showed a worsening of the underlying condition (hepatic encephalopathy) in 2 out of 10 patients exposed to 750 mg single doses of ceritinib under fasted conditions (see sections 4.2, 4.8 and 5.2). Other factors apart from study treatment could have impacted on observed events of hepatic encephalopathy, however, the relation between study treatment and events cannot be fully ruled out. No dose adjustment is necessary in patients with mild or moderate hepatic impairment (see section 4.2).

Interstitial lung disease/Pneumonitis

Severe, life-threatening or fatal ILD/pneumonitis have been observed in patients treated with ceritinib in clinical studies. Most of these severe/life-threatening cases improved or resolved with interruption of treatment.

Patients should be monitored for pulmonary symptoms indicative of ILD/pneumonitis. Other potential causes of ILD/pneumonitis should be excluded, and ceritinib should be permanently discontinued in patients diagnosed with any grade 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 ceritinib (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.

Use of ceritinib in patients with congenital long QT syndrome should be avoided. The benefits and potential risks of ceritinib should be considered before beginning therapy in patients who have pre-existing bradycardia (heart rate less than 60 beats per minute [bpm]), patients who have a history of or predisposition for QTc prolongation, patients who are taking anti-arrhythmics or other medicinal products that are known to prolong the QT interval and patients with relevant pre-existing cardiac disease and/or electrolyte disturbances. Periodic monitoring with ECGs and periodic monitoring of electrolytes (e.g. potassium) is recommended in these patients. In the event of vomiting, diarrhoea, dehydration or impaired renal function, correct electrolytes as clinically indicated. Ceritinib should be permanently discontinued in patients who develop QTc >500 msec or >60 msec change from baseline and torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia. Ceritinib should be withheld in patients who develop QTc >500 msec on at least two separate ECGs until recovery to baseline or a QTc ≤480 msec, then reinitiated with dose reduced by 150 mg (see sections 4.2, 4.8 and 5.2).

Bradycardia

Asymptomatic cases of bradycardia (heart rate less than 60 bpm) have been observed in 21 out of 925 (2.3%) patients treated with ceritinib in clinical studies.

Use of ceritinib in combination with other agents known to cause bradycardia (e.g. beta blockers, non-dihydropyridine calcium channel blockers, clonidine and digoxin) should be avoided as far as possible. Heart rate and blood pressure should be monitored regularly. In cases of symptomatic bradycardia that is not life-threatening, ceritinib should be withheld until recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, the use of concomitant medicinal products should be evaluated and the ceritinib dose adjusted if necessary. In the event of life-threatening bradycardia ceritinib should be permanently discontinued if no contributing concomitant medicinal product is identified; however, if associated with a concomitant medicinal product known to cause bradycardia or hypotension, ceritinib should be withheld until recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above. If the concomitant medicinal product can be adjusted or discontinued, ceritinib should be reinitiated with dose reduced by 150 mg on recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, with frequent monitoring (see sections 4.2 and 4.8).

Gastrointestinal adverse reactions

Diarrhoea, nausea, or vomiting occurred in 76.9% of 108 patients treated with ceritinib at the recommended dose of 450 mg taken with food in a dose optimisation study and were mainly grade 1 (52.8%) and grade 2 (22.2%) events. Two patients (1.9%) experienced one grade 3 event each (diarrhoea and vomiting respectively). Nine patients (8.3%) required study drug interruption due to diarrhoea, nausea or vomiting. One patient (0.9%) required dose adjustment due to vomiting. In the same study, the incidence and severity of gastrointestinal adverse drug reactions were higher for patients treated with ceritinib 750 mg fasted (diarrhoea 80.0%, nausea 60.0%, vomiting 65.5%; 17.3% reported a grade 3 event) compared to 450 mg with food (diarrhoea 59.3%, nausea 42.6%, vomiting 38.0%; 1.9% reported a grade 3).

In the 450 mg with food and 750 mg fasted arms of this dose optimisation study, no patients required discontinuation of ceritinib due to diarrhoea, nausea or vomiting (see section 4.8).

Patients should be monitored and managed using standards of care, including anti-diarrhoeals, anti-emetics or fluid replacement, as clinically indicated. Dose interruption and dose reduction should be employed as necessary (see sections 4.2 and 4.8). If vomiting occurs during the course of treatment, the patient should not take an additional dose, but should continue with the next scheduled dose.

Hyperglycaemia

Cases of hyperglycaemia (all grades) have been reported in less than 10% of patients treated with ceritinib in clinical studies; grade 3-4 hyperglycaemia was reported in 5.4% of patients. The risk of hyperglycaemia was higher in patients with diabetes mellitus and/or concurrent steroid use.

Patients should be monitored for fasting plasma glucose prior to the start of ceritinib treatment and periodically thereafter as clinically indicated. Anti-hyperglycaemic medicinal products should be initiated or optimised as indicated (see sections 4.2 and 4.8).

Lipase and/or amylase elevations

Elevations of lipase and/or amylase have occurred in patients treated with ceritinib in clinical studies. Patients should be monitored for lipase and amylase elevations prior to the start of ceritinib treatment and periodically thereafter as clinically indicated (see sections 4.2 and 4.8). Cases of pancreatitis have been reported in patients treated with ceritinib (see section 4.8).

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially “sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

Agents that may increase ceritinib plasma concentrations

Strong CYP3A inhibitors
In healthy subjects, co-administration of a single 450 mg fasted ceritinib dose with ketoconazole (200 mg twice daily for 14 days), a strong CYP3A/P-gp inhibitor, resulted in 2.9-fold and 1.2-fold increase in ceritinib AUC_{inf} and C_{max}, respectively, compared to when ceritinib was given alone. The steady-state AUC of ceritinib at reduced doses after co-administration with ketoconazole 200 mg twice daily for 14 days was predicted by simulations to be similar to the steady-state AUC of ceritinib alone. Concomitant use of strong CYP3A inhibitors should be avoided during treatment with ceritinib. If it is not possible to avoid concomitant use with strong CYP3A inhibitors (including, but not limited to, ritonavir, saquinavir, telithromycin, ketoconazole, itraconazole, voriconazole, posaconazole and nefazodone), the dose of ceritinib should be reduced by approximately one third, rounded to the nearest multiple of the 150 mg dose strength. After discontinuation of a strong CYP3A inhibitor, ceritinib should be resumed at the dose that was taken prior to initiating the strong CYP3A inhibitor.

P-gp inhibitors
Based on *in vitro* data, ceritinib is a substrate of the efflux transporter P-glycoprotein (P-gp). If ceritinib is administered with medicinal products that inhibit P-gp, an increase in ceritinib concentration is likely. Caution should be exercised with concomitant use of P-gp inhibitors and ADRs carefully monitored.

Agents that may decrease ceritinib plasma concentrations

Strong CYP3A and P-gp inducers
In healthy subjects, co-administration of a single 750 mg fasted ceritinib dose with rifampicin (600 mg daily for 14 days), a strong CYP3A/P-gp inducer, resulted in 70% and 44% decreases in ceritinib AUC_{inf} and C_{max}, respectively, compared to when ceritinib was given alone. Co-administration of ceritinib with strong CYP3A/P-gp inducers decreases ceritinib plasma concentrations. Concomitant use of strong CYP3A inducers should be avoided; this includes, but is not limited to, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampicin and St. John's Wort (*Hypericum perforatum*). Caution should be exercised with concomitant use of P-gp inducers.

Agents that affect gastric pH
Ceritinib demonstrates pH-dependent solubility and becomes poorly soluble as pH increases *in vitro*. Acid reducing agents (e.g., proton pump inhibitors, H_2-receptor antagonists, antacids) can alter the solubility of ceritinib and reduce its bioavailability. Co-administration of a single 750 mg fasted ceritinib dose with a proton pump inhibitor (esomeprazole) 40 mg daily for 6 days in healthy, fasting subjects decreased ceritinib AUC by 76% and C_{max} by 79%. The drug-drug interaction study was designed to observe the impact of proton pump inhibitor in the worst scenario, but in clinical use the impact of proton pump inhibitor on ceritinib exposure appears to be less pronounced. A dedicated study to evaluate the effect of gastric acid-reducing agents on the bioavailability of ceritinib under steady state has not been conducted. Caution is advised with concomitant use of proton pump inhibitors, as exposure of ceritinib may be reduced. There is no data with concomitant use of H_2 blockers or antacids. However, the risk for a clinically relevant decrease in bioavailability of ceritinib is possibly lower with concomitant use of H_2 blockers if they are administered 10 hours before or 2 hours after the ceritinib dose, and with antacids if they are administered 2 hours before or 2 hours after the ceritinib dose.

Agents whose plasma concentration may be altered by ceritinib

CYP3A and CYP2C9 substrates
Based on *in vitro* data, ceritinib competitively inhibits the metabolism of a CYP3A substrate, midazolam, and a CYP2C9 substrate, diclofenac. Time-dependent inhibition of CYP3A was also observed.

Ceritinib has been classified *in vivo* as a strong CYP3A4 inhibitor and has the potential to interact with medicinal products that are metabolised by CYP3A, which may lead to increased serum concentrations of the other product. Co-administration of a single dose of midazolam (a sensitive CYP3A substrate) following 3 weeks of ceritinib dosing in patients (750 mg daily fasted) increased the midazolam AUC_{inf} (90% CI) by 5.4-fold (4.6, 6.3) compared to midazolam alone.
Co-administration of ceritinib with substrates primarily metabolised by CYP3A or CYP3A substrates known to have narrow therapeutic indices (e.g. alfuzosin, amiodarone, cisapride, ciclosporin, dihydroergotamine, ergotamine, fentanyl, pimozide, quetiapine, quinidine, lovastatin, simvastatin, sildenafil, midazolam, triazolam, tacrolimus, alfentanil and sirolimus) should be avoided and alternative medicinal products that are less sensitive to CYP3A4 inhibition should be used if possible. If unavoidable, dose reduction for co-administered medicinal products that are CYP3A substrates with narrow therapeutic indices should be considered.

Ceritinib has been classified *in vivo* as a weak CYP2C9 inhibitor. Co-administration of a single dose of warfarin (a CYP2C9 substrate) following 3 weeks of ceritinib dosing in patients (750 mg daily fasted) increased the S-warfarin AUC_{inf} (90% CI) by 54% (36%, 75%) compared to warfarin alone. Co-administration of ceritinib with substrates primarily metabolised by CYP2C9 or CYP2C9 substrates known to have narrow therapeutic indices (e.g. phenytoin and warfarin) should be avoided. If unavoidable, dose reduction for co-administered medicinal products that are CYP2C9 substrates with narrow therapeutic indices should be considered. Increasing the frequency of international normalised ratio (INR) monitoring may be considered if co-administration with warfarin is unavoidable.

CYP2A6 and CYP2E1 substrates
Based on *in vitro* data, ceritinib also inhibits CYP2A6 and CYP2E1 at clinically relevant concentrations. Therefore, ceritinib may have the potential to increase plasma concentrations of co-administered medicinal products that are predominantly metabolised by these enzymes. Caution should be exercised with concomitant use of CYP2A6 and CYP2E1 substrates and ADRs carefully monitored.

A risk for induction of other PXR regulated enzymes apart from CYP3A4 cannot be completely excluded. The effectiveness of concomitant administration of oral contraceptives may be reduced.

Agents that are substrates of transporters

Based on *in vitro* data, ceritinib does not inhibit apical efflux transporter MRP2, hepatic uptake transporters OATP1B1 or OATP1B3, renal organic anion uptake transporters OAT1 and OAT3, or the organic cation uptake transporters OCT1 or OCT2 at clinically relevant concentrations. Therefore, clinical drug-drug interactions as a result of ceritinib-mediated inhibition of substrates for these transporters are unlikely to occur. Based on *in vitro* data, ceritinib is predicted to inhibit intestinal P-gp and BCRP at clinically relevant concentrations. Therefore, ceritinib may have the potential to increase plasma concentrations of co-administered medicinal products transported by these proteins. Caution should be exercised with concomitant use of BCRP substrates (e.g. rosuvastatin, topotecan, sulfasalazine) and P-gp substrates (digoxin, dabigatran, colchicine, pravastatin) and ADRs carefully monitored.

Pharmacodynamic interactions

In clinical studies, QT prolongation was observed with ceritinib. Therefore, ceritinib should be used with caution in patients who have or may develop prolongation of the QT interval, including those patients taking anti-arrhythmic medicinal products such as class I (e.g. quinidine, procainamide, disopyramide) or class III (e.g. amiodarone, sotalol, dofetilide, ibutilide) anti-arrhythmics or other medicinal products that may lead to QT prolongation such as domperidone, droperidol, chloroquine, halofantrine, clarithromycin, haloperidol, methadone, cisapride and moxifloxacin. Monitoring of the QT interval is indicated in the event of combinations of such medicinal products (see sections 4.2 and 4.4).

Food/drink interactions

Ceritinib should be taken with food. The bioavailability of ceritinib is increased in the presence of food.

For patients who develop a concurrent medical condition and are unable to take ceritinib with food, ceritinib can be taken on an empty stomach as the alternate continued treatment regimen, in which no food should be eaten for at least two hours before and one hour after the dose. Patients should not alternate between fasted and fed dosing. Dose must be adjusted properly, i.e for patients treated with 450 mg or 300 mg with food, the dose should be increased to 750 mg or 450 mg taken on an empty stomach, respectively (see section 5.2) and for patients treated with 150 mg with food treatment should be discontinued. For subsequent dose adjustment and management recommendations for ADRs, please follow table 1 (see section 4.2). The maximum allowable dose under fasted condition is 750 mg (see section 5.2).

Patients should be instructed to avoid grapefruit and grapefruit juice as they may inhibit CYP3A in the gut wall and may increase the bioavailability of ceritinib.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception

Women of childbearing potential should be advised to use a highly effective method of contraception while taking ceritinib and for up to 3 months after discontinuing treatment (see section 4.5).

Pregnancy

There are no or limited amount of data from the use of ceritinib in pregnant women.

Animal studies are insufficient with respect to reproductive toxicity (see section 5.3).

Ceritinib should not be used during pregnancy unless the clinical condition of the woman requires treatment with ceritinib.

Breast-feeding

It is unknown whether ceritinib/metabolites are excreted in human milk. A risk to the newborn/infant cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from ceritinib therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman (see section 5.3).

Fertility

The potential for ceritinib to cause infertility in male and female patients is unknown (see section 5.3).

4.7 Effects on ability to drive and use machines

Zykadia has minor influence on the ability to drive or use machines. Caution should be exercised when driving or using machines during treatment as patients may experience fatigue or vision disorders.

4.8 Undesirable effects

Summary of the safety profile

Adverse drug reactions (ADRs) described below reflect exposure to ceritinib 750 mg once daily fasted in 925 patients with ALK-positive advanced NSCLC across a pool of seven clinical studies including two randomised, active-controlled, phase 3 studies (studies A2301 and A2303).

The median duration of exposure to ceritinib 750 mg fasted was 44.9 weeks (range: 0.1 to 200.1 weeks).

ADRs with an incidence of ≥10% in patients treated with ceritinib 750 mg fasted were diarrhoea, nausea, vomiting, fatigue, liver laboratory test abnormalities, abdominal pain, decreased appetite, weight decreased, constipation, blood creatinine increased, rash, anaemia and oesophageal disorder.

Grade 3-4 ADRs with an incidence of ≥5% in patients treated with ceritinib 750 mg fasted were liver laboratory test abnormalities, fatigue, vomiting, hyperglycaemia, nausea and diarrhoea.

In the dose optimisation study A2112 (ASCEND-8) in both previously treated and untreated patients with ALK-positive advanced NSCLC, the overall safety profile of ceritinib at the recommended dose of 450 mg with food (N=108) was consistent with ceritinib 750 mg fasted (N=110), except for a reduction in gastrointestinal adverse drug reactions, while achieving comparable steady-state exposure (see section 5.1 and subsection 'Gastrointestinal adverse reactions' below).

Tabulated list of ADRs

Table 2 shows the frequency category of ADRs reported for ceritinib in patients treated at a dose of 750 mg fasted (N=925) in seven clinical studies. The frequency of selected gastrointestinal ADRs (diarrhoea, nausea and vomiting) are based on patients treated with a dose of 450 mg once-daily with food (N=108).

ADRs are listed according to MedDRA system organ class. Within each system organ class, the ADRs are ranked by frequency, with the most frequent reactions first. In addition, the corresponding frequency category using the following convention (CIOMS III) is also provided for each ADR: 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); and not known (cannot be estimated from the available data). Within each frequency grouping, ADRs are presented in the order of decreasing seriousness.

Table 2 ADRs in patients treated with ceritinib

System organ class	Ceritinib N=925 %	Frequency category
Blood and lymphatic system disorders		
Anaemia	15.2	Very common
Metabolism and nutrition disorders		
Decreased appetite	39.5	Very common
Hyperglycaemia	9.4	Common
Hypophosphataemia	5.3	Common
Eye disorders		
Vision disorder[a]	7.0	Common
Cardiac disorders		
Pericarditis[b]	5.8	Common
Bradycardia[c]	2.3	Common
Respiratory, thoracic and mediastinal disorders		
Pneumonitis[d]	2.1	Common

Gastrointestinal disorders		
Diarrhoea[e]	59.3	Very common
Nausea[e]	42.6	Very common
Vomiting[e]	38.0	Very common
Abdominal pain[f]	46.1	Very common
Constipation	24.0	Very common
Oesophageal disorder[g]	14.1	Very common
Pancreatitis	0.5	Uncommon
Hepatobiliary disorders		
Abnormal liver function tests[h]	2.2	Common
Hepatotoxicity[i]	1.1	Common
Skin and subcutaneous tissue disorders		
Rash[j]	19.6	Very common
Renal and urinary disorders		
Renal failure[k]	1.8	Common
Renal impairment[l]	1.0	Common
General disorders and administration site conditions		
Fatigue[m]	48.4	Very common
Investigations		
Liver laboratory test abnormalities[n]	60.5	Very common
Weight decreased	27.6	Very common
Blood creatinine increased	22.1	Very common
Electrocardiogram QT prolonged	9.7	Common
Lipase increased	4.8	Common
Amylase increased	7.0	Common

Includes cases reported within the clustered terms:

[a] Vision disorder (vision impairment, vision blurred, photopsia, vitreous floaters, visual acuity reduced, accommodation disorder, presbyopia)

[b] Pericarditis (pericardial effusion, pericarditis)

[c] Bradycardia (bradycardia, sinus bradycardia)

[d] Pneumonitis (interstitial lung disease, pneumonitis)

[e] The frequency of these selected gastrointestinal ADRs (diarrhoea, nausea and vomiting) is based on patients treated with the recommended dose of ceritinib 450 mg with food (N=108) in the study A2112 (ASCEND-8) (see subsection 'Gastrointestinal adverse reactions' below)

[f] Abdominal pain (abdominal pain, abdominal pain upper, abdominal discomfort, epigastric discomfort)

[g] Oesophageal disorder (dyspepsia, gastro-oesophageal reflux disease, dysphagia)

[h] Abnormal liver function test (hepatic function abnormal, hyperbilirubinaemia)

[i] Hepatotoxicity (drug-induced liver injury, hepatitis cholestatic, hepatocellular injury, hepatotoxicity)

[j] Rash (rash, dermatitis acneiform, rash maculopapular)

[k] Renal failure (acute renal injury, renal failure)

[l] Renal impairment (azotaemia, renal impairment)

[m] Fatigue (fatigue, asthenia)

[n] Liver laboratory test abnormalities (alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased, blood bilirubin increased, transaminases increased, hepatic enzyme increased, liver function test abnormal, liver function test increased, blood alkaline phosphatase increased)

Elderly (≥65 years)

Across seven clinical studies, 168 out of 925 patients (18.2%) treated with ceritinib were aged 65 years or older. The safety profile in patients aged 65 years or older was similar to that in patients less than 65 years of age (see section 4.2). There are no safety data in patients older than 85 years of age.

Hepatotoxicity

Concurrent elevations of ALT or AST greater than 3× ULN and total bilirubin greater than 2× ULN without elevated alkaline phosphatase have been observed in less than 1% of patients in clinical studies with ceritinib. Increases to grade 3 or 4 ALT elevations were observed in 25% of patients receiving ceritinib. Hepatotoxicity events were managed with dose interruptions or reductions in 40.6% of patients. 1% of patients required permanent discontinuation of treatment in clinical studies with ceritinib (see sections 4.2 and 4.4).

Liver laboratory tests including ALT, AST and total bilirubin should be performed prior to the start of treatment, every 2 weeks during the first three months of treatment and monthly thereafter, with more frequent testing for grade 2, 3 or 4 elevations. Patients should be monitored for liver laboratory test abnormalities and managed as recommended in sections 4.2 and 4.4.

Gastrointestinal adverse reactions

Nausea, diarrhoea and vomiting were among the most commonly reported gastrointestinal events. In the dose optimisation study A2112 (ASCEND-8) in both previously treated and untreated patients with ALK-positive advanced NSCLC at the recommended dose of ceritinib 450 mg taken with food (N=108), adverse events of diarrhoea, nausea and vomiting were mainly grade 1 (52.8%) and grade 2 (22.2%). Grade 3 events of diarrhoea and vomiting were each reported in two different patients (1.9%). Gastrointestinal events were managed primarily with concomitant medicinal products including anti-emetic/anti-diarrhoeal medicinal products. Nine patients (8.3%) required study drug interruption due to diarrhoea, nausea or vomiting. One patient (0.9%) required dose adjustment. In the 450 mg with food and 750 mg fasted arms, no patients had diarrhoea, nausea, or vomiting that required discontinuation of study drug. In the same study the incidence and severity of gastrointestinal adverse drug reactions were reduced for patients treated with ceritinib 450 mg with food (diarrhoea 59.3%, nausea 42.6%, vomiting 38.0%; 1.9% reported a grade 3 event) compared to 750 mg fasted (diarrhoea 80.0%, nausea 60.0%, vomiting 65.5%; 17.3% reported a grade 3 event). Patients should be managed as recommended in sections 4.2 and 4.4.

QT interval prolongation

QTc prolongation has been observed in patients treated with ceritinib. Across the seven clinical studies, 9.7% of patients treated with ceritinib had events of QT prolongation (any grade), including grade 3 or 4 events in 2.1% of patients. These events required dose reduction or interruption in 2.1% of patients and led to discontinuation in 0.2% of patients.

Treatment with ceritinib is not recommended in patients who have congenital long QT syndrome or who are taking medicinal products known to prolong the QTc interval (see sections 4.4 and 4.5). Particular care should be exercised when administering ceritinib to patients with an increased risk of experiencing torsade de pointes during treatment with a QTc-prolonging medicinal product.

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

Bradycardia

Across the seven clinical studies, bradycardia and/or sinus bradycardia (heart rate less than 60 bpm) events (all grade 1) were reported in 2.3% of patients. These events required dose reduction or interruption in 0.2% of patients. None of these events led to discontinuation of ceritinib treatment. The use of concomitant medicinal products associated with bradycardia should be carefully evaluated. Patients who develop symptomatic bradycardia should be managed as recommended in sections 4.2 and 4.4.

Interstitial lung disease/Pneumonitis

Severe, life-threatening, or fatal interstitial lung disease (ILD)/pneumonitis have been observed in patients treated with ceritinib. Across the seven clinical studies, any grade ILD/pneumonitis has been reported in 2.1% of patients treated with ceritinib, and grade 3 or 4 events have been reported in 1.2% of patients. These events required dose reduction or interruption in 1.1% of patients and led to discontinuation in 0.9% of patients. 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).

Hyperglycaemia

Hyperglycaemia (all grades) was reported in 9.4% of patients treated with ceritinib across the seven clinical studies; grade 3 or 4 events were reported in 5.4% of patients. These events required dose reduction or interruption in 1.4% of patients and led to discontinuation in 0.1% of patients. The risk of hyperglycaemia was higher in patients with diabetes mellitus and/or concurrent steroid use. Monitoring of fasting serum glucose is required prior to the start of ceritinib treatment and periodically thereafter as clinically indicated. Administration of anti-hyperglycaemic medicinal products should be initiated or optimised as indicated (see sections 4.2 and 4.4).

Reporting of suspected adverse reactions

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

4.9 Overdose

There is no reported experience with overdose in humans. General supportive measures should be initiated in all cases of overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, anaplastic lymphoma kinase (ALK) inhibitors, ATC code: L01ED02.

Mechanism of action

Ceritinib is an orally highly selective and potent ALK inhibitor. Ceritinib inhibits autophosphorylation of ALK, ALK-mediated phosphorylation of downstream signalling proteins and proliferation of ALK-dependent cancer cells both *in vitro* and *in vivo*.

ALK translocation determines expression of the resulting fusion protein and consequent aberrant ALK signaling in NSCLC. In the majority of NSCLC cases, EML4 is the translocation partner for ALK; this generates an EML4-ALK fusion protein containing the protein kinase domain of ALK fused to the N-terminal part of EML4. Ceritinib was demonstrated to be effective against EML4-ALK activity in a NSCLC cell line (H2228), resulting in inhibition of cell proliferation *in vitro* and regression of tumours in H2228-derived xenografts in mouse and rat.

Clinical efficacy and safety

Previously untreated ALK-positive advanced NSCLC - randomised phase 3 Study A2301 (ASCEND-4)
The efficacy and safety of ceritinib for the treatment of advanced ALK-positive NSCLC patients who have not received previous systemic treatment anti-cancer therapy (including ALK inhibitor) with the exception of neo-adjuvant or adjuvant therapy, was demonstrated in a global multicentre, randomised, open-label phase 3 Study A2301.

A total of 376 patients were randomised in a 1:1 ratio (stratified by WHO performance status, prior adjuvant/neoadjuvant chemotherapy and presence/absence of brain metastasis at screening) to receive either ceritinib (750 mg daily, fasted) or chemotherapy (based on investigator's choice - pemetrexed [500 mg/m^2] plus cisplatin [75 mg/m^2] or carboplatin [AUC 5-6], administered every 21 days). Patients who completed 4 cycles of chemotherapy (induction) without progressive disease subsequently received pemetrexed (500 mg/m^2) as single-agent maintenance therapy every 21 days. One hundred and eighty-nine (189) patients were randomised to ceritinib and one hundred eighty-seven (187) were randomised to chemotherapy.

The median age was 54 years (range: 22 to 81 years); 78.5% of patients were younger than 65 years. A total of 57.4% of patients were female. 53.7% of the study population was Caucasian, 42.0% Asian, 1.6% Black and 2.6% other races The majority of patients had adenocarcinoma (96.5%) and had either never smoked or were former smokers (92.0%). The Eastern Cooperative Oncology Group (ECOG) performance status was 0/1/2 in 37.0%/56.4%/6.4% of patients, and 32.2% had brain metastasis at baseline. 59.5% of patients with brain metastasis at baseline received no prior radiotherapy to the brain. Patients with symptomatic CNS (central nervous system) metastases who were neurologically unstable or had required increasing doses of steroids within the 2 weeks prior to screening to manage CNS symptoms, were excluded from the study.

Patients were allowed to continue the assigned study treatment beyond initial progression in case of continued clinical benefit as per the investigator's opinion. Patients randomised to the chemotherapy arm could cross-over to receive ceritinib upon RECIST-defined disease progression confirmed by blinded independent review committee (BIRC). One hundred and five (105) patients out of the 145 patients (72.4%) that discontinued treatment in the chemotherapy arm received subsequent ALK inhibitor as first antineoplastic therapy. Of these patients 81 received ceritinib.

The median duration of follow-up was 19.7 months (from randomisation to cut-off date) at the primary analysis.

The study met its primary objective demonstrating a statistically significant improvement in progression free survival (PFS) by BIRC (see Table 3 and Figure 1). The PFS benefit of ceritinib was consistent by investigator assessment and across various subgroups including age, gender, race, smoking class, ECOG performance status and disease burden.

At the time of the primary analysis, the overall survival (OS) data was not mature with 107 deaths representing approximately 42.3% of the required events for the final OS analysis.

Efficacy data from Study A2301 are summarised in Table 3, and the Kaplan-Meier curves for PFS and OS are shown in Figure 1 and Figure 2, respectively.

Table 3 ASCEND-4 (Study A2301) - Efficacy results in patients with previously untreated ALK-positive advanced NSCLC (primary analysis)

	Ceritinib (N=189)	Chemotherapy (N=187)
Progression-free survival (based on BIRC)		
Number of events, n (%)	89 (47.1)	113 (60.4)
Median, months[d] (95% CI)	16.6 (12.6, 27.2)	8.1 (5.8, 11.1)
HR (95% CI)[a]	0.55 (0.42, 0.73)	
p-value[b]	<0.001	
Overall survival[c]		
Number of events, n (%)	48 (25.4)	59 (31.6)
Median, months[d] (95% CI)	NE (29.3, NE)	26.2 (22.8, NE)
OS rate at 24 months[d], % (95% CI)	70.6 (62.2, 77.5)	58.2 (47.6, 67.5)
HR (95% CI)[a]	0.73 (0.50,1.08)	
p-value[b]	0.056	
Tumour response (based on BIRC)		
Overall response rate (95% CI)	72.5% (65.5, 78.7)	26.7% (20.5, 33.7)
Duration of response (based on BIRC)		
Number of responders	137	50
Median, months[d] (95% CI)	23.9 (16.6, NE)	11.1 (7.8, 16.4)
Event-free rate at 18 months[d], % (95% CI)	59.0 (49.3, 67.4)	30.4 (14.1, 48.6)

HR=hazard ratio; CI=confidence interval; BIRC=Blinded Independent Review Committee; NE=not estimable

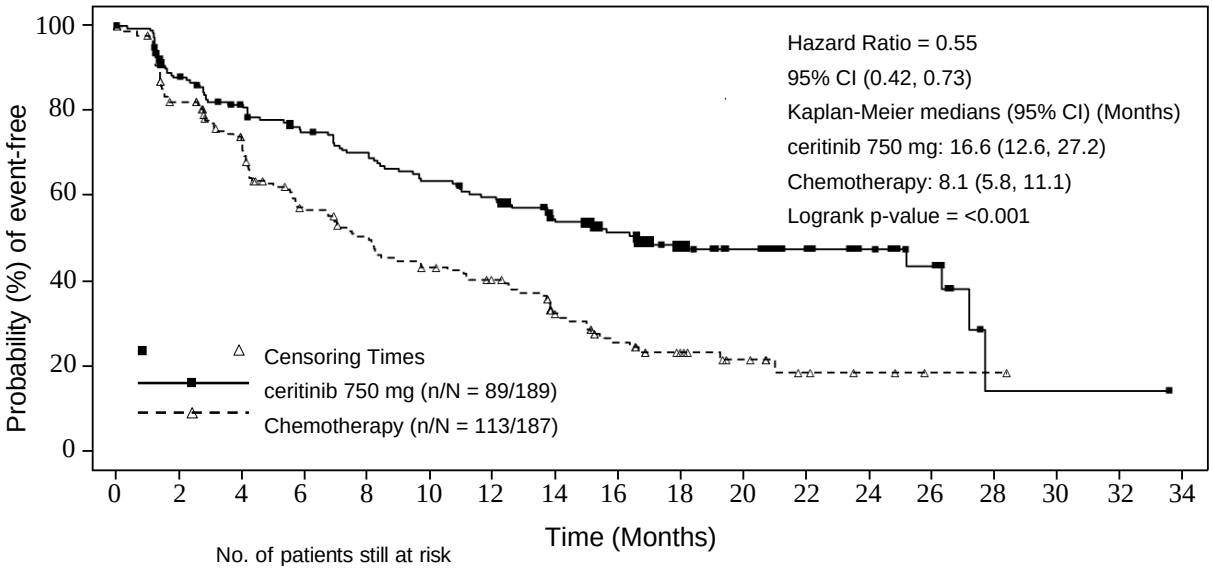
[a] Based on the Cox proportional hazards stratified analysis.

[b] Based on the stratified log-rank test.

[c] OS analysis was not adjusted for the effects of cross-over.

[d] Estimated using the Kaplan-Meier method.

Figure 1 ASCEND-4 (Study A2301) - Kaplan-Meier curves of progression-free survival as assessed by BIRC (primary analysis)

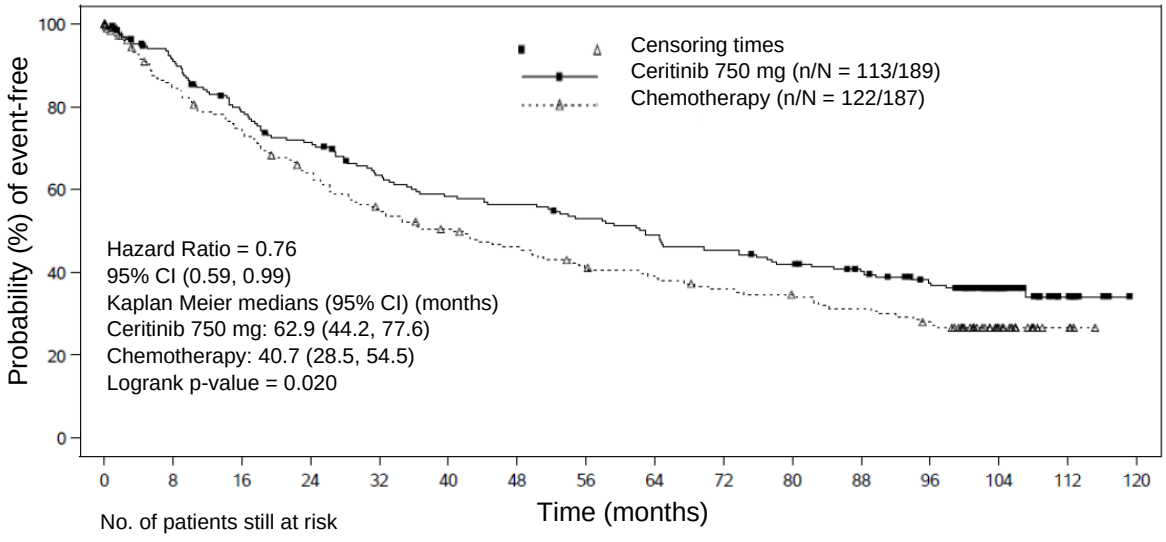


No. of patients still at risk

Time (Months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34
ceritinib 750 mg	189	155	139	125	116	105	98	76	59	43	32	23	16	11	1	1	1	0
Chemotherapy	187	136	114	82	71	60	53	35	24	16	11	5	3	1	1	0	0	0

At the final OS analysis, 113 (59.8%) patients had died in the ceritinib arm and 122 (65.2%) in the chemotherapy arm. The median OS was 62.9 months (95% CI: 44.2, 77.6) and 40.7 months (95% CI: 28.5, 54.5) for the ceritinib arm and the chemotherapy arm, respectively. There was a statistically significant 24% reduction in the risk of death in the ceritinib arm compared to the chemotherapy arm (HR 0.76; 95% CI: 0.59, 0.99; p=0.020). There was a high rate of crossover, with 61.5% of patients in the chemotherapy arm switching to receive ceritinib. Additionally, patients in both arms received next-line antineoplastic therapies, including other ALK inhibitors, which influenced the OS outcome.

Figure 2 ASCEND-4 (Study A2301)- Kaplan-Meier plot of overall survival by treatment arm (final OS analysis)



No. of patients still at risk

Time (months)	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	76	80	84	88	92	96	100	104	108	112	116	120
Ceritinib 750 mg	189	176	166	151	141	129	127	117	110	104	101	100	98	95	91	88	84	79	78	74	71	68	64	60	55	51	30	17	9	3	0
Chemotherapy	187	161	146	135	128	115	108	99	91	87	82	76	74	69	65	63	61	58	55	53	52	48	47	44	41	32	19	7	4	0	0

In Study A2301, 44 patients with measurable brain metastasis at baseline and at least one post-baseline brain radiological assessment (22 patients in the ceritinib arm and 22 patients in the chemotherapy arm) were assessed for intracranial response by BIRC neuro-radiologist per modified RECIST 1.1 (i.e. up to 5 lesions in the brain). The overall intracranial response rate (OIRR) was higher with ceritinib (72.7%, 95% CI: 49.8, 89.3) as compared to the chemotherapy arm (27.3%, 95% CI: 10.7, 50.2).

The median PFS by BIRC using RECIST 1.1 was longer in the ceritinib arm compared to the chemotherapy arm in both subgroups of patients with brain metastases and without brain metastases. The median PFS in patients with brain metastases was 10.7 months (95% CI: 8.1, 16.4) versus 6.7 months (95% CI: 4.1, 10.6) in the ceritinib and chemotherapy arms, respectively, with HR 0.70 (95% CI: 0.44, 1.12). The median PFS in patients without brain metastases was 26.3 months (95% CI: 15.4, 27.7) versus 8.3 months (95% CI: 6.0, 13.7) in the ceritinib and chemotherapy arms, respectively, with HR 0.48 (95% CI: 0.33, 0.69).

Previously treated ALK-positive advanced NSCLC - randomised phase 3 Study A2303 (ASCEND-5)
The efficacy and safety of ceritinib for the treatment of ALK-positive advanced NSCLC patients who have received previous treatment with crizotinib, was demonstrated in a global multicentre, randomised, open-label phase 3 Study A2303.

A total of 231 patients with advanced ALK positive NSCLC who have received prior treatment with crizotinib and chemotherapy (one or two regimen including a platinum-based doublet) were included in the analysis. One hundred fifteen (115) patients were randomised to ceritinib and one hundred sixteen (116) were randomised to chemotherapy (either pemetrexed or docetaxel). Seventy-three (73) patients received docetaxel and 40 received pemetrexed. In the ceritinib arm, 115 patients were treated with 750 mg once daily fasted. The median age was 54.0 years (range: 28 to 84 years); 77.1% of patients were younger than 65 years. A total of 55.8% of patients were female. 64.5% of the study population were Caucasian, 29.4% Asian, 0.4% Black and 2.6% other races. The majority of patients had adenocarcinoma (97.0%) and had either never smoked or were former smokers (96.1%). The ECOG performance status was 0/1/2 in 46.3%/47.6%/6.1% of patients respectively, and 58.0% had brain metastasis at baseline. All patients were treated with prior crizotinib. All except one patient received prior chemotherapy (including a platinum doublet) for advanced disease; 11.3% of the patients in the ceritinib arm and 12.1% of the patients in the chemotherapy arm were treated with two prior chemotherapy regimen for advanced disease.

Patients were allowed to continue the assigned study treatment beyond initial progression in case of continued clinical benefit as per the investigator's opinion. Patients randomised to the chemotherapy arm could further crossover to receive ceritinib upon RECIST-defined disease progression confirmed by BIRC.

The median duration of follow-up was 16.5 months (from randomisation to data cut-off date) at the primary analysis.

The study met its primary objective demonstrating a statistically significant improvement in PFS by BIRC with an estimated 51% risk reduction in the ceritinib arm compared to chemotherapy arm (see Table 4 and Figure 3). The PFS benefit of ceritinib was consistent across various subgroups including age, gender, race, smoking class, ECOG performance status, and presence of brain metastases or prior response to crizotinib. The PFS benefit was further supported by local investigator assessment, and analysis of overall response rate (ORR) and disease control rate (DCR).

At the primary analysis, OS data was immature with 48 (41.7%) events in the ceritinib arm and 50 (43.1%) events in the chemotherapy arm, corresponding to approximately 50% of the required events for the final OS analysis. In addition, 81 patients (69.8%) in the chemotherapy arm received subsequent ceritinib as first antineoplastic therapy after study treatment discontinuation.

Efficacy data from Study A2303 are summarised in Table 4, and the Kaplan-Meier curves for PFS and OS are shown in Figure 3 and 4, respectively.

Table 4 ASCEND-5 (Study A2303) – Efficacy results in patients with previously treated ALK-positive metastatic/advanced NSCLC (primary analysis)

	Ceritinib (N=115)	Chemotherapy (N=116)
Duration of follow-up Median (months) (min – max)	16.5 (2.8 – 30.9)	
Progression-free survival (based on BIRC)		
Number of events, n (%)	83 (72.2%)	89 (76.7%)
Median, months (95% CI)	5.4 (4.1, 6.9)	1.6 (1.4, 2.8)
HR (95% CI)[a]	0.49 (0.36, 0.67)	
p-value[b]	<0.001	
Overall survival[c]		
Number of events, n (%)	48 (41.7%)	50 (43.1%)
Median, months (95% CI)	18.1 (13.4, 23.9)	20.1 (11.9, 25.1)
HR (95% CI)[a]	1.00 (0.67,1.49)	
p-value[b]	0.496	
Tumour responses (based on BIRC)		
Objective response rate (95% CI)	39.1% (30.2, 48.7)	6.9% (3.0, 13.1)
Duration of response		
Number of responders	45	8
Median, months[d] (95% CI)	6.9 (5.4, 8.9)	8.3 (3.5, NE)
Event-free probability estimate at 9 months[d] (95% CI)	31.5% (16.7%, 47.3%)	45.7% (6.9%, 79.5%)

HR=hazard ratio; CI=confidence interval; BIRC=Blinded Independent Review Committee; NE=not estimable

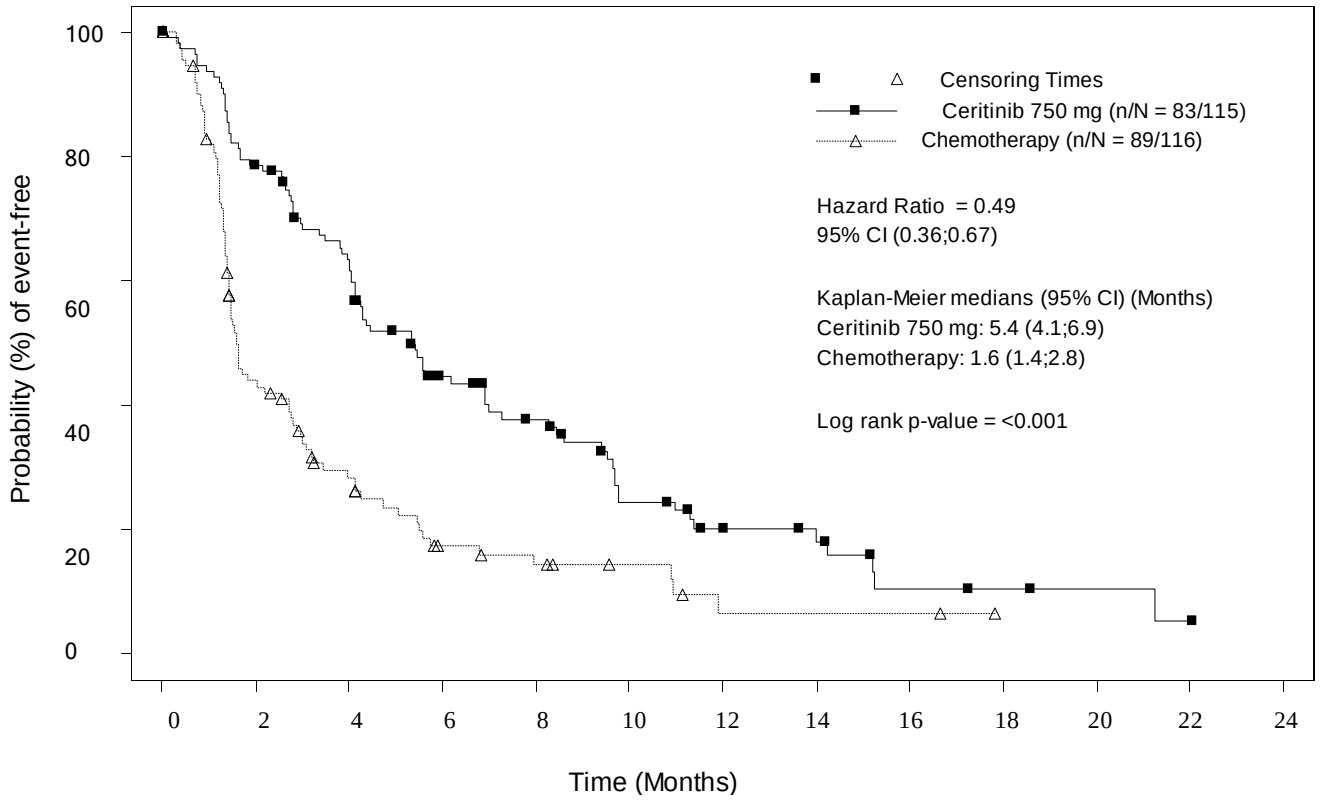
[a] Based on the stratified Cox proportional hazards analysis.

[b] Based on the stratified log-rank test.

[c] OS analysis was not adjusted for the potentially confounding effects of cross over.

[d] Estimated using the Kaplan-Meier method.

Figure 3 ASCEND-5 (Study A2303) – Kaplan-Meier plot of progression-free survival as assessed by BIRC (primary analysis)

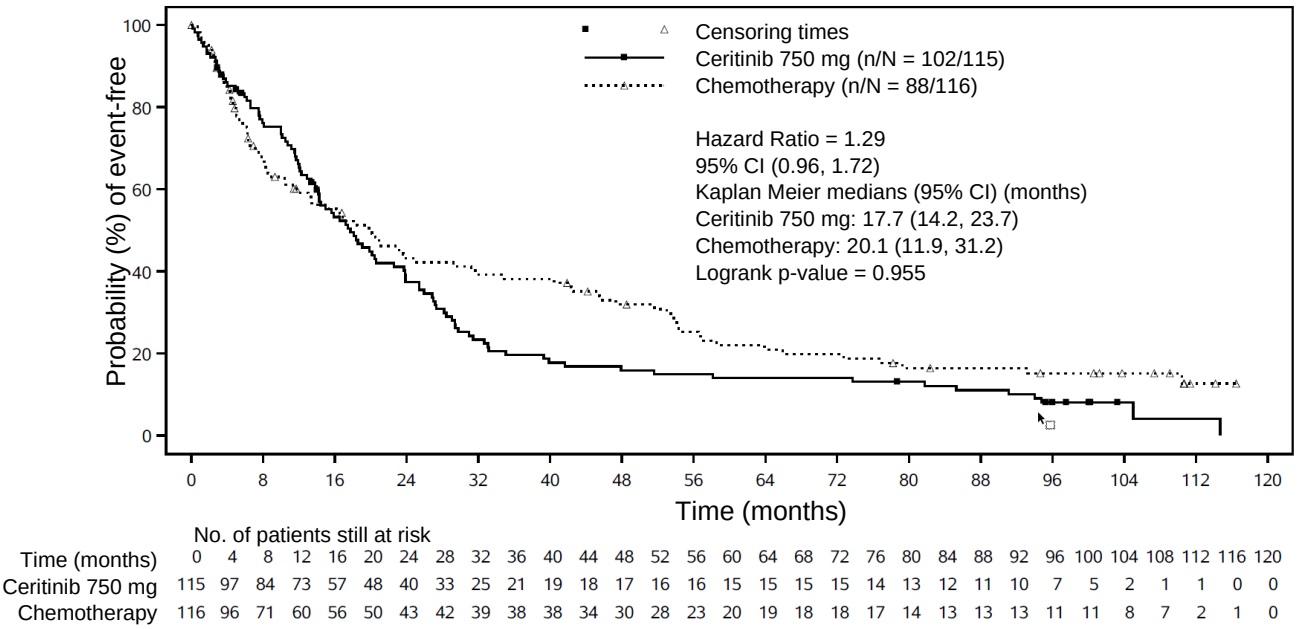


No. of patients still at risk

Time (Months)	0	2	4	6	8	10	12	14	16	18	20	22	24
Ceritinib 750 mg	115	87	68	40	31	18	12	9	4	3	2	1	0
Chemotherapy	116	45	26	12	9	6	2	2	2	0	0	0	0

At the final OS analysis, with a median duration of follow-up of 110 months, 102 (88.7%) patients had died in the ceritinib arm and 88 (75.9%) in the chemotherapy arm. The median OS was 17.7 months (95% CI: 14.2, 23.7) and 20.1 months (95% CI: 11.9, 31.2) for the ceritinib arm and the chemotherapy arm, respectively. There was no statistically significant difference in OS between the two treatment arms (HR 1.29; 95% CI: 0.96, 1.72; p=0.955). There was a high rate of early crossover, with 88 (76%) of patients in the chemotherapy arm switching to receive ceritinib. Additionally, patients in both arms received next-line antineoplastic therapies, including other ALK inhibitors. Overall, crossover and next-line therapies were a major confounding factor that may have diluted any potential difference in OS between the treatment arms.

Figure 4 ASCEND-5 (Study A2303) – Kaplan-Meier plot of overall survival by treatment arm (final OS analysis)



No. of patients still at risk

Time (months)	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	76	80	84	88	92	96	100	104	108	112	116	120
Ceritinib 750 mg	115	97	84	73	57	48	40	33	25	21	19	18	17	16	16	15	15	15	15	14	13	12	11	10	7	5	2	1	1	0	0
Chemotherapy	116	96	71	60	56	50	43	42	39	38	38	34	30	28	23	20	19	18	18	17	14	13	13	13	11	11	8	7	2	1	0

In Study A2303, 133 patients with baseline brain metastasis (66 patients in the ceritinib arm and 67 patients in the chemotherapy arm) were assessed for intracranial response by BIRC neuro-radiologist (per modified RECIST 1.1 (i.e. up to 5 lesions in the brain). The OIRR in patients with measurable disease in the brain at baseline and at least one post-baseline assessment was higher in the ceritinib arm (35.3%, 95% CI: 14.2, 61.7) compared to the chemotherapy arm (5.0%, 95% CI: 0.1, 24.9). The median PFS by BIRC using RECIST 1.1 was longer in the ceritinib arm compared to the chemotherapy arm in both subgroups of patients with brain metastases and without brain metastases. The median PFS in patients with brain metastases was 4.4 months (95% CI: 3.4, 6.2) versus 1.5 months (95% CI: 1.3, 1.8) in the ceritinib and chemotherapy arms, respectively with HR 0.54 (95% CI: 0.36, 0.80). The median PFS in patients without brain metastases was 8.3 months (95% CI: 4.1, 14.0) versus 2.8 months (95% CI: 1.4, 4.1) in the ceritinib and chemotherapy arms, respectively with HR 0.41 (95% CI: 0.24, 0.69).

Dose optimisation Study A2112 (ASCEND-8)

The efficacy of ceritinib 450 mg with food was evaluated in a multicentre, open-label dose optimisation study A2112 (ASCEND-8). A total of 147 previously untreated patients with ALK-positive locally advanced or metastatic NSCLC were randomised to receive ceritinib 450 mg once daily with food (N=73) or ceritinib 750 mg once daily under fasted conditions (N=74). A key secondary efficacy endpoint was ORR according to RECIST 1.1 as evaluated by BIRC.

The population characteristics of the previously untreated patients with ALK-positive locally advanced or metastatic NSCLC across the two arms, 450 mg with food (N=73) and 750 mg fasted (N=74), were: mean age 54.3 and 51.3 years, age less than 65 (78.1% and 83.8%), female (56.2% and 47.3%), Caucasian (49.3% and 54.1%), Asian (39.7% and 35.1%), never or former smoker (90.4% and 95.9%), WHO PS 0 or 1 (91.7% and 91.9%), adenocarcinoma histology (98.6% and 93.2%), and metastases to the brain (32.9% and 28.4%), respectively.

Efficacy results from ASCEND-8 are summarised in Table 5 below.

Table 5 ASCEND-8 (Study A2112) - Efficacy results in patients with previously untreated ALK-positive locally advanced or metastatic NSCLC by BIRC

Efficacy Parameter	Ceritinib 450 mg with food (N=73)	Ceritinib 750 mg fasted (N=74)
Overall Response Rate (ORR: CR+PR), n (%) (95% CI)[a]	57 (78.1) (66.9, 86.9)	56 (75.7) (64.3, 84.9)

CI: Confidence Interval
Complete Response (CR), Partial Response (PR) confirmed by repeat assessments performed not less than 4 weeks after response criteria were first met
Overall response rate determined based on BIRC assessment per RECIST 1.1
[a]Exact binomial 95% confidence interval

Single arm studies X2101 and A2201
The use of ceritinib in the treatment of ALK-positive NSCLC patients previously treated with an ALK inhibitor was investigated in two global, multicentre, open-label, single-arm phase 1/2 studies (Study X2101 and Study A2201).

In study X2101 a total of 246 ALK-positive NSCLC patients were treated at a ceritinib dose of 750 mg once daily fasted: 163 who had received prior treatment with an ALK inhibitor and 83 who were ALK inhibitor naïve. Of the 163 ALK-positive NSCLC patients who had received prior treatment with an ALK inhibitor, the median age was 52 years (range: 24-80 years); 86.5% were younger than 65 years and 54% were female. The majority of patients were Caucasian (66.3%) or Asian (28.8%). 93.3% had adenocarcinoma and 96.9% had either never been or were former smokers. All of the patients were treated with at least one regimen prior to enrolment into the study and 84.0% with two or more regimens.

Study A2201 involved 140 patients who had been previously treated with 1-3 lines of cytotoxic chemotherapy followed by treatment with crizotinib, and who had then progressed on crizotinib. The median age was 51 years (range: 29-80 years); 87.1% of patients were younger than 65 years and 50.0% were female. The majority of patients were Caucasian (60.0%) or Asian (37.9%). 92.1% of patients had adenocarcinoma.

The main efficacy data for both studies are summarised in Table 6. Final overall survival (OS) data are presented for Study A2201. For Study X2101, OS data were not yet mature at the time of the analysis.

Table 6 ALK-positive advanced NSCLC - overview of efficacy results from Studies X2101 and A2201

	Study X2101 ceritinib 750 mg N=163	Study A2201 ceritinib 750 mg N=140
Duration of follow-up Median (months) (min – max)	10.2 (0.1 – 24.1)	14.1 (0.1 – 35.5)
Overall response rate		
Investigator (95% CI)	56.4% (48.5, 64.2)	40.7% (32.5, 49.3)
BIRC (95% CI)	46.0% (38.2, 54.0)	35.7% (27.8, 44.2)
Duration of response*		
Investigator (months, 95% CI)	8.3 (6.8, 9.7)	10.6 (7.4, 14.7)
BIRC (months, 95% CI)	8.8 (6.0, 13.1)	12.9 (9.3, 18.4)
Progression-free survival		
Investigator (months, 95% CI)	6.9 (5.6, 8.7)	5.8 (5.4, 7.6)
BIRC (months, 95% CI)	7.0 (5.7, 8.7)	7.4 (5.6, 10.9)
Overall survival (months, 95% CI)	16.7 (14.8, NE)	15.6 (13.6, 24.2)

NE = not estimable
Study X2101: Responses assessed using RECIST 1.0
Study A2201: Responses assessed using RECIST 1.1
*Includes only patients with confirmed CR, PR

In Studies X2101 and A2201, brain metastases were seen in 60.1% and 71.4% of patients, respectively. The ORR, DOR and PFS (by BIRC assessment) for patients with brain metastases at baseline were in line with those reported for the overall population of these studies.

Non-adenocarcinoma histology

Limited information is available in ALK-positive NSCLC patients with non-adenocarcinoma histology.

Elderly

Limited efficacy data are available in elderly patients. No efficacy data are available in patients over 85 years of age.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with ceritinib in all subsets of the paediatric population in lung carcinoma (small cell and non-small cell carcinoma) (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Peak plasma levels (C_{max}) of ceritinib are achieved approximately 4 to 6 hours after a single oral administration in patients. Oral absorption was estimated to be ≥25% based on metabolite percentages in the faeces. The absolute bioavailability of ceritinib has not been determined.

Systemic exposure of ceritinib was increased when administered with food. Ceritinib AUC_{inf} values were approximately 39% and 64% higher (C_{max} approximately 42% and 58% higher) in healthy subjects when a single 750 mg ceritinib dose (tablet) was administered with a low fat meal (containing approximately 330 kcalories and 9 grams of fat) and a high fat meal (containing approximately 1000 kcalories and 58 grams of fat), respectively, as compared with the fasted state.

In a dose optimisation study A2112 (ASCEND-8) in patients comparing ceritinib 450 mg or 600 mg daily with food (approximately 100 to 500 kcalories and 1.5 to 15 grams of fat) to 750 mg daily under fasted conditions (dose and food condition of administration initially authorised), there was no clinically meaningful difference in the systemic steady-state exposure of ceritinib for the 450 mg with food arm (N=36) compared to the 750 mg fasted arm (N=31), with only small increases in steady-state AUC (90% CI) by 4% (-13%, 24%) and C_{max} (90% CI) by 3% (-14%, 22%). In contrast, the steady-state AUC (90% CI) and C_{max} (90% CI) for the 600 mg with food arm (N=30) increased by 24% (3%, 49%) and 25% (4%, 49%), respectively, compared to the 750 mg fasted arm. The maximum recommended dose of ceritinib is 450 mg taken orally once daily with food (see section 4.2).

After single oral administration of ceritinib in patients, plasma exposure to ceritinib, as represented by C_{max} and AUC_{last}, increased dose-proportionally over the 50 to 750 mg dose range under fasted conditions. In contrast with single-dose data, pre-dose concentration (C_{min}) after repeated daily dosing appeared to increase in a greater than dose-proportional manner.

Distribution

Binding of ceritinib to human plasma proteins *in vitro* is approximately 97% in a concentration independent manner, from 50 ng/ml to 10,000 ng/ml. Ceritinib also has a slight preferential distribution to red blood cells, relative to plasma, with a mean *in vitro* blood-to-plasma ratio of 1.35. *In vitro* studies suggest that ceritinib is a substrate for P-glycoprotein (P-gp), but not of breast cancer resistance protein (BCRP) or multi-resistance protein 2 (MRP2). The *in vitro* apparent passive permeability of ceritinib was determined to be low.

In rats, ceritinib crosses the intact blood brain barrier with a brain-to-blood exposure (AUC_{inf}) ratio of about 15%. There are no data related to brain-to-blood exposure ratio in humans.

Biotransformation

In vitro studies demonstrated that CYP3A was the major enzyme involved in the metabolic clearance of ceritinib.

Following a single oral administration of radioactive ceritinib dose at 750 mg fasted, ceritinib was the main circulating component in human plasma. A total of 11 metabolites were found circulating in plasma at low levels with mean contribution to the radioactivity AUC of ≤2.3% for each metabolite. Main biotransformation pathways identified in healthy subjects included mono-oxygenation, O-dealkylation, and N-formylation. Secondary biotransformation pathways involving the primary biotransformation products included glucuronidation and dehydrogenation. Addition of a thiol group to O-dealkylated ceritinib was also observed.

Elimination

Following single oral doses of ceritinib under fasted conditions, the geometric mean apparent plasma terminal half-life ($T_{½}$) of ceritinib ranged from 31 to 41 hours in patients over the 400 to 750 mg dose range. Daily oral dosing of ceritinib results in achievement of steady-state by approximately 15 days and remains stable afterwards, with a geometric mean accumulation ratio of 6.2 after 3 weeks of daily dosing. The geometric mean apparent clearance (CL/F) of ceritinib was lower at steady-state (33.2 litres/hour) after 750 mg daily oral dosing than after a single 750 mg oral dose (88.5 litres/hour), suggesting that ceritinib demonstrates non-linear pharmacokinetics over time.

The primary route of excretion of ceritinib and its metabolites is in the faeces. Recovery of unchanged ceritinib in the faeces accounts for a mean 68% of an oral dose. Only 1.3% of the administered oral dose is recovered in the urine.

Special populations

Hepatic impairment
The effect of hepatic impairment on the single-dose pharmacokinetics of ceritinib (750 mg under fasted conditions) was evaluated in subjects with mild (Child-Pugh class A; N=8), moderate (Child-Pugh class B; N=7), or severe (Child-Pugh class C; N=7) hepatic impairment and in 8 healthy subjects with normal hepatic function. The geometric mean AUC_{inf} (unbound AUC_{inf}) of ceritinib was increased by 18% (35%) and 2% (22%) in subjects with mild and moderate hepatic impairment, respectively, compared to subjects with normal hepatic function.

The geometric mean AUC_{inf} (unbound AUC_{inf}) of ceritinib was increased by 66% (108%) in subjects with severe hepatic impairment compared to subjects with normal hepatic function (see section 4.2). A dedicated pharmacokinetic study under steady-state in patients with hepatic impairment has not been conducted.

Renal impairment
A dedicated pharmacokinetic study in patients with renal impairment has not been conducted. Based on available data, ceritinib elimination via the kidney is negligible (1.3% of a single oral administered dose).

Based on a population pharmacokinetic analysis of 345 patients with mild renal impairment (CLcr 60 to <90 ml/min), 82 patients with moderate renal impairment (CLcr 30 to <60 ml/min) and 546 patients with normal renal function (≥90 ml/min), ceritinib exposures were similar in patients with mild and moderate renal impairment and normal renal function, suggesting that no dose adjustment is necessary in patients with mild to moderate renal impairment. Patients with severe renal impairment (CLcr <30 ml/min) were not included in the clinical studies of ceritinib (see section 4.2).

Effects of age, gender, and race
Population pharmacokinetic analyses showed that age, gender and race had no clinically meaningful influence on ceritinib exposure.

Cardiac electrophysiology
The potential for QT interval prolongation of ceritinib was assessed in seven clinical studies with ceritinib. Serial ECGs were collected following a single dose and at steady-state to evaluate the effect of ceritinib on the QT interval in 925 patients treated with ceritinib 750 mg once daily fasted. A categorical outlier analysis of ECG data demonstrated new QTc >500 msec in 12 patients (1.3%). There were 58 patients (6.3%) with a QTc increase from baseline >60 msec. A central tendency analysis of the QTc data at average steady-state concentration from Study A2301 demonstrated that the upper bound of the 2-sided 90% CI for QTc increase from baseline was 15.3 msec at ceritinib 750 mg fasted. A pharmacokinetic analysis suggested that ceritinib causes concentration-dependent increases in QTc (see section 4.4).

5.3 Preclinical safety data

Safety pharmacology studies indicate that ceritinib is unlikely to interfere with vital functions of the respiratory and central nervous systems. *In vitro* data show that the IC50 for the inhibitory effect of ceritinib on the hERG potassium channel was 0.4 micromolar. An *in vivo* telemetry study in monkeys showed a modest QT prolongation in 1 of 4 animals after receiving the highest dose of ceritinib. ECG studies in monkeys after 4- or 13-weeks of dosing with ceritinib have not shown QT prolongation or abnormal ECGs.

The micronucleus test in TK6 cells was positive. No signs of mutagenicity or clastogenicity were observed in other *in vitro* and *in vivo* genotoxicity studies with ceritinib. Therefore, genotoxic risk is not expected in humans.

Carcinogenicity studies have not been performed with ceritinib.

Reproductive toxicology studies (i.e. embryo-foetal development studies) in pregnant rats and rabbits indicated no foetotoxicity or teratogenicity after dosing with ceritinib during organogenesis; however, maternal plasma exposure was less than that observed at the recommended human dose. Formal non-clinical studies on the potential effects of ceritinib on fertility have not been conducted.

The principal toxicity related to ceritinib administration in rats and monkeys was inflammation of the extra-hepatic bile ducts accompanied by increased neutrophil counts in the peripheral blood. Mixed cell/neutrophilic inflammation of the extra-hepatic ducts extended to the pancreas and/or duodenum at higher doses. Gastrointestinal toxicity was observed in both species characterised by body weight loss, decreased food consumption, emesis (monkey), diarrhoea and, at high doses, by histopathological lesions including erosion, mucosal inflammation and foamy macrophages in the duodenal crypts and submucosa. The liver was also affected in both species, at exposures that approximate clinical exposures at the recommended human dose, and included minimal increases in liver transaminases in a few animals and vacuolation of the intra-hepatic bile duct epithelium. Alveolar foamy macrophages (confirmed phospholipidosis) were seen in the lungs of rats, but not in monkeys, and the lymph nodes of rats and monkeys had macrophage aggregates. Target organ effects showed partial to complete recovery.

Effects on the thyroid were observed in both rat (mild increases in thyroid stimulating hormone and triiodothyronine/thyroxine T3/T4 concentrations with no microscopic correlate) and monkey (depletion of colloid in males in 4-week study, and one monkey at high dose with diffuse follicular cell hyperplasia and increased thyroid stimulating hormone in 13-week study). As these non-clinical effects were mild, variable and inconsistent, the relationship between ceritinib and thyroid gland changes in animals is unclear.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Cellulose, microcrystalline
Hydroxypropylcellulose, low-substituted
Povidone
Croscarmellose sodium
Magnesium stearate
Silica, colloidal anhydrous

Film-coating

Hypromellose
Titanium dioxide (E171)
Macrogol
Talc
Indigo carmine aluminium lake (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PCTFE (polyvinylchloride/polychlorotrifluoroethylene) – Aluminium blister containing 21 film-coated tablets.

Pack containing 84 film-coated tablets (4 blisters per pack).

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

8. MARKETING AUTHORISATION NUMBERS

EU/1/15/999/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 06 May 2015
Date of latest renewal: 16 February 2022

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

150 mg hard capsules

Novartis Farmacéutica, S.A.
Gran Via de les Corts Catalanes, 764
08013 Barcelona
Spain

Novartis Pharmaceuticals S.R.L.
Str. Livezeni nr. 7A
540472 Targu Mures
Romania

Novartis Pharma GmbH
Roonstraße 25
D-90429 Nuremberg
Germany

Novartis Pharma GmbH
Sophie-Germain-Strasse 10
90443 Nuremberg
Germany

150 mg film-coated tablets

Novartis Pharmaceutical Manufacturing LLC
Verovškova ulica 57
1000 Ljubljana
Slovenia

Lek farmacevtska družba d.d., Poslovna enota PROIZVODNJA LENDAVA
Trimlini 2D
9220 Lendava
Slovenia

Novartis Pharma GmbH
Roonstraße 25
D-90429 Nuremberg
Germany

Novartis Pharma GmbH
Sophie-Germain-Strasse 10
90443 Nuremberg
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

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

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

- **Risk management plan (RMP)**

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

An updated RMP should be submitted:

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

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF UNIT PACK CONTAINING 40 OR 90 HARD CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

Zykadia 150 mg hard capsules
ceritinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 150 mg ceritinib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule

40 hard capsules
90 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/999/002	40 hard capsules (PVC/PCTFE/alu)
EU/1/15/999/003	90 hard capsules (PVC/PCTFE/alu)
EU/1/15/999/005	90 hard capsules (PVC/PE/PVDC/alu)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Zykadia 150 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF PACK (INCLUDING BLUE BOX) CONTAINING 150 (3 PACKS OF 50) HARD CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

Zykadia 150 mg hard capsules
ceritinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 150 mg ceritinib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule

150 (3 packs of 50) hard capsules.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/999/001	150 (3 packs of 50) hard capsules (PVC/PCTFE/alu)
EU/1/15/999/006	150 (3 packs of 50) hard capsules (PVC/PE/PVDC/alu)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Zykadia 150 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF PACK (WITHOUT BLUE BOX) CONTAINING 50 HARD CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

Zykadia 150 mg hard capsules
ceritinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 150 mg ceritinib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule

50 hard capsules. Cannot be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/999/001	150 (3 packs of 50) hard capsules (PVC/PCTFE/alu)
EU/1/15/999/006	150 (3 packs of 50) hard capsules (PVC/PE/PVDC/alu)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Zykadia 150 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Zykadia 150 mg hard capsules
ceritinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Zykadia 150 mg film-coated tablets
ceritinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 150 mg ceritinib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

84 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/999/004 84 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Zykadia 150 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Zykadia 150 mg tablets
ceritinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Zykadia 150 mg hard capsules
ceritinib

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

What is in this leaflet

1. What Zykadia is and what it is used for

What Zykadia is
Zykadia is a cancer medicine that contains the active substance ceritinib. It is used to treat adults with advanced stages of a form of lung cancer called non-small cell lung cancer (NSCLC). Zykadia is only given to patients whose disease is due to a defect in a gene called ALK (anaplastic lymphoma kinase).

How Zykadia works
In patients with ALK defects, an abnormal protein is produced that stimulates the growth of the cancer cells. Zykadia blocks the action of this abnormal protein and thus slows down the growth and spread of NSCLC.

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

2. What you need to know before you take Zykadia

Do not take Zykadia
- if you are allergic to ceritinib or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor or pharmacist before taking Zykadia:
- if you have problems with your liver.
- if you have problems with your lungs or problems breathing.
- if you have problems with your heart, including reduced heart rate, or if the results of an electrocardiogram (ECG) have shown that you have an abnormality of the electrical activity of your heart known as “prolonged QT interval”.
- if you have diabetes (high level of sugar in your blood).
- if you have problems with your pancreas.
- if you are currently taking steroids.

Tell your doctor or pharmacist immediately if you get any of the following signs or symptoms during treatment with Zykadia:
- tiredness, itchy skin, yellowing of your skin or the whites of your eyes, nausea (feeling sick) or vomiting, decreased appetite, pain on the right side of your abdomen (belly), dark or brown urine, bleeding or bruising more easily than normal. These may be signs or symptoms of liver problems.
- new or worsening cough with or without mucus, fever, chest pain, trouble breathing or shortness of breath. These may be symptoms of lung problems.
- chest pain or discomfort, changes in your heartbeat (fast or slow), light-headedness, fainting, dizziness, blue discoloration of your lips, shortness of breath, swelling of your lower limbs or skin. These may be signs or symptoms of heart problems.
- severe diarrhoea, nausea or vomiting. These are symptoms of digestive problems.
- excessive thirst or increased frequency of urination. These may be symptoms of a high level of sugar in the blood.

Your doctor may need to adjust your treatment or stop Zykadia temporarily or permanently.

Blood tests during treatment with Zykadia
Your doctor should perform blood tests before you start treatment, every 2 weeks during the first three months of treatment and monthly therafter. The purpose of these tests is to check your liver function. Your doctor should also perform blood tests to check the functioning of your pancreas and the level of sugar in your blood before you start treatment with Zykadia and regularly during treatment.

Children and adolescents
The use of Zykadia in children and adolescents up to 18 years of age is not recommended.

Other medicines and Zykadia
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription such as vitamins or herbal supplements, because they might interact with Zykadia. It is particularly important that you mention any of the following medicines.

Medicines which may increase the risk of side effects with Zykadia:
- medicines used to treat AIDS/HIV (e.g. ritonavir, saquinavir).
- medicines used to treat infections. These include medicines that treat fungal infections (antifungals such as ketoconazole, itraconazole, voriconazole, posaconazole) and medicines that treat certain types of bacterial infection (antibiotics such as telithromycin).

The following medicines may reduce the effectiveness of Zykadia:
- St. John’s Wort, a herbal medicine used to treat depression.
- medicines used to stop seizures or fits (anti-epileptics such as phenytoin, carbamazepine, or phenobarbital).
- medicines used to treat tuberculosis (e.g. rifampicin, rifabutin).

Zykadia may increase the side effects associated with the following medicines:
- medicines used to treat irregular heartbeat or other heart problems (e.g. amiodarone, disopyramide, procainamide, quinidine, sotalol, dofetilide, ibutilide and digoxin).
- medicines used to treat stomach problems (e.g. cisapride).
- medicines used to treat mental health problems (e.g. haloperidol, droperidol, pimozide).
- medicines used to treat depression (e.g. nefazodone).
- midazolam, a medicine used to treat acute seizures or as a sedative before or during surgery or medical procedures.
- warfarin and dabigatran, medicines used to prevent blood clots.
- diclofenac, a medicine used to treat joint pain and inflammation.
- alfentanil and fentanyl, medicines used to treat severe pain.

- ciclosporin, sirolimus and tacrolimus, medicines used in organ transplantation to prevent transplant organ rejection.
- dihydroergotamine and ergotamine, medicines used to treat migraine.
- domperidone, a medicine used to treat nausea and vomiting.
- moxifloxacin and clarithromycin, medicines used to treat bacterial infections.
- methadone, a medicine used to treat pain and for the treatment of opioid dependence.
- chloroquine and halofantrine, medicines used to treat malaria.
- topotecan, a medicine used to treat certain types of cancer.
- colchicine, a medicine used to treat gout.
- pravastatine and rosuvastatine, medicines used to reduce cholesterol levels.
- sulfasalazine, a medicine used to treat inflammatory bowel disease or rheumatoid arthritis.

Ask your doctor or pharmacist if you are not sure whether your medicine is one of the medicines listed above.

These medicines should be used with care or may need to be avoided during your treatment with Zykadia. If you are taking any of these, your doctor might need to prescribe an alternative medicine for you.

You should also tell your doctor if you are already taking Zykadia and you are prescribed a new medicine that you have not already taken at the same time as Zykadia.

Oral contraceptives
If you take Zykadia whilst using oral contraceptives, the oral contraceptives may become ineffective.

Zykadia with food and drink
You should not eat grapefruit or drink grapefruit juice during treatment. It may make the amount of Zykadia in your blood increase to a harmful level.

Pregnancy and breast-feeding
You must use a highly effective method of birth control during treatment with Zykadia and for 3 months after stopping treatment. Talk to your doctor about the birth control methods that may be right for you.

Zykadia is not recommended during pregnancy unless the potential benefit outweighs the potential risk to the baby. If you are pregnant, think you may be pregnant or are planing to have a baby, ask your doctor for advice before taking this medicine. Your doctor will discuss with you the potential risks of taking Zykadia during pregnancy.

Zykadia should not be used during breast-feeding. You and your doctor will decide together whether you should breast-feed or take Zykadia. You should not do both.

Driving and using machines
You should take special care when driving and using machines when taking Zykadia as you may experience visual disturbances or tiredness.

Zykadia contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially “sodium-free”.

3. How to take Zykadia

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

How much to take
The recommended dose is 450 mg (three capsules) taken once daily with food, although your doctor could modify this recommendation if needed. Your doctor will tell you exactly how many capsules you need to take. Do not change the dose without talking to your doctor.
– Take Zykadia once a day at about the same time each day with food (for example a snack or a full meal). If you cannot eat food while taking Zykadia, talk to your doctor.
– Swallow the capsules whole with water. Do not chew or crush them.
– If you vomit after you swallow the Zykadia capsules, do not take any more capsules until your next scheduled dose.

How long to take Zykadia
– Continue taking Zykadia for as long as your doctor tells you.
– This is a long-term treatment, possibly lasting for months. Your doctor will monitor your condition to see that the treatment is having the desired effect.

If you have questions about how long to take Zykadia, talk to your doctor or pharmacist.

If you take more Zykadia than you should
If you accidentally take too many capsules, or if someone else accidentally takes your medicine, contact a doctor or hospital for advice immediately. Medical treatment may be necessary.

If you forget to take Zykadia
What to do if you forget to take a dose depends on how long it is until your next dose.
- If your next dose is in 12 hours or more, take the missed capsules as soon as you remember. Then take the next capsules at the usual time.
- If your next dose is in less than 12 hours, skip the missed capsules. Then take the next capsules at the usual time.

Do not take a double dose to make up for a forgotten dose.

If you stop taking Zykadia
Do not stop taking this medicine before talking to your doctor.

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

4. Possible side effects

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

STOP taking Zykadia and seek medical help immediately if you experience any of the following, which may be signs of an allergic reaction:
– Difficulty in breathing or swallowing
– Swelling of the face, lips, tongue or throat
– Severe itching of the skin, with a red rash or raised bumps

Some side effects could be serious
If you experience any of the following side effects, tell your doctor or pharmacist immediately:
– Chest pain or discomfort, changes in your heartbeat (fast or slow), light-headedness, fainting, dizziness, blue discoloration of your lips, shortness of breath, swelling of your lower limbs or skin (potential signs or symptoms of heart problems)
– New or worsening cough with or without mucus, fever, chest pain, trouble breathing or shortness of breath (potential signs of lung problems)
– Tiredness, itchy skin, yellowing of your skin or the whites of your eyes, nausea (feeling sick) or vomiting, decreased appetite, pain on the right side of your abdomen (belly), dark or brown urine, bleeding or bruising more easily than normal (potential signs or symptoms of liver problems)

– Severe diarrhoea, nausea or vomiting
– Excessive thirst, increased frequency of urination (symptoms of high level of glucose in the blood)
– Severe upper stomach pain (sign of inflammation of the pancreas, also known as pancreatitis)

Other possible side effects
Other side effects are listed below. If these side effects become severe, please tell your doctor or pharmacist.

Very common (may affect more than 1 in 10 people):
– Tiredness (fatigue and asthenia)
– Abnormal results of blood tests to check liver function (high levels of enzymes called alanine aminotransferase and/or aspartate aminotransferase and/or gamma glutamyltransferase and/or blood alkaline phosphatase, high levels of bilirubin)
– Abdominal pain
– Decreased appetite
– Weight decreased
– Constipation
– Rash
– Abnormal results of blood tests to check kidney function (high level of creatinine)
– Heartburn (potential sign of a disorder of the digestive tract)
– Reduction in the number of red blood cells, known as anaemia

Common (may affect up to 1 in 10 people):
– Vision problems
– Low level of phosphate in the blood (this would be detected during blood tests)
– High level of enzymes called lipase and/or amylase in the blood (this would be detected during blood tests)
– Significantly decreased urine flow (potential sign of a kidney problem)

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

5. How to store Zykadia

– Keep this medicine out of the sight and reach of children.
– Do not use this medicine after the expiry date which is stated on the carton and blister after EXP. The expiry date refers to the last day of that month.
– This medicine does not require any special storage conditions.
– Do not use this medicine if you notice any damage to the packaging or if there are any signs of tampering.

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

6. Contents of the pack and other information

What Zykadia contains
- The active substance of Zykadia is ceritinib. Each hard capsule contains 150 mg of ceritinib.
- The other ingredients are:
  - Capsule contents: silica, colloidal anhydrous; hydroxypropylcellulose, low-substituted; sodium starch glycolate (type A) (see "Zykadia contains sodium" in section 2); magnesium stearate; cellulose, microcrystalline.
  - Capsule shell: gelatin, indigotine (E132) and titanium dioxide (E171).
  - Printing ink: Shellac (bleached, de-waxed) glaze 45%, iron oxide black (E172), propylene glycol and ammonium hydroxide 28%.

What Zykadia looks like and contents of the pack
Zykadia hard capsules have a white opaque body and blue opaque cap, are approximately 23.3 mm long, with "LDK 150MG" imprinted on the cap and "NVR" on the body. They contain white to almost white powder.

The capsules are provided in blisters and are available in packs containing 40, 90 or 150 (3 packs of 50) capsules. Not all pack sizes may be marketed in your country.

Marketing Authorisation Holder
Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

Manufacturer
Novartis Farmacéutica, S.A.
Gran Via de les Corts Catalanes, 764
08013 Barcelona
Spain

Novartis Pharmaceuticals S.R.L.
Str. Livezeni nr. 7A
540472 Targu Mures
Romania

Novartis Pharma GmbH
Roonstraße 25
D-90429 Nuremberg
Germany

Novartis Pharma GmbH
Sophie-Germain-Strasse 10
90443 Nuremberg
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Novartis Pharma N.V.
Tél/Tel: +32 2 246 16 11

Lietuva
SIA Novartis Baltics Lietuvos filialas
Tel: +370 5 269 16 50

България
Novartis Bulgaria EOOD
Тел: +359 2 489 98 28

Luxembourg/Luxemburg
Novartis Pharma N.V.
Tél/Tel: +32 2 246 16 11

Česká republika
Novartis s.r.o.
Tel: +420 225 775 111

Magyarország
Novartis Hungária Kft.
Tel.: +36 1 457 65 00

Danmark
Novartis Healthcare A/S
Tlf: +45 39 16 84 00

Malta
Novartis Pharma Services Inc.
Tel: +356 2122 2872

Deutschland
Novartis Pharma GmbH
Tel: +49 911 273 0

Nederland
Novartis Pharma B.V.
Tel: +31 88 04 52 555

Eesti
SIA Novartis Baltics Eesti filiaal
Tel: +372 66 30 810

Norge
Novartis Norge AS
Tlf: +47 23 05 20 00

Ελλάδα
Novartis (Hellas) A.E.B.E.
Τηλ: +30 210 281 17 12

Österreich
Novartis Pharma GmbH
Tel: +43 1 86 6570

España
Novartis Farmacéutica, S.A.
Tel: +34 93 306 42 00

Polska
Novartis Poland Sp. z o.o.
Tel.: +48 22 375 4888

France
Novartis Pharma S.A.S.
Tél: +33 1 55 47 66 00

Portugal
Novartis Farma - Produtos Farmacêuticos, S.A.
Tel: +351 21 000 8600

Hrvatska
Novartis Hrvatska d.o.o.
Tel. +385 1 6274 220

România
Novartis Pharma Services Romania SRL
Tel: +40 21 31299 01

Ireland
Novartis Ireland Limited
Tel: +353 1 260 12 55

Slovenija
Novartis Pharma Services Inc.
Tel: +386 1 300 75 50

Ísland
Vistor hf.
Sími: +354 535 7000

Slovenská republika
Novartis Slovakia s.r.o.
Tel: +421 2 5542 5439

Italia
Novartis Farma S.p.A.
Tel: +39 02 96 54 1

Suomi/Finland
Novartis Finland Oy
Puh/Tel: +358 (0)10 6133 200

Κύπρος
Novartis Pharma Services Inc.
Τηλ: +357 22 690 690

Latvija
SIA Novartis Baltics
Tel: +371 67 887 070

Sverige
Novartis Sverige AB
Tel: +46 8 732 32 00

This leaflet was last revised in

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

Package leaflet: Information for the patient

Zykadia 150 mg film-coated tablets
ceritinib

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What is in this leaflet

1. What Zykadia is and what it is used for

What Zykadia is
Zykadia is a cancer medicine that contains the active substance ceritinib. It is used to treat adults with advanced stages of a form of lung cancer called non-small cell lung cancer (NSCLC). Zykadia is only given to patients whose disease is due to a defect in a gene called ALK (anaplastic lymphoma kinase).

How Zykadia works
In patients with ALK defects, an abnormal protein is produced that stimulates the growth of the cancer cells. Zykadia blocks the action of this abnormal protein and thus slows down the growth and spread of NSCLC.

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

2. What you need to know before you take Zykadia

Do not take Zykadia
- if you are allergic to ceritinib or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor or pharmacist before taking Zykadia:
- if you have problems with your liver.
- if you have problems with your lungs or problems breathing.
- if you have problems with your heart, including reduced heart rate, or if the results of an electrocardiogram (ECG) have shown that you have an abnormality of the electrical activity of your heart known as “prolonged QT interval”.
- if you have diabetes (high level of sugar in your blood).
- if you have problems with your pancreas.
- if you are currently taking steroids.

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- tiredness, itchy skin, yellowing of your skin or the whites of your eyes, nausea (feeling sick) or vomiting, decreased appetite, pain on the right side of your abdomen (belly), dark or brown urine, bleeding or bruising more easily than normal. These may be signs or symptoms of liver problems.
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- severe diarrhoea, nausea or vomiting. These are symptoms of digestive problems.
- excessive thirst or increased frequency of urination. These may be symptoms of a high level of sugar in the blood.

Your doctor may need to adjust your treatment or stop Zykadia temporarily or permanently.

Blood tests during treatment with Zykadia
Your doctor should perform blood tests before you start treatment, every 2 weeks during the first three months of treatment and monthly therafter. The purpose of these tests is to check your liver function. Your doctor should also perform blood tests to check the functioning of your pancreas and the level of sugar in your blood before you start treatment with Zykadia and regularly during treatment.

Children and adolescents
The use of Zykadia in children and adolescents up to 18 years of age is not recommended.

Other medicines and Zykadia
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription such as vitamins or herbal supplements, because they might interact with Zykadia. It is particularly important that you mention any of the following medicines.

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- St. John’s Wort, a herbal medicine used to treat depression.
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- midazolam, a medicine used to treat acute seizures or as a sedative before or during surgery or medical procedures.
- warfarin and dabigatran, medicines used to prevent blood clots.
- diclofenac, a medicine used to treat joint pain and inflammation.
- alfentanil and fentanyl, medicines used to treat severe pain.

- ciclosporin, sirolimus and tacrolimus, medicines used in organ transplantation to prevent transplant organ rejection.
- dihydroergotamine and ergotamine, medicines used to treat migraine.
- domperidone, a medicine used to treat nausea and vomiting.
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- methadone, a medicine used to treat pain and for the treatment of opioid dependence.
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- topotecan, a medicine used to treat certain types of cancer.
- colchicine, a medicine used to treat gout.
- pravastatine and rosuvastatine, medicines used to reduce cholesterol levels.
- sulfasalazine, a medicine used to treat inflammatory bowel disease or rheumatoid arthritis.

Ask your doctor or pharmacist if you are not sure whether your medicine is one of the medicines listed above.

These medicines should be used with care or may need to be avoided during your treatment with Zykadia. If you are taking any of these, your doctor might need to prescribe an alternative medicine for you.

You should also tell your doctor if you are already taking Zykadia and you are prescribed a new medicine that you have not already taken at the same time as Zykadia.

Oral contraceptives
If you take Zykadia whilst using oral contraceptives, the oral contraceptives may become ineffective.

Zykadia with food and drink
You should not eat grapefruit or drink grapefruit juice during treatment. It may make the amount of Zykadia in your blood increase to a harmful level.

Pregnancy and breast-feeding
You must use a highly effective method of birth control during treatment with Zykadia and for 3 months after stopping treatment. Talk to your doctor about the birth control methods that may be right for you.

Zykadia is not recommended during pregnancy unless the potential benefit outweighs the potential risk to the baby. If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. Your doctor will discuss with you the potential risks of taking Zykadia during pregnancy.

Zykadia should not be used during breast-feeding. You and your doctor will decide together whether you should breast-feed or take Zykadia. You should not do both.

Driving and using machines
You should take special care when driving and using machines when taking Zykadia as you may experience visual disturbances or tiredness.

Zykadia contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially “sodium-free”.

3. How to take Zykadia

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

How much to take
The recommended dose is 450 mg (three tablets) taken once daily with food, although your doctor could modify this recommendation if needed. Your doctor will tell you exactly how many tablets you need to take. Do not change the dose without talking to your doctor.
– Take Zykadia once a day at about the same time each day with food (for example a snack or a full meal). If you cannot eat food while taking Zykadia, talk to your doctor.
– Swallow the tablets whole with water. Do not chew or crush them.
– If you vomit after you swallow the Zykadia tablets, do not take any more tablets until your next scheduled dose.

How long to take Zykadia
– Continue taking Zykadia for as long as your doctor tells you.
– This is a long-term treatment, possibly lasting for months. Your doctor will monitor your condition to see that the treatment is having the desired effect.

If you have questions about how long to take Zykadia, talk to your doctor or pharmacist.

If you take more Zykadia than you should
If you accidentally take too many tablets, or if someone else accidentally takes your medicine, contact a doctor or hospital for advice immediately. Medical treatment may be necessary.

If you forget to take Zykadia
What to do if you forget to take a dose depends on how long it is until your next dose.
- If your next dose is in 12 hours or more, take the missed tablets as soon as you remember. Then take the next tablets at the usual time.
- If your next dose is in less than 12 hours, skip the missed tablets. Then take the next tablets at the usual time.

Do not take a double dose to make up for a forgotten dose.

If you stop taking Zykadia
Do not stop taking this medicine before talking to your doctor.

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

4. Possible side effects

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

STOP taking Zykadia and seek medical help immediately if you experience any of the following, which may be signs of an allergic reaction:
– Difficulty in breathing or swallowing
– Swelling of the face, lips, tongue or throat
– Severe itching of the skin, with a red rash or raised bumps

Some side effects could be serious
If you experience any of the following side effects, tell your doctor or pharmacist immediately:
– Chest pain or discomfort, changes in your heartbeat (fast or slow), light-headedness, fainting, dizziness, blue discoloration of your lips, shortness of breath, swelling of your lower limbs or skin (potential signs or symptoms of heart problems)
– New or worsening cough with or without mucus, fever, chest pain, trouble breathing or shortness of breath (potential signs of lung problems)
– Tiredness, itchy skin, yellowing of your skin or the whites of your eyes, nausea (feeling sick) or vomiting, decreased appetite, pain on the right side of your abdomen (belly), dark or brown urine, bleeding or bruising more easily than normal (potential signs or symptoms of liver problems)

– Severe diarrhoea, nausea or vomiting
– Excessive thirst, increased frequency of urination (symptoms of high level of glucose in the blood)
– Severe upper stomach pain (sign of inflammation of the pancreas, also known as pancreatitis)

Other possible side effects
Other side effects are listed below. If these side effects become severe, please tell your doctor or pharmacist.

Very common (may affect more than 1 in 10 people):
– Tiredness (fatigue and asthenia)
– Abnormal results of blood tests to check liver function (high levels of enzymes called alanine aminotransferase and/or aspartate aminotransferase and/or gamma glutamyltransferase and/or blood alkaline phosphatase, high levels of bilirubin)
– Abdominal pain
– Decreased appetite
– Weight decreased
– Constipation
– Rash
– Abnormal results of blood tests to check kidney function (high level of creatinine)
– Heartburn (potential sign of a disorder of the digestive tract)
– Reduction in the number of red blood cells, known as anaemia

Common (may affect up to 1 in 10 people):
– Vision problems
– Low level of phosphate in the blood (this would be detected during blood tests)
– High level of enzymes called lipase and/or amylase in the blood (this would be detected during blood tests)
– Significantly decreased urine flow (potential sign of a kidney problem)

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

5. How to store Zykadia

– Keep this medicine out of the sight and reach of children.
– Do not use this medicine after the expiry date which is stated on the carton and blister after EXP. The expiry date refers to the last day of that month.
– This medicine does not require any special storage conditions.
– Do not use this medicine if you notice any damage to the packaging or if there are any signs of tampering.

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

6. Contents of the pack and other information

What Zykadia contains
- The active substance of Zykadia is ceritinib. Each film-coated tablet contains 150 mg of ceritinib.
- The other ingredients are:
  - Tablet core: cellulose, microcrystalline; hydroxypropylcellulose, low-substituted; povidone; croscarmellose sodium (see “Zykadia contains sodium” in section 2); magnesium stearate; silica, colloidal anhydrous.
  - Film-coating: hypromellose; titanium dioxide (E171); macrogol; talc; indigo carmine aluminium lake (E132).

What Zykadia looks like and contents of the pack
Zykadia film-coated tablets (tablets) are light blue, round (approximate diameter: 9.1 mm), biconvex with bevelled edges, without score, debossed with “NVR” on one side and “ZY1” on the other side.

The tablets are provided in blisters and are available in a pack containing 84 tablets (4 blisters of 21 tablets).

Marketing Authorisation Holder
Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

Manufacturer
Novartis Pharmaceutical Manufacturing LLC
Verovškova ulica 57
1000 Ljubljana
Slovenia

Lek farmacevtska družba d.d., Poslovna enota PROIZVODNJA LENDAVA
Trimlini 2D
9220 Lendava
Slovenia

Novartis Pharma GmbH
Roonstraße 25
D-90429 Nuremberg
Germany

Novartis Pharma GmbH
Sophie-Germain-Strasse 10
90443 Nuremberg
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Novartis Pharma N.V.
Tél/Tel: +32 2 246 16 11

България
Novartis Bulgaria EOOD
Тел: +359 2 489 98 28

Česká republika
Novartis s.r.o.
Tel: +420 225 775 111

Danmark
Novartis Healthcare A/S
Tlf: +45 39 16 84 00

Deutschland
Novartis Pharma GmbH
Tel: +49 911 273 0

Eesti
SIA Novartis Baltics Eesti filiaal
Tel: +372 66 30 810

Ελλάδα
Novartis (Hellas) A.E.B.E.
Τηλ: +30 210 281 17 12

España
Novartis Farmacéutica, S.A.
Tel: +34 93 306 42 00

France
Novartis Pharma S.A.S.
Tél: +33 1 55 47 66 00

Hrvatska
Novartis Hrvatska d.o.o.
Tel. +385 1 6274 220

Ireland
Novartis Ireland Limited
Tel: +353 1 260 12 55

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Novartis Farma S.p.A.
Tel: +39 02 96 54 1

Lietuva
SIA Novartis Baltics Lietuvos filialas
Tel: +370 5 269 16 50

Luxembourg/Luxemburg
Novartis Pharma N.V.
Tél/Tel: +32 2 246 16 11

Magyarország
Novartis Hungária Kft.
Tel.: +36 1 457 65 00

Malta
Novartis Pharma Services Inc.
Tel: +356 2122 2872

Nederland
Novartis Pharma B.V.
Tel: +31 88 04 52 555

Norge
Novartis Norge AS
Tlf: +47 23 05 20 00

Österreich
Novartis Pharma GmbH
Tel: +43 1 86 6570

Polska
Novartis Poland Sp. z o.o.
Tel.: +48 22 375 4888

Portugal
Novartis Farma - Produtos Farmacêuticos, S.A.
Tel: +351 21 000 8600

România
Novartis Pharma Services Romania SRL
Tel: +40 21 31299 01

Slovenija
Novartis Pharma Services Inc.
Tel: +386 1 300 75 50

Slovenská republika
Novartis Slovakia s.r.o.
Tel: +421 2 5542 5439

Suomi/Finland
Novartis Finland Oy
Puh/Tel: +358 (0)10 6133 200

Κύπρος
Novartis Pharma Services Inc.
Τηλ: +357 22 690 690

Latvija
SIA Novartis Baltics
Tel: +371 67 887 070

Sverige
Novartis Sverige AB
Tel: +46 8 732 32 00

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