26 February 2015
EMA/170114/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Zykadia

International non-proprietary name: CERITINIB

Procedure No. EMEA/H/C/003819/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Administrative information

Name of the medicinal product:	Zykadia
Applicant:	Novartis Europharm Ltd Wimblehurst Road Horsham West Sussex RH12 5AB UNITED KINGDOM
Active substance:	ceritinib
International Nonproprietary Name	ceritinib
Pharmaco-therapeutic group (ATC Code):	(L01XE)
Therapeutic indication(s):	Zykadia 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.
Pharmaceutical form:	Capsule, hard
Strength:	150 mg
Route of administration:	Oral use
Packaging:	Blister (PVC/PCTFE/Alu)
Package size:	150 (3 x 50) capsules (multipack)

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List of abbreviations

AE	Adverse event
AESI	Adverse event of special interest
ALCL	Anaplastic large cell lymphomas
ALK	Anaplastic lymphoma kinase
ALK-naive	Patients who were never treated with an ALK-inhibitor
ALK-positive	Patients with ALK gene rearrangements
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
BIRC	Blinded independent central review committee
BLRM	Bayesian logistic regression model
BOR	Best overall response
BSA	Body surface area
CDRH	Center for Devices and Radiological Health
CEAS	Central efficacy analysis set
cGMP	commercial Good Manufacturing Practice
CI	Confidence interval
CIRS	Cumulative illness rating scale
CL	Clearance
Cmax	Maximum drug concentration
c-MET	Mesenchymal epithelial growth factor
CNS	Central nervous system
CQA	Critical Quality Attribute
CR	Complete response
CrCL	Calculated creatinine clearance
CRF	Case Report/Record Form
CRO	Contract Research Organization

CSR Clinical study report

CT Computerized tomography

CTCAE Common terminology criteria for adverse events

CTD Common Technical Document

DBP Diastolic blood pressure

DDS Dose determining set

DILI Drug induced liver injury

DLT Dose limiting toxicity

DMC Data monitoring committee

DoE Design of Experiment

DOR Duration of response

DSC Differential Scanning Calorimetry

EAS Efficacy analysis set

ECG Electrocardiogram

ECOG Eastern Cooperative Oncology Group

eCRF Electronic case report form

EDC Electronic data capture

EGFR Epidermal growth factor receptor

EMEA European Medicines Agency

EOS End of study

EOT End of treatment

EWOC Escalation with overdose control

FAS Full analysis set

FAS-NSCLC subset of FAS including only ALK-positive NSCLC patients

FISH Fluorescent in situ hybridization

FMEA Failure Mode and Effect Analysis

FPFV First patient first visit

GC Gas Chromatography

GI Gastrointestinal

GLP Good Laboratory Practices

GMP Good Manufacturing Practice

Hb Hemoglobin

HIV	Human immunodeficiency virus
HNSTD	Highest non-severely toxic dose
HPLC	High Performance Liquid Chromatography
HR	Hazard ratio
IEC	Independent Ethics Committee
IGF1R	Insulin-like growth factor 1 receptor
IHC	Immunohistochemistry
ILD	Interstitial lung disease
INSR	Insulin receptor
IPC	In-process Control
IRB	Institutional Review Board
IV	Intravenous(ly)
KF	Karl Fischer (titration)
LC-MS	Liquid chromatography-tandem mass spectrometry
LLN	Lower limit of normal
LLOQ	Lower limit of quantitation
LoD	Loss on Drying
LOD	Limit of Detection
LOQ	Limit of Quantitation
LPLV	Last patient last visit
MedDRA	Medical dictionary for regulatory activities
MRI	Magnetic resonance imaging
ms	Millisecond
MTD	Maximum tolerated dose
MVTR	Moisture Vapour Transmission Rate
NA	Not applicable
NCI-H2228 cells	SCLC cell line carrying EML4-ALK rearrangements
ND	Not Detected
NLT	Not Less Than
NMT	Not More Than
NSCLC	Non-small cell lung cancer
OIRR	Overall intracranial response rate

ORR	Overall response rate
OS	Overall survival
PAR	Proven Acceptable Range
PAS	Pharmacokinetic analysis set
PD	Progressive disease
PFS	Progression free survival
PK	Pharmacokinetics
PP	Per protocol
ppm	part per million
PR	Partial response
PS	Performance status
PT	Preferred term
Pts.	Patients
QbD	Quality by Design
QTcF	Corrected QT interval using Frederica formula
QTPP	Quality Target Product Profile
RD	Recommended dose
RECIST	Response evaluation criteria in solid tumors
RH	Relative Humidity
RR	Respiration rate
RTK	Receptor tyrosine kinase
RT-PCR	Reverse transcriptase-polymerase chain reaction
SAE	Serious adverse event
SBP	Systolic blood pressure
SD	Stable disease
SGF	Simulated Gastric Fluid
SIF	Simulated Intestinal Fluid
SOC	System organ class
STD	Severely toxic dose
THF	Tetrahydrofuran
TTC	Threshold of Toxicological Concern
ULN	Upper limit of normal

UNK	Unknown
USP/NF	United States Pharmacopeia / National Formulary
UV	Ultraviolet
WHO	World health organization
XRPD	X-ray Powder Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Novartis Europharm Ltd submitted on 4 March 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Zykadia (ceritinib, LDK378, LDK378 Novartis Pharma AG), through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 27 June 2013.

The applicant applied for the following indication: "the treatment of adult patients with previously treated anaplastic lymphoma kinase (ALK)-positive locally advanced or metastatic non-small cell lung cancer (NSCLC)".

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that ceritinib was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision CW/1/2011 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Applicant's request for consideration

New active Substance status

The applicant requested the active substance ceritinib contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Scientific Advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

Zykadia has been given a Marketing Authorisation in the USA (2014-04-29), Guatemala (2014-12-05), Chile (2014-12-23), Ecuador (2015-01-09).

A new application was filed in the following countries: Switzerland and Canada.

1.2. Manufacturers

Manufacturer responsible for batch release

Novartis Pharma GmbH
Roonstraße 25
D-90429 Nürnberg
GERMANY

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Arantxa Sancho-Lopez

Co-Rapporteur: Ingunn Hagen Westgaard

- The application was received by the EMA on 4 March 2014.
- The procedure started on 26 March 2014.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 13 June 2014 (Annex 1). The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 13 June 2014 (Annex 2).
- During the PRAC meeting on 10 July 2014, the PRAC RMP Advice and assessment overview was adopted by PRAC (Annex 3).
- During the meeting on 24 July 2014, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 25 July 2014 (Annex 4).
- The applicant submitted the responses to the CHMP consolidated List of Questions on 15 October 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 24 November 2014 (Annex 5).
- During the CHMP meeting on 18 December 2014, the CHMP agreed on a list of outstanding issues to be addressed in writing and in an oral explanation by the applicant (Annex 6).
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 23 January 2015.
- During the PRAC meeting on 12 February 2015, the PRAC RMP Advice and assessment overview was adopted by PRAC (Annex 7).
- During the meeting on 26 February 2015, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Zykadia.

2. Scientific discussion

2.1. Introduction

Problem statement

Lung cancer has been among the most common cancers in the world for several decades. The 2012 worldwide estimates of cancer incidence and mortality by GLOBOCAN, indicate a total of 1.8 million new lung cancer cases and 1.6 million lung cancer related deaths, accounting for 13.0% of all cancer cases (except non-melanoma skin cancers) and 19.4% of all cancer deaths (except non-melanoma skin cancers). Furthermore, lung cancer incidence rates were two-fold higher in males compared to females (1,241,601 and 583,100, respectively). In 2013, the estimated number of lung cancer related deaths is 159,480 in the United States (Siegel et al 2013) and 269,610 in the European Union (Malvezzi et al 2013).

The two most prevalent sub-types of lung cancer are small cell lung cancer and non-small cell lung cancer (NSCLC). Approximately 85% of all lung cancers are NSCLC, which is frequently further subdivided into non-squamous carcinoma (including adenocarcinoma, large-cell carcinoma, and other cell types) and squamous cell (epidermoid) carcinoma.

Adenocarcinoma (40% of lung cancers) is the most common type of lung cancer, and is also the most frequently occurring in non-smokers as reported in United States (US) data (American Cancer Society 2013).

Non-small cell lung cancer is associated with high mortality rates as >70% of the patients are diagnosed with locally advanced or metastatic disease (Molina et al 2008) [stages III and IV according to the American joint committee on cancer staging (AJCC)]. Historically, patients with locally advanced or metastatic NSCLC have been treated with standard chemotherapy and/or radiation, and while these treatments may provide modest survival benefits, they are rarely curative.

Systemic chemotherapy is a cornerstone in the management of locally advanced or metastatic NSCLC. Standard first-line treatment typically consists of a platinum-based doublet (cisplatin or carboplatin in combination with other chemotherapy agents), unless a patient has a known mutation, candidate for targeted therapy (NCCN Guidelines v3.2012, Vansteenkiste et al 2013). The outcomes with this type of chemotherapy remain poor, with response rates of 15 to 35% and median progression-free survival (PFS) and overall survival (OS) of 4 to 7 months and 10 to 16 months, respectively (Scagliotti et al 2008, Ciuleanu et al 2009, Ettinger et al 2010, Paz-Ares et al 2012).

Pemetrexed/cisplatin (or carboplatin) combination therapy and carboplatin/paclitaxel with (or without) bevacizumab represent a therapeutic option in patients with advanced non-squamous NSCLC. These regimens are commonly used based on phase III randomised trials (NCCN version 1.2015)

Recently, pemetrexed-based regimens have been used in adenocarcinomas (if patients are not candidate for targeted therapy), because taxane-based regimens are associated with more toxicity (e.g. neurotoxicity).

The outcomes with second-line chemotherapy are dismal, with response rates of less than 10%, median PFS of 2 to 3 months, and median OS of 5 to 8 months (Shepherd et al 2000, Fossella et al 2000, Hanna et al 2004).

Although chemotherapy is appropriate for many patients with lung cancer, there is a sense that the use of traditional chemotherapeutic agents has reached a therapeutic plateau. Increased understanding of

cancer biology has revealed numerous potential therapeutic strategies targeting oncogenic signal transduction pathways. Where NSCLC was previously considered to be a single disease treated with standard cytotoxic chemotherapy, it is now becoming more appropriate to consider NSCLC as a collection of disease subtypes according to the driving oncogenic aberration, and to select treatment accordingly (Bang 2011).

Personalized targeted therapy for advanced NSCLC relies primarily on the concept of "oncogene addiction", in which cancers that contain multiple genetic abnormalities rely on only one or several genes for the maintenance of the malignant phenotype and their survival (Ma 2012). Several molecular aberrations have been identified in NSCLC, with subsequent development of drugs that target these aberrations. Gefitinib, afatinib and erlotinib for the treatment of NSCLC harbouring epidermal growth factor receptor (EGFR) mutations or overexpression, and crizotinib for the treatment of NSCLC with the anaplastic lymphoma kinase (ALK) fusion translocation oncogenes are examples of this rationale targeted approach to treating cancer (Ma 2012, Yang et al 2012a).

Multiple large randomized clinical trials have demonstrated that patients harbouring activating EGFR mutations benefit more from treatment with EGFR tyrosine kinase inhibitors (TKIs) than with standard chemotherapy in terms of response rate (62 to 85%), PFS, toxicity profile and quality of life (reviewed in NCCN Guidelines v3.2012, Gettinger and Lynch 2011). The success of EGFR TKIs highlights the importance of identifying specific NSCLC molecular drivers to appropriately develop targeted agents for treating specific patient populations.

Anaplastic lymphoma kinase, a receptor tyrosine kinase, was first identified as a fusion protein resulting from chromosomal translocation in the majority of anaplastic large cell lymphomas (ALCL). When fused to other proteins, ALK becomes constitutively active, leading to increased catalytic kinase function, signal transduction activity, and oncogenic function. ALK has since been linked with many different fusion partners in different tumour types (Soda et al 2007).

The frequency of ALK gene rearrangements in patients with NSCLC (referred to as ALK positive NSCLC from here onwards) is relatively low; it is present in approximately 2 to 7% of tumours tested. However, considering the high incidence of lung cancer, this small percentage translates into about 60,000 patients annually worldwide (Kwak et al 2010, Shaw et al 2013, Weickhardt et al 2012).

Patients with ALK-positive NSCLC are associated with specific demographic and clinical features, including never or light smoking history, younger age, and adenocarcinoma histology (Shaw et al 2009, Wong et al 2009, Rodig et al 2009). In addition, several reports have associated ALK positivity with a more advanced stage at diagnosis and worse prognosis (Shaw et al 2009, Yang et al 2012b). Further, ALK gene rearrangements are largely mutually exclusive with EGFR or KRAS mutations (Gainor et al 2013), consistent with the notion that ALK gene rearrangements defines a unique molecular subset of NSCLC. In these patients, ALK gene rearrangements serve as a key and strong oncogenic driver for NSCLC and represent a critical therapeutic target susceptible to targeted ALK kinase inhibition.

Crizotinib, a non-specific small molecule ALK inhibitor is the only targeted agent currently approved for the treatment of locally advanced or metastatic ALK-positive NSCLC. Early single-arm trials of crizotinib in patients with ALK-positive NSCLC demonstrated impressive activity and with clinical benefit response rates of 50 to 61% and duration of response of 6 to 10 months (Ou 2011). Based on these data, crizotinib (Xalkori) received conditional approval in the European Union (EU) (October 2012) for the treatment of adults with previously treated ALK-positive advanced NSCLC.

The clinical benefit of crizotinib treatment in patients with locally advanced or metastatic ALK-positive NSCLC in the second-line setting following treatment with at least one prior chemotherapy regimen has been confirmed in a phase III trial (PROFILE 1007). Crizotinib prolonged PFS to a median of 7.7 months

compared to 3.0 months in patients who received single-agent chemotherapy (Hazard ratio=0.49; 95% CI: 0.37–0.64; p<0.001). In addition, crizotinib significantly increased overall response rate over chemotherapy (65% vs. 20%, p<0.001), and improved symptom control and quality of life. The analysis of the OS rate was not sufficiently mature to draw conclusions, and was confounded by the cross-over of patients from chemotherapy to crizotinib (Shaw et al 2013).

While crizotinib is effective in patients with ALK-positive NSCLC, disease progression invariably occurs, typically within one year, due to the development of acquired drug resistance. Crizotinib resistant ALK-positive NSCLC frequently conserves the ALK gene rearrangements, but may result from the development of resistant ALK mutations, ALK amplification, and/or activation of alternate aberrant signalling pathways (Katayama et al 2012, Doebele et al 2012). Furthermore, not all patients respond to or tolerate crizotinib treatment.

About the product

Ceritinib is a selective and potent inhibitor of ALK. It inhibits autophosphorylation of ALK, and thus ALK-mediated phosphorylation of downstream signalling proteins, and proliferation of ALK-dependent cancer cells in both in vitro and in vivo models.

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 kinase 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.

The applicant applied for the following indication: Treatment of adult patients with previously treated anaplastic lymphoma kinase (ALK)-positive locally advanced or metastatic non-small cell lung cancer (NSCLC).

The recommended indication for approval is: Zykadia 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.

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

An accurate and validated ALK assay is necessary for the selection of ALK-positive NSCLC patients. 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.

The recommended dose of ceritinib is 750 mg taken orally once daily at the same time each day. Ceritinib capsules should be swallowed whole with water. The capsules should not be chewed or crushed. Ceritinib capsules must be taken on an empty stomach. No food should be eaten for at least two hours before and for two hours after the dose of ceritinib is taken.

The maximum recommended dose is 750 mg 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. However ceritinib should be discontinued in patients unable to tolerate 300 mg daily.

Temporary dose interruption and/or dose reduction of Zykadia may be required based on individual safety and tolerability. If dose reduction is required due to any adverse drug reaction (ADR), 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.

Approximately 54% of patients initiating treatment at the recommended dose of 750 mg required at least one dose adjustment due to adverse reaction, with a median time to first dose reduction of approximately 7 weeks.

The below table summarizes 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**
Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevation >5 times upper limit of normal (ULN) with total bilirubin ≤2 times ULN	Withhold Zykadia until recovery to baseline or ≤3 times ULN, then reinitiate with dose reduced by one decrement.
ALT or AST elevation >3 times ULN with concurrent total bilirubin elevation >2 times ULN (in the absence of cholestasis or haemolysis)	Permanently discontinue Zykadia.
Any grade treatment-related pneumonitis	Permanently discontinue Zykadia.
QT corrected for heart rate (QTc) >500 msec on at least 2 separate electrocardiograms (ECGs)	Withhold Zykadia until recovery to baseline or to a QTc ≤480 msec, check and if necessary correct electrolytes, then reinitiate with dose reduced by one decrement.
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 Zykadia.
Bradycardia[a] (symptomatic, may be severe and medically significant, medical intervention indicated)	Withhold Zykadia 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 Zykadia 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 Zykadia with dose reduced by one

	decrement 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 Zykadia if no contributing concomitant medicinal product is identified. If a contributing concomitant medicinal product is identified and discontinued, or its dose is adjusted, reinitiate Zykadia with dose reduced by two decrements upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, with frequent monitoring[b].
Severe (grade 3) or intolerable nausea, vomiting or diarrhoea despite optimal anti-emetic or anti-diarrhoeal therapy	Withhold Zykadia until improved, then reinitiate Zykadia with dose reduced by one decrement.
Persistent hyperglycaemia greater than 250 mg/dl despite optimal anti-hyperglycaemic therapy	Withhold Zykadia until hyperglycaemia is adequately controlled, then reinitiate Zykadia with dose reduced by one decrement. If adequate glucose control cannot be achieved with optimal medical management, permanently discontinue Zykadia.
[a] Heart rate less than 60 beats per minutes (bpm) [b] Permanently discontinue in the event of recurrence.	

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as hard capsules containing 150 mg of ceritinib as active substance.

Other ingredients are:

Capsule content: microcrystalline cellulose, *L*-hydroxypropylcellulose, sodium starch glycolate (type A), magnesium stearate, and colloidal anhydrous silica.

Capsule shell: gelatin, indigotine (E132), and titanium dioxide (E171).

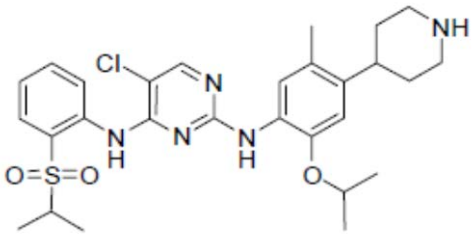
Printing ink: shellac glaze 45%. iron oxide black (E172), propylene glycol and ammonium hydroxide 28%.

The product is available in PVC/polychlorotrifluoroethylene (PCTFE) – Alu blisters.

2.2.2. Active substance

General information

The chemical name of ceritinib is 5-Chloro-2-*N*-{5-methyl-4-(piperidin-4-yl)-2-[(propan-2-yl)oxy]phenyl}-4-*N*-[2-(propane-2-sulfonyl)phenyl]pyrimidine-2,4-diamine and it has the following structure:



Ceritinib is a white to almost white or light yellow powder which has good solubility in very acidic aqueous medium. The solubility decreases significantly with increasing pH. A good solubility is found in the organic medium methanol.

The molecular structure has been fully characterised by elemental analysis, ultraviolet absorption spectroscopy, infrared spectroscopy, proton nuclear magnetic resonance (^{1}H-NMR) spectroscopy, carbon nuclear magnetic resonance (^{13}C-NMR) spectroscopy, mass spectrometry, X-ray powder diffraction (XRPD), and single crystal X-ray diffraction.

Ceritinib exists in two polymorphic forms: modification A and B. Modification B is thermodynamically unstable under the manufacturing process conditions of the active substance. The X-ray diffraction pattern of ceritinib batches manufactured to date demonstrate that the diffractograms correspond to that of modification A. Modification A was selected for development and commercial use.

Ceritinib is non-hygroscopic and achiral.

Manufacture, characterisation and process controls

Certinib is manufactured by a convergent six step synthesis (including salt formation and free base formation, excluding recrystallizations of wet isolated solids), followed by an additional milling step using three commercially available well-defined starting materials with acceptable specifications. The characterisation of the active substance and its impurities is in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

Specification

Certinib's specification includes tests for appearance, particle size (light diffraction), identity (IR, XRPD), assay (HPLC), residual solvents (GC), loss on drying, sulphated ash (Ph Eur), heavy metals (ICP-OES), trace metals (ICP-MS), clarity of solution (Ph Eur), colour of solution (Ph Eur), impurities (HPLC), and microbial enumeration test (Ph Eur).

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines.

Batch analysis data of 29 pilot and commercial scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

The 2 packaging formats used for stability studies were sealed polyethylene bag inside a quadruple laminated foil bag which simulates the actual packaging for bulk batches and two sealed flat LDPE bags inside steel drums with tight closures.

Three pilot scale batches of ceritinib from the proposed manufacturers stored for up to 12 months under long term conditions at 25°C / 60% RH and intermediate conditions at 30°C / 75% RH, up to 6 months under accelerated conditions at 40°C / 75% RH and up to 3 months at 50°C according to the ICH guidelines in tight packaging and very tight packaging were provided.

The parameters tested were appearance, identity (X-ray diffraction), related substances (HPLC), loss on drying, clarity of the solution, colour of the solution, assay (HPLC), and microbial enumeration tests.

The active substance is chemically stable since no significant changes and no degradation were observed under either long term or accelerated conditions in either packaging format. Neither polymorphic form nor the content of volatiles changed over the storage period.

Photostability testing following the ICH guideline Q1B was performed on two batches. Additionally, active substance from these two batches was exposed to stressed conditions (50 or 60 ^{o}C, <30 or 75% RH) in either open containers or in two LDPE bags inside steel drums with tight closure. Ceritinib was also tested at 80 ^{o}C stored in ampoules in the presence of N_2 (with and without water) or O_2. No degradation was observed under any condition. The only change was slight discoloration on exposure to light or under the severe stressed conditions.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period in the proposed container.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The finished product is formulated as immediate release solid dosage form for oral administration using compendial excipients. The active substance is dry blended with the excipients and the final blend is encapsulated in hard gelatin capsules.

For the manufacturing of the hard-gelatin capsule, a dry blending process with subsequent encapsulation was chosen. The process is rather simple and consists of several sieving and blending steps, followed by encapsulation. Sieving was performed with oscillating sieving equipment or with hand-sieve, based on the batch size, and blending was performed using a diffusion mixer. For encapsulation, an automatic encapsulation machine with dosing disk encapsulation principle was chosen. The encapsulation process step comprised also a weight check of all filled capsules after encapsulation. The powder blend showed good flowing property during encapsulation.

The impact of the active substance particle size on finished product processability was investigated, and no impact was observed on the blending and sieving processes or on the blend uniformity. However, smaller particles affect the bulk volume of the final blend, which makes encapsulation more challenging. Based on the experiences from pilot scale encapsulation, a lower particle size limit was proposed. The optimised powder blend showed good flowing property during encapsulation.

The choice of the excipients used in the capsule formulation was based on excipient compatibility studies and the functionality of excipients. Binary and ternary blends of different excipients and active substance were prepared and stored for 3 months at 40 °C under humid condition (75% RH) and under dry condition.

The excipients selected did not cause an increase in degradation products. They are commonly used for solid oral dosage forms and in compliance with pharmacopoeial standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

Two batches of dry blend containing the selected excipients were prepared for formulation development and encapsulated within hard gelatin capsules. The capsules were packaged in high density polyethylene (HDPE) bottles and placed on stability. Assay results after 3 months met the acceptance criteria and no significant degradation or other changes were observed. The total degradation products remained well below the specification limit, which at the beginning of development was the requirement for sum of degradation products. This requirement was tightened for the commercial product based on the availability of additional data and justification of the finished product specifications.

The finished product is packaged in PCTFE/PVC blister packs and consists of a PCTFE/PVC film backed with a heat sealable lacquered aluminium foil. Based on the available stability data provided, the proposed packaging is considered protective and compatible with the hard gelatine capsules. The container closure system complies with the new Commission Regulation (EU) No 10/2011 on plastic materials and articles intended to come into contact with food.

Manufacture of the product and process controls

A dry blending process with subsequent encapsulation was chosen as manufacturing process. It consists of 7 main steps: loading of the active substance and excipients, sieving, blending, sieving and mixing, blending, encapsulation and packaging. The process is considered to be a standard manufacturing process.

The robustness of the manufacturing process has been validated at production scale .Process validation utilizing the intended commercial process was performed on three consecutive batches prior to commercialization. This was considered satisfactory.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance of contents, appearance of shell, identity (UV, HPLC), mean mass of contents, dissolution (UV), impurities (HPLC), microbial enumeration test (Ph Eur), assay (HPLC) and uniformity of dosage units (Ph Eur). Batch analysis results are provided for nine batches used for clinical and/or stability studies confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data on 3 batches (2 pilot scale and 1 commercial scale) of finished product stored under long term conditions for 9 months at 25 ºC / 60% RH, for up 9 months under intermediate conditions at 30 °C / 75% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. The batches are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, appearance of the shell, assay (HPLC), dissolution (UV), and impurities (HPLC). The analytical procedures used are stability indicating. The analytical procedures used are stability indicating.

Supportive stability data for clinical and registration batches in HDPE bottles have been included. Data up to 6 months are available. In addition supportive data for 2 development clinical batches at lab scale packed in HDPE bottles have been submitted. Data up to 24 months and 12 months respectively are available. All supportive batches complied with specifications for appearance of capsule contents and shells, dissolution rate testing as well as assay and degradation products testing at all time points tested to date. Supportive bridging registration stability data up to 6 months in blister have been included for blue-white opaque coloured, size '00' capsules, representative to commercial capsule colour.

A freeze/thaw cycle stability test was performed for one batch. The samples were stored for four complete freeze and thaw cycles (one cycle consisted of -20 °C / ambient RH for 6 days, followed by 1 day at 25 °C / 60% RH) for a total of 28 days. After four complete cycles over a total of 28 days all tested quality parameters complied with specifications.

A photostability stability test was performed on one unpacked batch according to the ICH Q1B guideline for the 'Photostability testing of new active substances and medicinal products'. No significant changes or trends were observed for all the investigated parameters (assay, individual unspecified and total impurities, dissolution and appearance).

An open dish stability study was conducted for two batches by placing the capsules in an open glass dish stored for 0, 1 and 3 months at 25°C / 60% RH and 30°C / 75% RH. Samples were stored for 9 months at 25°C / 60% RH and 30°C / 75% RH in PCTFE/PVC blister packs. After this time period, the samples were unpacked and capsules were placed in an open glass dish. These samples were stored again at the original storage condition (25°C / 60% RH or 30°C / 75% RH) and subsequently tested after 1 and 3 months.

In all the stability studies no significant change and no trend were observed for all the investigated parameters. No formation or increase in levels of any degradation product was observed.

Based on available stability data, the shelf-life with no special storage conditions as stated in the SmPC is acceptable.

Adventitious agents

The gelatin in the capsule shell used in the finished product is of animal (bovine) origin. Current EDQM Certificates of Suitability are provided.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

N/A

2.3. Non-clinical aspects

2.3.1. Introduction

2.3.2. Pharmacology

Ceretinib is a selective and potent inhibitor of anaplastic lymphoma kinase (ALK). ALK is a receptor tyrosine kinase that is not normally expressed in the human adult. ALK genetic aberrations involving translocation of the kinase domain, gene amplification, or activating mutations occur, creating ALK fusion genes with ALK kinase domain fused to partner genes. For NSCLC, ALK aberrations are detected in approximately 2% to 8% of the patients.

Among thirteen fusion partner genes identified to date, NPM is the most common partner in anaplastic large-cell lymphoma (ALCL) and echinoderm microtubule-associated protein-like4 (EML4) is the main partner in NSCLC. The partner genes retain oligomerization domains, leading to ligand-independent dimerization or oligomerization, and thus constitutive activation of ALK kinase, which elicits downstream signalling pathways that play central roles in cell proliferation, growth and survival. As a consequence, NSCLC cells with ALK fusion genes are dependent on or addictive to the ALK fusion genes.

Primary pharmacodynamic studies
A number of biochemical, cellular, and in vivo studies have been conducted to characterize ceritinib pharmacology activity.

In vitro studies

In biochemical assays, ceritinib potently inhibits ALK kinase (IC50 = 0.15 nM). For INSR and IGF-1R, the IC50 levels are approximately 50 fold higher than for ALK, AURORA-A, cABL-T315I, and AXL, for which IC50s in the range 110-180 nM were determined. For the remaining 30 recombinant kinases tested, the selectivity in favour of ALK was at least 2600 fold.

In cell based assays, ceritinib had an IC50 of 27-35 nM against the fusion kinases EML4-ALK and NPM-ALK. The IC50s for IGF-1R, INSR and ROS1 were approximately 5-11 fold higher, while for the rest of the 40 kinases in the panel the IC50s were at least 1000 nM.

When compared to crizotinib in the same panel of recombinant kinases, ceritinib showed 20-fold greater potency than crizotinib against ALK kinase (ceritinib IC50=0.15 nM vs. crizotinib IC50= 3 nM) without inhibiting MET (ceritinib IC50= 3200 nM vs. crizotinib IC50= 8 nM).

Ceritinib showed less potency against crizotinib resistant EML4-ALK mutants compared to its corresponding activity against the non-mutated EML4-ALK.

Table 2: Potency of CERITINIB and crizotinib against ALK mutations

Assay	CERITINIB IC_{50}(nM)	Crizotinib IC_{50}(nM)
EML4-ALK	31	160
EML4-ALK C1156Y	160	440
EML4-ALK L1196M	69	1460
EML4-ALK G1202R	940	1370

The in vitro IC50 assay measurements on the 4 mutated ALKs were conducted in a medium consisting of 10% fetal bovine serum (FBS). The unbound fraction of ceritinib in 10% or 100% FBS has not been determined. However, a free fraction of 0.029 in 100% FBS was estimated utilizing the mean of unbound fractions in rat (fu=0.017), dog (fu= 0.015), monkey (fu = 0.054) and human plasma (fu = 0.028). The change in free fraction upon diluting plasma with buffer has been described in the literature (Kalvass 2002). The experiments conducted by Cyprotex demonstrate that free fraction in diluted plasma is nearly proportional to the plasma dilution factor. Using either equation 4 from Kalvass (**Figure 1: Equation 4 (where fu is the fraction unbound and D is the dilution factor)**) or the equation on the Cyprotex website, the unbound fraction of ceritinib in 10% FBS may be estimated to be 0.23.

$$\mathrm{fu}_{diluted} = \frac{1}{1 - \frac{1}{D} + \frac{1}{D\ \mathrm{fu}_{undiluted}}}$$

(Kalvass 2002)

Figure 1: Equation 4 (where fu is the fraction unbound and D is the dilution factor)

Applying this estimated fu in 10% FBS to the in vitro assays results in the following unbound IC50 estimates of ceritinib in the in vitro assays (Table 3):

Table 3: Ceritinib IC50

	Observed total IC50 (nM)	Estimated unbound IC50 (nM)
EML4-ALK	31	~ 7 (31*0.23)
EML4-ALK C1156Y	160	~ 37 (160*0.23)
EML4-ALK L1196M	69	~ 16 (69*0.23)
EML4-ALK G1202R	940	~ 216 (940*0.23)

The growth inhibitory effect of ceritinib was examined in a panel of 95 human NSCLC cell lines. Cell proliferation and growth were monitored by measuring the amount of ATP in cells after incubation with ceritinib. The ALK expression levels were determined in the 95 cell lines by RNA-seq technology as FPKM values calculated from RNA-seq data. NSCLC lines that do not harbour ALK rearrangements were not sensitive to ceritinib (CP or relative IC50 > 5.0 µM) regardless of their ALK expression level. NCI-H2228, the only line with the EML4-ALK translocation (and the highest expression level of ALK), was the most sensitive line, with the CP or relative IC50 of 0.8 µM.

In vivo studies

In vivo, ceritinib demonstrated a dose-dependent anti-tumour activity in several human tumour models expressing EML4-ALK or NPM-ALK. Complete or nearly complete anti-tumour efficacy (tumour regression) was observed at oral dose of 25 mg/kg/day in mice and rats. AUC levels were below human therapeutic exposure.

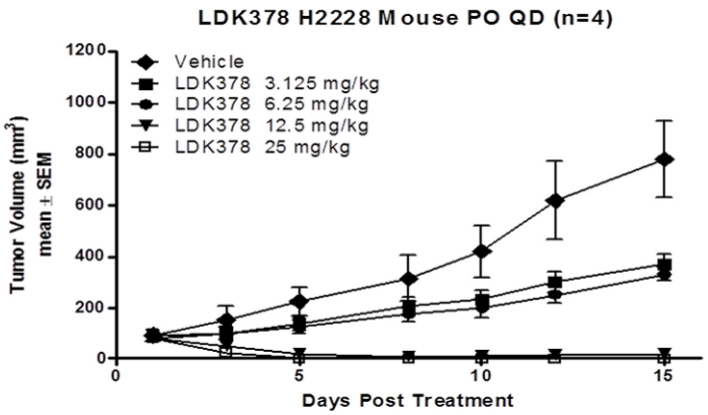


Figure 2: Anti-tumour activity of ceritinib in the NCI-H2228 tumour model in mouse (RD-2008-50926)

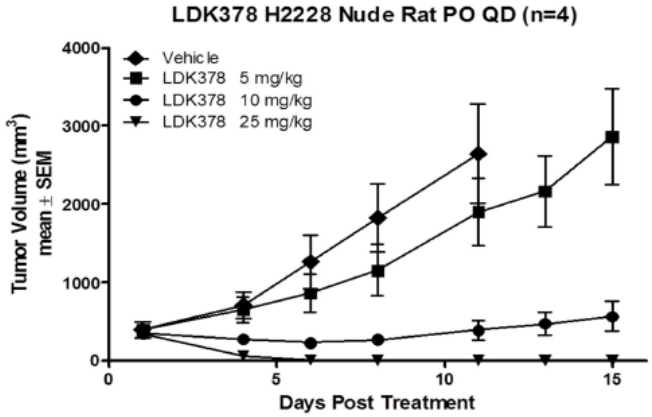


Figure 3: Anti-tumour activity of ceritinib in the NCI-H2228 tumour model in rat (RD-2008-50933)

Ceritinib was also evaluated in comparison with crizotinib in the mouse xenograft model derived from the EML4-ALK-positive NCI-H2228 cell line. Both compounds caused complete tumour regression, but the effect of ceritinib appeared to be more sustained than for crizotinib (150 days versus 1-2 weeks, respectively). The exposure at the dose required for crizotinib to achieve complete regression (mean $AUC_{0\text{-}24h}$ 49,059 ng*hr/mL, 100 mg/kg) is approximately 4 times higher than the exposure required for ceritinib (mean $AUC_{0\text{-}24h}$ 12,507 ng*hr/mL, 25 mg/kg), indicating that ceritinib is a more potent ALK inhibitor than crizotinib in vivo. The exposure to ceritinib is considered to be equal to the expected therapeutic exposure in patients.

In several NCI-H2228 xenograft tumour models that developed resistance to crizotinib, ceritinib showed strong anti-tumour activity at oral dose of 50 to 100 mg/kg/day. The exposures of ceritinib at these doses were in the clinically relevant range, 1.3- to 2.4- fold higher than the exposure observed at 750 mg/day in humans. One of these crizotinib-resistant models harboured the same secondary ALK mutation, C1156Y, as that identified from crizotinib-resistant patients. Another model did not harbour secondary mutations in the ALK kinase domain (or harbours wild type EML4-ALK) but retained the ALK translocation, which is similar to what has been observed in some patients who have developed resistance to crizotinib. The anti-tumour activity of ceritinib in these crizotinib-resistant models likely results from its inhibition of mutant ALK and/or more potent inhibition of wild type ALK.

Secondary pharmacodynamic studies

The selectivity of ceritinib was assessed in panels of GPCRs, transporters, ion channels, nuclear receptors, and enzymes. Activities were monitored initially at a single concentration of 10 µM in an 84-member target panel or by dose-response for a 72-member target panel.

Ceritinib was further tested in a functional calcium flux cellular assay of Somatostatin Sst2 and Sst4 and was found to be inactive up to 10 µM.

In biochemical assay ceritinib inhibited insulin receptor (INSR) and insulin-like growth factor 1 receptor (IGF-1R) with IC50 values lower than 55 nM. To assess its selectivity over INSR in vivo, ceritinib was evaluated in an oral glucose tolerance test in mice. Animals were dosed once daily with ceritinib at 25, 50, or 100 mg/kg for 7 days before the oral glucose tolerance test was conducted under fasting condition. Compared with the vehicle, ceritinib did not have a significant effect on glucose levels during the glucose tolerance test or on fasting plasma insulin level at all dose levels tested. Notably, these dose levels were able to induce 70- 90% inhibition of the ALK pathway and strong anti-tumour activity in treatment-naïve and crizotinib-resistant EML4-ALK-positive tumour models.

HSP90s are a family of chaperone proteins involved in folding and stabilization of a large number of client proteins, including EML4-ALK fusion proteins. An HSP90 inhibitor has been shown to induce the degradation of EML4-ALK and lead to tumour regression in an EML4-ALK-postive NSCLC model. The combination of an ALK kinase inhibitor with an HSP90 inhibitor has the potential to increase anti-tumour effects by combining two different mechanisms of targeting ALK fusion proteins. The combination of ceritinib with AUY922 (an HSP90 inhibitor) was evaluated in two different primary lung tumour xenograft models derived from patient tumour cells: HLUX1787, which harbours the EML4-ALK variant 2, and LUF-1656, which harbours the EML4-ALK variant 1. Both studies showed that the combinations improved anti-tumour activity compared with the monotherapy.

Safety pharmacology programme

The results of the safety pharmacology studies conducted with ceritinib are summarised in the below table.

Table 4: Summary of safety pharmacology studies

Safety pharmacology					
Organ systems evaluated	**Species / strain**	**Method of administration**	**Doses[a]**	**Gender and no. per group**	**Significant findings**
hERG-encoded channel GLP 0970418	HEK293 cells	*In vitro*	0.3, 0.4, 1.0, 2.4 µM	NA	The IC50 value was 0.4 µM.
Cardiovascular Non-GLP 0770889-01	Monkey/ Cynomolgus	Oral gavage	0, 250 mg/kg[b]	2 males	No effects on hemodynamic parameters (HR, BP, body temperature) or on ECG parameters (P duration, PR, QRS, QT and QTc intervals)
Cardiovascular	Monkey/ Cynomolgus	Oral gavage	0, 10, 30, 100 mg/kg[b]	4 males	CERITINIB at single oral doses up to 100 mg/kg had no effects on blood pressure, heart rate, body temperature, PR or QRS intervals and did not produce any arrhythmias. QT prolongation in ¼ animals at 100 mg/kg.
CNS/Respiratory GLP 0970415	Rat/Wistar Hannover	Oral gavage	0, 100 mg/kg	10 males	No effects on FOB. No effects on respiratory rate, tidal volume, minute volume.

[a]Single dose unless specified otherwise; b Single dose in a 4x4 Latin square cross-over design; CNS = Central nervous system, FOB = Functional observation battery, HEK=human embryonic kidney; hERG=human ether-a go go-related gene, HR=heart rate, BP=blood pressure, IC50= 50% inhibitory concentration; NA=not applicable

Ceritinib demonstrated adverse cardiac effects in safety pharmacology studies. In vitro, it inhibited hERG potassium channel (IC50=0.4 µM, 233 ng/mL). In vivo, ceritinib induced QT prolongation in 1 of 4 monkeys after receiving the highest dose of ceritinib, 100 mg/kg. No ECG abnormalities were detected in a 13-week toxicology study in monkeys at an average exposure (Cmax) up to 1590 and 1860 ng/mL for females and males, respectively.

Pharmacodynamic drug interactions

No non-clinical information on possible pharmacodynamic drug interactions has been submitted.

2.3.3. Pharmacokinetics

Non-clinical pharmacokinetics studies were conducted in rats, mice, monkeys and dogs.

Absorption and pharmacokinetics

Ceritinib was slowly absorbed in rats, monkeys and humans with a plasma T_{max} between 6-24 h after single dose. Oral absorption was moderate in rats and monkeys, 37% and $\geqslant$ 40%, respectively. In humans, oral absorption was estimated to be $\geqslant$ 25%.

Table 5: Absorption parameters following single dose ADME studies, single dose PK studies, and selected multiple dose TK studies

Species	Dose (mg/kg/day)	Time to Peak (h) in plasma [a]		% Dose absorbed [b]	Reference
		Radioactivity	LDK378	-	
Mouse	20 mg/kg [c]	-	7	-	RD-2008-50924
Rat	25 mg/kg [c]	12 [10]	12	37	R0900773a
	3 [d]	-	7, 10	-	R1270164
	10 [d]	-	5, 7	-	R1270164
	30 [d]	-	5, 5	-	R1270164
Dog	20 mg/kg [c]	-	8	-	R0700555-01
Monkey	30 mg/kg [c]	7-24 [7-24]	7-24	≥40	R1200422
	60 mg/kg [c]	-	13 ± 9.2	-	R0800227-01
	3 [d]	-	3-7, 3-5	-	R1270165
	10 [d]	-	3, 3-7	-	R1270165
	30 [d]	-	5-10, 5-7	-	R1270165
Human	750 mg/subject	6-10 [6-10]	6-12	≥25	CLDK378A2105

[a] Results in blood are given in brackets, [ ]; when two LDK378 values are shown, these represent male and female, respectively.

[b] Estimated based on either a comparison of the plasma radioactivity AUC following oral and intravenous dosing or on the % of the radioactivity dose in the excreta present as LDK378 or metabolites

[c] Single dose

[d] Multiple non-radiolabeled dose; 13-week duration; results from Day 73; males and females, respectively

The bioavailability of ceritinib was moderate in the mouse, rat and monkey (~ 40-60%). An oral bioavailability value of ~ 100 was obtained in fed dogs, suggesting the possible existence of a positive food effect. In humans, a positive food effect was also observed for ceritinib when administered under fed conditions with a high-fat, high-calorie meal (73% for AUC_{inf}, 72% for AUC_{last} and 41% for C_{max}).

Certinib exposure increased with the dose in an over-proportional manner in all species evaluated (rat, monkey and humans). There was no apparent gender difference in the exposure for monkeys and rats. No conclusive evidence of accumulation for rats was observed, while monkeys showed moderate accumulation (up to 2.7-fold on day 73). In humans accumulation was up to 6.2-fold after 3 weeks of once-daily dosing.

The terminal half-life after intravenous administration of ceritinib was long in the mouse, rat, dog and monkey (6.2-29 hours). In humans, the apparent terminal half-life was also long ~ 30-40 hours.

Plasma clearance of ceritinib following an intravenous dose was moderate in the mouse, rat and dog, 1.60 L/h/kg, 1.49 L/h/kg and 0.552 L/h/kg, respectively, and low to moderate in the monkey, 0.366-0.78 L/h/kg. The steady-state volume of distribution of ceritinib was high in the mouse (9.7 L/kg), rat (19.9 L/kg), dog (13.5 L/kg) and monkey (6.53-13.5 L/kg).

Distribution

In vivo, ceritinib was widely distributed with a T_{max} occurring at 4 h post-dose in most of the tissues. Concentration in tissues was generally higher than blood concentration. Ceritinib was mainly distributed to the intestinal wall, uveal tract, pituitary gland, bile, adrenal cortex, harderian gland, liver, spleen, lymph node, lung, kidney, thyroid, bone marrow, adrenal medulla, pancreas, thymus and salivary gland.

Ceritinib-derived radioactivity was retained in several other tissues (including testis, epididymis, and skin) and the elimination was not yet complete by 168 hours post-dose.

Ceritinib is distributed across the blood-brain barrier, but to a lower degree compared to other tissues and organs. It demonstrated a high affinity for melanin-rich tissues (uveal tract).

The compound distributed more to blood cells than to plasma in all tested species including humans.

In vitro, ceritinib was highly bound to protein. Mean plasma protein binding over the concentration range of 50-10,000 ng/mL was 98.5%, 98.3%, 97,2% and 94.6% for the dog, rat, human and monkey, respectively.

Ceritinib crosses the placental barrier in animals (rats and rabbits). Maternal ceritinib plasma concentrations were approximately 10- to 20-fold higher than the foetal ceritinib plasma concentration. Ceritinib should not be used during pregnancy.

Metabolism

Biotransformation of ceritinib has been examined in rats and monkeys, the species used for non-clinical general toxicity testing.

In general, metabolism of ceritinib is low across species and the biotransformation reactions observed *in vitro* were mainly the same as those observed in vivo in rats, monkeys and humans. These included mono-oxygenation, O-dealkylation, S-dealkylation, and N-formylation of ceritinib, and secondary di-oxygenation, glucuronidation, sulfation and dehydrogenation. After a single intravenous or oral dose of ceritinib, unchanged ceritinib was the only circulating component in plasma from rats, and the main component in plasma from monkeys (84.4%) and humans (81.6%). Eleven metabolites were found in the plasma of humans, each at levels $\leqslant$ 2.3% of the total drug-related AUC. Five of these eleven metabolites were not detected in the plasma of either the rat or monkey. However, two of them (M23.6 and M35.8) were observed in the faeces of both species. The remaining three unique human metabolites detected at low levels in plasma included M46.6 (1.7%), M48.8 (1.7%), and M52.0 (2%).

M35.8 was the most abundant metabolite in the faeces of the monkey. M33.4 was also relatively abundant in the faeces of both the rat and monkey. In orally dosed humans, the faecal route of excretion for ceritinib was also dominant over the urinary route. As with the monkey, the most abundant metabolite in human faeces after an oral dose of ceritinib was also M35.8. Of the metabolites found in rat, monkey, and human faeces, none were present at mean levels > 8.7% of the administered dose.

Metabolite profiles in urine were not determined for rat, monkey or human because only a small amount of the administered dose was eliminated by this route (<2%).

No studies on metabolism have been conducted in rabbit.

Excretion

The major route of excretion was the faeces in rats, monkeys and humans (approximately 90 to 100% after 168 h).

Table 6: Excretion of ceritinib and total radioactivity following a single oral dose of radiolabeled ceritinib

Amount Excreted (% of Dose)							
		Feces			Urine		
Species	Dose (mg/kg)	Radioactivity		Ceritinib	Radioactivity		Ceritinib
		0-24 h	0-168h	0-72h	0-24 h	0-168h	0-72h
Rat	25	33.2	101	80.4	0.0498	0.180	-
Monkey	30	18.4	92.3	60.2	0.41	0.71	-
Human	9.14	20.9	91.0	68	0.510	1.2	-

In cannulated rats, excretion was mainly into the faeces (65%) and bile (24.3%). Urinary excretion was 1.3 % in humans and ⩽3% in animals.

Studies on the excretion of ceritinib into milk were not conducted.

Pharmacokinetic drug interactions

In vitro interaction studies with ceritinib were performed in human liver microsomes,hepatocytes and other cellular systems.

Relative contribution of the individual CYP450 enzymes to the hepatic microsomal oxidative metabolism of ceritinib was assessed in pre-clinical study R0900839. Hepatic microsomal oxidative metabolism of ceritinib was primarily mediated by CYP3A, as selective inhibition of CYP3A by ketoconazole and azamulin produced maximum inhibition (>90%) of the metabolite rate formation, while inhibition of other CYPs tested produced maximum inhibitions ranging from 10-22%.

The recombinant human CYP enzymes found capable of metabolizing ceritinib were CYP3A4 and CYP1B1. Since CYP1B1 is not endogenously expressed in human liver under normal conditions, CYP3A4 is expected to contribute to the majority of hepatic oxidative clearance of ceritinib in humans (R0900839). Thus, due to the major involvement of CYP3A4 in the hepatic oxidative metabolic clearance of ceritinib, there is a potential for drug-drug interactions with co-medications that are CYP3A inhibitors.

Further, CYP450 inhibition by ceritinib in human liver microsomes was assessed in pre-clinical study R0900796. Ceritinib was found to be a reversible and time-dependent inhibitor of CYP3A4/5, with an unbound Ki value for reversible inhibition of 0.161 µM, and Ki and kinact values of 1.47 µM and 0.0642 min-1, respectively, for time-dependent inhibition. In addition to CYP3A4, in vitro inhibition results from this study indicated that ceritinib may inhibit the metabolic clearance of co-medications metabolized by CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP2E1 in vivo if sufficiently high concentrations are achieved.

Enzyme induction studies in primary human hepatocytes (study R1200856) revealed a dose dependent induction of CYP3A4 mRNA with the ceritinib treatment in hepatocytes from the three donor livers used. Ceritinib (0.25-2.5 µM) did not result in induction of CYP1A2 or CYP2B6 mRNA/activities (levels were <2-fold). Based on these in vitro results, ceritinib is unlikely to be a clinical inducer of CYP1A2, CYP2B6, or CYP2C9 in vivo. There is a potential for ceritinib to be an inducer of CYP3A4 in vivo. The relevance of these in vitro data to an induction response in vivo is dependent upon the actual dosing regimen and exposure of ceritinib clinically.

Ceritinib was classified as a low passive permeability compound. It is a substrate of the transporter P-gp. The uptake of ceritinib was stimulated 1.44 and 1.29-fold in cells stably expressing OAT2 and OATP1B1, respectively, but the uptake was minor compared to the uptake of the prototypic substrates of OAT2 (cGMP). Ceritinib did not appear to be a substrate of OCT1 or OATP2B1.

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. Studies in vitro showed that the IC50 values of hepatic uptake transporters OATP1B1 or OATP1B3 and renal organic anion uptake transporters OAT1 and OAT3 are higher than 5 µM.

2.3.4. Toxicology

A complete toxicity safety evaluation program (acute, subchronic, chronic, reproductive toxicology studies and genotoxicity studies) was conducted to support the administration of ceritinib to adult cancer patients. The toxicology program was consistent with the ICH S9 Guideline on Nonclinical Evaluation for Anticancer Pharmaceuticals as well as all other relevant ICH Guidelines on safety. All toxicology studies were performed either in accordance with GLP guidelines or with currently accepted guidelines with respect to animal numbers and dose levels.

Single dose toxicity

One single rising dose study was conducted with ceritinib in monkeys, while no single dose studies in rodents have been performed. The study and main findings are summarised in Table 7.

Table 7: Single dose toxicity studies with ceritinib

Species / Strain (Study ID)	Sex / Number	GLP	Dose (mg/kg) Route	Max non-lethal dose (mg/kg)	Major findings
Monkey / Cynomolgus (0770888)	M / 2	No	Rising dose study; 20, 60, 120, 250. Oral gavage	250	⩾120 mg/kg: Diarrhea, ↑ AST (3-5x), ↑ ALT (2x) 250 mg/kg: Diarrhea, emesis

Ceritinib was given as a 0.5% methyl cellulose (MC) solution to 2 male Cynomolgus monkeys in a single rising dose design of 20, 60, 120 and 250 mg/kg on days 1, 6, 12 and 19, respectively.

Diarrhoea was seen after a dose of 120 mg/kg and diarrhoea and emesis with food after 250 mg/kg. There were no changes in haematology parameters. Increased AST (3-5-fold over baseline) and ALT (2-fold over baseline) were observed in one animal at the two highest doses.

Repeat dose toxicity

Subacute, subchronic and chronic toxicity of ceritinib were assessed in oral repeat-dose toxicity studies in rats (up to 13 weeks) and cynomolgus monkey (up to 13 weeks). Major findings from the repeat dose toxicity studies are presented in Table 8.

Table 8: Repeat dose toxicity studies

Species /strain (Study ID) GLP status	Study Duration	Dose (mg/kg/day) Route Sex and number per group	Major findings NOAEL (mg/kg)

IGS Wistar Hannover Rat; Crl: WI(Han) (0770561) Non-GLP	2-weeks	0, 25, 100 Oral gavage 5M	25 mg/kg: *Clinical signs:* ↓ body weight gain *Haematology and clinical chemistry:* ↓ reticulocyte counts, ↓ mean corpuscular volume (MCV) and mean corpuscular haemoglobin (MCH), ↓ haematocrit and haemoglobin. ↓ triglycerides, ↓ glucose and albumin, ↑ globulin. *Microscopic findings:* Bile duct vacuolation / hypertrophy; Adrenal gland: ↑ cortical vacuolation and/or cortical single cell necrosis; Stomach: (glandular) erosion 100 mg/kg: *Clinical signs:* Piloerection, ↓ body weight (BW) *Haematology and clinical chemistry:* ↑ red blood cell (RBC) count and haemoglobin, ↑ platelet counts, ↑ total white blood cell count (WBC), neutrophil and monocyte counts. ↑ aspartate aminotransferase (AST), ↑ creatine kinase in one animal, ↓ urea, total bilirubin, and cholesterol, ↓ triglycerides, glucose, and albumin, ↑ globulin. *Macroscopic findings:* ↓ mean thymic and splenic weights. *Microscopic findings:* Bile duct vacuolation / hypertrophy; focal / multifocal or single cell necrosis of hepatocytes, peri- / cholangiolitis. Hypocellularity in bone marrow (sternum), absence of haemopoiesis in spleen. Mesenteric lymph nodes: focal / multifocal necrosis (cortex/paracortex), abscess formation (paracortex), and increase in aggregates of macrophages, subacute focal inflammation in the mesentery, reduction/absence of germinal center development. Thymus: cortical atrophy and/or lymphocytolysis. Adrenal gland: increase in cortical vacuolation and/or cortical single cell necrosis. Small intestine: minimal neutrophilic cell infiltration; Stomach: (glandular) erosion. NOAEL: ND
IGS Wistar Hannover Rat; Crl: WI(Han) (0870025) Non-GLP	2-weeks	0, 10, 50 and 100 Oral gavage 5M	≥ 50 mg/kg: ↓ body weight gain (BWG) and ↓ food consumption. NOAEL: 10 mg/kg
IGS Wistar Hannover Rat; Crl: WI(Han) 0970057-01 Non-GLP	4-weeks with 4 week recovery	0, 25, 50 for 4 weeks; 0, 50, 100 cyclic (Monday, Thursday, Saturday) Oral gavage 5M all doses, 5M recovery	25 mg/kg/day: Piloerection, decreased BWG, ↑ globulin. Biliopancreatic duct: inflammation and epithelial cytoplasmic vacuolation, erosion, and/or necrosis Liver: vacuolation in epithelium of bile duct; Lymph node: accumulation of macrophage aggregates. 50 mg/kg/day *Clinical signs:* Dehydration, hunched posture, ↓ locomotor activity, ↓ BWG *Haematology and clinical chemistry:* ↑ neutrophils, ↑ globulin, *Macroscopic findings:* ↑ liver and thyroid gland weights, ↓ thymus weight. *Microscopic findings:* Biliopancreatic duct: inflammation and epithelial cytoplasmic vacuolation, erosion, and/or necrosis; Pancreas: mixed cell inflammation; Liver: vacuolation of bile duct epithelium; Lymph node: accumulation of macrophage aggregates; Lung: foamy alveolar macrophages.

			50 mg/kg (cyclic): *Clinical signs:* Piloerection; ↓ BWG *Clinical chemistry:* ↑ globulin *Microscopic findings:* Biliopancreatic duct: inflammation and epithelial cytoplasmic vacuolation erosion, and/or necrosis; Liver: vacuolation epithelium of bile duct; Lymph node: accumulation of macrophage aggregates. 100 mg/kg (cyclic) *Clinical signs:* Piloerection, ↓ BWG *Haematology and clinical chemistry:* ↓ lymphocytes, ↑ globulin *Macroscopic findings:* ↓ spleen weight *Microscopic findings:* Biliopancreatic duct: inflammation and epithelial cytoplasmic vacuolation erosion, and/or necrosis; Pancreas: mixed cell inflammation; Liver: epithelium vacuolation of bile duct; Lymph node: accumulation of macrophage aggregates; Lung: foamy alveolar macrophages; Recovery: Partial recovery after 4 weeks NOAEL: ND
IGS Wistar Hannover Rat; Crl: WI(Han) 0970416 GLP	4-weeks with 4 week recovery	0, 7.5, 25, 75 → 50 10/sex/group 6/sex for recovery (high dose and vehicle)	≥25 mg/kg/day: *Clinical findings:* ↓ body weight gain *Clinical chemistry:* ↑ neutrophil, ↑ serum insulin concentration (M) 50 mg/kg/day: *Clinical signs:* ↓ body weight, ↓ food consumption. *Hematology:* Inflammation (↑ monocyte, ↑ platelet, ↑ plasma fibrinogen). ↑ lymphocyte counts (M). *Clinical chemistry:* ↑ insulin (F). ↑ serum liver enzyme activities (M), ↑ serum phosphorus concentration 75 mg/kg/day: Not tolerated and was reduced to 50 mg/kg due to adverse clinical signs (body weight loss, reduced food consumption, cold to touch, thin, hunched posture and/or piloerection) *Haematology:* ↓ reticulocyte counts *Clinical chemistry:* ↓ urea, ↓ phosphorus (M) and ↓ magnesium ↑. Glucose (F), and ↑ calcium (M). ↑ serum AST and ALT activities (M) Recovery Complete recovery, except for reductions in body weight (M) and food consumption (M), macroscopic dilatation of the extra-hepatic bile duct (M), inflammatory changes, necrosis and luminal dilatation of the biliopancreatic duct epithelium, and macrophage aggregates in the mesenteric lymph nodes. NOAEL: 7.5 mg/kg

IGS Wistar Hannover Rat; Crl: WI(Han) 1270164 GLP	13-weeks with 8 week recovery	0, 3, 10, 30 10/sex/group 6/sex for recovery (high dose and vehicle)	≥3 mg/kg/day: *Microscopic findings:* Major duodenal papilla (epithelial degeneration/necrosis (M), vacuolation (M), degeneration/necrosis, and erosion/ulcer). Biliopancreatic duct (chronic-active inflammation, epithelial vacuolation (M), hyperplasia (M) and luminal dilatation (M)) ≥10 mg/kg/day: *Clinical chemistry:* ↑ thyroid stimulating hormone concentration (M) *Microscopic findings:* Vacuolation of the intrahepatic bile duct epithelium. Major duodenal papilla (vacuolation (M+F)). Biliopancreatic duct (epithelial vacuolation, hyperplasia and luminal dilatation (M+F)) 30 mg/kg/day: *Clinical findings:* ↓ food consumption, ↓ body weight gain and ↓ body weights *Haematology and clinical chemistry:* ↑ platelet count and ↑ fibrinogen concentration. ↑ total protein concentration (M), ↓ albumin concentration (F), ↑ globulin concentration and ↓ albumin-to-globulin ratio, ↑ cholesterol concentration (F), ↓ triglyceride concentration, ↑ calcium concentration (M), ↑ thyroid stimulating hormone concentration, ↑ total triiodothyronine concentration (M), and ↑ total thyroxine concentration (F). *Microscopic findings:* Duodenum (chronic-active inflammation, hyperplasia and luminal dilatation), mesenteric lymph node and lung (↑ number of macrophages) Recovery: Complete recovery, except: degeneration/necrosis (M) and vacuolation (F) in the duodenal major papilla; chronic-active inflammation, epithelial vacuolation and hyperplasia, luminal dilatation, erosion/ulcer, and degeneration/necrosis of one or more sections of biliopancreatic bile duct; and ↑ macrophage aggregates in the mesenteric lymph node (M) NOAEL: ND
Cynmolgus monkey/Macaca fascicularis 0870126 Non-GLP	2-weeks	0, 10, 40, 100 1/sex for vehicle, low and mid doses, and 2/sex for high dose	≥40 mg/kg: *Clinical signs:* Circling, depression, cold to touch, dehydration, hunched posture, decreased locomotor activity (DLA), soft faeces/diarrhoea, and emesis *Microscopic findings:* Thymus (lymphoid depletion), pancreas (decreased zymogen) 100 mg/kg: *Clinical signs:* Decreased BW. *Clinical chemistry:* ↓ neutrophils, ↓ reticulocytes, ↓ cellularity in bone marrow smears. ↑ ALT (2-3-fold), ↑ total bilirubin, ↑ urea and ↑ creatinine. *Microscopic findings:* Bone marrow (↓ cellularity), pancreas (↓ zymogen) 1M euthanized on day 10 due to toxicological signs (↓ Food consumption, ↑ neutrophils and fibrinogen, ↓ lymphocytes, ↑ phosphorus; cause of morbidity was kidney toxicity (multifocal cortical interstitial mixed inflammation, tubular necrosis, mineralization, dilatation, and cast formation))

			NOAEL: 10 mg/kg
Cynomolgus monkey/Macaca fascicularis 0970612 GLP	4-weeks with 4 week recovery	0, 3, 10, 30 3/sex/group 2/sex for recovery (high dose and vehicle)	≥10 mg/kg/day: *Macroscopic findings:* ↓ Thyroid gland weights (M). Small thyroid gland (M). Small follicles and colloid depletion in thyroid gland (M). *Microscopic findings:* Sinus histiocytosis in mesenteric lymph nodes (F). 30 mg/kg/day: *Clinical chemistry:* ↑ serum ALT activity *Microscopic findings:* Erosion and vacuolation of the lining epithelium of duodenal ampulla, associated with epithelial hyperplasia, and foamy macrophage infiltration of the submucosa. Neutrophilic inflammation in duodenal ampulla and adjacent duodenal mucosa. ↓ zymogen in the acinar pancreas. Sinus histiocytosis in mesenteric lymph nodes. Thymic lymphoid depletion. Recovery: Complete recovery, except for reduced thyroid gland weight (M), and small follicles and colloid depletion in the thyroid glands (M). NOAEL: 10 mg/kg
Cynomolgus monkey/Macaca fascicularis 1270165 GLP	13-weeks with 8 week recovery	0, 3, 10, 30 4/sex/group 2/sex for recovery (high dose and vehicle)	≥3 mg/kg/day: *Clinical signs*: sporadic vomitus 30 mg/kg/day: *Clinical signs*: Liquid faeces *Clinical chemistry*: ↑ ALT activity, ↑ glucose, ↑ insulin (M) *Macroscopic findings*: Discoloured major duodenal papilla *Microscopic findings*: ↑ mixed cell inflammation in the cystic bile duct (M), hepatic bile duct (M), and the common bile duct (M). Mixed cell inflammation (mononuclear cells and neutrophils) in major duodenal papilla. Fine cytoplasmic vacuoles in duct epithelium of the cystic bile duct (M), hepatic bile duct (M), common bile duct (M), and lining cells of the major duodenal papilla (M). Minimal mixed cell peribiliary inflammation in the liver. Recovery: Complete recovery NOAEL: 10 mg/kg

ND: Not determined

Genotoxicity

The genotoxic potential of ceritinib was evaluated in a standard battery of genotoxicity tests.

Table 9: Summary of genotoxicity studies

Type of test	Test system	Concentrations	Major Findings

Miniscreen Ames Study 0613212 Non-GLP	S. typhimurium :TA 98 and TA 100 ± S9	10, 30, 100, 300 and 1000 µg/well	Not mutagenic
Chromosomal aberration screen Study 0870222 Non-GLP	Cultured human peripheral blood lymphocytes ± S9	3 + 17-hour ± S9 Tested up to 16 µg/mL, precipitation	Not aneugenic or clastogenic; polyploidy observed (anti-mitotic effect)
Micronucleus test *in vitro* Study 0714901 Non-GLP	Cultured human peripheral blood lymphocytes	3- or 20-hour –S9 and 3-hour +S9 Tested up to 18.6 µg/mL, cytotoxic	No increase in micronuclei; Not aneugenic or clastogenic
Micronucleus test *in vitro* Study 0614110 Non-GLP	TK6 cells	3- or 20-hour –S9 and 3-hour +S9 Tested up to 125 µg/mL, precipitation	Increased numbers of cells containing micronuclei after 20-hour treatment -S9, but not after 3-hour treatment ±S9 at cytotoxic concentrations only
Ames Study 0970421 GLP	Strains TA1535, TA97a, TA98, TA100, TA102 ± S9	1.563-100.0 µg/plate for TA100, TA1535 and TA97 -S-9, 0.781-50.00 µg/plate for TA102 - S-9 and 1.563-200.0 µg/plate for strain TA98 - S-9 and all strains +S-9	No increases in revertant colonies; not mutagenic
Chromosome aberration Study 0970419 GLP	Cultured human peripheral blood lymphocytes ± S9	3 + 17-hour ± S9, 20 +0 hour –S9; 3+17hour +S9; Tested up to 22 µg/mL, limited by cytotoxicity	Not aneugenic or clastogenic; polyploidy observed
Rat bone marrow micronucleus test Study 1370166	Rats	0, 200, 1000, 2000 mg/kg po × 2 days	No micronuclei observed in bone marrow 48h after the first dose

The Ames tests were negative and the chromosomal aberration studies gave no indication on structural changes. An increased number of cells with numerical aberrations were seen. This was predominantly associated with increases in polyploidy cells. The in vitro micronucleus test showed a weakly positive effect at moderate cytotoxic levels. However, the in vivo study gave a negative result. Ceritinib is considered as being neither mutagenic nor clastogenic in the conducted genotoxicity studies.

Carcinogenicity

No carcinogenicity studies were performed which in view of the applied indication is acceptable according to the guideline ICH S9 on Non Clinical Evaluation for Anticancer Pharmaceuticals.

Reproduction Toxicity

Fertility and early embryonic development studies were not conducted with ceritinib according to ICHS9 Guideline for the development of oncology drugs.

In the pivotal embryo-foetal development studies, no signs of foetotoxicity or teratogenicity were observed in rats and rabbits. At the embryo-foetal no effect levels, maternal exposures (AUC) in pregnant rats and rabbits were 0.65 and 0.49, respectively, of the exposure attained at the clinical dose of 750 mg. Though no effects of ceritinib were observed on the developing foetus, at maximum tolerated maternal doses the exposure margins are low so caution needs to be applied in extrapolating to potential human risk.

Prenatal and postnatal development and juvenile toxicity studies have not been conducted.

Local Tolerance

Local tolerance studies were not conducted with ceritinib as the route of administration is oral.

Other toxicity studies

Phototoxicity

The phototoxic potential of ceritinib was evaluated in the 3T3 NRU phototoxicity assay. The resulting Photo Irritation Factor values from two assays (8.1 and 5.1) indicated that ceritinib had a slight phototoxic potential (PIF>5.0). The in vivo phototoxic potential of ceritinib was also evaluated after oral administration to female BALB/c mice. Ceritinib did not have any phototoxic potential at a C_{max} that is 3-fold higher than the C_{max} at the clinical maximum tolerated dose (MTD) of 750 mg. According to the clinical overview, AEs associated with phototoxicity were reported in only 2.0% of 304 patients in Study X2101 and all were grade 1. These AEs had no impact on study treatment (i.e., no cases required drug interruption, dose reduction, or discontinuation).

Studies on impurities

Limits proposed for impurities 123-13 and 127-13 are above of qualification threshold. These impurities have been adequately qualified in the four weeks general toxicity study and in the micronucleus test performed in rats.

2.3.5. Ecotoxicity/environmental risk assessment

Table 10 Summary of main study results

Substance (INN/Invented Name):					
CAS-number (if available):					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD117	Log Pow = 3.1 (pH 4), 5.1 (pH 7), 5.0 (pH 9)			Potential PBT (Y)
PBT-assessment					
Not conducted					
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	3.75	µg/L			> 0.01 threshold (Y)
Other concerns (e.g. chemical class)					(Y/N)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD	*Ongoing*			
Ready Biodegradability Test	OECD 301	*Not biodegradable*			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	*Ongoing*			
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/ *Pseudokirchneriella subcapitata* D78373, GLP	OECD 201	72h-NOEC	0.0068	mg/L	Since the differences in growth rate between the treatments at 0.0068-0.12 mg/L
		72h-EC10	0.12		

					and the control were < 10% (without a concentration-effect relationship), the statistically determined NOEC was considered by the applicant to be replaced by the EC10-value.
Daphnia magna. Reproduction Test D78362, GLP	OECD 211	NOEC	0.41	mg/L	
Fish, Early Life Stage Toxicity Test/ Zebra Fish D78351, GLP	OECD 210	NOEC	0.045	mg/L	*Danio rerio*
Activated Sludge, Respiration Inhibition Test D78395, GLP	OECD 209	EC	⩾100	mg/L	

The octanol/water partition coefficient for ceritinib was determined to be 5.1 at pH=7. Ceritinib log D exceeds 4.5. Therefore, PBT screening is required.

Further, a Ready Biodegradability Test (OECD 301) was conducted and the results show that ceritinib is not readily biodegradable. A long-term toxicity test set on fish, daphnia and algae was performed to study potential effects on aquatic organisms.

The potential for adsorption to sewage sludge and soil, as well as partitioning to sediments, will be examined in further studies which are ongoing.

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends the following point to be addressed:

The Applicant will therefore submit a complete environmental risk assessment including studies to address the PBT assessment, adsorption to sewage sludge and soil and transformation in soil and aqueous sediment system by Q3 2015.

2.3.6. Discussion on non-clinical aspects

Pharmacology and Safety pharmacology

Ceritinib has been studied extensively in primary, secondary and safety pharmacology studies. Potent inhibition of ALK kinase with a high degree of selectivity has been demonstrated (IC_{50} = 0.15 nM). Compared to crizotinib, which inhibits both ALK, cABL and MET within the same concentration range, ceritinib appears to be a more selective ALK-inhibitor. However, at the therapeutic maximum dose of 750 mg/day, a maximum free plasma concentration of approximately 55 nM is expected, and a potential effect on some other kinases cannot be excluded. Functional effects on IGF-1R and INSR was not detected in specifically designed studies, but a tendency to mild increase in plasma glucose and insulin was observed in some general toxicity studies in both rat and monkey. Hyperglycaemia is also listed as an identified clinical risk in the Risk Management Plan (RMP). The mechanism inducing hyperglycaemia is unknown, however inhibition of the INSR cannot be excluded. For ROS1 no functional data are available.

Ceritinib was less potent against crizotinib resistant EML4-ALK mutants compared to its activity against the non-mutated EML4-ALK. Nonetheless, ceritinib showed strong activity against these ALK mutants with greater potency than crizotinib. The unbound fraction of ceritinib in the in vitro cellular assay on protein kinases and on crizotinib resistant EML4-ALK mutants has not been determined. Based on the

equation from Kalvass (2002) the unbound concentrations of ceritinib in 10% FBS was estimated to be 0.23. Applying this approximation the estimated unbound IC50 for EML4-ALK C1156Y, EML4-ALK L1196M and EML4-ALK are below the therapeutic concentration of ceritinib (55 nM). Clinical efficacy of ceritinib on EML4-ALK L1196M and EML4-ALK has been demonstrated. However, clinical data about effects on EML4-AL C1156Y are not available. Regarding to EML4-ALK G1202R, the estimated unbound IC50 is above the 55 nM and this mutation has been detected in patients who progressed on ceritinib.

In xenograft tumour models derived from NCI-H2228 (EML4-ALK variant 3) and Karpas299 (NPM-ALK+) cells, ceritinib induced a dose-dependent tumour regression that was complete, or nearly complete. Interestingly, the effect of ceritinib appeared to be much more sustained than for crizotinib, and a strong anti-tumour effect by ceritinib was also observed in crizotinib-resistant models. However, only one of these crizotinib-resistant models harboured a secondary ALK mutation, C1156Y, which has been identified in crizotinib-resistant patients. Another model did not harbour secondary mutations in the ALK kinase domain but retained the ALK translocation. Ceritinib exposure levels that induced complete tumour regression in these models were equal to or 2.4 fold higher, than clinical exposure, suggesting that compared to crizotinib naïve subjects, higher doses are necessary to induce tumour regression. This is also consistent with results from cell lines expressing ALK mutants, which were less sensitive to ceritinib than the EML4-ALK WT. Although it is plausible that a higher concentration of ceritinib is required to inhibit mutant ALK, loss of selectivity and inhibition of kinases different from ALK (e.g. ROS1, AURORA, ABL, AXL) could potentially also contribute to the anti tumourigenic effect in these models.

In the secondary pharmacology studies, a screening for potential effects of ceritinib was conducted in two large panels of GPCRs, ion channels, transporters and receptors. For study RD-2008-50904 the Applicant states that a dose response has been performed for 9 of 15 targets with more than 50% inhibition at 10 µM ceritinib. Targets included in the dose-response follow up were the ones where at least 90% inhibition at 10 µM ceritinib was detected, pharmacologically related targets, and in addition the 5-HTa receptor (71% inhibition in the screening). Otherwise, IC50's that have been presented are in general in large excess of the expected free concentration in patients (55 nM) and most targets with an IC50 > 1 µM have been further examined in cellular functional assays. Results have not shown any effects considered to be clinically relevant. Overall, data presented in the dossier support a high degree of selectivity for ceritinib at therapeutic doses; no obvious secondary non-kinase targets have been identified.

The studies to evaluate the acute effects of ceritinib on vital organ system functions were conducted according to the requirements established in the ICH S7a and S7b guidelines. These studies indicate that ceritinib is unlikely to interfere with vital functions of the respiratory and central nervous systems.

Ceritinib inhibited the hERG current at all tested concentrations, with an estimated IC_{50} of 0.4 µM (233 ng/mL). Based on an average C_{max} of 1100 ng/mL in humans at the current therapeutic dose of 750 mg and that ceritinib is approximately 97.2% bound to plasma proteins, this equates to a maximal free drug concentration of 30.8 ng/mL. The difference between maximal free drug concentration in plasma and the estimated IC_{50} value in the hERG-assay is approximately 7 fold.

In clinical studies with ceritinib there have been observations of QT/QTc prolongation in 18 patients (5.9%). According to the Applicant, no patient discontinued the study drug due to QT prolongation events, nor were there any reported deaths due to treatment-related cardiac events. These findings are further discussed in the clinical part of the assessment. The detectable effects on the hERG channel and QT interval prolongation warrant caution when using co-medications that carry this risk, or in patients that may experience unusually high plasma concentrations or have risk factors for QT prolongation. QT prolongation is however listed as an important identified risk in the Risk Management Plan (RMP) and information about the non-clinical findings is adequately presented in the SPC. Further non-clinical studies are not considered necessary.

Pharmacokinetics

ADME-studies were conducted in rat and monkey, the species used for general toxicity testing.

Three unique human metabolites have been detected, namely M46.6 (1.7%), M48.8 (1.7%), and M52.0 (2%). Considering the low levels of these human metabolites, and the fact that ceritinib is a product under the scope of ICH S9, no further qualification of human metabolites is considered warranted.

No PK-studies have been conducted in rabbit, one of the species used for reproductive toxicity testing. However, biotransformation reactions appear similar and occur only to a limited extent across tested species (rat, monkey and human). In view of this, and with reference to ICH S9, metabolic profiling for ceritinib in rabbit is not considered necessary.

No data on excretion in milk are available. Since ceritinib is not intended to be used in pregnant or lactating women, this is considered acceptable. Adequate information and warning has been included in section 4.6 of the SPC.

PK interaction

Ceritinib at clinically relevant concentration will likely inhibit the in vivo clearance of drugs metabolized by CYP2A6, CYP2C9, CYP3A (reversible and time-dependent), and CYP2E1 but not CYP1A2, CYP2B6, CYP2C8, CYP2C19, and CYP2D6. Additionally, ceritinib can inhibit CYP3A4. This effect will likely be masked by the time-dependent inhibition of CYP3A. The apparent passive permeability of ceritinib was determined to be low indicating that ceritinib efflux is through transporters. It was showed that ceritinib is a substrate of P-gp but not of OAT1, OAT2, OATP1B1 and OATP2B1. It is unlikely that ceritinib administered at dose of 750 mg once-day will alter the pharmacokinetics of co-medications that are substrates for any of the following transporters, OATP1B1, OATP1B3, OAT1, OAT3 and OCT2.

Since ceritinib is predicted to inhibit intestinal P gp and BCRP at clinically relevant concentrations, it may have the potential to increase plasma concentrations of co administered medicinal products transported by these proteins.

Toxicology

A complete toxicity safety evaluation program (acute, subchronic, chronic and reproductive toxicology studies and genotoxicity studies) was conducted to support the administration of ceritinib to adult cancer patients. The toxicology program was consistent with the ICH S9 Guideline on Nonclinical Evaluation for Anticancer Pharmaceuticals as well as all other relevant ICH Guidelines on safety. All toxicology studies were performed either in accordance with GLP guidelines or with currently accepted guidelines with respect to animal numbers and dose levels.

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. Liver was also affected in both species, but only at the highest dose levels studied, 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.

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, which is considered acceptable according to ICH S9.

No fertility, early embryonic development, pre-/postnatal or juvenile toxicology studies have been conducted. This is in line with guidelines for pharmaceuticals intended for treatment of patients with advanced cancer. The potential for ceritinib to cause infertility in male and female patients is therefore unknown.

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 dose of 750 mg in clinical trials. The potential risk in humans is unknown. Women of childbearing potential should therefore be advised to use a highly effective method of contraception while taking ceritinib and for up to 3 months after discontinuing treatment (see sections 4.5 and 4.6 of the SmPC).

Ceritinib showed a low potential for phototoxicity in the 3T3 NRU *in vitro* assay and was confirmed to be non-phototoxic in the UV mouse LLNA.

An environmental risk assessment (ERA) has been submitted but the available data are not sufficient to conclude on the environmental risk of ceritinib. The Applicant will therefore submit a complete environmental risk assessment including studies to address the PBT assessment, adsorption to sewage sludge and soil and transformation in soil and aqueous sediment system by Q3 2015.

2.3.7. Conclusion on the non-clinical aspects

The pharmacologic, pharmacokinetic, and toxicological profile of ceritinib is well characterized. Data from Pharmacodynamic studies suggest that ceritinib has an effect on both tumour cell growth and proliferation.

Modest QT prolongation has been observed in safety pharmacology studies.

The toxicology program was consistent with the ICH S9 Guideline and the principal toxicity identified was inflammation of the extra hepatic bile ducts and gastrointestinal toxicity.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study (Status) /cut-off date		Primary endpoint	No. of patients	Ceritinib dose
Registration studies for efficacy and safety				
Study X2101 (ongoing; enrolment complete) 14-Apr-2014	Phase 1, multi-center, dose-escalation study in patients with ALK-positive tumors; prior ALK inhibitor therapy was allowed	Escalation phase: MTD Efficacy endpoint: ORR by Investigator per RECIST 1.0	Escalation phase: 59 Expansion phase: 245 Total at 750 mg: 255 [a]	Escalation phase: 50 to 750 mg Expansion phase: 750 mg
Study A2201 (ongoing; enrolment complete) 13-Aug-2014	Phase 2, multi-center, single-arm study in adult patients with ALK-activated NSCLC previously treated with chemotherapy and crizotinib	ORR by Investigator per RECIST 1.1	140	750 mg
Study A2203 (ongoing; enrolment complete) 26-Feb-2014	Phase 2, multi-center, single-arm study in crizotinib naïve adult patients with ALK-activated NSCLC	ORR by Investigator per RECIST 1.1	124	750 mg
Phase 1 study with efficacy and safety data				
Study X1101 (enrolment complete for dose-escalation, ongoing for expansion) 02-Aug-2013	Phase 1, multi-center, dose-escalation study in Japanese patients with ALK-positive tumours; prior ALK inhibitor therapy was allowed	Escalation phase: MTD Efficacy endpoint: ORR by Investigator per RECIST 1.1	Escalation phase: 19[b] Expansion phase: 0 Total at 750 mg: 6[b]	Escalation phase: 300 to 750 mg Expansion phase: 750 mg
Studies contributing safety data				
Study A2303 (enrolling) 27-Jun-2014	Phase 3, multi-center, randomized, open-label study of ceritinib vs. standard second-line chemotherapy (pemetrexed or docetaxel) in patients previously treated with chemotherapy and crizotinib; patients had to have progressed on crizotinib.	PFS by BIRC per RECIST 1.1	Total (ceritinib and comparator): 81[c] Ceritinib: ~41	750 mg
Study A2301 (enrolling) 27-Jun-2014	Phase 3 multi-center, randomized, open-label study of ceritinib vs. chemotherapy (pemetrexed plus cisplatin) in previously untreated patients with advanced ALK-positive NSCLC	PFS by BIRC per RECIST 1.1	Total (ceritinib and comparator): 70[c] Ceritinib: ~35	750 mg
Study A2402 (enrolling) 27-Jun-2014	Open-label, multi-center, expanded treatment protocol of ceritinib in adult patients with ALK-positive NSCLC previously treated with an ALK inhibitor	Safety	64	750 mg
Study A2109 (enrolling) 27-Jun-2014	Phase 1/2 study in Chinese patients with ALK-positive NSCLC previously treated with crizotinib	Characterize PK in Chinese patients	31	750 mg
Study X2103 (enrolling) 27-Jun-2014	Phase 1 dose-finding study of ceritinib in pediatric patients with ALK-positive malignancies	Determine MTD	17	Starting dose 300 mg/m2
Study X2102 (terminated)[d] 27-Jun-2014	Phase Ib, open-label, dose-escalation study of ceritinib and AUY922 in patients with ALK-positive NSCLC previously treated with ALK inhibitor	Escalation phase: MTD	Escalation phase: 17 [e]	ceritinib 600 mg AUY922 40 mg/m2 /week

Study A2110 (enrolling) 27-Jun-2014	A phase I, open label, multi-center, single dose study to evaluate the pharmacokinetics of ceritinib in healthy subjects with normal hepatic function and subjects with impaired hepatic function	Characterize PK in subjects with impaired hepatic function	23 subjects	750 mg
StudyA2108 (enrolling) 27-June-2014	Phase 1 bioavailability and food effect study of two new tablet formulations vs reference capsule formulation in healthy subjects	Characterize PK to evaluate the relative bioavailability	12 healthy subjects	750 mg
Studies contributing to the clinical pharmacology				
Study A2101 (completed)	Food-drug interaction study	Food effect	28 healthy subjects (50 mg and 150 mg capsules)	Single dose: 500 mg
Study A2105 (completed)	Mass balance study (ADME)	Human ADME	6 healthy subjects (150 mg capsule)	Single dose: 750 mg
Study A2104 (completed)	Drug-drug interaction study	Drug-drug interaction with ketoconazole	19 Healthy subjects (150 mg capsule)	Single dose: 450 mg
Study A2106 (completed)	Drug-drug interaction study	Drug-drug interaction with rifampin	19 Healthy subjects (150 mg capsule)	Single dose: 750 mg
Studies X2101, X1101, A2101, A2104, A2105 and A2106	Basic PK	Characterise PK	See above	
Study X2101	Population PK	Characterize PK with respect to inter-patient variability; test effects of demographic covariates (gender, age, weight, race, baseline renal/hepatic condition) and concomitant medications	See above	
Study X2101	Exposure response relationship	Exposure-efficacy; exposure-safety, including concentration-QTc relationship	See above	

ORR: overall response rate; PFS: progression-free survival; BIRC: blinded independent review committee; ADME: absorption, distribution, metabolism, excretion; PK: pharmacokinetic; MTD: maximum tolerated dose

[a] 246 patients with NSCLC and 9 patients with another malignancy

[b] 18 patients with NSCLC (5 treated at 750 mg) and 1 patient with another malignancy (treated at 750 mg)

[c] Includes patients randomized to both the chemotherapy and ceritinib arms

[d] Study X2102: dose escalation completed, dose expansion terminated

[e] Study X2102: some patients could receive AUY922 on Day 1 and initiate ceritinib on Day 2

2.4.2. Pharmacokinetics

The PK characteristics of ceritinib have mainly been investigated in four studies in healthy subjects (A2101, A2104, A2105, A2106) and two clinical studies in patients (X1101 and X2101). There is an ongoing study in hepatic impaired subjects.

Absorption

Peak plasma levels (C_{max}) of ceritinib are achieved approximately 4 to 6 hours after oral administration in patients, and approximately 6 to 8 h in healthy subjects.

In study A2105, following administration of single oral dose of 750 mg [14C] ceritinib, median maximum plasma concentrations were reached after 8 hr with mean C_{max} of 228 ng/mL and $AUC_{0-\infty}$ of 11300 (ng*h/mL)/mg. Oral absorption was estimated to be $\geqslant$25% based on metabolite percentages in the faeces. The absolute bioavailability of ceritinib has not been determined.

The slow absorption of ceritinib was further confirmed in drug-interaction studies A2104 and A2106

In study X2101, C_{max} and AUC_{last} increased dose-proportionally across the 50-750 mg dose range following a single oral dose; however, pre-dose C_{trough} appeared to increase with dose in a greater than-proportional manner following multiple daily doses at steady-state. Overall, the inter-patient variability in exposure parameter estimates was high, with coefficients of variation of 93% and 87% for AUC_{last} and C_{max}, respectively.

Following dosing at the recommended dose of 750 mg daily, steady-state conditions were achieved by approximately 15 days, with geometric mean accumulation (assessed by AUC_{tau}) of 4.7-fold after 1 week and 6.2-fold after 3 weeks: exposure stayed relatively stable over the 12-week treatment period. Ceritinib demonstrated nonlinear PK over time, as indicated by the observed difference in apparent clearance (CL/F) between single-dose administration (88.5 L/h at 750 mg) and at steady-state (33.2 L/h at 750 mg).

Influence of food on drug exposure

Results from the food effect study A2101 in healthy volunteers showed that the bioavailability of ceritinib is increased when given with a meal. Ceritinib AUC_{inf} values were approximately 58% and 73% higher (C_{max} approximately 43% and 41% higher) when administered with a low fat meal and a high fat meal, respectively. No food should be eaten for at least 2 hours before, and for 2 hours after the dose of ceritinib is taken.

Table 11: Summary statistics of ceritinib pharmacokinetic parameters under fasted or fed conditions (Study A2101-PAS)

Parameter[a]	LDK378 (500 mg), fasted (Treatment A) N=27	LDK378 (500 mg), low-fat (Treatment B) N=14	LDK378 (500 mg), high-fat (Treatment C) N=14	Comparison	Geo-mean Ratio (90%CI)
Tmax (h)	8.00 (6.00-12.0)	7.00 (3.00-12.1)	10.0 (6.00-12.0)	B-A	-2.00 (-6.00-6.10)
	n=27	n=14	n=14	C-A	0 (-4.00-6.00)
Cmax (ng/mL)	159 (43.5)	220 (19.7)	235 (29.4)	B/A	1.43 (1.21-1.71)
	n=27	n=14	n=14	C/A	1.41 (1.18-1.68)
AUCinf (ng*h/mL)	6910 (41.8)	10300 (22.6)	12700 (31.7)	B/A	1.58 (1.34-1.86)
	n=27	n=14	n=14	C/A	1.73 (1.46-2.05)
AUClast (ng*h/mL)	6630 (42.2)	9910 (22.6)	12200 (31.9)	B/A	1.59 (1.35-1.87)
	n=27	n=14	n=14	C/A	1.72 (1.45-2.03)
T1/2 (h)	36.2 (23.9)	34.6 (11.9)	34.2 (15.2)		
	n=27	n=14	n=14		
CL/F (L/h)	72.3 (41.8)	48.4 (22.6)	39.3 (31.7)		
	n=27	n=14	n=14		
Vz/F (L)	3770 (55.1)	2410 (28.0)	1940 (35.2)		
	n=27	n=14	n=14		

n: number of subjects with non-missing values

[a] Values are median (range) for Tmax, geometric mean (CV% of geometric mean) for all others.

Distribution

The geometric mean apparent volume of distribution (Vz/F) ranged from 1990 to 6230 L across the 400 to 750 mg dose groups [Study X2101], suggesting that ceritinib is extensively distributed. The fraction of ceritinib bound to human plasma proteins *in vitro* is approximately 97% and is independent of

concentration 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 concentration ratio of 1.35.

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.

Metabolism

Hepatic microsomal oxidative metabolism of ceritinib is primarily mediated by CYP3A, based on vitro drug metabolism studies. In humans, the main biotransformation pathways of ceritinib included mono-oxygenation, O-dealkylation, and N-formylation. Secondary biotransformation pathways involving the primary biotransformation products included glucuronidation, dehydrogenation and the addition of a thiol group to O-dealkylated ceritinib. Unchanged ceritinib was the most abundant drug-related chemical species found in both the plasma and excreta. On average, 82% of the circulating radioactivity in plasma was attributable to ceritinib. A total of eleven metabolites were found circulating in plasma at low levels (mean contribution to the radioactivity AUC ≤ 2.3% for each metabolite). Additionally, no single metabolite contributed >5.8% to the plasma radioactivity AUC of any individual subject in the study.

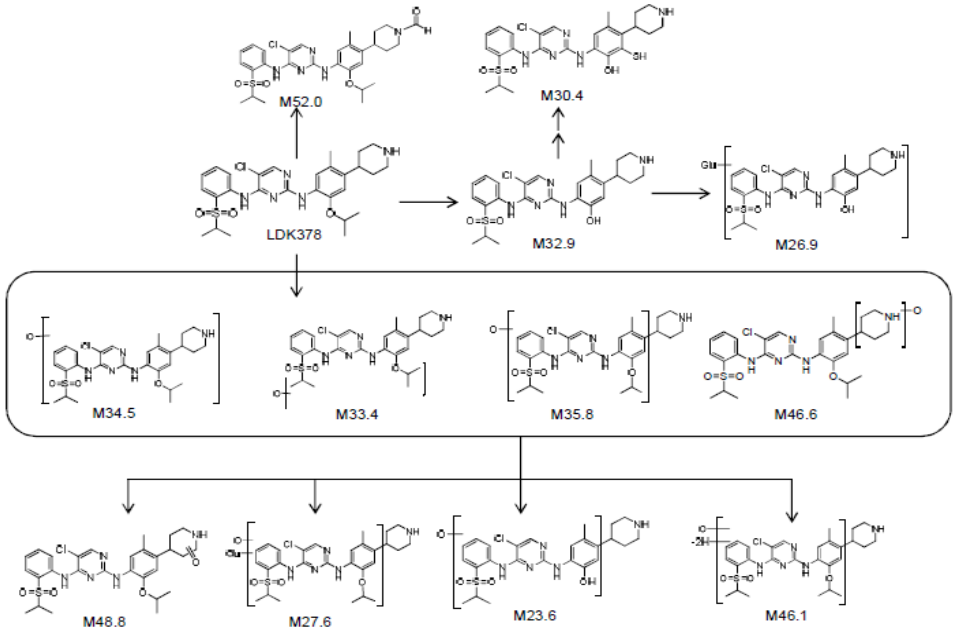


Figure 4: Biotransformation scheme for ceritinib in humans

Elimination

Following single oral doses of ceritinib, the geometric mean apparent plasma terminal half-life ($T_{½}$) ranged from 31 to 41 h across doses of 400 to 750 mg in patients, and 36 to 48 h across doses of 450 to 750 mg in healthy subjects. Consistent with preclinical studies in rats [Study R0900773a] and monkeys [Study R1200422], the majority of the radioactivity dose in humans was eliminated in the faeces (mean: 91.0%) with only a minor amount eliminated in the urine (mean: 1.3%) following a single oral dose of 750 mg of [14C]ceritinib to healthy male subjects [Study A2105]. The mean percentage of the dose eliminated in the feces as unchanged ceritinib was 68.0% while all the metabolites were present at low levels, with no individual metabolite contributing greater than 2.3% to the radioactivity AUC. Hepatic metabolism and potentially biliary excretion and gastrointestinal secretion all contribute to ceritinib elimination in humans while the kidney appears to play a negligible role.

Special populations

No dedicated pharmacokinetic study has been conducted in patients with renal or hepatic impairment.

Based on a population pharmacokinetic analysis of 97 patients with mild renal impairment (CLcr 60 to <90 ml/min), 22 patients with moderate renal impairment (CLcr 30 to <60 ml/min) and 183 patients with normal renal function (≥90 ml/min), ceritinib exposures were similar in patients with mild and moderate renal impairment and normal renal function. Patients with severe renal impairment (CLcr <30 ml/min) were not included in the clinical studies of ceritinib.

Based on a population pharmacokinetic analysis of 48 patients with mild hepatic impairment (total bilirubin ⩽ULN and AST >ULN or total bilirubin >1.0 to 1.5 times ULN and any AST) and 254 patients with normal hepatic function (total bilirubin ⩽ULN and AST ⩽ULN), ceritinib exposures were similar in patients with mild hepatic impairment and normal hepatic function. The pharmacokinetics of ceritinib have not been studied in patients with moderate to severe hepatic impairment.

No formal studies were conducted to examine the effects of gender, race, weight or age on the PK of ceritinib. In the population PK model, gender had no statistically significant effect on the systemic exposures of ceritinib. The population PK model predicted that the steady-state AUC_{tau} in females (32351 ng*h/mL) was 14% higher than that in males (28425 ng*h/mL). This magnitude of increase is unlikely to be clinically meaningful.

The final population PK model predicted that Asian patients had approximately 10% higher steady-state exposures (AUC_{tau}, C_{max} and C_{min}) than non-Asian patients.

Among the patients included in the population PK analysis, 207 patients were non-Asians (Caucasian, Black, and other) and 95 patients were Asians. Race and body weight effects were simultaneously evaluated along with other covariates of interest.

Race had no statistically significant effect on CL/F of ceritinib, and it was suggested that the slightly higher exposure estimated in Asian patients was likely explained by the lower body weight observed in Asians (mean ± SD: 61.3 ± 10.4 kg) than non-Asians (mean ± SD: 72.3 ± 16.4 kg). The current analysis results suggest the use of the same dosing regimen (750 mg qd) in Asian and non-Asian patients.

Weight was found to have a significant effect on the PK of ceritinib in the PopPK analysis. Exposure of ceritinib decreased with increasing body weight. Relative to the group of patients of 60-80 kg, the $AUC_{ô,ss}$ predicted by the PopPK model increased by 20% for a patient below 60 kg, and decreased by 18% for a patient over 80-kg. No dose adjustment from the recommended 750 mg qd dose is required on the basis of body weight.

A dedicated pharmacokinetic study in elderly patients has not been conducted.

No significant difference in the predicted steady-state exposure of ceritinib was observed between patients aged ⩾ 65 years and aged < 65 years. Hence, no dose adjustment is required on the basis of age. However, there are limited PK data in patients >75 years and no data in patients over 85 years of age (see section 4.2 of the SmPC).

No studies investigating PK of ceritinib in paediatric populations have been conducted.

Pharmacokinetic interaction studies

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

Effect of other medicinal products on ceritinib pharmacokinetics

CYP3A/P-gp inhibitors

In healthy subjects, co-administration of a single 450 mg 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 (study A2104). 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.

Table 12: Summary statistics of LDK378 pharmacokinetic parameters in healthy subjects when LDK378 was administered alone or co-administered with ketoconazole (Study A2104–PAS)

Parameter[a]	LDK378 (450 mg) alone (Treatment A) N=19	LDK378 (450 mg) with ketoconazole (200 mg bid for 14 days) (Treatment B) N=19	Comparison	Geo-mean Ratio (90% CI)
Tmax (h)	6.00 (6.00-12.0) n=18	10.0 (6.00-11.9) n=19		
Cmax (ng/mL)	133 (34.9) n=18	164 (40.3) n=19	B / A	1.22 (1.07-1.39)
AUCinf (ng*h/mL)	5760 (43.4) n=18	16600 (47.2) n=19	B / A	2.86 (2.46-3.33)
AUClast (ng*h/mL)	5640 (44.3) n=18	16300 (47.0) n=19	B / A	2.86 (2.45-3.34)
T1/2 (h)	47.7 (32.9) n=18	52.0 (30.1) n=19		
CL/F (L/h)	78.1 (43.4) n=18	27.1 (47.2) n=19		
Vz/F (L)	5380 (34.8) n=18	2030 (62.3) n=19		

n: number of subjects with non-missing values

[a] Values are median (range) for Tmax, geometric mean (CV% of geometric mean) for all others.

Source(s): [Study LDK378A2104-Table 11-3], [Study LDK378A2104-Table 11-4] and [Study LDK378A2104-Table 11-5]

CYP3A inducers

In healthy subjects, co-administration of a single 750 mg 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 (study A2106).

Table 13: Summary statistics of LDK378 pharmacokinetic parameters in subjects at baseline and during rifampin treatment (Study A2106 – PAS)

Parameter[a]	LDK378 (750 mg) alone (Treatment A) N=19	LDK378 (750 mg) with rifampin (600 mg qd for 14 days) (Treatment B) N=18	Comparison	Geo-mean Ratio (90% CI)
Tmax (h)	8.02 (6.00-24.0) n=17	6.00 (4.00-10.0) n=17		
Cmax (ng/mL)	219 (93.6) n=17	122 (85.1) n=17	B / A	0.559 (0.412-0.760)
AUCinf (ng*h/mL)	10600 (72.1) n=17	3210 (85.4) n=17	B / A	0.299 (0.230-0.388)
AUClast (ng*h/mL)	10100 (74.2) n=17	3130 (87.8) n=17	B / A	0.308 (0.236-0.403)
T1/2 (h)	38.9 (18.5) n=17	30.3 (23.0) n=17		
CL/F (L/h)	70.6 (72.1) n=17	234 (85.4) n=17		
Vz/F (L)	3970 (84.4) n=17	10200 (68.6) n=17		

n: number of subjects with non-missing values

[a] Values are median (range) for Tmax, geometric mean (CV% of geometric mean) for all others.

Source(s): [Study LDK378A2106-Table 11-3], [Study LDK378A2106-Table 11-4] and [Study LDK378A2106-Table 11-5]

pH-elevating agents

A dedicated study to evaluate the effect of gastric acid-reducing agents on the bioavailability of ceritinib has not been conducted. Gastric acid-reducing agents (e.g. proton pump inhibitors, H2-receptor antagonists, antacids) may alter the solubility of ceritinib and reduce its bioavailability as ceritinib demonstrates pH-dependent solubility and becomes poorly soluble as pH increases in vitro.

Hepatic Transporters

Ceritinib was found to be a substrate of the hepatic efflux transporter P-gp but was found not to be a substrate of the major hepatic uptake transporters organic cation transporter (OCT1), organic anion transporter (OAT2), OATP1B1, or OATP2B1 [Study R1000083] or the hepatic efflux transporters multidrug resistance protein (MRP2) or breast cancer resistance protein (BCRP) [Study R1000482].

Effect of ceritinib on the pharmacokinetics of other medicinal products

Based on *in vitro* data, ceritinib competitively inhibits the metabolism of a CYP3A substrate, midazolam, and a CYP2C9 substrate, diclofenac.

Table 14: Reversible inhibition of cytochrome P450 enzymes by ceritinib tested in human liver microsomes

CYP Enzyme	Probe reaction	IC_{50} value[a] (unbound)[b] (μM)	K_I value (unbound) (μM) Inhibition mechanism
CYP1A2	phenacetin *O*-de-ethylation	> 100 (2.5)	--[c]
CYP2A6	coumarin 7-hydroxylation	~ 5 (1.5)	0.0316 (0.00920) ± 0.00993 mixed (partial)
CYP2B6	bupropion hydroxylation	~ 2 (0.3)	5.34 (0.780) ± 0.985 competitive (full)
CYP2C8	paclitaxel 6α-hydroxylation	~ 25 (0.6)	--
CYP2C8	amodiaquine *N*-de-ethylation	~ 2 (0.6)	16.7 (4.86) ± 8.89 mixed (full)
CYP2C9	diclofenac 4′-hydroxylation	~ 2 (0.6)	0.241 (0.0701) ± 0.0306 competitive (partial)
CYP2C19	*S*-mephenytoin 4′-hydroxylation	~ 70 (1.8)	--
CYP2D6	bufuralol 1′-hydroxylation	~ 20 (2.9)	--
CYP2E1	chlorzoxazone 6-hydroxylation	~ 30 (4.4)	--
CYP3A4/5	midazolam 1′-hydroxylation	~ 0.2 (0.06)	0.161 (0.0469) ± 0.0554 competitive (partial)
CYP3A4/5	testosterone 6β-hydroxylation	~ 0.2 (0.06)	--

[a] LDK378 concentration estimated to inhibit probe substrate reaction by 50%.
[b] Unbound values corrected for microsomal protein binding: unbound fractions were 0.291, 0.146 and 0.0253 for 0.025, 0.05 and 0.5 mg/mL protein, respectively.
[c] --, not determined

Time-dependent inhibition of CYP3A was also observed. The steady-state C_{max} value of ceritinib at the recommended clinical dose of 750 mg daily may exceed the Ki values for CYP3A and CYP2C9, suggesting that ceritinib could inhibit the clearance of other medicinal products metabolised by these enzymes at clinically relevant concentrations.

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.

In vitro data suggest that ceritinib might induce CYPs regulated by PXR, as indicated in vitro by one marker enzyme for PXR induction, CYP3A4.

Based on *in vitro* data, ceritinib does not inhibit apical efflux transporters 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.

2.4.3. Pharmacodynamics

Mechanism of action

See non-clinical aspects.

Primary and Secondary pharmacology

No dedicated pharmacodynamics study has been conducted; however relationship between plasma concentration and effect has been investigated within study X2101.

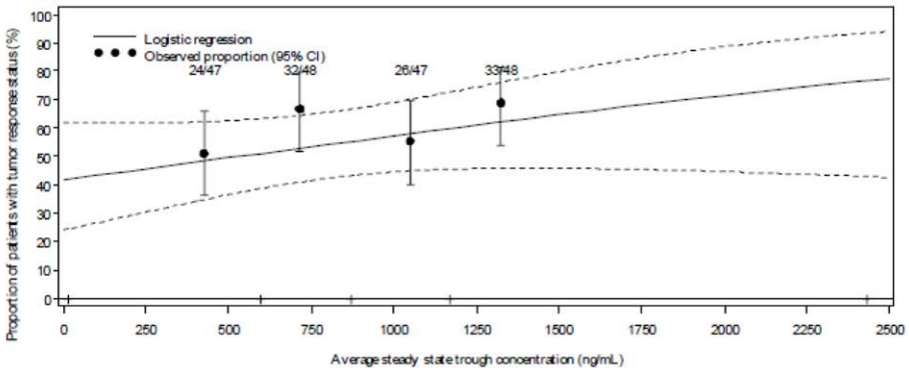
Exposure-response relationship

The relationship between steady-state exposure of LDK378, as assessed by average $C_{trough,ss}$, and BOR of confirmed PR/CR by investigator assessment, was investigated in all ALK-positive NSCLC patients in the Efficacy Analysis Set (EAS) with an available average $C_{trough,ss}$. Patients were grouped by quartiles of average $C_{trough,ss}$ and the proportion of patients with response (BOR of confirmed CR/PR by investigator assessment) was presented separately for each quartile range. The average $C_{trough,ss}$ quartile ranges and the corresponding frequency and proportion of patients with response are shown in Table 15. The result of logistic regression analysis, after adjusting for other covariates, showed a trend for an increase of response rate with exposure. With a 200 ng/mL (approximately the increase in $C_{trough,ss}$ from 600 mg qd to 750 mg qd) increase in LDK378 average $C_{trough,ss}$, the estimated odds ratio of having a BOR of confirmed PR/CR is 1.13 (95% CI: 0.96, 1.34), in the presence of other covariates.

Table 15: Incidence of tumour response status (confirmed CR/PR by investigator assessment) by quartile of average $C_{trough,ss}$

LDK378 Ctrough,ss quartiles	<Q1 (14 –< 598 ng/mL) N=47	Q1- <Q2 (598 –< 871 ng/mL) N=48	Q2- <Q3 (871 –< 1170 ng/mL) N=47	>=Q3 (1170 - 2432 ng/mL) N=48
Confirmed PR/CR by Investigator Assessment , n (%), 95% CI	24 (51.1) (36.1, 65.9)	32 (66.7) (51.6, 79.6)	26 (55.3) (40.1, 69.8)	33 (68.8) (53.7, 81.3)

Source: [SCP Appendix I - Table 5-16]



- Covariates include age, gender, race, weight, baseline ECOG status, and baseline SLD.
- Dashed curves are the 95% CI of the logistic regression model estimation.
- The logistic regression model estimation is generated as follows: numeric covariates at the median, categorical covariates at the highest frequency level.
- Observed proportions are calculated for each quartile range of average SS trough concentration (<25%, 25-<50%, 50-<75%, >=75%).
- n/N is the number of patients with events/total number of patients in the quartile range.
- Includes patients in the EAS with evaluable Ctrough concentration.

Figure 5: Logistic regression of tumour response status (confirmed CR/PR by investigator assessment) versus average $C_{trough,ss}$, overlaid with observed data

The potential for QT interval prolongation of ceritinib was assessed in four clinical studies with Zykadia. Serial ECGs were collected following a single dose and at steady-state to evaluate the effect of ceritinib on the QT interval. A central analysis of ECG data demonstrated new QTc >500 msec in one patient (0.2%). There were 23 patients (4.4%) with a QTc increase from baseline >60 msec.

Data from Study X2101 was also used to characterise the exposure-QTc response for ceritinib based on concentration-ECG time-matched data available for patients from a wide dose range (50 to 750 mg dose of ceritinib). The analysis of these data showed that increased exposure of ceritinib is associated with increased QTc changes from baseline; at median steady-state C_{max} the upper bound of the 90% CI for mean QTc change from baseline was < 20 ms regardless of the heart rate correction used.

Table 16: Summary of estimated QTc change from baseline at ceritinib peak concentrations (Study X2101)

Heart Rate Correction	Concentration levels	Concentration (ng/mL)	Median baseline QTc (ms)	Estimated mean (90% CI) QTc change from baseline (ms)
QTcF	25% percentile of Cmax	730.5	404.2	11.6 (9.7; 13.6)
	Mean Cmax	1073.3		16.9 (14.8; 19.0)
	Median Cmax	1080.0		17.0 (14.9; 19.1)
	75% percentile of Cmax	1350.0		21.2 (18.8; 23.5)
QTcB	25% percentile of Cmax	730.5	423.0	9.2 (7.3; 11.2)
	Mean Cmax	1073.3		12.6 (10.4; 14.8)
	Median Cmax	1080.0		12.7 (10.5; 14.9)
	75% percentile of Cmax	1350.0		15.4 (12.9; 17.8)
QTcP	25% percentile of Cmax	730.5	415.4	9.4 (7.7; 11.2)
	Mean Cmax	1073.3		13.5 (11.6; 15.5)
	Median Cmax	1080.0		13.6 (11.7; 15.5)
	75% percentile of Cmax	1350.0		16.8 (14.7; 19.0)

* Cmax is calculated based on evaluable concentrations collected on Cycle 2 Day 1 in all patients (133 patients from 750 mg dose group , and 6 patients from dose groups < 750 mg)

Source(s): [Study X2101-Table 14.2-3.9], [Study X2101-Table 14.2-3.10], [Study X2101-Table 14.2-3.11]

2.4.4. Discussion on clinical pharmacology

No apparent differences in the PK of ceritinib were observed between healthy volunteers and patients. Observations made in healthy volunteers receiving ceritinib monotherapy are therefore considered to be transferrable to the target population.

Ceritinib demonstrated non-linear PK in patients over time with lower apparent clearance at steady state after daily oral dosing at MTD of 750 mg than after a single oral dose. Highest dose investigated in the dose-escalation study was 750 mg; thus PK above this dose is not known. The bioavailability of ceritinib was increased when given with a meal depending on the fat content.

Ceritinib is extensively distributed and the fraction bound to human plasma proteins *in vitro* is approximately 97%.

As ceritinib is eliminated primarily by the liver, hepatic impairment is likely to increase the systemic exposure of ceritinib. However, the extent of increase is not anticipated to be substantial, as ceritinib is not extensively metabolized based on results from human ADME study. Based on the results of a population pharmacokinetic analysis, dose adjustment is not recommended for patients with mild hepatic impairment.

A study in subjects with varying degrees of hepatic impairment (mild, moderate, severe, based on Child-Pugh classification) and matched subjects with normal hepatic function is ongoing (Study A2110) and the CSR will be submitted by June 2016. Until these data are available, a precautionary statement recommending not using ceritinib in patients with moderate-severe hepatic impairment has been included in sections 4.2 and 5.2 of the SmPC.

As ceritinib is minimally eliminated by the kidney (1.3% of a single oral administered dose) no studies have been carried out in impaired renal patients. However, taking into account both, the population PK analysis and the mass balance study, no dose adjustment is necessary in patients with mild to moderate renal impairment (see section 4.2 and 5.2 of the SmPC). Patients with severe renal impairment patients were excluded from clinical studies and therefore no data have been collected and caution should be used in this population.

In vivo and in vitro data have shown that the concomitant use of CYP3A/P-gp inhibitors can increase the ceritinib plasma concentrations. As a consequence, 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), reduce the ceritinib dose by approximately one third, rounded to the nearest multiple of the 150 mg dosage strength. After discontinuation of a strong CYP3A inhibitor, resume the ceritinib dose that was taken prior to initiating the strong CYP3A inhibitor (see section 4.5 of the SmPC). Patients should also be instructed to avoid grapefruit and grapefruit juice as they may inhibit CYP3A in the gut wall and may increase the bioavailability of ceritinib.

Results from a DDI study with rifampin clearly indicate that co-administration of ceritinib with strong CYP3A/P-gp inducers decreases ceritinib plasma concentrations. Concomitant use of strong CYP3A inducers should therefore 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 (see section 4.5 of the SmPC).

Gastric acid-reducing agents (H2-blockers/proton pump inhibitors) may alter the solubility of ceritinib and reduce its bioavailability. In order to investigate the interaction with pH-elevating agents, the applicant

will conduct a post-approval study with esomeprazole and submit the results by March 2016 (see RMP). In the meantime, the potential for interaction has been reflected in the SmPC (see section 4.5).

Ceritinib was found to be a reversible and time-dependent inhibitor of CYP3A4/5 in vitro, but it also has a potential to be an inducer of CYP3A4 in vivo. Due to the concomitant time-dependent inhibition of CYP3A and the observed decrease in apparent clearance (CL/F) of ceritinib after multiple dosing relative to a single dose [Study X2101], it is unlikely that ceritinib would act as a CYP3A inducer clinically. In addition, time–dependent inhibition of other major CYPs was evaluated in another study.

In another study (data not shown) ceritinib showed no apparent time-dependent inhibition of CYP2B6, CYP2C8, or CYP2C19 at concentrations of up to 50 μM. It was also shown that ceritinib competitively inhibits the metabolism of a CYP2C9 substrate. In order to ensure characterization of the maximal ceritinib-mediated inhibition of CYP3A4 and CYP2C9, the applicant will submit the results of a study with warfarin(CYP2C9 substrate) and midazolam (CYP3A4 substrate) administered as a two- drug cocktail in patients with ALK-positive advanced tumours including NSCLC by September 2018 (see RMP).

Dose reduction may be needed for co-administered medicinal products that are predominantly metabolised by CYP3A and CYP2C9. Co-administration of ceritinib with CYP3A substrates known to have narrow therapeutic indices (e.g. astemizole, cisapride, ciclosporin, ergotamine, fentanyl, pimozide, quinidine, tacrolimus, alfentanil and sirolimus) and CYP2C9 substrates known to have narrow therapeutic indices (e.g. phenytoin and warfarin) should be avoided. However, for other PXR-regulated enzymes and transporters (including UGTs) the net effect may be induction. In particular, there may be a risk for reduced efficacy of hormonal contraceptives (see section 4.5 of the SmPC).

In vitro data also showed that ceritinib inhibits CYP2A6 and CYP2E1. Therefore, ceritinib may have the potential to increase plasma concentrations of co administered medicinal products that are predominantly metabolised by these enzymes. Caution should therefore be exercised with concomitant use of CYP2A6 and CYP2E1 substrates and ADRs carefully monitored.

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 (see section 4.5).

Because of the potential for ceritinib to inhibit intestinal P-gp and BCRP at clinically relevant concentrations, there could be a potential increase of the 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 (see section 4.5 of the SmPC).

Molecular profiling of patient samples both at the gene and protein levels are important to further explore deviations and/or explanations at molecular levels in relation with ceritinib therapy. The applicant is therefore recommended to submit yearly updates on the biomarker program.

The identification of which chimeric fusion protein/proteins (result of the chromosomal rearrangements of the ALK gene) present in a tumour may be important for predicting responders, as there is a possibility that ceritinib may not be equally sensitive to all chimeric proteins. The response to ceritinib may be depending on which fusions are present, in addition to other ALK-independent mechanisms (eg. in NSCLC the predominant fusion partner with the ALK-kinase domain is the EML4 gene). Thirteen variants of the EML4-ALK chimeric protein has so far been identified, several possibly being functional kinases. The biomarker program described above would provide useful information to address this issue.

The specificity and performance of the pivotal FISH test were discussed during the procedure. This is a critical test and a proper selection of patients for treatment with ceritinib is dependent on its validity. The FISH test is based on two selected probes to detect rearrangements in the ALK gene. It is a qualitative assay, and is designed to detect only the break-up of the ALK gene, and not to identify the nature of the fusion partners.

Information and descriptions for different alternatives to determine ALK arrangements, like the RT-PCR, immunohistochemical (IHC) assays, direct sequencing, were adequately provided by the Applicant. The choice of the validated and standardised IHC was also adequately justified.

In the initial submission, twenty-eight of the patients enrolled in study 2101 appeared with no response neither on crizotinib nor ceritinib (non- responders on ALK-TKIs), and it was questioned whether these patients could have been false positives. The Applicant suggested that other mechanisms could contribute to explain the lack of effectiveness of these ALK receptor tyrosine kinase inhibitors (eg. additional oncogenic driver mutations (in the EGFR gene) or other types of resistance (like epithelial-mesenchymal transition); even if the tumour is determined positive in ALK gene rearrangement by the validated FISH assay .Investigations of tumour biopsies from patients both at the gene and protein levels are important to be able to predict response to ceritinib. A biomarker plan will be conducted by the Applicant.

Ceritinib is claimed to have both a higher potency and to be more specific than crizotinib and has been shown to have significant activity in crizotinib-resistant patients. In a recent paper, it is observed that ceritinib may supress resistance mutations promoted by crizotinib in vivo, and that rarer mutations may be selected by treatment with ceritinib (Friboulet et al., 2014). More knowledge about the resistance mechanisms for ceritinib seems important for making treatment decisions.

The applicant presented results from study A2203, which indicated that percent positive cells above the 15% cut-off seemingly are not a determinant for response.

Dose investigations presented for ceritinib were limited by few patients. A proper titration according to DLTs was not performed, and results from dose-efficacy analyses were not submitted. Preliminary statistical exposure-response analyses suggest only a trend regarding a relationship between higher steady-state exposure of ceritinib and higher ORR. However, a rather clear relationship is indicated between exposure of ceritinib and increases in more serious adverse events (elevation of transaminases, hyperglycemia, QT/QTc- prolongation).

A pharmacokinetic analysis suggested that ceritinib causes concentration dependent increases in QTc. 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 astemizole, 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. The important risk related to QT interval prolongation has been reflected in sections 4.2, 4.4, 4.5, 4.8, 5.2 and 5.3 of the SmPC.

2.4.5. Conclusions on clinical pharmacology

The pharmacokinetic data in support of the approval of ceritinib sufficiently supports the approval in the final indication. The Applicant will conduct a number of post-authorisation measures (PAMs) to further clarify the PK/PD profile:

- In order to evaluate the PK of ceritinib in subjects with hepatic impairment compared to subjects with

normal hepatic function, the applicant will conduct and submit the results of a single dose study by 30 June 2016;

- In order to assess the effect of ceritinib on the PK of warfarin and midazolam administered as a two-drug cocktail in patients with ALK-positive advanced tumours, the applicant will conduct and submit the results of a DDI study;

- In order to assess the effect of esomeprazole (proton pump inhibitor) on the PK of ceritinib in healthy volunteers, the applicant will conduct and submit the results of a single dose DDI study.

In addition, the applicant is recommended to develop a biomarker program to further explore deviations and/or explanations at molecular levels in relation with ceritinib therapy.

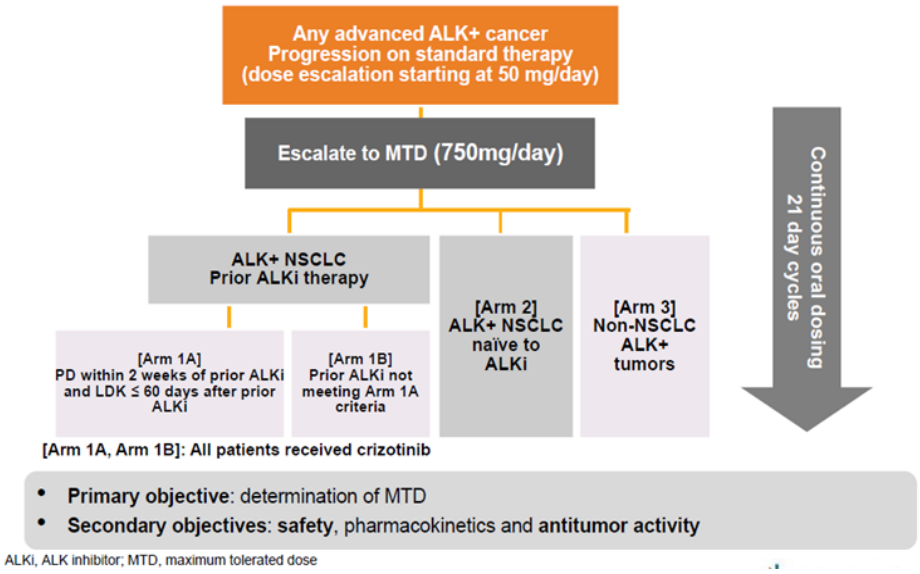
Awaiting data from the planned studies, the lack of information has been reflected in the SmPC.

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

Study X2101

Determination of MTD has been conducted as part of registration study X2101. This study was originally designed as a phase I dose escalation trial for the definition of the MTD. It was a first-in-human, open-label, Phase I study that comprised a dose-escalation phase (to determine the MTD and recommended dose [RD]), and an expansion phase to characterize the efficacy, safety and pharmacokinetics (PK) of ceritinib.



Dose-escalation

The dose-escalation phase included a 3-day single dose PK run-in and the 750mg OD dose was selected for further testing into the following period of daily dosing in continuous 21-day treatment cycles. Patients could continue treatment until disease progression or unacceptable toxicity. Patients treated at the RD during the dose-escalation phase and who met the criteria for one of the four expansion arms were considered to be included in the appropriate expansion arm.

The MTD/RD was determined based on the BLRM model assessing the probability of DLTs in Cycle 1 and the clinical assessment of safety and efficacy data.

In the dose-escalation phase, 59 patients were treated in 15 cohorts across nine different dose levels (50 mg to 750 mg), and 54 patients were included in the Dose Determining Set (DDS).

At the time that the MTD was determined, eight DLTs had occurred during the first cycle of treatment in six patients (Table 11-13).

• At 400 mg: grade 3 hypophosphatemia in one patient, and grade 3 transaminase increased evolving from grade 2 ALT increased in one patient.

• At 600 mg: grade 3 diarrhoea and grade 3 dehydration, in one patient each.

• At 750 mg: grade 3 diarrhoea with grade 3 vomiting in one patient and intolerable grade 2 diarrhoea in one patient.

Additional support to establish MTD/RD at 750 mg came from the experience of the first 10 patients in the expansion phase (no DLTs were observed) and the preliminary data on tumour activity, which had shown tumour response with doses >400mg.

2.5.2. Main study

A phase I, multicentre, open-label, dose-escalation study of LDK378, administered orally in adult patients with tumours characterized by genetic abnormalities in anaplastic lymphoma kinase (ALK)

Methods

Study Participants

Main inclusion criteria:

1. Patients diagnosed with a locally advanced or metastatic malignancy that has progressed despite standard therapy, or for which no effective standard therapy exists. Only patients with tumours characterized by genetic abnormalities in ALK were enrolled. An ALK translocation must be detected by FISH in $\geqslant$ 15% of tumour cells. In patients with diseases other than NSCLC, ALK translocation is not required and overexpression of ALK protein may be considered indicative of a genetic abnormality in ALK.

2. Presence of at least one measurable lesion as determined by modified RECIST version 1.0.

3. Age $\geqslant$ 18 years.

4. Eastern Cooperative Oncology Group (ECOG) performance status $\leqslant$ 2.

5. Life expectancy $\geqslant$ 12 weeks.

6. Patients had the following laboratory values (obtained within 14 days of enrollment):

- Absolute neutrophil count (ANC) $\geqslant$ 1.5 x 10^9/L.

- Hemoglobin (Hgb) $\geqslant$ 9 g/dL ($\geqslant$ 90 g/L).

- Platelets $\geqslant$ 100 x 10^9/L.

- Serum total bilirubin $\leqslant$ 1.5 x upper limit of normal (ULN), except for patients with Gilbert's syndrome who may be included if total bilirubin $\leqslant$ 3.0 x ULN and direct bilirubin $\leqslant$ 1.5 x ULN.

- Aspartate aminotransferase (AST) and ALT ⩽ 2.5 x ULN, except for patients with tumour involvement of the liver who had ALT and AST ⩽ 5 x ULN.

- Calculated creatinine clearance (CrCL) ⩾ 50 mL/min (⩾ 0.835 mL/s) (Cockcroft-Gault formula).

- Serum amylase ⩽ ULN (the patient was enrolled if amylase > ULN but there was no evidence of pancreatic disease).

- Serum lipase ⩽ ULN (the patient was enrolled if lipase > ULN but there was no evidence of pancreatic disease).

- Fasting plasma glucose ⩽ 200 mg/dL (⩽ 11.1 mmol/L).

7. Prior treatment with LDK378 was not permitted.

8. Expansion phase:

- Arm 1A: Patients with NSCLC that had progressed during treatment with a prior ALK inhibitor or within 2 weeks of the last dose of a prior ALK inhibitor, and the first dose of LDK378 was expected to be ⩽ 60 days since the last dose of the prior ALK inhibitor.

- Arm 1B: Patients with NSCLC that had progressed since treatment with prior ALK inhibitor, but that need not have been the last prior therapy, and they did not meet the criteria for Arm 1A.

- Arm 2: Patients with NSCLC that had not been previously treated with an ALK inhibitor.

- Arm 3: Patients with a malignancy other than NSCLC, and there was no requirement regarding therapy with a prior ALK inhibitor.

Main exclusion criteria:

1. Patients with symptomatic central nervous system (CNS) metastases who were neurologically unstable or required increasing doses of steroids to control their CNS disease.

2. Patients with unresolved nausea, vomiting or diarrhoea > CTCAE grade 1.

3. Impairment of gastrointestinal (GI) function or GI disease that significantly altered the absorption of LDK378 (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhoea, malabsorption syndrome, or small bowel resection).

4. History of pancreatitis or history of increased amylase or lipase that was due to pancreatic disease.

5. Acute or chronic liver disease. Evidence of active viral hepatitis, including Hepatitis A, B or C (testing for viral hepatitis was not mandatory).

6. Known diagnosis of human immunodeficiency virus (HIV) infection.

7. Patients with a prior or current history of a second malignancy (except adequately treated in situ carcinoma of the cervix or non-melanoma carcinoma of the skin, or any other curatively treated malignancy that had not been treated or recurred in the prior 3 years).

8. Clinically significant cardiac disease including congestive heart failure (New York Heart Association Class III or IV), arrhythmia or conduction abnormality requiring medication, or cardiomyopathy; or clinically uncontrolled hypertension (systolic blood pressure [SBP] > 140 mmHg or diastolic blood pressure [DBP] > 90 mmHg). Impaired cardiac function or clinically significant cardiac diseases;

9. Other concurrent severe and/or uncontrolled medical conditions that could cause unacceptable safety risks or compromised compliance with the protocol.

10. Patients treated with chemotherapy or biologic therapy or other investigational agent < 2 weeks prior to starting study drug for compounds with a half-life ⩽ 3 days, and < 4 weeks prior to starting study drug for compounds with a prolonged half-life.

11. Unresolved toxicity greater than CTCAE grade 1 from previous anti-cancer therapy or radiotherapy (excluding neurotoxicity, alopecia, ototoxicity, lymphopenia), or incomplete recovery from previous surgery, unless agreed by the sponsor and the Principal Investigator and was documented.

12. Patients who received radiotherapy to a large volume (including whole brain radiotherapy) < 2 weeks prior to starting study drug, and patients who had received radiotherapy to a small volume (including stereotactic radiotherapy to the CNS) < 1 week prior to starting study drug.

13. Patients who had underwent major surgery < 2 weeks prior to starting study drug or who had not recovered from the surgical procedure.

14. Patients treated with medications that were known to be strong inhibitors or inducers of CYP3A4/5 that could not be discontinued at least a week prior to start of treatment with LDK378 and for the duration of the study.

15. Patients receiving medications that were mainly metabolized by CYP3A4/5 and had low therapeutic index that could not be discontinued at least a week prior to start of treatment with LDK378, and for the duration of the study.

16. CYP2C9: patients receiving warfarin and phenytoin that could not be discontinued at least a week prior to start of treatment with LDK378 and for the duration of the study.

17. Medications with a known risk of prolonging the QT interval or inducing Torsades de Pointes

18. Anticoagulants: Patients receiving coumarin-type anticoagulants who could not discontinue at least a week prior to start of treatment and for the duration of the study. Treatment with therapeutic doses of coumarin-type anticoagulants for line patency (maximum daily dose of 2 mg) was permitted. Low molecular weight heparin (LMWH) was permitted.

20. Patients receiving concurrent investigational drugs, radiotherapy or chemotherapy.

21. Pregnant or nursing (lactating) women, where pregnancy was defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.

22. Women of child-bearing potential, unless they were using effective methods of contraception during dosing of study treatment through the study completion visit, 28 days after the last dose of study drug.

23. Sexually active males had to use a condom during intercourse while taking the drug and for 28 days after the last dose of study drug, and could not father a child in this period.

24. Patients using illegal drugs.

Treatments

Treatment allocated

Once the MTD/RD was established in the dose-escalation phase, all patients enrolled in the expansion phase of the study were treated at that dose (750mg).

LDK378 was administered continuously, orally every day and it was taken with a glass of water and consumed over a short period of time (e.g. 1 capsule every 2 minutes). Each daily dose of LDK378 was taken at least 2 hours after the last meal and patients could not eat for at least 2 hours after LDK378 was taken.

Duration /Discontinuation

In both the dose-escalation and expansion phases patients were treated with LDK378 until they experienced unacceptable toxicity that precluded any further treatment, disease progression, and/or treatment was discontinued at the discretion of the Investigator or by patient request. Patients could also continue treatment with LDK378 after disease progression if in the opinion of the Investigator the patients were still experiencing clinical benefit.

Dose reductions/Interruptions

Dose adjustments were permitted for patients who experienced a DLT with LDK378, if it was considered in the best interest of the patient to continue therapy. If a patient experienced a DLT, the Investigators were generally advised to interrupt treatment with LDK378 until the event resolved to grade 1 or the patient's baseline, and if continued treatment was considered to be in the best interest of the patient, to resume LDK378 at one dose-level lower.

Unauthorised Concomitant medications

Concomitant antineoplastic therapy (including radiotherapy and surgery) was prohibited, except for patients deriving clinical benefit with LDK378 as described above. Other prohibited concomitant therapies included CYP3A4/5 substrates with narrow therapeutic index, strong inhibitors and inducers of CYP3A4/5, and CYP2C9 substrates with narrow therapeutic index. Medications with a known risk of prolonging the QT interval or inducing Torsade de Pointes, as well as concurrent investigational drugs were not allowed.

Objectives

Primary objective:

To determine the maximum tolerated dose (MTD)/recommended dose (RD) of LDK378 (dose-escalation phase).

Secondary objectives (main objective in the expansion phase):

To characterise the safety, tolerability, PK, and anti-tumour activity of LDK378 at the RD in four different ALK-positive patient populations.

Exploratory objectives:

To identify mutations in the ALK gene or other molecular abnormalities associated with clinical progression after treatment with an ALK inhibitor in tumour samples collected during the pre-screening period in cases where ALK testing was performed centrally; to assess overall survival (OS) in patients treated with LDK378.

Outcomes/endpoints

Primary efficacy endpoints:

Overall response rate (ORR, CR+PR) and duration of response (DOR) as assessed by the investigator per RECIST 1.0.

These endpoints were also derived separately based on BIRC assessment.

- Overall response rate (ORR) was defined as the proportion of patients with a best overall response of CR or PR.

- Duration of response was defined as the time from first documented response (PR or CR) to the date of first documented disease progression (PD) or death due to any cause, among patients with a confirmed PR or CR.

Secondary efficacy endpoints:

- Progression free survival (PFS): the time from the start date of study drug to the date of the first radiologically documented PD or death due to any cause, assessed by Investigator and by BIRC. If a patient had not progressed or was not known to have died at the date of analysis cut-off or had received any further anticancer therapy, PFS was censored at the date of the last adequate tumour evaluation before the cut-off date or before the start of the new anticancer therapy date, whichever was earlier. Clinical deterioration was not considered as a qualifying event for progression.
- Overall survival (OS): time from the start date of study drug to the date of death due to any cause. If the patient was alive at the date of the analysis cut-off or lost to follow-up, then OS was censored at the last contact date prior to data cut-off date.

Sample size

No formal statistical power calculations to determine sample size were performed for this study. During the expansion phase, up to 310 patients could be enrolled (including all patients treated at the RD during the dose-escalation phase who were eligible for the safety set) with at least 25 and up to 100 patients in each of NSCLC arms (Arms 1A, 1B and 2), and approximately 10 patients in Arm 3.

Randomisation

This was a non-comparative, single arm, open-label study.

Blinding (masking)

N/A

Statistical methods

Qualitative data was summarized by frequency counts and percentages. Percentages were calculated using the number of patients in the relevant population or subgroup as the denominator.

Continuous data were summarized by appropriate descriptive statistics (i.e. mean, standard deviation, median, minimum, and maximum).

The analysis cut-off date was determined to ensure that at least 120 patients with ALK-positive NSCLC in the 750 mg dose group (from dose-escalation or expansion phases) who had received prior treatment with crizotinib, had received the first dose of LDK378 at least 18 weeks prior to the analysis cut-off date. Of these, a minimum of 80 patients were expected to have at least a baseline and a post-baseline scan available for central review.

Analyses sets

- Full Analysis Set (FAS): all patients (NSCLC and non-NSCLC) who received at least one dose of LDK378. Patients were classified according to the intended treatment dose group. The subset of FAS including only ALK-positive NSCLC patients across all doses (FAS NSCLC) was used for the supportive analysis of tumour response data (ORR, DOR, and PFS based on Investigator assessments) and for analysis of OS.

- Efficacy Analysis Set (EAS): subset of the FAS-NSCLC consisting of patients with ALK-positive NSCLC across all doses who received the first dose of LDK378 at least 18 weeks prior to the analysis cut-off date.

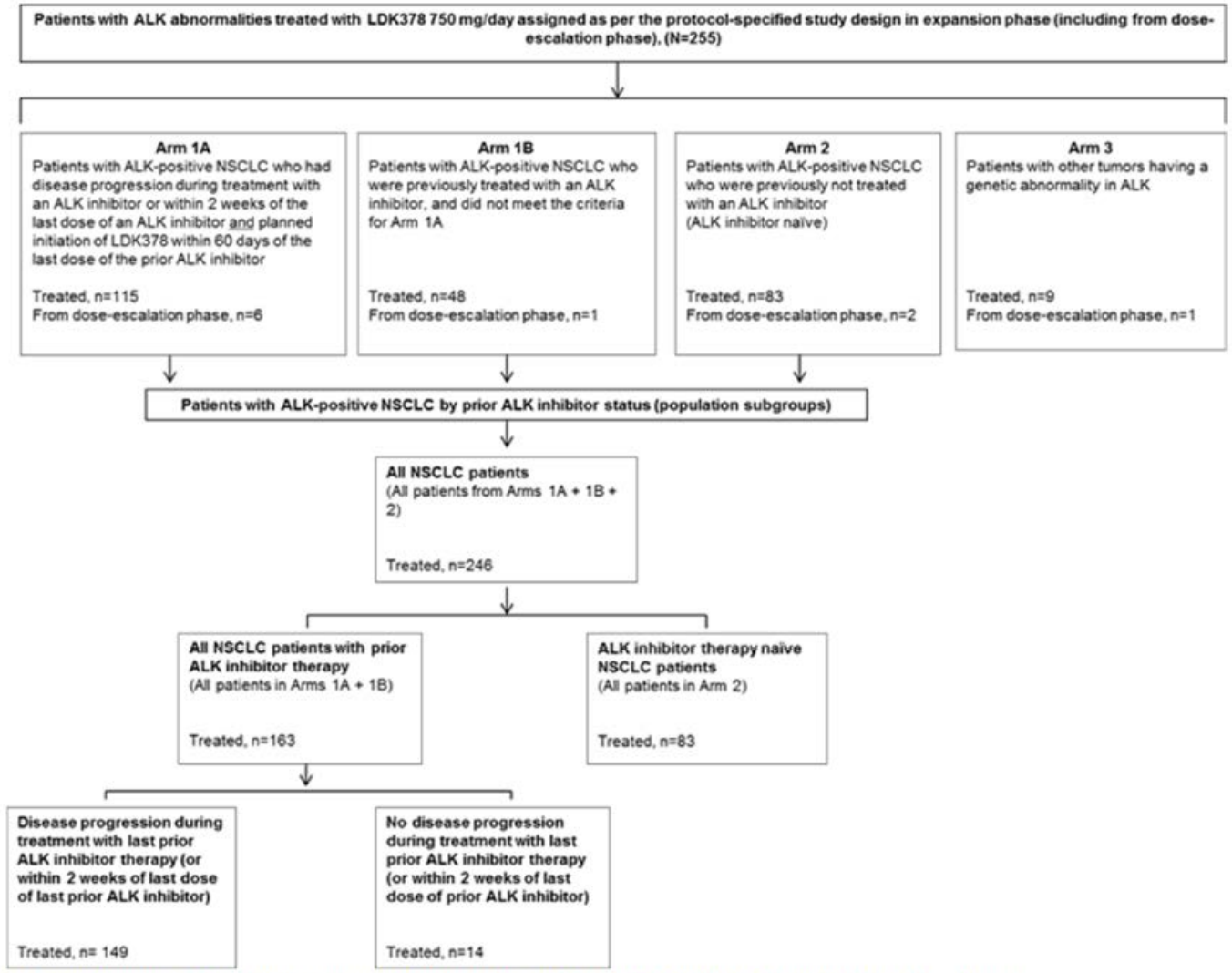
The EAS is the primary data set used for the analysis of tumour response data (ORR, DOR, and PFS based on Investigator assessments) and for the analysis of OS.

- Central Efficacy Analysis Set (CEAS) is used for the analysis of tumour response data based on independent central review assessments. It is a subset of the EAS including all NSCLC patients for whom EITHER the baseline scan and at least one post-baseline scan were available and evaluable by the BIRC OR no post-baseline scan was performed due to early death or discontinuation.

- Safety Set consists of all patients (including NSCLC and non-NSCLC) who received at least one dose of LDK378. The Safety set was used for all safety analyses with the exception of the analyses based on DLTs which used the dose-determining set.

Results

Participant flow



Patients treated at 750 mg in dose-escalation phase (n = 10) were programmatically mapped to study "Arms".
Listing 16.1.7-1.1

Recruitment

The study started on 24 January 2011 and it is currently on-going (data cut-off date 2 August 2013). The

study was closed to enrolment on 31 July 2013. It is being conducted at 20 centres in 11 countries: Australia (1 centre), Belgium (1 centre), Germany (4 centres), Italy (2 centres), Netherlands (1 centre), Spain (1 centre), UK (1 centre), Canada (1 centre), Singapore (1 centre), Korea (1 centre), and US (6 centres).

Conduct of the study

Protocol amendments

The study protocol was amended six times, mainly to increase the sample size and allow characterisation of further efficacy and safety of ceritinib.

Amendment 1 (20 June 2011): modifications requested by HAs, IRBs, ethics committees and several changes to inclusion and exclusion criteria. Patients with NSCLC were only eligible if they had evidence of ALK translocation in ≥ 15% of tumour cells as assessed by FISH.

Amendment 2 (22 March 2012): modifications to the classification of patients in Arms 1A, 1B, and 2 based on exposure and response to prior ALK inhibitors. Confirmatory ALK testing by a central laboratory was no longer required.

Amendment 3 (4 July 2012): to increase the sample size of the expansion arms 1A, 1B, and 2 by an additional 75 patients (i.e. up to 100 patients total) in each arm. The amendment also increased the number of allowed dose reductions from 2 to 3.

Amendment 4 (16 January 2013): to accommodate collection of imaging data for independent radiological review by an imaging CRO. In order to more fully assess the LDK378 PK profile, PK samples were to be collected at all time points from all patients enrolled in the expansion phase of the study; the full profile was no longer only collected from the first 10 expansion phase patients.

Amendment 5 (10 April 2013): to define the analysis cut-off point for the primary analyses, to specify that the primary analyses of antitumor activity would be performed in patients with ALK-positive NSCLC who had previously received crizotinib and were treated with LDK378 at a dose of 750 mg once-daily, and to provide additional details on the statistical analyses that were to be performed for tumour response data both based on Investigator assessment and an independent review of imaging. The inclusion/exclusion criteria were updated to exclude patients taking concomitant medications with a known risk of prolonging the QT interval or inducing Torsade de Pointes.

Amendment 6 (29 August 2013): to update the available safety and efficacy information regarding LDK378, add guidance for treatment of patients who develop pneumonitis/interstitial lung disease that is considered related to LDK378, and to remove phototoxicity precautions. The definition of duration of response (DOR) was changed from time from first documented response to the date of first documented disease progression or death due to underlying cancer to the date of first documented disease progression or death due to any cause.

Protocol deviations:

Protocol deviations were reported in 23.2% of the 246 ALK-positive NSCLC patients at 750 mg. The deviation categories reported were: use of prohibited concomitant medications (8.9%, 22 patients), deviations in treatment where patients did not take LDK378 dosing as per protocol (8.1%, 20 patients), deviations in selection criteria (3.3%, 8 patients – for 2 patients ALK expression/translocation was detected by a method other than FISH and 1 patient did not have a tumor with evidence of ALK expression), key procedures not performed as per protocol (2.8%, 7 patients) and subject not withdrawn as per the protocol (0.4%, 1 patient).

Baseline data

The baseline characteristics from the pivotal study X2101 are summarised in the table below.

Table 17: Demographic characteristics in NSCLC patients at 750 mg, by prior ALK inhibitor status (Study X2101 – FAS-NSCLC 750 mg

	NSCLC with prior ALK inhibitor			NSCLC ALK inhibitor naïve patients	All NSCLC patients[4]
	All patients with prior ALK inhibitor[1]	Patients with PD during last prior ALK inhibitor [2]	Patients without PD during last prior ALK inhibitor [3]		
	N=163	N=149	N=14	N=83	N=246
Age (years)					
n	163	149	14	83	246
Mean (SD)	51.5 (11.63)	51.6 (11.60)	51.2 (12.42)	53.9 (12.03)	52.3 (11.80)
Median	52.0	51.0	54.0	55.0	53.0
Min-Max	24.0-80.0	24.0-80.0	29.0-66.0	22.0-80.0	22.0-80.0
Age category (years) – n (%)					
< 65	141 (86.5)	129 (86.6)	12 (85.7)	66 (79.5)	207 (84.1)
≥ 65	22 (13.5)	20 (13.4)	2 (14.3)	17 (20.5)	39 (15.9)
Sex – n (%)					
Male	75 (46.0)	71 (47.7)	4 (28.6)	39 (47.0)	114 (46.3)
Female	88 (54.0)	78 (52.3)	10 (71.4)	44 (53.0)	132 (53.7)
Predominant race – n (%)					
Caucasian	108 (66.3)	100 (67.1)	8 (57.1)	48 (57.8)	156 (63.4)
Black	4 (2.5)	3 (2.0)	1 (7.1)	0	4 (1.6)
Asian	47 (28.8)	42 (28.2)	5 (35.7)	35 (42.2)	82 (33.3)
Native American	1 (0.6)	1 (0.7)	0	0	1 (0.4)
Other	3 (1.8)	3 (2.0)	0	0	3 (1.2)
Ethnicity – n (%)					
Hispanic/Latino	16 (9.8)	14 (9.4)	2 (14.3)	10 (12.0)	26 (10.6)
Chinese	12 (7.4)	12 (8.1)	0	5 (6.0)	17 (6.9)
Indian (Indian subcontinent)	3 (1.8)	2 (1.3)	1 (7.1)	3 (3.6)	6 (2.4)
Mixed ethnicity	1 (0.6)	1 (0.7)	0	0	1 (0.4)
Other	131 (80.4)	120 (80.5)	11 (78.6)	65 (78.3)	196 (79.7)
BMI (kg/m^2)					
n	162	148	14	83	245
Mean (SD)	25.1 (4.58)	25.1 (4.63)	24.8 (4.24)	23.6 (3.90)	24.6 (4.41)
Median	24.6	24.7	24.3	23.0	24.3
Min-Max	16.6 - 42.5	16.6 - 42.5	19.7 - 37.4	16.7 - 41.8	16.6 - 42.5
ECOG performance status – n (%)[5]					
0	38 (23.3)	34 (22.8)	4 (28.6)	25 (30.1)	63 (25.6)
1	104 (63.8)	96 (64.4)	8 (57.1)	51 (61.4)	155 (63.0)
2	20 (12.3)	19 (12.8)	1 (7.1)	7 (8.4)	27 (11.0)
>2	1 (0.6)	0	1 (7.1)	0	1 (0.4)
Smoking history – n (%)					
Never smoked	109 (66.9)	100 (67.1)	9 (64.3)	44 (53.0)	153 (62.2)
Ex-smoker	49 (30.1)	44 (29.5)	5 (35.7)	38 (45.8)	87 (35.4)
Current smoker	5 (3.1)	5 (3.4)	0	1 (1.2)	6 (2.4)

This table presents data for patients with NSCLC treated with LDK378 750 mg (750 mg treatment dose group from FAS-NSCLC, a subset of FAS).
[1] All patients with prior ALK inhibitor were treated with crizotinib, in addition 5 patients received CH5424802 as their last prior ALK inhibitor.
[2] Patients who had disease progression (PD) during treatment with (or within 2 weeks of last dose of) last prior ALK inhibitor therapy.
[3] Patients who did not have PD during treatment with (or within 2 weeks of last dose of) last prior ALK inhibitor therapy.
[4] All patients include all ALK-positive NSCLC patients treated with LDK378 750 mg.
[5] 0 – Fully active, able to carry on all pre-disease performance without restriction; 1 – Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work; 2 – Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours;3 – Capable of only limited self-care, confined to bed or chair more than 50% of waking hours; 4 – Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
SD=standard deviation; BMI: body mass index
Source: [Study X2101-Table 14.1-3.1b]

The baseline characteristics presented in the table below summarise data from the phase I study X2101 and phase II studies A2201 and A2203 further described under supportive studies.

Table 18: Demographic characteristics in NSCLC patients at 750 mg, by prior ALK inhibitor status (Study X2101, Study A2201 and Study A2203)

	NSCLC patients with prior ALK inhibitor		ALK inhibitor naïve NSCLC patients	
	Study X2101 ceritinib 750 mg N=163	Study A2201 ceritinib 750 mg N=140	Study X2101 ceritinib 750 mg N=83	Study A2203 ceritinib 750 mg N=124
Age (years)				
Mean (SD)	51.5 (11.63)	51.2 (11.62)	53.9 (12.03)	54.8 (12.16)
Median	52.0	51.0	55.0	56.0
Min-Max	24.0-80.0	29.0 – 80.0	22.0-80.0	27.0-82.0
Age category (years) – n (%)				
< 65	141 (86.5)	122 (87.1)	66 (79.5)	94 (75.8)
≥ 65	22 (13.5)	18 (12.9)	17 (20.5)	30 (24.2)
Sex – n (%)				
Male	75 (46.0)	70 (50.0)	39 (47.0)	50 (40.3)
Female	88 (54.0)	70 (50.0)	44 (53.0)	74 (59.7)
Predominant race – n (%)				
Caucasian	108 (66.3)	84 (60.0)	48 (57.8)	48 (38.7)
Black	4 (2.5)	0	0	1 (0.8)
Asian	47 (28.8)	53 (37.9)	35 (42.2)	74 (59.7)
Native American	1 (0.6)	0	0	0
Other	3 (1.8)	3 (2.1)	0	1 (0.8)
ECOG perf. status – n (%)				
0	38 (23.3)	42 (30.0)	25 (30.1)	46 (37.1)
1	104 (63.8)	78 (55.7)	51 (61.4)	69 (55.6)
2	20 (12.3)	20 (14.3)	7 (8.4)	9 (7.3)
>2	1 (0.6)	0	0	0
Metastatic sites* – n (%)				
Brain	98 (60.1) [a]	100 (71.4)	26 (31.3)	50 (40.3)
Liver	68 (41.7)	52 (37.1)	30 (36.1)	33 (26.6)
Bone	69 (42.3)	81 (57.9)	26 (31.3)	55 (44.4)
Thoracic involvement of cancer - n (%)				
Lung or pleura/pleural effusion or thoracic lymph nodes	155 (95.1)	129 (92.1)	82 (98.8)	123 (99.2)
Lung	126 (77.3)	115 (82.1)	79 (95.2)	123 (99.2)
Pleura/pleural effusion	64 (39.3)	60 (42.9)	34 (41.0)	56 (45.2)
Thoracic lymph nodes	102 (62.6)	59 (42.1)	53 (63.9)	68 (54.8)
Disease burden (SLD/SOD of target lesions), cm**				
n	163	140	83	124
mean (SD)	9.2 (6.80)	6.7 (6.21)	8.7 (6.10)	6.4 (4.53)
median (min-max)	8.0 (1.0-42.4)	4.3 (1.0-38.0)	6.60 (1.3-25.1)	5.8 (0.0-25.2)
Number of target lesions – n (%)**				
0				1 (0.8)
1	41 (25.2)	60 (42.9)	20 (24.1)	45 (36.3)
2	34 (20.9)	38 (27.1)	22 (26.5)	36 (29.0)
3	30 (18.4)	18 (12.9)	12 (14.5)	29 (23.4)
4	25 (15.3)	13 (9.3)	12 (14.5)	6 (4.8)
5	13 (8.0)	11 (7.9)	6 (7.2)	7 (5.6)
6 or more	20 (12.3)	NA [b]	11 (13.3)	NA [b]
Number of prior regimens – n (%)				
0	0	0	16 (19.3)	2 (1.6)
1	26 (16.0)	0	38 (45.8)	54 (43.5)
2	45 (27.6)	61 (43.6)	16 (19.3)	37 (29.8)
3	35 (21.5)	50 (35.7)	7 (8.4)	24 (19.4)
>3	57 (35.0)	29 (20.7)	6 (7.2)	7 (5.6)

Metastatic sites as collected in CRF page of diagnosis and extent of cancer. Thoracic involvement is based on the Investigator reported lesion location for the baseline RECIST evaluation and was complemented by the metastatic site of cancer at baseline as reported in the 'Diagnosis and Extent of Cancer' eCRF when no thoracic lesion was identified from the RECIST evaluation. For further details please refer to [D120-Appendix 1-X1101-Table 14.1-3.15c], [Study A2201-Appendix 16.1.9b], [Study A2203-Appendix 16.1.9b]. [a] includes one patient with metastatic site in the meninges [b] Per RECIST 1.1, only up to 5 target lesions are recorded. SLD = sum of longest diameters in X2101 per RECIST 1.0; SOD = sum of diameters in A2201 and A2203 per RECIST 1.1.

The most frequent tumour histology was adenocarcinoma (92.7%), and most of the patients had Stage IV at baseline. The population included was heavily pre-treated with antineoplastic agents, including

platinum based chemotherapy (80.5%). The majority of patients (66.3%) were treated with prior ALK inhibitor (mostly crizotinib).

The subjects recruited in this trial consisted in a heavily pre-treated population with 163 patients previously exposed to an ALK inhibitor. Of them, 121 subjects received the first dose of ceritinib at least 18 weeks prior of the cut-off date, being the target population of this application.

Table 19: **NSCLC patient in the primary efficacy analysis of Study X2101**

All patients with prior ALK inhibitor treatment		163
	Patients with PD during treatment with (or within 2 weeks of last dose) last prior ALK inhibitor therapy	149
	Patients without PD during treatment with (or within 2 weeks of last dose of) last prior ALK inhibitor therapy	14
ALK inhibitor therapy naïve		83
All NSCLC		246

Numbers analysed

Table 20: **Analysis sets in NSCLC patients at 750 mg, by prior ALK inhibitor status (Study X2101 – FAS–NSCLC 750 mg)**

	NSCLC with prior ALK inhibitor			NSCLC ALK inhibitor naïve patients	All NSCLC patients[4]
	All patients with prior ALK inhibitor[1]	Patients with PD during last prior ALK inhibitor [2]	Patients without PD during last prior ALK inhibitor [3]		
	N=163	N=149	N=14	N=83	N=246
	n (%)	n (%)	n (%)	n (%)	n (%)
Full analysis set (FAS-NSCLC 750mg)	163 (100)	149 (100)	14 (100)	83 (100)	246 (100)
Efficacy analysis set (EAS-NSCLC 750 mg)	121 (74.2)	110 (73.8)	11 (78.6)	59 (71.1)	180 (73.2)
Central efficacy analysis set (CEAS-NSCLC 750 mg)	118 (72.4)	108 (72.5)	10 (71.4)	59 (71.1)	177 (72.0)

This table presents data for patients with NSCLC treated with LDK378 750 mg (750 mg treatment dose group from FAS-NSCLC, a subset of FAS). [1] All patients with prior ALK inhibitor were treated with crizotinib, in addition 5 patients received CH5424802 as their last prior ALK inhibitor. [2] Patients who had disease progression (PD) during treatment with (or within 2 weeks of last dose of) last prior ALK inhibitor therapy. [3] Patients who did not have PD during treatment with (or within 2 weeks of last dose of) last prior ALK inhibitor therapy. [4] All patients include all ALK-positive NSCLC patients treated with LDK378 750 mg. Source: [Study X2101-Table 14.1-2.1b]**.**

Outcomes and estimation

- Primary endpoints:
    - Overall response rate and duration of response

The primary efficacy analysis was performed using the EAS (NSCLC patients who received the first dose of LDK378 at least 18 weeks prior to the data cut-off date).

Table 21: Tumour response based on Investigator assessment in NSCLC patients at 750 mg, by prior ALK inhibitor status in Study X2101 (EAS-NSCLC 750 mg)

	NSCLC with prior ALK inhibitor			NSCLC ALK inhibitor naïve patients	All NSCLC patients
	Patients with prior ALK inhibitor	Patients with PD during last prior ALK inhibitor	Patients without PD during last prior ALK inhibitor		
	N=121	N=110	N=11	N=59	N=180
Best overall response, n (%)					
Complete response (CR)	2 (1.7)	2 (1.8)	0	1 (1.7)	3 (1.7)
Partial response (PR)	65 (53.7)	61 (55.5)	4 (36.4)	40 (67.8)	105 (58.3)
Stable disease (SD)	23 (19.0)	22 (20.0)	1 (9.1)	13 (22.0)	36 (20.0)
Progressive disease (PD)	13 (10.7)	12 (10.9)	1 (9.1)	0	13 (7.2)
Unknown	18 (14.9)	13 (11.8)	5 (45.5)	5 (8.5)	23 (12.8)
Overall response rate (ORR) (CR or PR), n (%)	**67 (55.4)**	**63 (57.3)**	**4 (36.4)**	**41 (69.5)**	**108 (60.0)**
95% CI	(46.1-64.4)	(47.5-66.7)	(10.9-69.2)	(56.1-80.8)	(52.4-67.2)
Duration of response	**N=67**	**N=63**	**N=4**	**N=41**	**N=108**
Median (month) [95%CI]	7.39 [5.42,10.12]	7.29 [5.09,10.12]	NE [7.85, NE]	NE [5.55, NE]	9.69 [6.93,11.40]
6 month DOR rate [95% CI]	58.5 [43.5,70.8]	56.1 [40.7,68.9]	100 [100, 100]	71.1 [49.8,84.6]	63.2 [51.2,72.9]

This table presents data for patients with ALK-positive NSCLC in the 750 mg treatment dose group who received the first dose of LDK378 at least 18 weeks prior to the analysis cut-off date, **EAS-NSCLC 750 mg group**.

The Central Efficacy Analysis Set (CEAS) was used for the analysis of tumour response data based on BIRC assessment.

Table 22: Tumour response based on BIRC in NSCLC patients at 750 mg, by prior ALK inhibitor status in Study X2101 (CEAS-NSCLC 750 mg)

	NSCLC with prior ALK inhibitor			NSCLC ALK inhibitor naïve patients	All NSCLC patients
	Patients with prior ALK inhibitor	Patients with PD during last prior ALK inhibitor	Patients without PD during last prior ALK inhibitor		
	N=118	N=108	N=10	N=59	N=177
Best overall response, n (%)					
Complete response (CR)	1 (0.8)	1 (0.9)	0	0	1 (0.6)
Partial response (PR)	51 (43.2)	49 (45.4)	2 (20.0)	38 (64.4)	89 (50.3)
Stable disease (SD)	28 (23.7)	27 (25.0)	1 (10.0)	11 (18.6)	39 (22.0)
Progressive disease (PD)	23 (19.5)	22 (20.4)	1 (10.0)	5 (8.5)	28 (15.8)
Unknown	15 (12.7)	9 (8.3)	6 (60.0)	5 (8.5)	20 (11.3)
Overall response rate (ORR) (CR or PR), n (%)	**52 (44.1)**	**50 (46.3)**	**2 (20.0)**	**38 (64.4)**	**90 (50.8)**
95% CI	[34.9, 53.5]	[36.7, 56.2]	[2.5, 55.6]	[50.9, 76.4]	[43.2, 58.4]
Duration of response	**N=52**	**N=50**	**N=2**	**N=38**	**N=90**
Median (month) [95%CI]	7.06 [4.80, NE]	7.06 [5.52, NE]	NE [2.79, NE]	NE [5.91, NE]	9.69 [5.98, NE]
6 month DOR rate [95% CI]	56.2 [36.5, 71.9]	57.3 [37.2, 73.1]	NE [NE, NE]	83.0 [49.0, 95.3]	66.1 [50.0, 78.2]

This table presents data for patients with ALK-positive NSCLC in the 750 mg treatment dose group who received the first dose of LDK378 at least 18 weeks prior to the analysis cut-off date and for whom EITHER the baseline scan and at least one post-baseline scan are available and can be evaluated by BIRC OR no post-baseline scan was performed in the study due to early death or discontinuation, **CEAS-NSCLC 750 mg group**

- Secondary endpoints
    - PFS

Table 23: Analysis of PFS based on Investigator assessment in NSCLC patients at 750 mg, by prior ALK inhibitor status (Study X2101 – EAS-NSCLC 750 mg)

	NSCLC with prior ALK inhibitor			NSCLC ALK inhibitor naïve patients	All NSCLC patients[4]
	All patients with prior ALK inhibitor[1]	Patients with PD during last prior ALK inhibitor[2]	Patients without PD during last prior ALK inhibitor [3]		
	N=121	N=110	N=11	N=59	N=180
Number of PFS events, n (%)	63 (52.1)	58 (52.7)	5 (45.5)	19 (32.2)	82 (45.6)
Progression	55 (45.5)	52 (47.3)	3 (27.3)	16 (27.1)	71 (39.4)
Death	8 (6.6)	6 (5.5)	2 (18.2)	3 (5.1)	11 (6.1)
Number of patients Censored	58 (47.9)	52 (47.3)	6 (54.5)	40 (67.8)	98 (54.4)
Kaplan-Meier estimates (%)					
PFS rate [95% CI] at					
3 months	75.9 [66.8, 82.8]	76.8 [67.4, 83.8]	64.8 [25.3, 87.2]	85.8 [73.5, 92.6]	79.2 [72.2, 84.6]
6 months	54.4 [44.1, 63.7]	54.7 [43.8, 64.3]	51.9 [16.4, 78.8]	67.0 [51.2, 78.7]	58.7 [50.3, 66.3]
12 months	25.5 [13.0, 40.0]	25.3 [11.7, 41.3]	25.9 [1.5, 64.9]	58.1 [41.6, 71.5]	36.6 [25.5, 47.6]
18 months	NE [NE, NE]	0 [NE, NE]	NE [NE, NE]	NE [NE, NE]	NE [NE, NE]
25th percentile PFS (month) [95% CI]	3.06 [2.66, 4.63]	4.01 [2.69, 4.73]	1.45 [0.13, 9.03]	5.52 [2.79, 6.77]	4.17 [2.79, 4.73]
Median PFS (month) [95% CI]	6.90 [5.39, 8.67]	6.90 [5.39, 8.67]	9.03 [0.13, NE]	NE [6.67, NE]	6.97 [6.21, 10.12]
75th percentile PFS (month) [95% CI]	12.45 [9.03, NE]	12.45 [8.67, 12.78]	NE [3.06, NE]	NE [NE, NE]	12.78 [12.45, NE]

This table presents data for patients with ALK-positive NSCLC in the 750 mg treatment dose group who received the first dose of ceritinib at least 18 weeks prior to the analysis cut-off date, EAS-NSCLC 750 mg group
[1] All patients with prior ALK inhibitor were treated with crizotinib, in addition 5 patients received CH5424802 as their last prior ALK inhibitor.
[2] Patients who had disease progression (PD) during treatment with (or within 2 weeks of last dose of) last prior ALK inhibitor therapy.
[3] Patients who did not have PD during treatment with (or within 2 weeks of last dose of) last prior ALK inhibitor therapy.
[4] All patients include all ALK-positive NSCLC patients treated with ceritinib 750 mg
Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982).
% Event-free probability estimate is the estimated probability that a patient will remain event-free up to the specified time point.
% Event-free probability estimates are obtained from the Kaplan-Meier survival estimates; Greenwood formula is used for CIs of KM estimates.
N: Total number of patients included in the analysis.

PFS results using BIRC assessment showed that the median PFS was 8.34 months (6.67, 11.07), and the 6- and 12-month PFS rates were 61.6% and 38.2% respectively.

Updated results

During the procedure, the applicant provided an update on the efficacy data from the phase I study X2101 (cut-off date: 14-Apr-2014), and both phase II studies (A2201 [cut-off date: 26-Feb-2014] and A2203 [cut off-date: 27-Jun-2014]). No new efficacy data has been provided for the Japanese Phase 1 Study X1101 (only SAE and death data has been captured in the global safety database). The results are summarized in the following tables:

Table 24: Response rates and duration of response in patients with ALK positive NSCLC by Investigator assessment (Study X2101, Study A2201, Study A2203)

	NSCLC patients with prior ALK inhibitor		ALK inhibitor naïve NSCLC patients	
	Study X2101 ceritinib 750 mg N=163	Study A2201 ceritinib 750 mg N=140	Study X2101 ceritinib 750 mg N=83	Study A2203 ceritinib 750 mg N=124
Overall response rate (CR+PR), n (%)	**92 (56.4)**	**52 (37.1)**	**60 (72.3)**	**79 (63.7)**
95% CI	(48.5-64.2)	(29.1, 45.7)	(61.4, 81.6)	(54.6, 72.2)
CR	3 (1.8)	3 (2.1)	1 (1.2)	0
PR	89 (54.6)	49 (35.0)	59 (71.1)	79 (63.7)
SD	29 (17.8)	56 (40.0)	14 (16.9)	32 (25.8)
PD	16 (9.8)	19 (13.6)	0	5 (4.0)
Non-CR/Non-PD	-	0	-	1 (0.8)
UNK	26 (16.0)	13 (9.3)	9 (10.8)	7 (5.6)
Disease control rate (CR+PR+SD)	Not Estimated**	108 (77.1)	Not Estimated**	111 (89.5)
(95% CI)	-	(69.3, 83.8)	-	(82.7, 94.3)
Duration of response*				
Median (month) (95%CI)	8.25 (6.80, 9.69)	9.2 (5.6, NE)	17.02 (11.27, NE)	9.3 (9.1, NE)

NE = not estimable.
Study X2101: Responses assessed by Investigator using RECIST 1.0.
Study A2201, A2203: Responses assessed by Investigator using RECIST 1.1.
CR, PR confirmed by repeat assessments performed not less than 4 weeks after response criteria were first met.
* Includes only patients with confirmed CR, PR.
** DCR was not a pre-defined endpoint in Study X2101
Source: [D120 Appendix 1-X2101-Table 14.2-1.1h], [D120 Appendix 1-X2101-Table 14.2-1.4h],[Study A2201-Table 14.2-1.1a], [Study A2203-Table 14.2-1.1a], [Study A2201-Table 14.2-1.3a], [Study A2203-Table 14.2-1.3a]

Table 25: Response rates in patients with ALK positive NSCLC by BIRC (Study X2101, Study A2201, Study A2203)

	Patients with prior ALK inhibitor treatment		ALK inhibitor naïve patients	
	Study X2101 ceritinib 750 mg N=163	Study A2201 ceritinib 750 mg N=140	Study X2101 ceritinib 750 mg N=83	Study A2203 ceritinib 750 mg N=124
Overall response rate (CR + PR)				
BIRC				
n (%)	75 (46.0)	48 (34.3)	53 (63.9)	73 (58.9)
(95% CI)	(38.2, 54.0)	(26.5, 42.8)	(52.6, 74.1)	(49.7, 67.6)

Study X2101: Responses assessed using RECIST 1.0
Studies A2203 and A2201: Responses assessed using RECIST 1.1
CR, PR confirmed by repeat assessments performed not less than 4 weeks after response criteria were first met

Table 26: **Progression-free survival in patients with ALK-positive NSCLC by Investigator assessment (Study X2101, Study A2201, Study A2203)**

	NSCLC patients with prior ALK inhibitor		ALK inhibitor naïve NSCLC patients	
	Study X2101 ceritinib 750 mg N=163	**Study A2201 ceritinib 750 mg N=140**	**Study X2101 ceritinib 750 mg N=83**	**Study A2203 ceritinib 750 mg N=124**
Number of patients with PFS event, n (%)	**113 (69.3%)**	**82 (58.6)**	**33 (39.8)**	**40 (32.3)**
Number of patients censored, n (%)	**50 (30.7)**	**58 (41.4)**	**50 (60.2)**	**84 (67.7)**
Reasons for censoring				
Ongoing without event	29 (17.8)	51 (36.4)	42 (50.6)	77 (62.1)
Lost to follow-up	1 (0.6)	1 (0.7)	0	0
Withdrew consent	5 (3.1)	2 (1.4)	1 (1.2)	2 (1.6)
Initiation of new anticancer therapy	7 (4.3)	2 (1.4)	3 (3.6)	1 (0.8)
Event documented after ≥ 2 missing tumor assessments [a]	5 (3.1)	1 (0.7)	2 (2.4)	0
Adequate assessment no longer available	3 (1.8)	1 (0.7)	2 (2.4)	4 (3.2)
Median PFS (months) (95% CI)	6.9 (5.6, 8.7)	5.7 (5.3, 7.4)	18.4 (11.1, NE)	11.1 (9.3, NE)
12-month PFS rate	27.2 (19.8, 35.1)	24.5 (14.4, 35.9)	62.3 (50.0, 72.4)	40.3 (19.7, 60.2)

NE = not estimable.
[a] No adequate evaluations for a specific period (more than 4 cycles + 2-week window) prior to data cut-off or without baseline assessment.
Study X2101: Responses assessed by Investigator using RECIST 1.0.
Study A2201, A2203: Responses assessed by Investigator using RECIST 1.1.
Source: [D120 Appendix 1-X2101-Table 14.2-1.5h],[D120 Appendix 1-X2101-Table 14.2-1.6f], [Study A2201-Table 14.2-1.6a], [Study A2201-Table 14.2-1.7], [Study A2203-Table 14.2-1.6a], [Study A2203-Table 14.2-1.7]

Table 27: **Overall survival in patients with ALK-positive NSCLC (Study X2101, Study A2201, Study A2203)**

	NSCLC patients with prior ALK inhibitor		ALK inhibitor naïve NSCLC patients	
	Study X2101 ceritinib 750 mg N=163	**Study A2201 ceritinib 750 mg N=140**	**Study X2101 ceritinib 750 mg N=83**	**Study A2203 ceritinib 750 mg N=124**
Number of deaths, n (%)	**63 (38.7)**	**39 (27.9)**	**16 (19.3)**	**13 (10.5)**
Number of patients censored, n (%)	**100 (61.3)**	**101 (72.1)**	**67 (80.7)**	**111 (89.5)**
Reasons for censoring				
Alive	73 (44.8)	100 (71.4)	58 (69.9)	110 (88.7)
Lost to follow-up	27 (16.6) [a]	1 (0.7)	9 (10.8)[b]	1 (0.8)
Median (month) (95%CI)	**16.7 (14.8, NE)**	**14.0 (10.3, 14.0)**	**NE (19.61, NE)**	**NE**
12-month OS rate (95% CI)	67.2 (58.9, 74.1)	54.9 (38.5, 68.6)	83.0 (72.4, 89.8)	81.5 (64.8, 90.8)

NE = not estimable.
[a] 2 patients classified by the investigator as lost to follow-up, and 24 patients for whom no survival information was available within 14 weeks prior to the cut-off date
[b] 1 patient classified by the investigator as lost to follow-up, and 8 patients for whom no survival information was available within 14 weeks prior to the cut-off date
Source: [D120 Appendix 1-X2101-Table 14.2-2.1d], [D120 Appendix 1-X2101-Table 14.2-1.6f], [Study A2201-Table 14.2-2.1], [Study A2203-Table 14.2-2.1], [Study A2201-Table 14.2-1.7], [Study A2203-Table 14.2-1.7]

Table 28: **Progression-free survival in ALK inhibitor naïve NSCLC patients treated with ceritinib 750 mg (FAS)**

	Investigator assessment		**BIRC assessment**	
	Study X2101 ceritinib 750 mg N=83	Study A2203 ceritinib 750 mg N=124	Study X2101 ceritinib 750 mg N=83	Study A2203 ceritinib 750 mg N=124
Number of patients with PFS event, n (%)	33 (39.8)	40 (32.3)	29 (34.9)	41 (33.1)
Number of patients censored, n (%)	50 (60.2)	84 (67.7)	54 (65.1)	83 (66.9)
Reasons for censoring				
- Ongoing without event				
- Lost to follow-up	0	0	1 (1.2)	0
- Withdrew consent	1 (1.2)	2 (1.6)	1 (1.2)	2 (1.6)
- Initiation of new anticancer therapy	3 (3.6)	1 (0.8)	9 (10.8)	5 (4.0)
- Event documented after ≥ 2 missing tumour assessments [a]	2 (2.4)	0	0	0
- Adequate assessment no longer available	2 (2.4)	4 (3.2)	3 (3.6)	8 (6.5)
Median PFS (months) (95% CI)	18.4 (11.1, NE)	11.1 (9.3, NE)	18.4 (15.2, NE)	NE (9.2, NE)

NE = not estimable; PFS = progression-free survival
[a] No adequate evaluations for a specific period (more than 4 cycles + 2-week window) prior to data cut-off or without baseline assessment. Study X2101: Responses assessed by Investigator using RECIST 1.0. Data cut-off: 14-Apr-2014. Study A2203: Responses assessed by Investigator using RECIST 1.1.
Source: [Day 120 response to Question 59 - Table 2-4], [Day 120 response to Question 87 -Table 3-39

Ancillary analyses

Analyses of ORR in study X2101 were performed in subgroups of patients based on demographic characteristics and prognostic factors, by brain metastases at baseline and by prior ALK inhibitor history.

Table 29: **ORR, DOR and PFS by Investigator in NSCLC patients at 750 mg by demographic characteristics and prognostic factors (EAS – NSCLC 750 mg)**

Subgroups	n	ORR (95% CI) n (%)	n#	Median DOR months (95% CI)	n	Median PFS months (95% CI)
Region						
North America	81	55.6 (44.1, 66.6)	45	7.39 (4.50, 11.04)	81	6.90 (5.32, 9.03)
Europe	48	56.3 (41.2, 70.5)	27	11.40 (4.21, NE)	48	6.67 (4.63, NE)
Asia Pacific	51	70.6 (56.2, 82.5)	36	10.12 (7.29, NE)	51	11.50 (6.77, NE)
Age						
< 65 years	151	61.6 (53.3, 69.4)	93	7.85 (6.93, 11.40)	151	6.97 (5.68, 10.12)
≥ 65 years	29	51.7 (32.5, 70.6)	15	10.12 (4.14, NE)	29	11.50 (4.63, NE)
Gender						
Male	79	63.3 (51.7, 73.9)	50	9.69 (7.29, 11.04)	79	8.67 (6.21, 12.45)
Female	101	57.4 (47.2, 67.2)	58	7.85 (5.09, NE)	101	6.77 (5.32, NE)
Race*						
Caucasian	118	56.8 (47.3, 65.9)	67	6.93 (4.50, 11.40)	118	6.67 (5.32, 8.41)
Asian	55	69.1 (55.2, 80.9)	38	10.12 (7.29, NE)	55	11.50 (6.90, NE)
ECOG status						
0	49	73.5 (58.9, 85.1)	36	NE (9.69, NE)	49	12.45 (6.97, NE)
≥ 1	131	55.0 (46.0, 63.7)	72	7.29 (5.42, 11.04)	131	6.21 (5.32, 8.41)
Disease burden						
Baseline SLD for target lesion < median	90	62.2 (51.4, 72.2)	56	NE (7.29, NE)	90	12.45 (6.90, NE)
Baseline SLD for target lesion ≥ median	90	57.8 (46.9, 68.1)	52	6.93 (5.09, 11.04)	90	6.47 (4.73, 7.00)
ALK positive by FISH, using Vysis probe and positivity definition ≥ 15%						
Met the criteria	129	58.9 (49.9, 67.5)	76	9.69 (6.93, 11.40)	129	6.97 (6.21, 10.12)
Did not meet the criteria	50	64.0 (49.2, 77.1)	32	NE (4.17, NE)	50	8.67 (4.73, NE)

*The number of patients in the "Black" (n=4) and "Other" (n=3) ethnicities was too low to enable meaningful comparisons.#EAS - NSCLC 750 mg patients with confirmed CR or PR

Table 30: **ORR, DOR and PFS in NSCLC patients at 750 mg, by brain metastases at baseline (EAS- NSCLC 750 mg)**

Efficacy parameters	Brain metastases at baseline		No brain metastases at baseline	
	n	Parameter (95% CI)	n	Parameter (95% CI)
ORR, n (%)				
By Investigator assessment	95	54.7 (44.2, 65.0)	85	65.9 (54.8, 75.8)
By BIRC assessment	93	45.2 (34.8, 55.8)	84	57.1 (45.9, 67.9)
Median DOR, months				
By Investigator assessment	52	7.39 (5.45, 11.04)	56	10.12 (5.52, NE)
By BIRC assessment	42	9.69 (5.62, NE)	48	8.31 (5.91, NE)
Median PFS, months				
By Investigator assessment	95	6.90 (5.39, 9.03]	85	11.50 (5.62, NE)
By BIRC assessment	93	8.21 (5.55, 11.07)	84	9.69 (6.97, NE)

The ORR, DOR and PFS is based on systemic response (all tumour lesions including brain) per RECIST

Table 31: ORR, DOR and PFS by Investigator in NSCLC patients at 750 mg, by prior ALK inhibitor history (EAS- NSCLC 750 mg)

Subgroups	n	ORR (95% CI)	n*	Median DOR months (95% CI)	n	Median PFS months (95% CI)
Prior response to ALK inhibitors						
Yes	68	61.8% (49.2, 73.3)	42	7.29 (4.21, 11.04)	68	6.80 (5.32, 8.41)
No	53	47.2% (33.3, 61.4)	25	10.12 (4.50, 11.40)	53	6.90 (4.63, 12.78)
Time from last dose of last prior ALK inhibitor to first dose of LDK378						
≤ 2 months	92	57.6% (46.9, 67.9)	53	7.29 (5.09, 10.12)	92	6.97 (5.32, 10.12)
> 2 months and ≤ 4 months	15	40.0% (16.3, 67.7)	6	NE (4.01, NE)	15	5.39 (1.45, NE)
> 4 months	14	57.1% (28.9, 82.3)	8	7.85 (3.15, 7.85)	14	6.21 (4.17, 9.03)

* EAS - NSCLC 750 mg patients with confirmed CR or PR

Although ORR was better in subjects that had previous response with an ALK inhibitor (61.8%), subjects that did not respond on prior ALK inhibitor also experienced substantial response (47.2%). Response in patients with primary resistance to previous ALK inhibitor (mainly crizotinib) further indicates that ceritinib may have different mechanisms of action.

Table 32: ALK-positive advanced NSCLC patients previously treated with AlK inhibitor with brain metastases at baseline - overview of efficacy data, by BIRC assessment

	Study X2101 ceritinib 750 mg N=98	Study A2201 ceritinib 750 mg N=100
Overall response rate (CR + PR)		
n (%)	41 (41.8)	31 (31.0)
(95% CI)	(31.9, 52.2)	(22.1, 41.0)
Duration of response*		
Median (months)	8.2	6.3
(95% CI)	(5.6, 13.1)	(3.9, 9.5)
Progression-free survival		
Median (months)	6.7	5.6
(95% CI)	(5.4, 9.5)	(5.4, 7.2)

NE = not estimable
Study X2101: Responses assessed by BIRC using RECIST 1.0
Study A2201: Responses assessed by BIRC using RECIST 1.1
CR, PR confirmed by repeat assessments performed not less than 4 weeks after response criteria were first met
*Includes only patients with confirmed CR, PR

Overall intracranial response rate (OIRR)

For all patients in the registration trial, an OIRR of 45.5% (95% CI: 16.7, 76.6) was shown (initial submission). This is considered to be of significant clinical importance, but as only a small number of patients (11/180) had brain metastases at baseline considered as target lesions uncertainty is associated with the results.

Summary of main study

The following tables summarise the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 33. Summary of Efficacy for trial X2101

Title:
A phase I, multicenter, open-label, dose-escalation study of LDK378, administered orally in adult patients with tumors characterized by genetic abnormalities in ALK.

Study identifier	CLDK378X2101; EudraCT no. 2010-019827-70		
Design	first-in-human, phase 1, open-label, dose-escalation and expansion study investigating the safety, pharmacokinetics (PK), and anti-tumor activity of oral, once daily, continuous dosing of LDK378 in adult patients with advanced tumors confirmed to have genetic abnormalities in ALK (ALK-positive).		
	Duration of main phase:		Study treatment was to be continued until the occurrence of disease progression or clinical deterioration, unacceptable toxicity, patient's withdrawal of consent, or protocol noncompliance. Treatment could be continued after disease progression if the patient was considered to be deriving clinical benefit as judged by the investigator.
Hypothesis	Exploratory		
Treatments groups	Dose Escalation Phase		Ceritinib once daily was administered continuously in 21-days cycles. Doses ranged from 50mf to 750mg.
	Expansion phase group 1A ALK-positive NSCLC previously treated with an ALK-inhibitor and progressed during treatment with an ALK inhibitor or within two weeks of the last dose of an ALK inhibitor and with planned initiation of LDK378 within 60 days of the last dose of the prior ALK inhibitor		Ceritinib 750mg QD was the starting dose to be administered orally in 21-day cycles.
	Expansion phase group 1B ALK-positive NSCLC previously treated with an ALK-inhibitor who did not meet criteria for 1A.		Ceritinib 750mg QD was the starting dose to be administered orally in 21
	Expansion phase group 1C ALK-positive NSCLC naïve to ALK-inhibitor treatment		Ceritinib 750mg QD was the starting dose to be administered orally in 21
Endpoints and definitions	Overall response rate	ORR	The proportion of patients with a best overall response of CR or PR. according to RECIST version 1.0.
	Duration of Response	DOR	Time from first documented response (PR or CR) to the date of first documented disease progression (PD) or death due to any cause, among patients with a confirmed PR or CR per RECIST 1.0.

	Progression Free Survival	PFS	Time from the start date of study drug to the date of the first radiologically documented PD per RECIST 1.0 or death due to any cause
	Overall Survival	OS	Time from the start date of study drug to the date of death due to any cause.
Database lock	14-Apr-2014		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Efficacy Analysis Set (**EAS**): patients with ALK-positive NSCLC across all doses who received the first dose of LDK378 at least 18 weeks prior to the analysis cut-off date.		
Descriptive statistics and estimate variability	Treatment group 750 mg/cohort	ALK-positive NSCLC previously treated with an ALK-inhibitor	ALK-positive NSCLC naïve to ALK-inhibitor treatment
	Number of subject	163	83
	ORR (%)	56.4%	72.3%
	95% CI	[48.5, 64.2]	[61.4, 81.6]
	DOR	8.25	17.0
	95% CI	[6.80, 9.69]	[11.27, NE]
Effect estimate per comparison	Not Applicable		
Analysis description	**Secondary analysis**		
Descriptive statistics and estimate variability	Treatment group 750 mg/cohort	ALK-positive NSCLC previously treated with an ALK-inhibitor	ALK-positive NSCLC naïve to ALK-inhibitor treatment
	Number of subject	163	83
	PFS (months)	6.9	18.4
	95% CI	[5.6, 8.7]	[11.1, NE]
	OS (months)	16.7	NE

	95% CI	[14.8, NE]	[19.6, NE]

Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

Clinical studies in special populations

No dedicated clinical studies were conducted in special populations.

Severe hepatic impairment:

Additional data have been requested and the Applicant agreed to conduct a study in patients with hepatic impairment (see section 2.7).

Elderly patients:

The below table provide information on the number of patients enrolled in the clinical development programme of ceritinib by age group and treated at the recommended dose of 750 mg.

Table 34: **Efficacy in special populations for the 750 mg ceritinib group (Full analysis set – NSCLC - 750 mg)**

Study	Age < 65 yrs n (%)	Age 65-<75 yrs n (%)	Age 75-<85 yrs n (%)
A2201 (N=140)	122 (87.1)	16 (11.4)	2 (1.4)
A2203 (N=124)	94 (75.8)	24 (19.4)	6 (4.8)
X1101 750 mg (N=5)	4 (80.0)	1 (20.0)	0
X2101 750 mg (N=246)	207 (84.1)	37 (15.0)	2 (0.8)
750 mg Pooled (A2201, A2203, X1101 and X2101) (N=515)	427 (82.9)	78 (15.1)	10 (1.9)

The denominator to calculate each percentage is N, the number of patients in the full analysis set for the 750 mg dose group.
Data cut-off for X2101: 14-Apr-2014, X1101: 02-Aug-2013, A2201: 26-Feb-2014, A2203: 27-Jun-2014
Source: [D120 Appendix 7-Table D120Q95-2b], [X1101 CSR – Table 14.1-4.1b]

Supportive studies

Study X1101

This is a phase I, open-label, dose-escalation and expansion study in Japanese patients, currently on-going. The dose-escalation phase enrolled patients with tumours characterized by genetic alterations in ALK to determine the MTD/RD, and to evaluate the safety, PK, and anti-tumour activity of LDK378. In the expansion phase additional patients will be enrolled to further evaluate the safety, tolerability, PK, and anti-tumour activity of LDK378 at the RD.

The study included a 3-day single dose PK run-in period to fully characterize the PK of LDK378 followed by a period of daily dosing in continuous 21-day treatment cycles.

In the **dose-escalation phase,** successive cohorts of patients received increasing doses of LDK378 (from 300 mg to 750 mg), until the MTD was determined. A two-parameter BLRM which employed the EWOC principle was used during the dose-escalation phase for dose level selection and for determination of the MTD. Dose-escalation decisions were based on safety information including both DLTs and other adverse events during Cycle 1 (including the PK run-in period).

The **expansion phase** was to be started after the MTD was determined (Note: as of the 02- Aug-2013 cut-off date, no patients were enrolled in the expansion phase).

In the dose-escalation phase patients were treated with LDK378 until they experienced unacceptable toxicity that precluded any further treatment, disease progression, and/or treatment was discontinued at the discretion of the Investigator or by patient request. The same would apply to patients who will be enrolled in the expansion phase.

The **efficacy endpoints** used to evaluate the anti-tumour activity of LDK378 are ORR, DOR and PFS as assessed by the Investigator per RECIST 1.1.

As of the cut-off date 02-Aug-2013, a total of 19 patients with locally advanced or metastatic, ALK-positive disease were enrolled in the dose-escalation phase of Study X1101: 300 mg (n=3), 450 mg (n=6), 600 mg (n=4), 750 mg (n=6), between 2-Jul-2012 and 4-Dec-2012.

Among these were 18 patients with ALK-positive NSCLC as determined by FISH and one patient (750 mg dose cohort) had a non-NSCLC tumour with ALK abnormality (inflammatory myofibroblastic tumour). No patients were enrolled in the expansion phase prior to the cut-off date.

All patients (19) reported in this study received the first dose of study drug more than 6 months prior to the analysis cut-off date. One patient treated in the study (in the 750 mg dose cohort) did not have NSCLC and is, therefore, not included in the EAS.

Based on the Investigator assessments using RECIST 1.1 criteria, there were 10 confirmed PRs out of the 18 EAS-NSCLC ALK-positive patients. The responses were observed in all dose cohorts (300 mg to 750 mg) and were regardless of the prior ALK inhibitor used (crizotinib, CH5424802 or ASP3026).

Four DOR events (progressions) (300 mg=2, 450 mg=1 and 600 mg=1) were observed in the 10 patients who had partial responses across all the dose cohorts. The median DOR in the 300 mg dose cohort based on Investigator assessment was 4.2 months (95% CI: 4.2, NE). The median DOR in the other dose cohorts were not estimable due to very few events.

Study A2201

This is a single-arm, open-label, multicentre, Phase II study with a single stage design to evaluate the efficacy and safety of single-agent ceritinib in patients with locally advanced or metastatic ALK-positive NSCLC previously treated with cytotoxic chemotherapy (one to three prior lines, of which 1 must have been a platinum doublet) and then with crizotinib.

The key inclusion criteria included patients ≥ 18 years with histologically or cytologically confirmed diagnosis of stage IIIB or IV NSCLC carrying an ALK rearrangement. NSCLC at patient study entry should have progressed during therapy with crizotinib. In addition, patients had to be previously treated with cytotoxic chemotherapy (one to three prior lines, of which one must have been a platinum doublet). Patients needed to have a WHO Performance Status 0 to 2 and life expectancy of ≥ 12 weeks at study entry. Also, patients had to have at least one measurable lesion as defined by RECIST 1.1.

Patients with known hypersensitivity to any of the excipients of ceritinib were excluded. The following patients were excluded: symptomatic CNS metastases history of interstitial lung disease or interstitial pneumonitis, history of a second malignancy, impaired GI function, history of carcinomatous meningitis, or clinically significant cardiac disease.

The treatment period began on Day 1 of Cycle 1. All patients were treated with ceritinib 750 mg administered orally on a once-daily dosing schedule. Each treatment cycle was 28 days (the 28 day cycle length was fixed regardless of whether the dose of ceritinib was withheld). Treatment with ceritinib was

continued until the patient experienced unacceptable toxicity that precluded further treatment, discontinued treatment at the discretion of the patient or investigator started a new anti-cancer therapy or died.

The primary objective of the study was to demonstrate the anti-tumour activity of ceritinib, as measured by ORR by Investigator assessment. The secondary objectives included the evaluation of:

- ORR as assessed by BIRC;

- DOR, DCR, TTR, OIRR, PFS as assessed by both Investigator and BIRC;

- OS;

- Safety profile.

The baseline characteristics and study results have been presented in the main study section (see above).

In response to the CHMP request, the applicant was requested to provide a summary of the initial and updated efficacy data by investigator and BIRC assessment (see Table).

Table 35: **Overall summary of efficacy (FAS, Study A2201) Efficacy endpoints, by Investigator and BIRC assessments**

Efficacy endpoint	Investigator assessment		BIRC assessment	
	Data cut-off 13-Aug-2014	Data cut-off 26-Feb-2014	Data cut-off 13-Aug-2014	Data cut-off 26-Feb-2014
ORR – n (%) [95% CI]	54 (38.6) [30.5, 47.2]	52 (37.1) [29.1, 45.7]	50 (35.7) [27.8, 44.2]	48 (34.3) [26.5, 42.8]
DOR – Median (Min-Max), months	9.7 [7.1, 11.1]	9.2 [5.6, NE]	9.7 [5.6, 12.9]	9.2 [5.5, NE]
PFS – Median [95% CI], months	5.7 [5.4, 7.6]	5.7 [5.3, 7.4]	7.2 [5.4, 9.0]	6.1 [5.4, 7.4]

ORR = Objective response rate, DOR = Duration of response, PFS = Progression free survival

FAS = Full analysis set consisting of all patients who received at least one dose of study drug

Source: [Day 180 Appendix 2-Table 14.2-1.1a], [Day 180 Appendix 2-Table 14.2-1.1b], [Day 180 Appendix 2-Table 14.2-1.3a], [Day 180 Appendix 2-Table 14.2-1.3b], [Day 180 Appendix 2-Table 14.2-1.6a], [Day 180 Appendix 2-Table 14.2-1.6b], [A2201 CSR-Table 14.2-1.1a], [A2201 CSR-Table 14.2-1.1b], [A2201 CSR-Table 14.2-1.3a], [A2201 CSR-Table 14.2-1.3b], [A2201 CSR-Table 14.2-1.6a], [A2201 CSR-Table 14.2-1.6b]

Study A2203

This is a single-arm, open-label, multicentre, Phase II study with a single stage design to evaluate the efficacy and safety of single-agent ceritinib in patients with locally advanced or metastatic ALK-positive NSCLC previously treated with cytotoxic chemotherapy and naïve to ALK-inhibitor treatment.

The main differences with study A2201 regarding inclusion and exclusion criteria were that study A2203 included chemotherapy-naïve patients as of protocol amendment 2 and excluded patients previously treated with crizotinib.

All patients were treated with ceritinib 750 mg administered orally on a once daily schedule and each treatment cycle lasted 28 days. Treatment with ceritinib continued until the patient experienced unacceptable toxicity that precluded further treatment, discontinued treatment at the discretion of the patient or Investigator, started a new anti-cancer therapy or died.

The primary objective of the study was to demonstrate the anti-tumour activity of ceritinib, as measured by ORR by Investigator assessment. The secondary objectives included the evaluation of:

- ORR as assessed by BIRC;

- DOR, DCR, TTR, OIRR, PFS as assessed by both Investigator and BIRC;

- OS;

- Safety profile.

The baseline characteristics and study results have been presented in the main study section (see above).

2.5.3. Discussion on clinical efficacy

The efficacy (and safety) database provided with the original submission was quite limited, since just one phase I study was submitted to support this application.

During the procedure, the Applicant has provided an update on the efficacy data from the phase I study X2101 with a data cut-off date of 13 August 2014 (performed when all patients had either completed 48 weeks of treatment or discontinued study drug earlier) for the key efficacy endpoints (OS not updated).

The applicant also provided updates from both phase II studies (A2201 [cut-off date: 26 February 2014] and A2203 [cut off-date: 27 June 2014]). No new efficacy data has been provided for the Japanese Phase 1 Study X1101 (only SAE and death data has been captured in the global safety database).

Design and conduct of clinical studies

Overall, 515 ALK-positive NSCLC patients have been treated with ceritinib 750 mg (83 ALK inhibitor naïve and 163 ALK inhibitor pretreated patients in study X2101; 140 ALK inhibitor pretreated patients in study A2201 and 124 ALK inhibitor naïve patients in study A2203; 6 additional patients have been treated at the proposed dose in study X1101).

With regards to patients' disposition, a relevant portion of patients are still on-going in the 3 studies (99 of 246 in study X2101, 75 of 140 in A2201 and 91 of 124 in A2203). This means that for both phase II studies, full OS data is not yet available.

Sixty-eight patients out of the 246 patients treated at 750 mg in the FAS for study X2101 were enrolled in the EU, 101 patients from North America, and 77 in Asia. Of the 246 NSCLC, 180 patients (73.2%) who received the first dose of LDK378 at least 18 weeks prior to the data cut-off date were included in the EAS-NSCLC 750 mg group. The 18-week period was prospectively selected (as per Protocol Amendment 5) so that patients would have sufficient follow-up for assessment and/or confirmation of response, and because DOR data would be limited if patients with less than 18 weeks of exposure were included.

The primary efficacy endpoints are overall response rate (ORR) and duration of response (DOR), as assessed by the Investigator per RECIST 1.0. Taking into consideration that ORR is a measure of anti-tumour activity and does not provide direct evidence on patient's benefit, PFS/OS (included as secondary endpoints in the registration study) would have been preferred as primary efficacy endpoints over ORR.

Efficacy data and additional analyses

Overall, the profile of the patient population in study X2101 largely resembles the population included in the pivotal studies that led to crizotinib conditional approval.

The ALK inhibitor (ALKi) pre-treated patient population comprises heavily pre-treated patients, with more than half of the patients having received at least 3 prior regimens, including crizotinib. The ORR (56.4% and 37.1%) seen in these patients exceed that expected with chemotherapy. The DOR was similarly long in both studies (median 8.3 and 9.2 months, respectively). Furthermore, the PFS seen in these patients

ranged from a median of 6.9 months in Study X2101 to a median of 5.7 months in Study A2201, whilst for OS preliminary data show a median of 16.7 and 14.0 months, respectively.

The updated results for the primary endpoint ORR by investigator and secondary endpoints of PFS and OS, show a lower magnitude of effect in the phase II studies than in the phase I study. These findings are unexpected to some extent, because although the population in study X2101 is more heavily treated, efficacy results seem to be better.

The population recruited into the study A2201 could be considered the actual target population to be treated in clinical practice, i.e. those patients with 2 prior treatments (chemo + crizotinib).

In the ALKi pre-treated patients in X2101, the ORR reported by BIRC assessment was 46%, compared to 56.4% by investigator´s assessment (approximatively 10% difference). For ALKi naïve patients, the difference is around the same size (63.9% by BIRC, versus 72.3% by investigator assessment).

The Applicant stated that these differences could partly be explained by inter-observer variability, which can be agreed with, to some extent. However, an overestimation of the effect in study X2101 due to the nature of its design (being a first administration to humans, open-label, uncontrolled study which included an advanced patient population with limited options) could not be completely ruled out. The fact that both assessments (by BIRC and by investigator) in the phase II studies are concordant and that the BIRC assessment of study X2101 seems to be in line with those results is at least reassuring.

The indication applied for “treatment of adult patients with previously treated anaplastic lymphoma kinase (ALK) positive locally advanced or metastatic non-small cell lung cancer (NSCLC)” is broad, including ALKi pre-treated patients as well as ALKi naïve patients (previously treated with chemotherapy). It is agreed that ceritinib answers an unmet medical need in the treatment of ALKi previously treated patients whom experienced disease progression.

For patients who progress on or shortly after treatment with an ALK-inhibitor there are very limited treatment options. In this patient population, ceritinib appears to be a more efficacious treatment option than other currently available salvage therapies (Chemotherapy regimens). Available data indicate that ceritinib provides a clinically relevant benefit in those patients previously treated with an ALKi, however there is a need to further confirm the benefit/risk of the product before a full approval can be granted.

The Applicant has provided the expected timelines for the presentation of the results from the on-going confirmatory phase II (A2201) and phase III (A2303) studies in the ALKi previously treated population and has proposed these 2 studies to be specific obligations for the approval. The final CSR for Study A2201 is estimated to be available towards Q2 2016 and the final CSR for Study A2303 is estimated to be available towards Q3 2018.

The evidence supporting the use as an alternative to crizotinib for ALKi naïve NSCLC patients is considered weak, being based on uncontrolled, open label studies and lower than that required for currently available alternatives.

In addition, the sequential use of ALKi is also a remaining concern, due to the very limited data available. The whole evidence available comes from studies X2101 and A2201, in which a total of 303 patients received ceritinib after crizotinib treatment. No data is available to date on patients receiving an ALKi after ceritinib treatment. Consequently, the applicant has no data to rule out that ALKi naïve patients receiving ceritinib could consequently fail to respond to post-progression therapy with crizotinib or other ALKi.

It should be noted that the crizotinib authorization was based on data from a phase II + top-line data from a controlled phase III trial. No further controlled data would be expected for ceritinib in ALKi naïve subjects.

In addition, relevant efficacy endpoints, such as PFS and OS, are still not fully mature, since a large number of patients are currently on-going without an event (50.6% and 62.1%, in X2101 and A2203, respectively). There is therefore a high level of uncertainty to the magnitude of the clinical benefit. During the procedure, the applicant notified of their decision to only pursue the indication in ALKi pre-treated patients.

Finally, data related to the anti-tumour activity of ceritinib in brain metastases have been submitted. This might be of clinical value for a population in which the available alternatives provide limited activity. Data from study A2205, will likely add more information on this regard. Until more data is available, only descriptive information has been included in section 5.1 of the SmPC.

Additional efficacy data needed in the context of a conditional MA

The updated information from the phase I and the phase II studies supporting the ALKi pretreated indication confirm the efficacy results initially observed, and provide reassurance on the robustness of these results. Although a positive benefit-risk profile can be concluded, the data have limitations inherent to the non-comparative nature of the studies supporting the recommendation for a conditional MA.

In order to confirm the positive benefit-risk profile, the applicant will submit the final results of the phase II study A2201 expected by Q2 2016. In addition, 177 patients out of the target 236 patients (75% completed) have been randomized in the ongoing phase III comparative study (A2303). Enrolment is expected to be completed by end of August 2015 and the approval of ceritinib in the EU is not expected to impact completion of recruitment in this study. The final study report of study A2303 will allow a more comprehensive data package to be submitted in Q3 2018.

2.5.4. Conclusions on the clinical efficacy

In conclusion, the efficacy of ceritinib in the treatment of ALK-positive NSCLC is currently based on the results of three uncontrolled, open label studies (the extension phase of one phase I and two phase II clinical trials). The absence of direct comparative data with other agents represents an important limitation. Although more mature data has been provided, the absence of controlled studies dot not allow a better understanding of the benefit on PFS, the real effect on PROs and on OS. Despite these limitations, it is acknowledged that results in patients with prior ALK inhibitor treatment have a meaningful clinical value since there is an unmet medical need.

For ALK inhibitor naïve patients the evidence provided was insufficient to fulfil requirements for a conditional approval. .

The CHMP considers the following measures necessary to address the missing efficacy data in the context of a conditional MA:

- To submit the final clinical study report of phase II study A2201 by Q2 2016;

- To submit the final clinical study report of phase III study A2303 by Q3 2018.

2.6. Clinical safety

The safety profile provided with the initial submission was mainly based on study X2101, an open-label, uncontrolled study, which included a total of 304 patients (main safety set: 290 patients with ALK-positive NSCLC and 14 patients with non-NSCL tumours), 255 treated at the proposed dose of 750mg. Available data from the other phase I open-label study (X1101) was also provided (n=19), along with available data on SAEs and deaths for patients included in the on-going phase II studies with LDK378 (A2201 and A2203). The cut-off date used for most of the data analyses was 2 August 2013.

Patient exposure

In the initial submission, patients from the safety set treated with the proposed dose (n=255), the median duration of exposure was only 19.6 weeks, with almost half of patients having an exposure <18 week. A total of 133 (52.2%) patients in the 750 mg dose group required a dose reduction, all of them due to AEs. At least one dose interruption was observed in 155 patients (60.8%) in this group. AEs were the reason for dose interruption in 134 (86.5%) of these patients. These data suggest that the proposed dose of 750mg is not well-tolerated.

During the procedure, the Applicant provided an updated safety dataset. As a result, the safety dataset includes 525 patients exposed to ceritinib in the clinical studies (studies X2101, A2201, A2203 and X1101) and treated at the proposed dose of 750mg, as well as 62 patients treated with lower doses (from studies X2101 and X1101). Information on deaths and SAE reported to the Novartis safety database has also been provided. The duration of exposure in the pooled dataset is summarised in the table below.

Table 36: Duration of exposure to study drug in the pooled dataset (Safety set)

	X2101 Ceritinib 750 mg N=255	A2201 Ceritinib 750 mg N=140	A2203 Ceritinib 750 mg N=124	X1101 Ceritinib 750 mg N=6	All patients pool Ceritinib 750 mg N=525
Exposure category, weeks – n (%)					
<1	2 (0.8)	3 (2.1)	1 (0.8)	0	6 (1.1)
1 - <12	48 (18.8)	22 (15.7)	11 (8.9)	2 (33.3)	83 (15.8)
12 - <24	34 (13.3)	16 (11.4)	10 (8.1)	0	60 (11.4)
24 - <36	32 (12.5)	58 (41.4)	41 (33.1)	2 (33.3)	133 (25.3)
36 -<48	38 (14.9)	22 (15.7)	46 (37.1)	2 (33.3)	108 (20.6)
48 - <60	37 (14.5)	18 (12.9)	12 (9.7)	0	67 (12.8)
≥ 60	64 (25.1)	1 (0.7)	3 (2.4)	0	68 (13.0)
Duration of exposure (weeks)					
Mean (SD)	40.1 (26.63)	28.5 (15.17)	33.7 (14.01)	25.7 (17.57)	35.3 (21.89)
Median	38.7	28.1	34.9	34.6	33.0
Min-Max	0.4-106.1	0.3-60.1	0.4-70.3	3.0-39.7	0.3-106.1

A patient is counted in only one duration range.
Duration of exposure (weeks) = (Last dosing date – First dosing date + 1)/7.
Data cut-off dates for the individual studies: X2101: 14-Apr-2014, A2201: 26-Feb-2014, A2203: 27-Jun-2014, X1101: 02-Aug-2013,
Source: [D120 Appendix 5-Pool-Table 14.3-1.1]

Adverse events

The table below summarises the frequency of adverse events by grade and by study.

Table 37: Frequent adverse events (All patients pool, >5% of patients for all grades, or >2.0% of patients for grade 3-4) (Safety set)

	X2101 Ceritinib 750 mg N=255		A2201 Ceritinib 750 mg N=140		A2203 Ceritinib 750 mg N=124		X1101 Ceritinib 750 mg N=6		All patients Ceritinib 750 mg N=525	
	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Total	255 (100)	206 (80.8)	140 (100)	94 (67.1)	123 (99.2)	80 (64.5)	6 (100)	4 (66.7)	524 (99.8)	384 (73.1)
Diarrhoea	221 (86.7)	15 (5.9)	112 (80.0)	9 (6.4)	102 (82.3)	4 (3.2)	5 (83.3)	0	440 (83.8)	28 (5.3)
Nausea	211 (82.7)	15 (5.9)	111 (79.3)	9 (6.4)	92 (74.2)	4 (3.2)	5 (83.3)	0	419 (79.8)	28 (5.3)
Vomiting	157 (61.6)	12 (4.7)	87 (62.1)	6 (4.3)	83 (66.9)	6 (4.8)	3 (50.0)	0	330 (62.9)	24 (4.6)
Alanine Aminotransferase Increased	112 (43.9)	76 (29.8)	56 (40.0)	19 (13.6)	50 (40.3)	19 (15.3)	1 (16.7)	1 (16.7)	219 (41.7)	115 (21.9)
Decreased Appetite	95 (37.3)	4 (1.6)	56 (40.0)	5 (3.6)	61 (49.2)	2 (1.6)	4 (66.7)	0	216 (41.1)	11 (2.1)
Fatigue	110 (43.1)	13 (5.1)	46 (32.9)	9 (6.4)	40 (32.3)	7 (5.6)	3 (50.0)	0	199 (37.9)	29 (5.5)
Abdominal Pain	98 (38.4)	3 (1.2)	43 (30.7)	2 (1.4)	41 (33.1)	0	2 (33.3)	0	184 (35.0)	5 (1.0)
Aspartate Aminotransferase Increased	83 (32.5)	25 (9.8)	42 (30.0)	7 (5.0)	38 (30.6)	9 (7.3)	1 (16.7)	0	164 (31.2)	41 (7.8)
Constipation	79 (31.0)	0	33 (23.6)	3 (2.1)	19 (15.3)	0	1 (16.7)	0	132 (25.1)	3 (0.6)
Weight Decreased	46 (18.0)	5 (2.0)	45 (32.1)	6 (4.3)	36 (29.0)	1 (0.8)	0	0	127 (24.2)	12 (2.3)
Cough	74 (29.0)	0	26 (18.6)	0	21 (16.9)	0	0	0	121 (23.0)	0
Dyspnoea	63 (24.7)	11 (4.3)	25 (17.9)	7 (5.0)	17 (13.7)	1 (0.8)	0	0	105 (20.0)	19 (3.6)
Blood Creatinine Increased	43 (16.9)	0	20 (14.3)	0	26 (21.0)	0	4 (66.7)	0	93 (17.7)	0
Blood Alkaline Phosphatase Increased	45 (17.6)	13 (5.1)	21 (15.0)	4 (2.9)	25 (20.2)	8 (6.5)	1 (16.7)	0	92 (17.5)	25 (4.8)
Asthenia	50 (19.6)	2 (0.8)	22 (15.7)	6 (4.3)	18 (14.5)	2 (1.6)	0	0	90 (17.1)	10 (1.9)
Abdominal Pain Upper	60 (23.5)	2 (0.8)	16 (11.4)	1 (0.7)	11 (8.9)	0	1 (16.7)	0	88 (16.8)	3 (0.6)
Back Pain	50 (19.6)	1 (0.4)	18 (12.9)	1 (0.7)	19 (15.3)	1 (0.8)	0	0	87 (16.6)	3 (0.6)
Pyrexia	42 (16.5)	0	29 (20.7)	4 (2.9)	13 (10.5)	1 (0.8)	2 (33.3)	0	86 (16.4)	5 (1.0)
Headache	51 (20.0)	4 (1.6)	20 (14.3)	0	11 (8.9)	1 (0.8)	0	0	82 (15.6)	5 (1.0)
Rash	34 (13.3)	0	20 (14.3)	0	19 (15.3)	1 (0.8)	1 (16.7)	0	74 (14.1)	1 (0.2)
Gamma-Glutamyltransferase Increased	14 (5.5)	7 (2.7)	25 (17.9)	17 (12.1)	33 (26.6)	23 (18.5)	0	0	72 (13.7)	47 (9.0)

	X2101 Ceritinib 750 mg N=255		A2201 Ceritinib 750 mg N=140		A2203 Ceritinib 750 mg N=124		X1101 Ceritinib 750 mg N=6		All patients Ceritinib 750 mg N=525	
	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Non-Cardiac Chest Pain	26 (10.2)	2 (0.8)	23 (16.4)	2 (1.4)	16 (12.9)	1 (0.8)	0	0	65 (12.4)	5 (1.0)
Anaemia	31 (12.2)	13 (5.1)	20 (14.3)	3 (2.1)	8 (6.5)	1 (0.8)	1 (16.7)	0	60 (11.4)	17 (3.2)
Insomnia	39 (15.3)	0	12 (8.6)	0	7 (5.6)	0	0	0	58 (11.0)	0
Musculoskeletal Pain	37 (14.5)	0	8 (5.7)	0	9 (7.3)	0	0	0	54 (10.3)	0
Dizziness	31 (12.2)	0	8 (5.7)	0	11 (8.9)	0	0	0	50 (9.5)	0
Dyspepsia	32 (12.5)	1 (0.4)	7 (5.0)	0	10 (8.1)	0	0	0	49 (9.3)	1 (0.2)
Hypokalaemia	29 (11.4)	11 (4.3)	8 (5.7)	4 (2.9)	11 (8.9)	5 (4.0)	0	0	48 (9.1)	20 (3.8)
Arthralgia	26 (10.2)	0	11 (7.9)	0	9 (7.3)	0	0	0	46 (8.8)	0
Oedema Peripheral	28 (11.0)	0	13 (9.3)	0	4 (3.2)	0	0	0	45 (8.6)	0
Upper Respiratory Tract Infection	25 (9.8)	0	11 (7.9)	0	9 (7.3)	0	0	0	45 (8.6)	0
Pneumonia	25 (9.8)	12 (4.7)	9 (6.4)	5 (3.6)	8 (6.5)	4 (3.2)	0	0	42 (8.0)	21 (4.0)
Hyperglycaemia	21 (8.2)	15 (5.9)	6 (4.3)	3 (2.1)	13 (10.5)	7 (5.6)	1 (16.7)	1 (16.7)	41 (7.8)	26 (5.0)
Musculoskeletal Chest Pain	27 (10.6)	0	7 (5.0)	0	3 (2.4)	0	0	0	37 (7.0)	0
Nasopharyngitis	19 (7.5)	0	6 (4.3)	0	10 (8.1)	0	0	0	35 (6.7)	0
Pruritus	17 (6.7)	1 (0.4)	6 (4.3)	0	12 (9.7)	0	0	0	35 (6.7)	1 (0.2)
Dry Skin	17 (6.7)	0	9 (6.4)	0	7 (5.6)	0	1 (16.7)	0	34 (6.5)	0
Electrocardiogram Qt Prolonged	10 (3.9)	3 (1.2)	9 (6.4)	0	15 (12.1)	1 (0.8)	0	0	34 (6.5)	4 (0.8)
Hypomagnesaemia	23 (9.0)	0	7 (5.0)	0	3 (2.4)	1 (0.8)	1 (16.7)	0	34 (6.5)	1 (0.2)
Productive Cough	24 (9.4)	0	3 (2.1)	0	7 (5.6)	0	0	0	34 (6.5)	0
Dysgeusia	18 (7.1)	0	10 (7.1)	0	5 (4.0)	0	0	0	33 (6.3)	0
Anxiety	20 (7.8)	2 (0.8)	8 (5.7)	0	2 (1.6)	0	0	0	30 (5.7)	2 (0.4)
Stomatitis	13 (5.1)	0	10 (7.1)	0	7 (5.6)	1 (0.8)	0	0	30 (5.7)	1 (0.2)
Hypophosphataemia	16 (6.3)	8 (3.1)	6 (4.3)	2 (1.4)	5 (4.0)	1 (0.8)	1 (16.7)	0	28 (5.3)	11 (2.1)
Pain In Extremity	19 (7.5)	0	7 (5.0)	0	2 (1.6)	0	0	0	28 (5.3)	0
Urinary Tract Infection	18 (7.1)	2 (0.8)	4 (2.9)	0	6 (4.8)	0	0	0	28 (5.3)	2 (0.4)
Lipase Increased	24 (9.4)	16 (6.3)	0	0	0	0	0	0	24 (4.6)	16 (3.0)
Hyponatraemia	19 (7.5)	11 (4.3)	0	0	1 (0.7)	0	4 (3.2)	3 (2.4)	24 (4.6)	14 (2.7)

Source: [D120-Appendix 5-Pool-Table Table 14.3.1-1.4]

The most frequently observed SOCs wherein at least 50% of all patients reported one or more events were: gastrointestinal disorders (97.9%), investigations (73.5%), general disorders and administrative site conditions (68.0%), metabolism and nutrition disorders (59.6%) and respiratory, thoracic and mediastinal disorders (50.3).

The AEs suspected to be study drug related (all grades, by PT) reported in ≥ 25% of the patients were: GI toxicity events (diarrhoea 81.7%, nausea 77.7%, vomiting 60.0%) and increased transaminases (ALT 39.2%, AST 29.1%); decreased appetite (34.9%), abdominal pain (30.9%), fatigue (29.3%) and constipation (25.1%) were also reported in ⩾25% of patients. The most frequent (>3% of patients) grade 3-4 AEs assessed as related to study drug were ALT increased (20.2%), AST increased (6.9%), GGT increased (6.9%) diarrhoea (5.0%), ALP increased (4.4%), nausea (4.4%), vomiting (4.0%), and fatigue (3.4%).

Findings across the different dose ranges (50-750mg) in the safety set followed the same trend observed for the 750mg group (data not shown).

Dose reduction and dose interruptions

In Studies X2101, A2201 and A2203, a maximum of three dose reductions were allowed for each patient, after which the patient was discontinued from the study drug. Dose reductions permitted were 750 mg to 600 mg, 600 mg to 450 mg and 450 mg to 300 mg. In Study X1101, dose reductions were allowed for each patient until a minimum dose of 150 mg was reached after which the patient was discontinued from the study. For each patient, once a dose level reduction occurred, re-escalation to the higher dose was not allowed during subsequent treatment cycles. The table below summarizes doses reductions observed in the safety dataset.

Table 38: Dose reductions for patients in the 750 mg dose group in Studies X2101, A2201, A2203 and X1101

	X2101	A2201	A2203	X1101	All patients
	Ceritinib 750 mg	Ceritinib 750 mg	Ceritinib 750 mg	Ceritinib 750 mg	Ceritinib 750 mg
	N=255	N=140	N=124	N=6	N=525
	n (%)	n (%)	n (%)	n (%)	n (%)
Number of patients					
Without dose reduction	99 (38.8)	70 (50.0)	51 (41.1)	2 (33.3)	222 (42.3)
With at least one dose reduction	156 (61.2)	70 (50.0)	73 (58.9)	4 (66.7)	303 (57.7)
Only one dose reduction	90 (35.3)	32 (22.9)	29 (23.4)	3 (50.0)	154 (29.3)
More than one dose reduction	66 (25.9)	38 (27.1)	44 (35.5)	1 (16.7)	149 (28.4)
2 dose reductions	49 (19.2)	26 (18.6)	30 (24.2)	1 (16.7)	106 (20.2)
3 dose reductions	16 (6.3)	9 (6.4)	12 (9.7)	0	37 (7.0)
>3 dose reductions	1 (0.4)	3 (2.1)	2 (1.6)	0	6 (1.1)
Number of patients with at least one dose reduction by reason #					
As per protocol	2 (1.3)	8 (11.4)	4 (5.5)	0	14 (4.6)
Adverse event	153 (98.1)	60 (85.7)	66 (90.4)	4 (100.0)	283 (93.4)
Dosing error	3 (1.9)	7 (10.0)	4 (5.5)	0	14 (4.6)
Dispensing error	1	0	0	0	1 (0.3)
Physician decision	0	6 (8.6)	6 (8.2)	0	12 (4.0)
Subject/Guardian decision	0	6 (8.6)	6 (8.2)	0	12 (4.0)

[a] Dispensing error reported due to the cessation of drug supply of 50 mg capsules (drug dose level was 450 mg instead of 500 mg
A patient with multiple occurrences of a reason for dose reduction is only counted once in that category.
A patient with multiple reasons for dose reduction is only counted once in the total row.
The denominator to calculate percentages is the number of patients with at least one dose reduction
Source: [Appendix 1- X2101 -Table 14.3-1.3b], [Study A2201-Table 14.3-1.3a], [Study A2203–Table 14.3-1.3a] [Study X1101-Table 14.3-1.3a]

Adverse drug reactions

ADRs were screened and identified based on a number of factors such as investigator's causality (e.g., related AEs/SAEs), frequency and consistency of reporting, biological plausibility, class effects, and dechallenge and rechallenge information. Once the ADRs were selected, their frequency calculation was made from the totality of the events reported for each AE. The ADRs and respective frequencies are summarised in the table below.

Table 39: ADRs in patients treated with Ceritinib at a dose of 750 mg

Primary system organ class Preferred term	**Ceritinib** **N=525, n (%)**
Blood and lymphatic system disorders	
Anaemia	60 (11.4)
Metabolism and nutrition disorders	
Decreased appetite	216 (41.1)
Hyperglycaemia	41 (7.8)
Hypophosphataemia	28 (5.3)
Eye disorders	
Vision disorder[a]	39 (7.4)
Cardiac disorders	
Pericarditis[b]	31 (5.9)
Bradycardia[c]	10 (1.9)
Respiratory, thoracic and mediastinal disorders	
Pneumonitis[d]	17 (3.2)
Gastrointestinal disorders	
Diarrhoea	440 (83.8)
Nausea	419 (79.8)
Vomiting	330 (62.9)
Abdominal pain[e]	253 (48.2)
Constipation	132 (25.1)
Oesophageal disorder[f]	79 (15.0)
Hepatobiliary disorders	
Abnormal liver function tests[g]	11 (2.1)
Hepatotoxicity[h]	3 (0.6)
Skin and subcutaneous tissue disorders	
Rash[i]	100 (19.0)
Renal and urinary disorders	
Renal failure[j]	11 (2.1)
Renal impairment[k]	7 (1.3)
General disorders and administration site conditions	
Fatigue[l]	265 (50.5)
Investigations	
Liver laboratory test abnormalities[m]	265 (50.5)
Blood creatinine increased	93 (17.7)
Electrocardiogram QT prolonged	34 (6.5)
Lipase increased	24 (4.6)
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)
[cd] Pneumonitis (interstitial lung disease, pneumonitis)
[de] Abdominal pain (abdominal pain, abdominal pain upper, abdominal discomfort, epigastric discomfort)
[ef] Oesophageal disorder (dyspepsia, gastro-oesophageal reflux disease, dysphagia)
[g] Abnormal liver function test (hepatic function abnormal, hyperbilirubinaemia)
[h] Hepatotoxicity (drug-induced liver injury, hepatitis cholestatic, hepatocellular injury, hepatotoxicity)
[fi] Rash (rash, dermatitis acneiform, rash maculopapular)
[gj] Renal failure (renal failure acute, renal failure)
[hk] Renal impairment (azotaemia, renal impairment)
[il] Fatigue (fatigue, asthenia)
[m] 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)

Serious adverse event / deaths / other significant events

An overview of deaths and other serious or clinically relevant AEs in the pooled dataset is provided in Table 40.

SAEs (irrespective of causality) were reported in 38.3% of patients. The majority of these patients had SAEs associated with the underlying disease, including events of disease progression and deteriorating pulmonary status/respiratory complications.

Of the 68 deaths reported on-treatment in the pooled dataset, 49 deaths were directly attributed to study indication. Of the 19 patients with cause of death listed as "Other", 15 patients died from co-morbidities and/or conditions associated with progression of the underlying malignancy, and were assessed as not related to study drug by the Investigator. For one patient, the cause of death was reported as unknown; prior to the death, the patient experienced disease progression. The remaining 3 deaths (2 in Study X2101 and 1 in Study A2201) were considered related to study drug by the Investigator. In Study X2101, one death was due to ILD and the second was due to multi-organ failure that occurred in the context of infection and ischemic hepatitis. The third death reported in Study A2201 was due to pneumonia.

Table 40: Overview of deaths and other serious or clinically relevant adverse events in the pooled dataset (Safety set)

	X2101 N=255	A2201 N=140	A2203 N=124	X1101 N=6	All patients N=525
All deaths [a]	83 (32.5)	**39 (27.9)**	**13 (10.5)**	**0**	**135 (25.7)**
On-treatment deaths [b]	41 (16.1)	17 (12.1)	10 (8.1)	0	68 (13.0)
Study indication	26 (10.2)	15 (10.7)	8 (6.5)	0	49 (9.3)
Other	15 (5.9)	2 (1.4)	2 (1.6)	0	19 (3.6)
Serious adverse events	**121 (47.5)**	**51 (36.4)**	**27 (21.8)**	**2 (33.3)**	**201 (38.3)**
Suspected to be drug related	32 (12.5)	25 (17.9)	10 (8.1)	2 (33.3)	69 (13.1)
AEs leading to discontinuation	**26 (10.2)**	**10 (7.1)**	**9 (7.3)**	**1 (16.7)**	**46 (8.8)**
AEs requiring dose adjustment or interruption	**197 (77.3)**	**101 (72.1)**	**90 (72.6)**	**5 (83.3)**	**393 (74.9)**
AEs requiring additional therapy	**254 (99.6)**	**130 (92.9)**	**117 (94.4)**	**6 (100.0)**	**507 (96.6)**
AEs of special interest					
Hepatotoxicity	126 (49.4)	73 (52.1)	75 (60.5)	5 (83.3)	279 (53.1)
ILD/pneumonitis	12 (4.7)	3 (2.1)	2 (1.6)	1 (16.7)	18 (3.4)
QT prolongation	16 (6.3)	9 (6.4)	15 (12.1)	0	40 (7.6)
Hyperglycemia	32 (12.5)	11 (7.9)	15 (12.1)	2 (33.3)	60 (11.4)
Bradycardia	21 (8.2)	10 (7.1)	17 (13.7)	0	48 (9.1)
GI toxicity [c]	246 (96.5)	134 (95.7)	118 (95.2)	6 (100)	504 (96.0)

Categories are not mutually exclusive. Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.
[a] All deaths, including those > 30 days after last dose of study drug.
[b] Deaths occurring >30 days after last dose of study drug are not included.
[c] GI toxicity: nausea, diarrhoea, vomiting
Only AEs occurring during treatment or within 30 days of the last dose of study drug are reported.
Source: [D120 Appendix 5-Pool-Table 14.3.1-1.21], [RMP V2 Annex 12-Table 8-16p], [D120 Appendix 5-Pool-Table 14.3.1-1.5]

Adverse events of special interest (AESIs)

Adverse events of special interest have been identified based on emerging clinical information from the ongoing clinical studies. According to the applicant, the AESIs for ceritinib are hepatotoxicity, interstitial lung disease (ILD)/pneumonitis, QT prolongation, bradycardia, hyperglycaemia, and GI toxicity.

Hepatotoxicity

Hepatotoxicity AEs (primarily ALT increased and AST increased) were reported in 53.1% of patients, with grade 3-4 AEs reported in 31.0% of patients. The event required dose adjustment or interruption in 34.9% of patients and led to discontinuation in 0.8% of patients. The event was serious in 2.3% of patients. There were no deaths due to a hepatotoxicity AE.

Concurrent elevations of ALT 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.

Table 41: Hepatotoxicity events in the pooled dataset (Safety set)

Hepatotoxicity AEs	X2101 N=255 n (%)	A2201 N=140 n (%)	A2203 N=124 n (%)	X1101 N=6 n (%)	All patients N=525 n (%)
All AEs	126 (49.4)	73 (52.1)	75 (60.5)	5 (83.3)	279 (53.1)
Alanine Aminotransferase Increased	112 (43.9)	56 (40.0)	50 (40.3)	1 (16.7)	219 (41.7)
Aspartate Aminotransferase Increased	83 (32.5)	42 (30.0)	38 (30.6)	1 (16.7)	164 (31.2)
Gamma-Glutamyltransferase Increased	14 (5.5)	25 (17.9)	33 (26.6)	0	72 (13.7)
Blood Bilirubin Increased	9 (3.5)	0	5 (4.0)	0	14 (2.7)
Transaminases Increased	9 (3.5)	0	2 (1.6)	0	11 (2.1)
Hepatic Function Abnormal	0	4 (2.9)	4 (3.2)	2 (33.3)	10 (1.9)
Hepatic Enzyme Increased	0	3 (2.1)	4 (3.2)	1 (16.7)	8 (1.5)
Liver Function Test Abnormal	1 (0.4)	2 (1.4)	3 (2.4)	0	6 (1.1)
Bilirubin Conjugated Increased	3 (1.2)	0	0	0	3 (0.6)
Ascites	2 (0.8)	0	0	0	2 (0.4)
Drug-Induced Liver Injury	1 (0.4)	0	0	1 (16.7)	2 (0.4)
Hepatitis	0	0	2 (1.6)	0	2 (0.4)
Ammonia Increased	0	0	1 (0.8)	0	1 (0.2)
Asterixis	0	1 (0.7)	0	0	1 (0.2)
Hepatic Encephalopathy	0	1 (0.7)	0	0	1 (0.2)
Hepatitis Cholestatic	1 (0.4)	0	0	0	1 (0.2)
Hepatocellular Injury	0	1 (0.7)	0	0	1 (0.2)
Hepatotoxicity	0	1 (0.7)	0	0	1 (0.2)
Hyperbilirubinaemia	1 (0.4)	0	0	0	1 (0.2)
Ischaemic Hepatitis	1 (0.4)	0	0	0	1 (0.2)
Jaundice	1 (0.4)	0	0	0	1 (0.2)
CTC grade 3/4 AEs	82 (32.2)	35 (25.0)	43 (34.7)	3 (50.0)	163 (31.0)
AEs suspected to be drug related	117 (45.9)	68 (48.6)	66 (53.2)	5 (83.3)	256 (48.8)
SAEs	5 (2.0)	4 (2.9)	1 (0.8)	2 (33.3)	12 (2.3)
Alanine Aminotransferase Increased	4 (1.6)	1 (0.7)	0	0	5 (1.0)
Aspartate Aminotransferase Increased	2 (0.8)	1 (0.7)	0	0	3 (0.6)
Drug-Induced Liver Injury	1 (0.4)	0	0	1 (16.7)	2 (0.4)
Hepatic Function Abnormal	0	1 (0.7)	0	1 (16.7)	2 (0.4)
Hepatic Encephalopathy	0	1 (0.7)	0	0	1 (0.2)
Hepatitis	0	0	1 (0.8)	0	1 (0.2)
Hepatitis Cholestatic	1 (0.4)	0	0	0	1 (0.2)
Hepatocellular Injury	0	1 (0.7)	0	0	1 (0.2)
AEs leading to discontinuation	1 (0.4)	1 (0.7)	1 (0.8)	1 (16.7)	4 (0.8)
AEs requiring dose adjustment/interruption	85 (33.3)	45 (32.1)	50 (40.3)	3 (50.0)	183 (34.9)
Deaths	0	0	0	0	0

Source: [D120 Appendix 5-Pool-14.3.1-1.22a], [RMP V2 Annex 12 RMP Table 8-1p2]

ILD / pneumonitis

ILD/pneumonitis AEs were reported in 3.4% of patients, with grade 3-4 AEs reported in 1.9% of patients. The event required dose adjustment or interruption in 2.1% of patients and led to discontinuation in 1.1% of patients. The event was serious in 2.9% of patients. Fifteen patients in the pooled dataset had an ILD/pneumonitis SAE, one of them with an outcome of death.

Table 42: ILD / pneumonitis events in the pooled dataset (Safety set)

ILD/pneumonitis AEs	X2101 N=255 n (%)	A2201 N=140 n (%)	A2203 N=124 n (%)	X1101 N=6 n (%)	All patients N=525 n (%)
All AEs	12 (4.7)	3 (2.1)	2 (1.6)	1 (16.7)	18 (3.4)
Pneumonitis	9 (3.5)	3 (2.1)	1 (0.8)	1 (16.7)	14 (2.7)
ILD	2 (0.8)	0	1 (0.8)	0	3 (0.6)
Lung Infiltration	1 (0.4)	0	0	0	1 (0.2)
CTC grade 3/4 AEs	9 (3.5)	1 (0.7)	0	0	10 (1.9)
AEs suspected to be drug related	11 (4.3)	2 (1.4)	2 (1.6)	1 (16.7)	16 (3.0)
SAEs	12 (4.7)	3 (2.1)	0	0	15 (2.9)
Pneumonitis	9 (3.5)	3 (2.1)	0	0	12 (2.3)
Interstitial Lung Disease	2 (0.8)	0	0	0	2 (0.4)
Lung Infiltration	1 (0.4)	0	0	0	1 (0.2)
AEs leading to discontinuation	3 (1.2)	2 (1.4)	1 (0.8)	0	6 (1.1)
AEs requiring dose adjustment/interruption	8 (3.1)	1 (0.7)	1 (0.8)	1 (16.7)	11 (2.1)
Deaths	1 (0.4)	0	0	0	1 (0.2)

Source: [D120 Appendix 5-Pool-14.3.1-1.22a], [RMP V2 Annex 12 RMP Table 8-3p2

QT interval prolongation

QT prolongation AEs (primarily ECG QT prolonged) were reported in 7.6% of patients, with grade 3-4 AEs reported in 1.5% of patients. The event required dose adjustment or interruption in 1.0% of patients and led to discontinuation in 0.2% of patients. The event was serious in 0.4% of patients.

Table 43: QT prolongation events in the pooled dataset (Safety set)

QT prolongation AEs	X2101 N=255 n (%)	A2201 N=140 n (%)	A2203 N=124 n (%)	X1101 N=6 n (%)	All patients N=525 n (%)
All AEs	16 (6.3)	9 (6.4)	15 (12.1)	0	40 (7.6)
Electrocardiogram QT Prolonged	10 (3.9)	9 (6.4)	15 (12.1)	0	34 (6.5)
Syncope	4 (1.6)	0	0	0	4 (0.8)
Cardio-Respiratory Arrest	1 (0.4)	0	0	0	1 (0.2)
Loss Of Consciousness	1 (0.4)	0	0	0	1 (0.2)
Ventricular Arrhythmia	0	0	1 (0.8)	0	1 (0.2)
CTC grade 3/4 AEs	7 (2.7)	0	1 (0.8)	0	8 (1.5)
Electrocardiogram QT Prolonged	3 (1.2)	0	1 (0.8)	0	4 (0.8)
Syncope	3 (1.2)	0	0	0	3 (0.6)
Cardio-Respiratory Arrest	1 (0.4)	0	0	0	1 (0.2)
AEs suspected to be drug related	9 (3.5)	8 (5.7)	15 (12.1)	0	32 (6.1)
Electrocardiogram QT Prolonged	9 (3.5)	8 (5.7)	15 (12.1)	0	32 (6.1)
Ventricular Arrhythmia	0	0	1 (0.8)	0	1 (0.2)
SAEs	2 (0.8)	0	0	0	2 (0.4)
Cardio-Respiratory Arrest	1 (0.4)	0	0	0	1 (0.2)
Loss Of Consciousness	1 (0.4)	0	0	0	1 (0.2)
AEs leading to discontinuation	0	0	1 (0.8)	0	1 (0.2)
Electrocardiogram QT Prolonged	0	0	1 (0.8)	0	1 (0.2)
AEs requiring dose adjustment/interruption	4 (1.6)	0	1 (0.8)	0	5 (1.0)
Electrocardiogram QT Prolonged	4 (1.6)	0	1 (0.8)	0	5 (1.0)
Deaths	0	0	0	0	0

Source: [RMP V2 Annex 12-RMP Table 8-2p], [RMP V2 Annex 12-RMP Table 8-2p2]

Bradycardia

Bradycardia and sinus bradycardia AEs were reported in 1.0% of patients each (all grade 1), with 1.9% of patients having either a bradycardia and/or a sinus bradycardia event. No bradycardia SAEs or deaths due to bradycardia were reported.

Table 44: Bradycardia-associated events in the pooled dataset (Safety set)

Bradycardia AEs	X2101 N=255 n (%)	A2201 N=140 n (%)	A2203 N=124 n (%)	X1101 N=6 n (%)	All patients N=525 n (%)
All AEs	21 (8.2)	10 (7.1)	17 (13.7)	0	48 (9.1)
Electrocardiogram QT Prolonged	10 (3.9)	9 (6.4)	15 (12.1)	0	34 (6.5)
Bradycardia	4 (1.6)	1 (0.7)	0	0	5 (1.0)
Sinus Bradycardia	4 (1.6)	0	1 (0.8)	0	5 (1.0)
Syncope	4 (1.6)	0	0	0	4 (0.8)
Atrioventricular Block	0	0	1 (0.8)	0	1 (0.2)
Bundle Branch Block Right	0	1 (0.7)	0	0	1 (0.2)
CTC grade 3/4 AEs	6 (2.4)	0	1 (0.8)	0	7 (1.3)
Electrocardiogram QT Prolonged	3 (1.2)	0	1 (0.8)	0	4 (0.8)
Syncope	3 (1.2)	0	0	0	3 (0.6)
AEs suspected to be drug related	13 (5.1)	9 (6.4)	16 (12.9)	0	38 (7.2)
Electrocardiogram QT Prolonged	9 (3.5)	8 (5.7)	15 (12.1)	0	32 (6.1)
Bradycardia	2 (0.8)	1 (0.7)	0	0	3 (0.6)
Sinus Bradycardia	3 (1.2)	0	0	0	3 (0.6)
Atrioventricular Block	0	0	1 (0.8)	0	1 (0.2)
Bundle Branch Block Right	0	1 (0.7)	0	0	1 (0.2)
SAEs	0	0	0	0	0
AEs leading to discontinuation	0	0	1 (0.8)	0	1 (0.2)
Electrocardiogram QT Prolonged	0	0	1 (0.8)	0	1 (0.2)
AEs requiring dose adjustment/interruption	4 (1.6)	0	1 (0.8)	0	5 (1.0)
Electrocardiogram QT Prolonged	4 (1.6)	0	1 (0.8)	0	5 (1.0)
Deaths	0	0	0	0	0

Source: [RMP V2 Annex 12-RMP Table 8-8p], [RMP V2 Annex 12-RMP Table 8-8p2]

Hyperglycaemia

Hyperglycaemia AEs (primarily hyperglycaemia and diabetes mellitus) were reported in 11.4% of patients with grade 3-4 AEs in 6.1% (5.0% for hyperglycaemia). The event required dose adjustment or interruption in 2.1% of patients and led to discontinuation in 0.2%. The event was serious in 2.3% of patients. There were no deaths due to a hyperglycaemia AE.

Table 45: Hyperglycaemia events in the pooled dataset (Safety set)

Hyperglycemia AEs	X2101 N=255 n (%)	A2201 N=140 n (%)	A2203 N=124 n (%)	X1101 N=6 n (%)	All patients N=525 n (%)
All AEs	32 (12.5)	11 (7.9)	15 (12.1)	2 (33.3)	60 (11.4)
Hyperglycaemia	21 (8.2)	6 (4.3)	13 (10.5)	1 (16.7)	41 (7.8)
Diabetes Mellitus	10 (3.9)	3 (2.1)	3 (2.4)	1 (16.7)	17 (3.2)
Blood Glucose Increased	2 (0.8)	1 (0.7)	0	0	3 (0.6)
Diabetic Ketoacidosis	1 (0.4)	0	1 (0.8)	0	2 (0.4)
Blood Glucose Abnormal	1 (0.4)	0	0	0	1 (0.2)
Glucose Tolerance Impaired	1 (0.4)	0	0	0	1 (0.2)
Type 2 Diabetes Mellitus		1 (0.7)	0	0	1 (0.2)
CTC grade 3/4 AEs	17 (6.7)	5 (3.6)	9 (7.3)	1 (16.7)	32 (6.1)
AEs suspected to be drug related	7 (2.7)	2 (1.4)	4 (3.2)	1 (16.7)	14 (2.7)
SAEs	7 (2.7)	0	5 (4.0)	0	12 (2.3)
Hyperglycaemia	6 (2.4)	0	3 (2.4)	0	9 (1.7)
Diabetic Ketoacidosis	1 (0.4)	0	1 (0.8)	0	2 (0.4)
Diabetes Mellitus	0	0	1 (0.8)	0	1 (0.2)
AEs leading to discontinuation	0	0	1 (0.8)	0	1 (0.2)
AEs requiring dose adjustment/interruption	7 (2.7)	0	3 (2.4)	1 (16.7)	11 (2.1)
Deaths	0	0	0	0	0

Source: [D120 Appendix 5-Pool-14.3.1-1.22a]

GI toxicity

GI AEs (i.e., diarrhoea, nausea, vomiting) were reported in 96.0% patients and were suspected to be related to study drug by the Investigator in 94.9%. Most of the AEs were grade 1-2; grade 3-4 AEs were reported in 12.2% of patients. The event required dose adjustment or interruption in 33.0% of patients. The proportion of patients with SAEs was low (3.6%) the AEs led to discontinuation in 0.6% of patients. GI AEs were managed primarily with concomitant medications (reported in 84.8% of patients) and/or with dose adjustment or interruption of study drug (reported in 33.0% of patients).

Table 46: GI adverse events in the pooled dataset (Safety set)

GI AEs	X2101 N=255 n (%)	A2201 N=140 n (%)	A2203 N=124 n (%)	X1101 N=6 n (%)	All patients N=525 n (%)
All AEs	246 (96.5)	134 (95.7)	118 (95.2)	6 (100.0)	504 (96.0)
Diarrhea	221 (86.7)	112 (80.0)	102 (82.3)	5 (83.3)	440 (83.8)
Nausea	211 (82.7)	111 (79.3)	92 (74.2)	5 (83.3)	419 (79.8)
Vomiting	157 (61.6)	87 (62.1)	83 (66.9)	3 (50.0)	330 (62.9)
CTC grade 3/4 AEs	34 (13.3)	18 (12.9)	12 (9.7)	0	64 (12.2)
AEs suspected to be drug related	214 (94.5)	133 (95.0)	118 (95.2)	6 (100.0)	498 (94.9)
SAEs	11 (4.3)	5 (3.6)	3 (2.4)	0	19 (3.6)
Diarrhea	3 (1.2)	0	1 (0.8)	0	4 (0.8)
Nausea	6 (2.4)	3 (2.1)	1 (0.8)	0	10 (1.9)
Vomiting	3 (1.2)	3 (2.1)	1 (0.8)	0	7 (1.3)
AEs leading to discontinuation	1 (0.4)	2 (1.4)	0	0	3 (0.6)
AEs requiring dose adjustment/interruption	90 (35.3)	52 (37.1)	30 (24.2)	1 (16.7)	173 (33.0)
Deaths	0	0	0	0	0

Source: [D120 Appendix 7-Table D120Q99-2.1p], [D120 Appendix 7-Table D120Q99-2.2p]

Laboratory findings

Lymphocytes (hypo)

Baseline abnormalities in lymphocytes (hypo) were common. At baseline, 60.8% (319/525) patients had grade 0, 16.2% (85/525) patients had grade 1, 17.0% (89/525) patients had grade 2, 5.5% (29/525) patients had grade 3, and 0.4% (2/525) had grade 4. 275/518 patients (53.1%) had new or worsened post-baseline decreases (any grade) in lymphocytes. New or worsened grade 3 occurrences were reported for 89/489 patients (18.2%). New or worsened grade 4 occurrences were reported for 16/516 patients (3.1%). AEs associated with decreased lymphocytes were reported in <2% of patients. Lymphocyte count decreased was reported in 1.7% of patients (0.4% grade 3-4), and lymphopenia in 0.4% of patients (all grade 1-2). None of the patients had a serious event, 0.2% had dose adjustment or interruption, and none had an event that led to discontinuation.

White blood cells (WBCs)

Most patients had grade 0 at baseline (89.3%, 469/525 patients). 194/518 patients (37.5%) had new or worsened post-baseline decreases (any grade) in WBC. New or worsened grade 3 occurrences were reported for 7/518 patients (1.4%). New or worsened grade 4 occurrences were reported for 1/518 patient (0.2%). AEs associated with leukopenia were reported in 10.7% of patients, with 3.4% of patients reporting a grade 3-4 AE. The event was considered related to study drug for 7.8% of patients, was serious in 0.8% of patients, and 2.3% required dose adjustment or interruption. None of these events led to discontinuation.

Neutrophils

Most patients had grade 0 at baseline (96.0%, 504/525 patients). 129/518 patients (24.9%) had new or worsened post-baseline decreases (any grade) in neutrophils. New or worsened grade 3 occurrences were reported for 6/517 patients (1.2%). New or worsened grade 4 occurrences were reported for 7/518 patients (1.4%).Febrile neutropenia was reported as an AE in 0.4% of patients, and neutropenic sepsis in 0.2% of patients (all were grade 3-4, and all were serious). None of the events were considered related to study drug, and none required any action taken with study drug.

Hemoglobin

Most patients had grade 0 (47.0%, 247/525 patients) or grade 1 (43.8%, 230/525 patients) at baseline. 220/518 patients (42.5%) had new or worsened post-baseline decreases (any grade) in haemoglobin. New or worsened grade 3 occurrences were reported for 24/514 patients (4.7%). No new or worsened grade 4 occurrences were reported. AEs associated with decreased haemoglobin (including PTs of decreased haemoglobin and anaemia) were reported in 11.6% of patients, with 3.4% of patients reporting a grade 3-4 AE. None of these events led to discontinuation, and 1.1% of patients had an event that required dose adjustment/interruption.

Platelet counts

Most patients had grade 0 values at baseline (94.1%, 494 patients). 69/517 patients (13.3%) had new or worsened post-baseline decreases (any grade) in platelet counts. New or worsened grade 3 occurrences were reported for 6/517 patients (1.2%). New or worsened grade 4 occurrences were reported for 5/517 patients (1.0%). AEs associated with thrombocytopenia (including PTs of platelet count decreased and thrombocytopenia) were reported in 2.9% of patients, with 1.1% of patients reporting grade 3- 4 AE. None of these events led to discontinuation; one patient (0.2%) had a dose interruption.

In the pooled dataset, the most frequent post-baseline newly occurred or worsened grade 3-4 chemistry abnormalities were seen for ALT, AST, ALP, and glucose.

ALT

At baseline, 84.4% (443/525) patients had a grade 0 value; 14.7% (77/525) had grade 1,and 1.0% (5/525) had grade 2 ALT. New or worsened grade 3 or 4 increased ALT was seen in 23.1% (120/519) and 1.9% (10/519) patients, respectively.

AST

At baseline, 85.9% (451/525) patients had a grade 0 value; 13.7% (72/525) had grade 1,and 0.4% (2/525) had grade 2 AST. New or worsened grade 3 or 4 increased AST was seen in10.6% (55/519) and 1.7% (9/519) patients, respectively.

ALP

At baseline, 67.6% (355/525) patients had a grade 0 value; 25.5% (134/525) had grade1, 6.3% (33/525) had grade 2, and 0.6% (3/525) had grade 3 ALP. New or worsened grade 3 or 4 increased ALP was seen in 10.3% (53/515) and 0% patients, respectively.

Glucose

At baseline, 77.5% (407/525) patients had a grade 0 value; 22.5% (118/525) had an elevated value as follows: grade 1: 19.2%, grade 2: 2.9%, and grade 3: 0.4% of patients. 259/517 patients (50.1%) had new or worsened post-baseline increases (any grade) in glucose. New or worsened grade 3 and grade 4 increased glucose was seen in 11.1% (57/515) and 1.0% (5/517), respectively.

Safety in special populations

Subgroup analysis of safety by age, race and gender, assessed by the incidence of AEs and AESIs, did not reveal relevant clinically meaningful differences.

Table 47: Integrated Adverse Event Summary for the Patients in the 750 mg Dose Group by Age (Safety Set)

	<65 yrs N=436	65-<75 yrs N=79	75-<85 yrs N=10	All patients N=525
Any adverse events				
Number of patients with at least one event (PT), n(%)	436 (100)	78 (98.7)	10 (100)	524 (99.8)
Number of events (PTs)	9324	1627	206	11157
Serious adverse events				
Number of patients with at least one event (PT), n(%)	166 (38.1)	33 (41.8)	2 (20.0)	201 (38.3)
Number of events (PTs)	367	54	2	423
Adverse events leading to discontinuation				
Number of patients with at least one event (PT), n(%)	35 (8.0)	8 (10.1)	3 (30.0)	46 (8.8)
Psychiatric disorders				
Number of patients with at least one event (PT), n(%)	98 (22.5)	19 (24.1)	1 (10.0)	118 (22.5)
Number of events (PTs)	123	22	1	146
Nervous system disorders				
Number of patients with at least one event (PT), n(%)	199 (45.6)	28 (35.4)	5 (50.0)	232 (44.2)
Number of events (PTs)	406	57	8	471
Accidents and injuries				
Number of patients with at least one event (PT), n(%)	31 (7.1)	6 (7.6)	1 (10.0)	38 (7.2)
Number of events (PTs)	49	7	2	58
Cardiac disorders				
Number of patients with at least one event (PT), n(%)	62 (14.2)	10 (12.7)	0	72 (13.7)
Number of events (PTs)	85	14	0	99
Vascular disorders				
Number of patients with at least one event (PT), n(%)	37 (8.5)	6 (7.6)	1 (10.0)	44 (8.4)
Number of events (PTs)	54	6	2	62
Cerebrovascular disorders				
Number of patients with at least one event (PT), n(%)	4 (0.9)	0	0	4 (0.8)
Number of events (PTs)	4	0	0	4
Infections and infestations				
Number of patients with at least one event (PT), n(%)	213 (48.9)	33 (41.8)	3 (30.0)	249 (47.4)
Number of events (PTs)	383	57	5	445
Anticholinergic syndrome				
Number of patients with at least one event (PT), n(%)	0	0	0	0
Number of events (PTs)	0	0	0	0
Quality of life decreased				
Number of patients with at least one event (PT), n(%)	0	0	0	0
Number of events (PTs)	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures				
Number of patients with at least one event (PT), n(%)	64 (14.7)	16 (20.3)	2 (20.0)	82 (15.6)
Number of events (PTs)	93	17	3	113

Data pooled from X2101, X1101, A2201 and A2203.
Only AEs occuring during treatment or within 30 days of the last dose of study drug are reported.
MedDRA version 17.0 is used.
Data cut-off for X2101: 14APR2014, X1101: 02AUG2013, A2201: 26FEB2014, A2203: 27JUN2014.
Source: [D120 Appendix 7-Table D120Q106-1p], [D120 Appendix 7-Table D120Q106-2p]

There are no data regarding the use of ceritinib in pregnant women.

Safety related to drug-drug interactions and other interactions

There were no dedicated PD interaction studies, with respect to PK interactions, see section 2.4.2.

Discontinuation due to adverse events

AEs leading to discontinuation were reported in 8.8% of the patients treated at the 750 mg dose (safety set).

The table below summarises the AEs leading to drug discontinuation in Studies X2101, A2201, and A2203.

Table 48: AEs Leading to Study Drug Discontinuation in Patients Treated at 750 mg of ceritinib in Studies X2101, A2201, and A2203

Preferred Term	Study X2101 N=255 n (%)	Study A2201 N=140 n (%)	Study A2203 N=124 n (%)
All AEs	**26 (10.2)**	**10 (7.1)**	**9 (7.3)**
Pneumonia	3 (1.2)	1 (0.7)	0
Pneumonitis	2 (0.8)	2 (1.4)	0
Respiratory failure	2 (0.8)	0	0
Decreased appetite	2 (0.8)	0	0
General physical health deterioration	2 (0.8)	0	0
Nausea	1 (0.4)	2 (1.4)	0
Dyspnoea	1 (0.4)	0	0
Haemoptysis	1 (0.4)	0	0
Interstitial lung disease	1 (0.4)	0	1 (0.8)
Pleural effusion	1 (0.4)	0	0
Pleuritic pain	1 (0.4)	0	0
Pneumonia aspiration	1 (0.4)	0	1 (0.8)
Pneumothorax	1 (0.4)	0	0
Fatigue	1 (0.4)	1 (0.7)	0
Performance status decreased	1 (0.4)	0	0
Sepsis	1 (0.4)	0	0
Cauda equina syndrome	1 (0.4)	0	0
Haemorrhage intracranial	1 (0.4)	0	0
Monoplegia	1 (0.4)	0	0
Alanine aminotransferase increased	1 (0.4)	0	0
Aspartate aminotransferase increased	1 (0.4)	0	1 (0.8)
Blood alkaline phosphatase increased	1 (0.4)	0	0
Weight decreased	1 (0.4)	0	0
Cardiac tamponade	1 (0.4)	0	1 (0.8)
Corneal infiltrates	1 (0.4)	0	0
Hepatitis cholestatic	1 (0.4)	0	0
Malignant neoplasm of thorax	1 (0.4)	0	0
Renal failure acute	1 (0.4)	0	0
Faecaloma	0	1 (0.7)	0
Intestinal perforation	0	1 (0.7)	0
Vomiting	0	1 (0.7)	0
Empyema	0	1 (0.7)	0
Gamma-glutamyltransferase increased	0	1 (0.7)	0
Cancer pain	0	1 (0.7)	0
Pericarditis	0	0	1 (0.8)
Respiratory tract infection	0	0	1 (0.8)
Electrocardiogram Qt prolonged	0	0	1 (0.8)
Hyperglycaemia	0	0	1 (0.8)
Parkinson's disease	0	0	1 (0.8)

Source: [Day 120 Appendix 5 –Pool-Table 14.3.1-1.15]

2.6.1. Discussion on clinical safety

The median duration of exposure to ceritinib 750 mg is 38.7 weeks (range 0.4-106.1) in Study X2101; 28.1 weeks (range 0.3-60.1) in study A2201; 34.9 weeks (range 0.4-70.3) in study A2203; and 33.0 weeks (range 0.3-106.1) in the pooled dataset.

In the pooled dataset, almost all patients (99.8%) experienced an AE, 73% being grade 3-4, and over half of the AEs were suspected to be drug-related. The majority of patients (78%) experienced >10 AEs, with a median of 17 AEs (ranging from 1 to 171). Almost half of the AEs (4483/11157) required additional therapy. Dose reductions were performed at least once in more than half of the patients (57.8%) treated with ceritinib however treatment discontinuations due to AEs were not frequent (8.8%).

ADRs with an incidence of ⩾10% were diarrhoea, nausea, vomiting, fatigue, liver laboratory test abnormalities, abdominal pain, decreased appetite, constipation, rash, blood creatinine increased, oesophageal disorder and anaemia. The most frequently reported Grade 3-4 adverse reactions (⩾5%) were liver laboratory test abnormalities, fatigue, diarrhoea, nausea and hyperglycaemia.

The most frequently observed SOC was gastrointestinal disorders (97.9%). In terms of duration, these events were persistent (median duration of 62.0 days, 53.0 days, 19.0 days and 81 days, for diarrhoea AEs, nausea AEs, vomiting AEs and their combination, respectively) and recurrent. Grade 3-4 events of diarrhoea, nausea or vomiting were reported in 12.2% of patients. 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. If vomiting occurs during the course of treatment, the patient should not take an additional dose, but should continue with the next scheduled dose. (see sections 4.2, 4.4 and 4.8 of the SmPC)

Hepatic enzyme elevations were frequently reported and led to dose adjustments or temporary interruptions, but no permanent drug discontinuations.

Cases of hepatotoxicity occurred in less than 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 for the first month 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. Ceritinib is not recommended in patients with moderate or severe hepatic impairment.

Severe, life threatening or fatal interstitial lung disease (ILD) / pneumonitis have been observed in patients treated with ceritinib in clinical studies. Most cases improved or resolved with interruption of treatment. Patients should therefore be monitored for pulmonary symptoms indicative of pneumonitis. Other potential causes of pneumonitis should be excluded, and ceritinib permanently discontinued in patients diagnosed with treatment related pneumonitis.

QTc prolongation has been observed in clinical studies in patients treated with ceritinib, which may lead to an increased risk for ventricular tachyarrhythmias (e.g. torsade de pointes) or sudden death. A clear trend towards increased QTc-interval prolongation with increasing doses was observed in a linear mixed effects model (see clinical pharmacology). In addition, preclinical studies showed increases in QT/QTc in one of four monkeys exposed with ceritinib concentrations twice the C_{max} in patients, and indirect and probable influence on the QT-interval was demonstrated by in vitro blocking of hERG ion channels.

The use of ceritinib in patients with congenital long QT syndrome should therefore be avoided. The benefits and potential risks of ceritinib should be considered before beginning therapy in patients who have pre-existing bradycardia, 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 one decrement.

Asymptomatic cases of bradycardia have been observed in 10 out of 525 (1.9%) patients treated with ceritinib in clinical studies. The 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 two decrements on recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, with frequent monitoring (see sections 4.2, 4.4 and 4.8 of the SmPC).

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% 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, 4.4 and 4.8 of the SmPC).

Available safety data for specific patient subgroups, such as ALK-inhibitor pre-treated patients (with/without progressing during treatment) and ALK-inhibitor naïve patients, indicate a similar profile.

The profile observed in the 65 to 75 years old subgroup is similar to that of the <65 year old subgroup, with a numerically higher frequency for some events (GI AEs, Psychiatric disorders, age-related AEs such as syncope, injuries, and falls). AEs leading to discontinuation and SAEs were also numerically higher in the >65-75 years old subgroup. There are no data in the older patient subgroup (patients over the age of 85) which has been reflected in the SmPC.
Ceritinib should not be used during pregnancy unless the clinical condition of the woman requires treatment with ceritinib.
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 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 sections 4.6 and 5.3 of the SmPC).
Effects on ability to drive and use machines
Ceritinib 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.
Overdose
There is no reported experience with overdose in humans. General supportive measures should be initiated in all cases of overdose.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Additional safety data needed in the context of a conditional MA
The submission of the final CSRs for the phase II study A2201 and phase III study A2303 will provide additional information regarding the safety profile of ceritinib.

2.6.2. Conclusions on the clinical safety

The most frequent ADRs are gastrointestinal disorders and increased liver enzymes. The most serious ADRs are hepatotoxicity, ILD/pneumonitis, QT prolongation and bradycardia. Although ceritinib is not a well-tolerated treatment, the safety profile appears to be clinically manageable.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 2.1 could be acceptable if the applicant implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur assessment report.

The CHMP endorsed this advice without changes.

The applicant implemented the changes in the RMP as requested by PRAC.

The CHMP endorsed the Risk Management Plan version 2.4 with the following content:

Safety concerns

Table 49: Summary table of safety concerns

Important identified risks	Hepatotoxicity QT prolongation Interstitial Lung Disease/Pneumonitis Hyperglycemia GI toxicity (nausea, vomiting, diarrhea) Bradycardia
Important potential risks	Neuropathy Concomitant use of ceritinib and strong CYP3A inhibitors or strong CYP3A inducers
Missing information	Patients with hepatic impairment Patients with severe renal impairment Patients with severe cardiac impairment Elderly patients Paediatric patients Pregnant and lactating women, and women of childbearing potential Long-term safety Concomitant use of ceritinib and CYP3A, CYP2C9, CYP2A6 or CYP2E1 substrates; ceritinib and drugs that may prolong the QT interval Concomitant use of ceritinib and gastric acid reducing agents such as PPIs

Pharmacovigilance plan

Table 50: Table of on-going and planned additional PhV studies/activities in the Pharmacovigilance Plan

Study/activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status** (planned, started)	**Date for submission of interim or final Reports** (planned or actual)
LDK378A2110/ A Phase I, open label, multi-center, single dose study to evaluate the PK of ceritinib in subjects with hepatic impairment compared to subjects with normal hepatic function (3).	To evaluate the PK of a single oral dose of ceritinib in subjects with impaired hepatic function as compared to healthy subjects with normal hepatic function.	Use in patients with hepatic impairment	Started	Final study report Jun-2016 (planned)
LDK378A2103/ A Phase I, multi-center, open label, drug-drug interaction study to assess the effect of ceritinib on the pharmacokinetics of warfarin and midazolam administered as a two- drug cocktail in patients with ALK-positive advanced tumors including non-small cell lung cancer (3)	To assess the effect of ceritinib on the PK of warfarin and midazolam administered as a two-drug cocktail in patients with ALK-positive advanced tumors including NSCLC	Concomitant use of ceritinib and CYP2C9 and CYP3A substrates	Planned	Final study report Mar-2017 (planned)
LDK378A2113 /A Phase I, open label, two-period, single-center, single dose study to assess the effect of esomeprazole (proton pump inhibitor) on the pharmacokinetics of ceritinib in healthy volunteers (3)	To assess the effect of esomeprazole on the PK of a single 750 mg ceritinib in healthy adult subjects.	Concomitant use of ceritinib and gastric acid reducing agents such as PPIs	Planned	Final study report Mar-2016 (planned)

Risk minimisation measures

Table 51: Summary table of Risk Minimization Measures

Safety concern	**Routine risk minimization measures**	**Additional risk minimization measures**
Hepatotoxicity	Dose modification recommendations provided in SmPC Section 4.2 Posology and method of administration. Description of frequency and severity of events, and guidelines on monitoring of liver laboratory tests (including ALT, AST and total bilirubin) prior to and after start of treatment are provided in SmPC Section 4.4 Special warnings and precautions for use. Abnormal liver function tests (including hepatic function abnormal, hyperbilirubinaemia), hepatotoxicity (including DILI, hepatitis cholestatic, hepatocellular injury, hepatotoxicity), and Liver laboratory test abnormalities (including alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased, blood bilirubin increased, transaminases increased, hepatic enzyme increased, liver function test abnormal) are listed as ADRs in SmPC Section 4.8 Undesirable effects. Treatment should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products.	None.
QT prolongation	Dose modification recommendations in SmPC Section 4.2 Posology and method of administration. Section 4.4 Special warnings and precautions for use provides dose modification recommendations, guidelines on periodic monitoring of ECGs and electrolytes,	None.

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	correction of electrolytes as clinically indicated, avoiding use of Zykadia in patients with congenital long QT syndrome. SmPC Section 4.5 Interaction with other medicinal products and other forms of interactions: Provides caution with use in patients who have or may develop prolongation of the QT interval, including those patients taking anti-arrhythmic medicinal products or other medicinal products that may lead to QT prolongation. Electrocardiogram QT prolonged is listed as an ADR in SmPC Section 4.8 Undesirable effects. Treatment should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products.	
Interstitial lung disease/ pneumonitis	Dose modification recommendations in SmPC Section 4.2 Posology and method of administration Dose modification recommendations and guideline on periodic monitoring of pulmonary symptoms indicative of pneumonitis in SmPC Section 4.4 Special warnings and precautions for use. Pneumonitis (including ILD, pneumonitis) is listed as an ADR in SmPC Section 4.8 Undesirable effects. Treatment should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products.	None.
Hyperglycemia	Dose modification recommendations in SmPC Section 4.2 Posology and method of administration. SmPC Section 4.4 Special warnings and precautions for use provides details regarding the description of frequency and severity of events, guidance on monitoring of fasting glucose prior to and after start of Zykadia treatment, use of anti-hyperglycaemic medication, and risk of hyperglycaemia being higher in patients with diabetes mellitus and/or concurrent steroid use. Hyperglycaemia is listed as an ADR in SmPC Section 4.8 Undesirable effects. Treatment should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products.	None.
GI toxicity (nausea, vomiting, diarrhea)	Dose modification recommendations in SmPC Section 4.2 Posology and method of administration. Description of frequency and severity of events, dose modification recommendations and recommendations for supportive treatment using standards of care in SmPC Section 4.4 Special Warnings and Precautions for use. Nausea, vomiting, and diarrhea are listed as very common ADRs in SmPC Section 4.8 Undesirable effects. Treatment should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products.	None.
Bradycardia	Dose modification recommendations in SmPC Section 4.2 Posology and method of administration. SmPC Section 4.4 Special warnings and precautions for use provides dose modification recommendations, guidelines on regular monitoring of heart rate and blood pressure, and instructions on avoiding use Zykadia in combination with other agents known to cause bradycardia. Bradycardia (including bradycardia, sinus bradycardia) is listed as an ADR in SmPC Section 4.8 Undesirable effects. Treatment should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products.	None.
Neuropathy	Currently available data do not support the need for risk minimization. Treatment should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products.	None.
Concomitant use of ceritinib and strong CYP3A inhibitors or strong CYP3A inducers	SmPC Sections 4.2 and 4.5 provide recommendations to avoid concomitant use of strong CYP3A inhibitors during treatment with ceritinib, and to reduce the dose if concomitant use of a strong CYP3A inhibitor is unavoidable. Treatment should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products. The Patient Leaflet provides detailed instructions to the patients on the drugs that may interact with ceritinib and to notify the doctor or pharmacist if using any of these drugs.	None.
Patients with hepatic	SmPC Section 4.2 Posology and method of administration states that no dose adjustment is necessary in patients with mild hepatic impairment, and that	None.

Safety concern	Routine risk minimization measures	Additional risk minimization measures
impairment	ceritinib is not recommended in patients with moderate and severe hepatic impairmentPK information in SmPC Section 5.2 Pharmacokinetic properties. Treatment should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products.	
Patients with severe renal impairment	Caution of use in patients with severe renal impairment in SmPC Section 4.2 Posology and method of administration. PK information in SmPC Section 5.2 Pharmacokinetic properties. Treatment should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products.	None.
Patients with severe cardiac impairment	Currently available data do not support the need for risk minimization. Treatment should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products.	None.
Elderly patients	Paucity of data and that no dose modification is required in this patient population is detailed in SmPC Section 4.2 Posology and method of administration. SmPC Section 4.8 Undesirable effects that the safety profile in patients aged 65 years or older was similar to that in patients less than 65 years of age. There are no available data on patients over 85 years of age. SmPC Section 5.2 Pharmacokinetic properties details that the PK analyses showed that age had no clinically meaningful influence on ceritinib exposure. Treatment should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products.	None.
Paediatric patients	SmPC Section 4.2 Posology and method of administration details that there is no data in this patient population. SmPC Section 5.1 pharmacodynamics properties details that The European Medicines Agency has waived the obligation to submit the results of studies with Zykadia in all subsets of the paediatric population in lung carcinoma (small cell and non-small cell carcinoma). Treatment should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products.	None.
Pregnant and lactating women, and women of childbearing potential	Adequate information and guidance to help the prescriber and the patient is provided in Section 4.6 (Fertility, pregnancy, and lactation) of the SmPC. Preclinical safety data on reproductive toxicology studies (i.e. embryo-foetal development studies) and the potential effects of ceritinib on fertility are detailed in SmPC Section 5.3 (Preclinical safety data). Treatment should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products.	None.
Long-term safety	Currently available data do not support the need for risk minimization. Treatment should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products.	None.
Concomitant use of ceritinib and CYP3A, CYP2C9, CYP2A6 or CYP2E1 substrates; ceritinib and drugs that may prolong the QT interval	Guidelines on periodic monitoring of ECGs and electrolytes in patients taking medications known to prolong QT interval in SmPC Section 4.4 Special warning and precaution for use SmPC Section 4.5 Interaction with other medicinal products and other forms of interactions cautions on the concomitant use. Treatment should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products. The Patient Leaflet provides detailed instructions to the patients on the drugs that may interact with ceritinib and to notify the doctor or pharmacist if using any of these drugs.	None.
Concomitant use of ceritinib and gastric acid reducing agents such as PPIs	SmPC Section 4.5 Interaction with other medicinal products and other forms of interactions states that gastric acid reducing agents may alter the solubility of ceritinib and reduce its bioavailability. Treatment should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products.	None.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

Overall, 515 ALK-positive NSCLC patients have been treated with ceritinib 750 mg (83 ALK inhibitor naïve and 163 ALK inhibitor pretreated patients in study X2101; 140 ALK inhibitor pretreated patients in study A2201 and 124 ALK inhibitor naïve patients in study A2203; 5 additional patients have been treated at the proposed dose in study X1101).

The ALK inhibitor pretreated patients comprise a heavily pretreated patient population, with more than half of the patients having received at least 3 prior regimens, including crizotinib. The ORR (56.4% in study X2101 and 37.1% in study A2201) seen in these patients exceed that expected with chemotherapy and indicate that patients who have progressed on a prior ALK inhibitor have a high likelihood of responding to ceritinib. The DOR was similarly long in both studies (median 8.3 and 9.2 months, respectively). Furthermore, the PFS seen in these patients ranged from a median of 6.9 months in Study X2101 to a median of 5.7 months in Study A2201, whilst for OS preliminary data show a median of 16.7 and 14.0 months, respectively.

For the ALK inhibitor naïve population, the majority of the patients had received at least a platinum agent (Study X2101), or a platinum doublet (Study A2203). An ORR of 72.3% was shown in the updated results from study X2101, which is in line with the primary analysis (69.5%). A lower response was seen in Study A2203 (63.7%). DOR is still immature for Study X2101 [17.02 (11.27, NE) months] as for Study A2203 [9.3 (9.1, NE) months]. At the time of the last data cut-off available, a PFS event had been experienced by 39.8% in Study X2101 and 32.3% in Study X2203. Although the PFS analyses are immature, a substantially longer median PFS was seen in Study X2101 [18.4 (11.1, NE)] than in Study 2203 [11.1 (9.3, NE) months]. Survival data is not yet available.

Uncertainty in the knowledge about the beneficial effects.

The efficacy of ceritinib in the treatment of ALK-positive NSCLC is based on the results of three uncontrolled, open label clinical trials (one phase I, 2 phase II studies). The absence of direct comparative data with other agents is an important limitation.

The Applicant initially claimed a broad indication in the treatment of previously treated ALK positive NSCLC, which includes ALKi naïve and ALKi previously treated patients. Overall, the available efficacy data for **ALKi naïve** patients with NSCLC is limited and most of the efficacy endpoints are still immature, which brings uncertainty to the magnitude of the clinical benefit. Considering that for these patients, a treatment option is currently approved, and that efficacy assessment in single arm studies involves substantial uncertainties, it cannot be justified to conclude on benefit/risk based on partially immature data from two single arm studies. No results from the ongoing phase III Study A2301 (ceritinib vs. chemotherapy) could be provided during this procedure, and there is no data available comparing ceritinib to crizotinib.

In addition, there are concerns that ALKi naïve patients receiving ceritinib could consequently fail to respond to post-progression therapy with crizotinib. According to the applicant there are no non-clinical or clinical data comparing sequential therapy with ALK inhibitors (i.e., crizotinib followed by ceritinib versus ceritinib followed by crizotinib). Concerning mutation status, the applicant has presented data suggesting that patients resistant to crizotinib can be sensitive to ceritinib. However, the applicant has not provided any data suggesting that patients resistant to ceritinib are sensitive to crizotinib. Consequently, the applicant has no data to alleviate the concern that ALKi naïve patients receiving ceritinib could consequently fail to respond to post-progression therapy with crizotinib or other ALKi.

The data supporting the **ALKi pretreated** indications also have limitations given the non-comparative nature of the studies presented. The phase III comparative study has just started, but no data has been available during the procedure. It is nevertheless acknowledged that the updated information from the phase I and the phase II studies confirm the efficacy results initially observed, and provide reassurance on the robustness of these results.

While some differences are observed for all three studies between investigator´s and BIRC assessment, these differences are more evident for study X2101, and more particularly for the ORR results. The Applicant stated that these differences could partly be explained by inter-observer variability, which can be agreed with to some extent. However, an overestimation of the effect in study X2101 due to the nature of its design (being a first administration to humans, open-label, uncontrolled study including an advanced patient population with limited options) could not be completely ruled out. The fact that assessments by BIRC and by investigator in the phase II studies are very concordant and that the BIRC assessment of study X2101 seems to be in line with those results is reassuring.

Risks

Unfavourable effects

The pooled safety dataset includes 525 patients exposed to ceritinib 750 mg, with a mean duration of treatment of 35.3 (21.89) weeks.

The most common adverse reactions observed across studies were GI disorders (nausea, diarrhea, vomiting, and constipation), followed by general disorders and administrative site conditions, and investigations. The most frequently reported Grade 3-4 adverse reactions were increased ALT, increased AST, diarrhea, lipase increased, and hyperglycemia.

Hepatic enzyme elevations were frequently reported and led to dose adjustments or temporary interruptions, but no permanent drug discontinuations. There were 2 DILI cases in the original submission, one on each phase I study.

Ceritinib has been associated with study-drug related pneumonitis/ ILD, a class-effect known for some tyrosine kinase targeting drugs. Out of the 525 patients across the 4 clinical studies, a total of 17 cases were detected, including one case of pneumonitis with fatal outcome.

Cardiac disorders including bradycardia and ECG abnormalities have also been observed during the conducted studies.

The safety profile of ceritinib is somewhat similar to that seen with crizotinib. Considering that the intended target population is patients previously treated with crizotinib, a subset of the studied population, no meaningful differences were observed with AE profile shown for ALKi naïve patients. Although patients treated with ceritinib experience a high incidence of adverse drug reactions, the safety profile of ceritinib seems to be clinically manageable.

Uncertainty in the knowledge about the unfavourable effects

The safety profile appears reasonably well characterized with respect to the most frequent AEs, which overall seem to be clinically manageable. However there are uncertainties related to the overall limited database and the long term safety given that the median duration of exposure in the pooled dataset is 33 weeks. There are also uncertainties concerning some drug-drug interactions as well as use in patients with moderate and severe hepatic impairment, and their potential safety implications, which will be addressed as post-approval commitments. In addition, the limited available safety data in elderly patients (>75 years of age) preclude firm conclusions on the safety in this group of patients, but based on data available there are not specific reasons to limit use of ceritinib in this population.

Benefit-risk balance

Importance of favourable and unfavourable effects

Patients for whom the disease progresses on or shortly after treatment with an ALK-inhibitor have limited treatment options and therefore there is a high unmet medical need. In this patient population, ceritinib appears a more efficacious treatment option compared to currently available therapies.

For ALKi naïve patients, the presently available information on efficacy is limited since most of the time-to-event analyses are still immature. No data comparing the efficacy of ceritinib versus crizotinib is available and the concern regarding sequential treatment with crizotinib after ceritinib has not been elucidated. Therefore efficacy in the ALKI naïve population is not considered demonstrated.

The use of ceritinib is associated with relevant toxicities, and the tolerability of this treatment should be considered in the context of a pre-treated population with not optimal performance status. Therefore, although the AEs seem to be clinically manageable, ceritinib is not well tolerated. This is further supported by the persistent and recurrent nature of the most frequent AEs.

Benefit-risk balance

The benefits in the population of patients previously treated with an ALK inhibitor outweigh the risks related to the use of ceritinib.

Discussion on the benefit-risk balance

The effect of ceritinib on tumour burden is relevant in a population with limited treatment options. This ORR is not usually observed in solid tumours and especially after several lines of chemotherapy. Historical data in patients treated with chemotherapy (pemetrexed) in second line have shown ORR of 29% at best, with median of PFS of 4.2 months.

Despite the fact that the ORR in the phase II studies seem to be lower than initially reported (based on both IRC analyses and updated outcomes), these results are considered relevant.

However in ALKi naïve patients, the available efficacy data is limited and most of the efficacy endpoints are still immature which brings uncertainty to the magnitude of the clinical benefit. Considering that for these patients, a valid treatment option is available, and that efficacy assessment in single arm studies involves substantial uncertainties, it cannot be justified to base the efficacy assessment solely on partially immature data from two single arm studies. No results from the ongoing phase III Study A2301 (ceritinib vs. chemotherapy) will be provided during this procedure, and there is no data available comparing ceritinib to crizotinib.

It is agreed that there is a need for new therapies able to improve the unfavourable prognostic of these patients. However crizotinib is currently available for these patients and ceritinib has not yet robustly demonstrated a significant benefit compared to crizotinib. In addition, none of the proposed studies are aimed to provide confirmatory data on the efficacy of ceritinib in the treatment of ALKi naïve patients

previously exposed to chemotherapy. Study 2301 will provide data in the first line clinical setting, while Study 2205 will only provide data from a cohort of patients previously exposed to chemotherapy. The benefit risk balance of the ALKi naïve patients indication is considered negative.

Patients for whom the disease progresses on or shortly after treatment with an ALK-inhibitor have limited treatment options and therefore a high unmet medical need. An ORR in the range of 37-56%, and a DOR of approximately 8-9 months confirm that ceritinib has a strong anti-tumour activity in these patients. Median PFS was 6.9 (5.6, 8.7) months in Phase I study X2101 and 5.7 (5.3, 7.4) months in Phase II study A2201. The median PFS in the two studies are thus very similar, and considered to represent a reliable estimate of a PFS following treatment with ceritinib in prior ALKi treated patients. A PFS of 6-7 months is also considered of clinical benefit to these patients, since in this setting; the experience is that chemotherapy results in median PFS of approximately 3 months. In addition, although not fully mature, median overall survival data represents a clinical benefit when compared to existing treatment options.

Taking into account the risk related to the open-label nature of the data, it is considered that the available data is considered sufficient to conclude that the benefit-risk of ceritinib in the ALKi pre-treated patient population is positive although the clinical data package supporting the benefit-risk is not considered comprehensive.

The CHMP considered that Zykadia falls under the scope of Article 2(1) of Commission Regulation (EC) No 507/2006:

- Medicinal products which aim at the treatment, the prevention or the medical diagnosis of seriously debilitating diseases or life-threatening diseases

and is thus eligible for a Conditional Marketing Authorisation.

Furthermore, all the requirements listed in Article 4(1) of the Commission Regulation (EC) No. 507/2006 apply to Zykadia on the basis of the following reasons:

a) The risk-benefit balance of the product is positive.

See Discussion on benefit-risk balance.

b) It is likely that the applicant will be able to provide comprehensive clinical data:

The applicant will provide further comprehensive clinical data to confirm efficacy of ceritinib in the proposed indication from the final results of the phase II study A2201 expected by Q2 2016. In addition, the results of an ongoing phase III comparative study (A2303) in patients previously treated with crizotinib will further support the benefit-risk evaluation of ceritinib. The final study report of study A2303 is expected to be submitted by Q3 2018.

c) Fulfilment of unmet medical need in the proposed indications:

Currently there are no approved treatment options for patients with ALK-positive NSCLC who have progressed on or after treatment with crizotinib. The efficacy data supporting the MA indicate that patients who have progressed on or after treatment with crizotinib have a high likelihood of responding to ceritinib.

d) The benefits to patients of the immediate availability outweigh the risks inherent in the fact that additional data are still required:

In view of the favourable benefit-risk profile and the unmet medical need (see above), the immediate availability of Zykadia outweighs the risk inherent in the fact that additional data are still required.

The CHMP concluded that all the requirements for the granting of a conditional marketing authorisation had been met.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Zykadia in the treatment of adult patients with anaplastic lymphoma kinase (ALK) positive advanced non-small cell lung cancer (NSCLC) previously treated with crizotinib., is favourable and therefore recommends the granting of the conditional marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

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

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The 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.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14(7) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to further confirm the efficacy of ceritinib in the treatment of patients previously treated with crizotinib, the MAH should submit the final results of the phase III efficacy study A2303 comparing ceritinib to chemotherapy.	30 September 2018
In order to further confirm the efficacy of ceritinib in the treatment of patients previously treated with crizotinib, the MAH should submit the final results of the phase	30 June 2016

Description	Due date
II single-arm efficacy study A2201.	

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that ceritinib is qualified as a new active substance.