Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Ceritinib

Proprietary Product Name: Zykadia

Sponsor: Novartis Pharmaceuticals Aust Pty Ltd

February 2018

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
ADME	Absorption, Distribution, Metabolism, and Excretion
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
AJCC	American Joint Committee on Cancer
ALCL	Anaplastic large cell lymphoma
ALK	Anaplastic lymphoma kinase
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
AUCtau	Area under the plasma concentration-time curve for each dosing interval (from time 0 to 24 hours sample) determined using the linear trapezoidal rule
AUC_{inf}	The area under the blood or plasma concentration-time curve from time zero extrapolated to infinity when feasible.
AUC_{last}	The area under the blood or plasma concentration-time curve from time zero to last sampling time
BIRC	Blinded Independent Review Committee
BLRM	Bayesian Logistic Regression Model
BOR	Best overall response
bpm	Beats per minute
BUN	Blood urea nitrogen
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval

Abbreviation	Meaning
CL/F	Total body clearance divided by the oral bioavailability
C_{max}	The maximum (peak) blood or plasma concentration after single dose administration
C_{trough}	trough concentration
$C_{trough,ss}$	steady state trough concentration
CEAS	Central Efficacy Analysis Set
CMI	Consumer Medicines Information
CNS	Central nervous system
CR	Complete response
CrCL	Creatinine clearance
CSF	Clinical Service Formulation
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease control rate
DDI	Drug-drug interaction
DLT	Dose-limiting toxicity
DOR	Duration of response
DSC	Differential Scanning Calorimeter
EAS	Efficacy Analysis Set
ECG	Electrocardiogram
ECOG	Eastern cooperative oncology group
EDTA	Ethylene diamine tetra acetic acid
EGFR	Epidermal growth factor receptor
EU	European Union
EWOC	Escalation with overdose control
FAS	Full Analysis Set
FDA	Food and Drug Administration

Abbreviation	Meaning
FISH	Fluorescence In Situ Hybridisation
FMI	Final Market Image
GGT	Gamma-glutamyl transpeptidase
GI	Gastrointestinal
HIV	Human immunodeficiency virus
HR	Hazard ratio
ILD	Interstitial lung disease
Lambda_z	Terminal elimination rate constant
LC-MS/MS	Liquid Chromatography-Tandem Mass Spectrometry
LDK378	Ceritinib
LLOQ	Lower Limit Of Quantification
LMWH	Low Molecular Weight Heparin
LSC	Liquid Scintillation Counting
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NE	Not Estimable
NSCLC	Non-Small Cell Lung Cancer
OIRR	Overall intracranial response rate
ORR	Overall response rate
OS	Overall Survival
PAS	Pharmacokinetic Analysis Set
PD	Progressive Disease
PFS	Progression-free survival
P-gp	P-glycoprotein
PI	Product Information
PK	Pharmacokinetics

Abbreviation	Meaning
pKa	Dissociation constant
PPS	Per-Protocol Set
PR	partial response
PRO	Patient reported outcome
PS	Performance status
PXR	Pregnane X receptor
QTc	Corrected QT interval
QTcB	Corrected QT interval using Bazett's formula
QTcF	Corrected QT interval using Frederica formula
Racc	Accumulation ratio
RD	Recommended dose
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious adverse event
SD	Standard deviation
SOC	System organ classes
SOD	Sum of diameters
SPC	Summary of Product Characteristic
SS	Steady state
T1/2	Elimination half-life associated with the terminal slope of a semi logarithmic concentration-time curve
TKI	Tyrosine kinase inhibitor
Tlast	Last sampling time T
Tmax	The time to reach maximum blood or plasma concentration following drug administration
TTR	Time to response
ULN	Upper limit of normal
US	United States

Abbreviation	Meaning
Vz/F	Volume of distribution divided by the oral bioavailability
WHO	World Health Organisation

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Decision:	Approved
Date of decision:	29 March 2016
Date of entry onto ARTG	31 March 2016
Active ingredient(s):	Ceritinib
Product name(s):	Zykadia
Sponsor's name and address:	Novartis Pharmaceuticals Aust Pty Ltd 54 Waterloo Road, North Ryde NSW 2113
Dose form(s):	Hard capsule
Strength(s):	150 mg
Container(s):	Blister pack
Pack size(s):	One blister strip contains 10 hard capsules. Multipacks containing 150 (3 packs of 50) hard capsules.
Approved therapeutic use:	*Zykadia is indicated as monotherapy for the treatment of adult patients with ALK-positive locally advanced or metastatic non-small cell lung cancer (NSCLC) whose disease has progressed on or who are intolerant of crizotinib.* *Note to the Indication: This indication is approved based on tumour response rate and duration of response. An improvement in survival or disease-related symptoms has not been established.*
Route(s) of administration:	Oral (PO)
Dosage:	The recommended dose of Zykadia is 750 mg taken orally once daily at the same time each day. Continue treatment as long as the patient is deriving clinical benefit from therapy. The maximum recommended dose is 750 mg daily.
ARTG number (s):	235737

Product background

This AusPAR describes the application by the sponsor to register the new chemical entity Ceritinib as Zykadia *for the treatment of adult patients with ALK-positive locally advanced or metastatic non-small cell lung cancer (NSCLC) previously treated with an ALK-inhibitor.*

Anaplastic lymphoma kinase (ALK), a receptor tyrosine kinase, was first identified as a fusion protein resulting from chromosomal translocation in the majority of anaplastic

large cell lymphoma (ALCL). When fused to other proteins, ALK becomes constitutively active, leading to increased catalytic kinase function, signal transduction activity, and oncogenic function. ALK gene rearrangement is found in about 5% of patients with NSCLC[1] and is thought to be mutually exclusive with epidermal growth factor receptor (EGFR) and KRAS[2] mutations[3]. It has been associated with a younger age, non-smoking status and adenocarcinoma histology and a more advanced state at presentation.[4] Thus ALK gene rearrangements define a unique molecular subset of non–small-cell lung cancers (NSCLC).[1]

The prevalence of ALK-positive lung cancer in Australia was estimated by the TGA to be approximately 1200 in 2015 with an estimated annual incidence of 720 in Australia.

ALK gene rearrangements were identified as an oncogenic driver in this subset of NSCLC and this potential target has been confirmed by the improvement in response rates and progression free survival with crizotinib. Crizotinib is a non-specific small molecule ALK, Mesenchymal Epithelial Transition Factor (cMET) and proto-oncogene tyrosine-protein kinase (ROS-1) inhibitor and the only targeted agent currently approved for the treatment of locally advanced or metastatic ALK-positive NSCLC.

Phase III trials in patients who had received one prior line of chemotherapy demonstrated a response rate of 65% (95% CI: 58, 72) for crizotinib compared with 20% (95% CI: 14, 26) with chemotherapy (P<0.001). The median progression free survival (PFS) was 7.7 months compared with 3.0 months in patients who received single-agent chemotherapy (Hazard ratio 0.49; 95% confidence interval (CI): 0.37, 0.64; p<0.001). Improvement in overall survival (OS) was not demonstrated and crossover to crizotinib on progression in the chemotherapy arm is likely to account for this. This study also includes one of the first reports of chemotherapy response rates in ALK-positive NSCLC (compared with NSCLC not otherwise specified) which is relevant for this application as the studies presented lack a control arm. This trial followed single-arm trials of crizotinib in patients with ALK-positive NSCLC where response rates of 50 to 61% and duration of response of 6 to 10 months were reported.[5]

In a Phase III open label trial in the first line setting, crizotinib resulted in a significantly increased median PFS compared with pemetrexed and platinum doublet chemotherapy;10 months versus 7.0 months , HR 0.45; 95% CI:0.35, 0.6, p<0.001. Quality of life and symptom control were also reported to be improved with crizotinib.[6] The OS data are still immature but the trial's crossover design may well preclude demonstration of an OS benefit. This confirms the current standard of care to be crizotinib in patients newly diagnosed with locally advanced or metastatic ALK-positive NSCLC. Crizotinib (Xalkori) is registered by the TGA for the treatment of patients with ALK-positive advanced non-small cell lung cancer for the treatment of adults with Stage IIIB or IV non-squamous type of NSCLC harbouring an ALK gene rearrangement in tumour material, defined as 15% (or greater) positive cells by fluorescence in situ hybridisation (FISH) testing.

Acquired drug resistance to crizotinib remains a problem and may result from the development of resistant ALK mutations, ALK amplification and/or activation of alternate

[1] Shaw AT et al. Crizotinib versus chemotherapy in ALK positive lung cancer. N Engl J Med 2013;368:2385-94

[2] KRAS (K-ras or Ki-ras) is proto-oncogene corresponding to the oncogene first identified in Kirsten rat sarcoma virus and the gene product was first found as a p21 GTPase.

[3] Gainor JF et al. ALK rearrangements are mutually exclusive with mutations in EGFR or KRAS: an analysis of 1,683 patients with non-small cell lung cancer. Clin Cancer Res 2013;19:4273-81.

[4] Shaw AT et al. Clinical features and outcome of patients with non-small-cell lung cancer who harbor EML4-ALK. J Clin Oncol 2009;27:4247-53.

[5] Ou SH. Crizotinib: a novel and first-in-class multitargeted tyrosine kinase inhibitor for the treatment of anaplastic lymphoma kinase rearranged non-small cell lung cancer and beyond. Drug Des Devel Ther 2011;5:471-85.

[6] Solomon, B et al NEJM 2015 accessed 20 February 2016 at http://www.nejm.org/doi/full/10.1056/NEJMoa1408440

aberrant signalling pathways.[7] Brain metastases are common in NSCLC and the first site of progression on crizotinib.[8] Furthermore, not all patients respond to or tolerate crizotinib treatment.

Crizotinib has the following significant toxicities: hepatotoxicity (including fatal cases), pneumonitis (including fatal cases), QT prolongation, bradycardia (usually asymptomatic), and vision disorders. It was uncertain as to whether these are a class effect of ALK tyrosine kinase inhibitors.

Ceritinib is an oral medicine stated in the application to primarily be a potent inhibitor of ALK kinase, with activity against ALK-positive NSCLC that has developed resistance to crizotinib. The TGA nonclinical evaluator removed the reference in the PI to it being a highly selective ALK inhibitor, identifying potential activity against the insulin like growth factor 1 (IGF1) superfamily, including ROS-1, INSR, and IGF1R.

Patients with intolerance of or progression on crizotinib have few remaining effective treatment options and this application seeks to register ceritinib for this population. It is also being tested in crizotinib-naïve ALK-positive NSCLC but pursuit of registration in that indicated population was dropped following the presubmission meeting with the TGA following concerns that the study design was not appropriate to support an adequate demonstration of safety and efficacy.

Regulatory status

The product is a new chemical entity in Australia and was first registered on the Australian Register of Therapeutic Goods (ARTG) on 31 March 2016.

Zykadia has been designated as an orphan drug, pursuant to subregulation 16J (2) of the Therapeutic Goods Regulations 1990. The indication is for the treatment of patients with NSCLC that is ALK-positive. The indication sought in this submission does not differ from the designated orphan indication.

At the time the TGA considered this application, a similar application had been granted accelerated approval in the USA and given conditional marketing authorisation in the European Union (EU) and Canada (see Table 1).

Table 1: Overseas regulatory submission history for ceritinib

Country	Submission Date	Outcome
European Union Conditional	Positive CHMP opinion on 26 February 2015	Conditional Marketing Authorisation *ZYKADIA is indicated for the treatment of adult patients with ALK positive advanced NSCLC previously treated with crizotinib.*
USA	Approved in	Accelerated approval for the following (taken

[7] Katayama R et al. Mechanisms of acquired crizotinib resistance in ALK-rearranged lung cancers. Sci Transl Med 2012;4:120ra17
Doebele RC et al. Mechanisms of resistance to crizotinib in patients with ALK gene rearranged non-small cell lung cancer. Clin Cancer Res 2012;18:1472-82
[8] Camidge DR et al. Activity and safety of crizotinib in patients with ALK-positive non-small-cell lung cancer: updated results from a phase 1 study. Lancet 2012;13:1011-9.
Yang P et al. Worse disease-free survival in never-smokers with ALK+ lung adenocarcinoma. J Thorac Oncol 2012;7:90-7.
Camidge DR and Doebele RC. Treating ALK-positive lung cancer – early successes and future challenges. Nature 2012;9:268-77

Country	Submission Date	Outcome
Accelerated approval	April 2014	from FDA label): *ZYKADIA is indicated for the treatment of patients with ALK-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib. This indication is approved under accelerated approval based on tumor response rate and duration of response. An improvement in survival or disease-related symptoms has not been established. Continued approval may be contingent upon verification and description of clinical benefit in confirmatory trials.*
Canada Conditional	Approved 27 March 2015	*ZYKADIA is indicated as monotherapy for use in patients with ALK-positive locally advanced (not amenable to curative therapy) or metastatic NSCLC who have progressed on or who were intolerant to crizotinib*. This approval was issued with conditions, pending the results of studies to verify its clinical benefit.

The TGA Delegate notes the later lodgement of the submission with the TGA compared with other agencies. As the reports and product monographs and so on are available from other agencies, these have been used as references by the Delegate. The clarity with which the early dataset and evidence base for the decisions made in the FDA, EU and by Health Canada are noted as well as prominent discussion of the conditional nature of the registration.

The proposed indication, dosage regimen and patient population for which this TGA approval is being sought in Australia is the same as those approved overseas.

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration timeline

Table 2: Registration timeline for Submission PM-2015-00418-1-4

Description	Date
Submission dossier accepted and 1st round evaluation commenced	30 April 2015
1st round evaluation completed	8 October 2015
Sponsor provides responses on questions raised in 1st round evaluation	18 December 2015

Description	Date
2nd round evaluation completed	15 February 2016
Request for Advisory Committee advice and/or Delegate's Overview	1 March 2016
Sponsor's response to Delegate's Overview	7 March 2016
Advisory Committee meeting	Not applicable
Registration decision	29 March 2016
Entry onto ARTG	31 March 2016
Number of TGA working days from commencement of evaluation to registration decision *	228

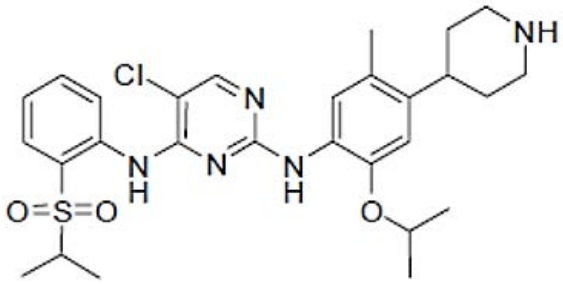
* Target timeframe for standard applications: 220 working days. Statutory timeframe: 255 working days.

III. Quality findings

Introduction

The sponsor has applied to register the new chemical entity ceritinib 150 mg hard capsules in blister packs of 50 and 150 capsules. The chemical structure is shown in Figure 1 below.

Figure 1: Chemical structure of ceritinib



Ceritinib is an achiral, synthetic drug soluble in acid, but much less soluble at higher pH.

The proposed drug product is a white opaque hard capsule with a blue cap. The opaque blue cap is marked with black ink 'LDK 150 mg' and the opaque white body is marked with black ink 'NVR'. The capsule contains a white to almost white powder. Ceritinib capsules are formulated with standard excipients (microcrystalline cellulose, hydroxypropyl cellulose, sodium starch glycolate type A, magnesium stearate, and silica colloidal anhydrous) in a gelatin capsule shell.

Ceritinib is classified as Biopharmaceutics Classification. System (BCS) Class IV (low solubility/low permeability).[9]

[9] The drugs are classified in BCS on the basis of solubility, permeability and dissolution.

A Food-effect study (#LDK378A2101) was conducted in 28 healthy subjects. The recommended dose of ceritinib is 750 mg (as 5 x 150 mg capsules) taken orally once daily at the same time each day. The dose should be taken on an empty stomach.

Quality comments and recommendation

Some changes to the Provisional ARTG Records are required (see appended sample PAR).

Acceptability of the proposed trade name Zykadia is a decision for the clinical Delegate (compare to Zylap olanzapine tablets Aspen Pharma Pty Ltd; Kadian morphine sulfate sustained release capsule Mayne Pharma are export only).

The low solubility except in acid is drawn to the attention of the Delegate (the potential risk of low bioavailability in achlorhydric patients or if dosed with antacids and so forth).

The labels require revision.

The capsule dissolution limit should be reviewed by Novartis or a tighter limit could be made a condition of registration.[10]

Otherwise registration is recommended with respect to quality and bioavailability aspects.

IV. Nonclinical findings

Introduction

General comments

Nonclinical studies submitted are compliant with the relevant International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) S9 guideline *Nonclinical Evaluation for Anti-cancer Pharmaceuticals*. Pivotal toxicity studies were conducted under Good Laboratory Practice (GLP) conditions.

Pharmacology

Primary pharmacology

The pharmacological activity of ceritinib was investigated in recombinant human kinases and cancer cells in vitro and in animal tumour models in vivo.

In vitro studies demonstrated that ceritinib was most active against ALK among a panel of 36 recombinant human protein kinases. ALK is a receptor tyrosine kinase of the insulin receptor superfamily. The activity of ceritinib against ALK (50% inhibitory concentration (IC_{50}) 0.15 nM) was around 50 fold higher than that against two other receptor tyrosine kinases of the insulin receptor superfamily, InsR (insulin receptor, IC_{50} 7 nM) and IGF-1 receptor (IGF1R) IC_{50} 8 nM), and >730 fold higher than other protein kinases. A parallel study with crizotinib showed that crizotinib is less active against ALK (IC_{50} 3 nM) than ceritinib and crizotinib also has potent inhibitory activity against Met and cABL (IC_{50} 8 and 6 nM, respectively).

In cell proliferation studies using a variety of cancer cells, ceritinib inhibited proliferation of cancer cells transfected with fused nucleophosmin (NPM)-ALK or echinoderm microtubule associated protein-like 4 (EML4)-ALK or ALK activated by fusion with TEL.

[10] The specifications were subsequently tightened by the sponsor.

The IC_{50} values (20-60 nM) in the cell proliferation assays were comparable with the unbound clinical peak plasma concentration (C_{max}; approximately 60 nM) at the proposed dose of 750 mg.

In human lung cancer NSCLC cell lines, ceritinib inhibited proliferation and growth of NCI-H2228, which carries the EML4-ALK gene fusion but had no significant activity against 94 other NSCLC cell lines that do not harbor ALK translocations although the cell lines expressed ALK protein. Ceritinib also had anti-proliferative activity in a neuroblastoma cell line (NB-1-luc-Blast) with ALK gene amplification (IC_{50} 24 nM), and the antiproliferative activity correlated with inhibition of ALK phosphorylation and the downstream signalling protein STAT3 (IC_{50} 46 and 150 nM, respectively).

In vivo studies showed that ceritinib administration in mice resulted in a dose dependent inhibition of H2228 and Karapas299 (expressing EML4-ALK and NPM-ALK, respectively) xenograft growth in SCID mice[11] as well as nude rats, with complete or nearly complete tumour regression at well tolerated oral doses of 25-100 mg/kg/day in mice and rats. In these studies, tumour regression was observed at clinically relevant concentrations. In the tumour models, ceritinib also exhibited dose and concentration dependent inhibition of the ALK signalling pathway. Phosphorylation of STAT3 in tumour tissues was dose-dependently inhibited by ceritinib in the mouse Karapas299 xenograft model. Ceritinib doses (≥ 25 mg/kg/day) resulting in significant tumour growth regression were associated with 60 to 80% inhibition of STAT3.

Ceritinib was more effective than crizotinib in the treatment of crizotinib sensitive tumours in a mouse xenograft model. Treatment with crizotinib (100 mg/kg/day) and ceritinib (at 25, 50 mg/kg/day) for 14 consecutive days in mice with H2228 xenograft tumours resulted in complete tumour regression. Remission was maintained for ≥ 4 months in 50% of the animals administered 25 mg/kg/day ceritinib and all animals administered 50 mg/kg/day of ceritinib. In comparison, tumours rapidly recurred within 2 weeks in all animals treated with 100 mg/kg/day of crizotinib.

Activity against crizotinib-resistant tumours

Ceritinib was active against crizotinib resistant tumour cells with a variety of ALK mutations. In Ba/F3 cells transduced with EML4-ALK mutants the antiproliferative activity of ceritinib was 2 to 21 fold higher than that of crizotinib, depending on the mutation. Ceritinib IC_{50} values ranged from 38 to 940 nM as compared to IC_{50} values 340 to 2140 nM for crizotinib.

Activity against crizotinib-resistant tumours was also demonstrated in animal tumour xenograft models. Ceritinib inhibited crizotinib resistant NSCLC H2228 tumours with ALK-I1171T or ALK C1156Y mutations or unknown mechanism of resistance in mice. Treatment with ceritinib (50-100 mg/kg/day, plasma C_{max} approximately 1.2-4 fold higher than the clinical C_{max}) exhibited significant anti-tumour activity.

Overall, in vivo studies demonstrated that treatment with ceritinib in mice and rats produced a dose dependent inhibition of xenograft growth with a more sustained anti-tumour response than crizotinib. Ceritinib also inhibits growth of crizotinib-resistant tumours.

Secondary pharmacology

In vitro assays screening for off-target activity against 139 G protein-coupled receptors (GPCRs), ion channels, nuclear receptors and enzymes showed that ceritinib (10 μM) interacted with 42 (approximately 30%) of the targets with > 50% inhibition. Targets with

[11] Also known as NOD scid, NOD SCID. Mice homozygous for the severe combined immune deficiency spontaneous mutation Prkdcscid, commonly referred to as scid, are characterised by an absence of functional T cells and B cells, lymphopenia, hypogammaglobulinaemia, and a normal haematopoietic microenvironment.

IC_{50} values < 2 μM included histamine H2 receptor (0.67 μM), opiate kappa receptor melanocortin 3 receptor (0.67 μM), melanocortin 4 receptor (0.6 μM), adenosine 3 receptor (0.73 μM), tachykinin NK1 receptor (0.99 μM), dopamine 2 receptor (long form) (1.2 μM), and norepinephrine transporter (1.7 μM). Binding to the following targets was also observed (IC_{50} in brackets): transporter monoamine (0.331 μM), potassium channel (0.682 μM), somatostatin SST1 (2.42 μM), SST2 (2.25 μM), SST3 (5.12 μM) and SST4 (1.88 μM). However, functional assays of the above targets showed agonist or antagonist activity only at high concentrations approximately 10 μM or higher compared to the unbound clinical C_{max} of approximately 60 nM, suggesting the above off-target binding is unlikely to be clinically relevant.

Ceritinib inhibited InsR and IGF-1R kinase activity (discussed above), although the inhibitory activity against these receptor kinases was around 50 fold less than against ALK. Inhibition of InsR and IGF-1R was also demonstrated in cells transduced with these receptors and ROS-1 (IC_{50} 180, 220 and 400 nM against ROS1, IGF-1R and InsR, respectively as comparted to IC_{50} 60 nM against cells expressing ALK and unbound clinical C_{max} approximately 60 nM). Thus, ceritinib is only 3 to 7 fold more selective for ALK than the three receptor kinases of the insulin receptor superfamily in the cell proliferation assay. Low antiproliferative activity was observed against Ba/F3 cells transduced with other tyrosine kinases of the insulin receptor superfamily (IC_{50} >1 μM). Activity against IGF-1R was not seen in vivo. A single oral dose of ceritinib at up to 100 mg/kg in nude mice did not inhibit IGF-1R or AKT (IGF-1/AKT pathway) in the NIH3T3 tumour stably expressing human IGF-1R and IGF-2. Nor did ceritinib at up to 100 mg/kg/day (plasma C_{max} approximately 4 times the clinical C_{max}) for 7 days show off-target effects on glucose metabolism or insulin resistance in mice. Off-target inhibition of InsR, IGF-1R and ROS1 is a potential risk in patients at the proposed clinical dose.

IGF-1 blockade is associated with hyperglycaemia.[12] Increased plasma glucose levels (hyperglycaemia) were observed in repeat dose toxicity studies (Monkeys; 3 month study) and reported in patients treated with ceritinib.

Safety pharmacology

The potential effects of ceritinib on cardiovascular, respiratory and central nervous system (CNS) functions were investigated in in vitro assays and in monkeys and rats. Ceritinib inhibited potassium hERG channel activity in human embryonic kidney cells expressing hERG and the IC_{50} (0.4 μM) was approximately 7 fold higher than the unbound clinical C_{max} (approximately 60 nM). In monkeys, QT/QTc prolongation[13] (by 14-44 ms) was observed in one out of 4 monkeys at 10-19 h after a single oral dose of 100 mg/kg ceritinib (plasma concentrations at 10-19 h similar to the clinical C_{max} based on toxicokinetic data in the single dose toxicity study). No significant cardiovascular effects were seen at lower doses (10 or 30 mg/kg); nor was QT prolongation in a non-GLP study in 2 monkeys at 250 mg/kg PO (C_{max} similar to the clinical value) or at lower doses in the 4 and 13 week repeat dose studies. The nonclinical study findings indicate QT prolongation is a risk in patients.

No behavioural changes were observed in a rat observational battery test following a single oral dose of 100 mg/kg ceritinib (C_{max} approximately 2 times the clinical C_{max} based on toxicokinetic data from the toxicity studies). A transient increase in respiratory rate (by

[12] Janssen JAMJL and Varewijck AJ (2014). IGF-IR Targeted Therapy: Past, Present and Future. Front Endocrinol (Lausanne). 2014; 5: 224.
Chen HX and Sharon E. (2013). IGF-1R as an anti-cancer target—trials and tribulations. Chin J Cancer. 2013 May; 32(5): 242–252.

[13] In cardiology, the QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. The QT interval represents electrical depolarization and repolarization of the ventricles. An abnormally prolonged QT is associated with an increased risk of ventricular arrhythmias, especially Torsades de Pointes.

approximately 20%) was recorded 35 to 60 min after dosing but tidal volume and minute volume were unchanged. No signs of neurological toxicity or effects on respiration were observed in repeat dose toxicity studies. Ceritinib is not expected to cause effects on vital functions of the central nervous and respiratory system in patients.

Pharmacokinetics

Absorption, distribution, metabolism and excretion were studied in animal species, which were used in pharmacology and toxicology studies. The time to C_{max} (T_{max}) values (7 to 18 h) after oral administration of ceritinib in animal species (mice, rats and monkeys) indicated a slow rate of absorption, compared with the human T_{max} of 4 to 6 h. Oral bioavailability was moderate (mice: 55%; rats: 48%; monkeys: 43-58%; no human data for comparison).

Ceritinib has a long elimination half-life in rats and monkeys (12 to 16 h), which is shorter than the half-life ($t_{1/2}$) in humans (approximately 40 h). The plasma clearance was low to moderate (approximately 1.5 L/h/kg in mice and rats, 0.4-0.8 L/h/kg in monkeys). Steady state volume of distribution (V_{ss}) was high in all animal species (9.7 L/kg in mice, 19.9 L/kg in rats and 6.5-13.5 L/kg in monkeys), indicating extensive tissue distribution, consistent with rat tissue distribution study results (discussed below).

Protein binding is high and concentration independent in plasma of all species tested (rat approximately 98%, monkey approximately 95%, human approximately 97%; similar protein binding in human plasma and serum). The distribution of ceritinib to blood cells is higher than in plasma; in vitro blood distribution assays showed blood/plasma concentration ratios of 1.72 (rat), 2.59 (monkey) and 1.35 (human). Quantitative whole body autoradiography of rats dosed with radiolabelled ceritinib intravenously (IV) or PO showed rapid and wide distribution of drug-related materials to tissues, with higher concentrations in most tissues than in blood. Maximum concentration in blood and most tissues was reached at 4 h post-dose. Tissues with highest radioactivity concentrations after an oral dose were GIT and excretory and highly vascular organs, and included (in descending order based on C_{max}, excluding GIT) bile, adrenal, liver, spleen, lung/lymph node/thyroid/kidney (similar levels) and pancreas. Low levels were detected in brain, testis and epididymis, indicating that drug-related radioactivity crossed the blood-brain/testis/epididymis barrier. Results from pigmented rats at 168 h post-dose showed relatively high levels of radioactivity in the uveal tract, indicating binding of ceritinib or metabolites to melanin. Relatively high levels were also observed in pituitary and Harderian glands at 168 h.

Studies in rats, monkeys and humans indicated that the primary biotransformation pathways of ceritinib included mono-oxygenation, O-dealkylation, S-dealkylation and N-formylation, with secondary pathways including di-oxygenation, glucuronidation, sulfation and dehydrogenation. Unchanged ceritinib is the major species in plasma of rats and monkeys after IV or PO administration (85-90% of total drug-related components in monkey plasma; no metabolites in rat plasma), similar to humans (82%). Unchanged ceritinib was also the major component in faeces (rat and monkey; also in humans) and bile (rat; bile not collected in monkey studies).

Nine metabolites were identified in monkey plasma (each at levels of ≤ 3.6% the total drug-related AUC) and eleven metabolites in human plasma (each at levels ≤ 2.3% of the total drug-related AUC). Most metabolites formed in humans were detected in rats and/or monkeys. Five metabolites (M23.6, M35.8, M46.6, M48.8 and M52.0) identified in human plasma were not detected in rat or monkey plasma, but these metabolites accounted for only ≤ 2% of total drug-related species, and M23.6 and M35.8 were detected in rat and monkey bile and/or faeces.

The major excretory route in all species (rat, monkey and human) was faecal (approximately 100% of dose), with ≤ 1% of the dose excreted in urine. Studies in bile duct-cannulated rats and tissue distribution study in the same species (discussed above) showed extensive biliary excretion (PO: 24% of dose; IV: 65% of dose). The biliary and faecal excretion data in rats dosed with ceritinib by the IV route suggest that both biliary excretion and gastrointestinal secretion contributed to the elimination of ceritinib and metabolites.

Overall, the pharmacokinetic profiles in rats and monkeys were sufficiently similar to that in humans to allow them to serve as appropriate models for the assessment of drug toxicity in humans.

Pharmacokinetic drug interactions

In vitro studies with recombinant cytochrome P450 (CYP450) isozymes and human hepatic microsomes and selective CYP450 inhibitors showed that CYP3A is the major enzyme in the metabolism of ceritinib. Thus, CYP3A inhibitors and inducers are expected to increase and decrease, respectively, plasma ceritinib concentrations in patients. This has been confirmed in human subjects co-administered with ceritinib and ketoconazole (CYP3A inhibitor) or rifampicin (CYP3A inducer).

Assays using human liver microsomes showed that ceritinib is a potent inhibitor of CYP3A, CYP2A6 and CYP2C9 with unbound K_i values of 47, 9.2 and 70 nM, respectively, similar to or below the unbound human C_{max} of approximately 60 nM at the proposed clinical dose of 750 mg. Ceritinib also showed time-dependent inhibition of CYP3A (K_{inact} 0.0642 min^{-1}). Thus, ceritinib may increase plasma concentrations of drugs that are predominantly metabolised by CYP3A, 2A6 or 2C9 in patients. Moderate inhibition was observed against CYP2B6 (unbound K_i 780 nM) and CYP2C8 (unbound IC_{50} 600 nM but high K_i 4860 nM) and weak inhibition of CYP1A2, 2C19, 2D6 and 2E1 (unbound IC_{50} ≥1.8 μM, >30 times the clinical unbound C_{max}), which are of low clinical relevance.

In vitro assays using human hepatocytes demonstrated induction of CYP3A4 mRNA expression (by 3-9 fold from all 3 donors) by ceritinib but only marginal increases in CYP3A activity (by 2 fold at 2.5 μM) in hepatocytes of one out of 3 donors. The lack of correlation in the induction of CYP3A mRNA and activity may be due to the time-dependent inhibition of this enzyme (discussed above). Given the inhibitory activity of ceritinib against CYP3A ceritinib is unlikely to increase the activity of this enzyme in vivo. In addition, ceritinib was not an activator of human Pregnane X-receptor, which is used to investigate the potential of chemicals to induce the CYP3A4 gene in humans at up to 1 μM (the highest non-cytotoxic concentration). Ceritinib at up to 2.5 μM did not induce the activity or mRNA expression of CYP1A2, 2B6 or 2C9.

Ceritinib is a substrate of P-glycoprotein (P-gp). Absorption and distribution to tissues expressing P-gp may be altered by P-gp inhibitors and/or inducers. Hepatic uptake transporters, organic cation transporter 1 (OCT1), organic anion transporter 2 (OAT2), OATP1B1 and OATP2B1 have little to no effects on the uptake of ceritinib in genetically engineered cells expressing these transporters.

Ceritinib (1.5 μM, test concentration limited by solubility) is not an inhibitor of P-gp, BCRP or MRP2. No inhibition of organic anion/cation transporters, OAT3 and OCT2 and only weak inhibition of OAT1, OCT1, OATP1B1 and OATP1B3 (<40% inhibition at 5 μM) was observed. As the unbound clinical C_{max} is approximately 60 nM, inhibition of these transporters is not expected clinically.

Toxicology

Acute toxicity

A study investigating single dose toxicity in monkeys found no significant treatment related changes in haematology parameters, body weight gain or food consumption. A mild increase in serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) was observed 2 to 3 weeks after dosing at 120 and 250 mg/kg (C_{max} similar to the clinical C_{max} at the proposed daily dose of 750 mg).

Repeat-dose toxicity

Repeat dose toxicity studies of 2 weeks to 3 months in Wistar rats and cynomolgus monkeys assessed the toxicity profile of daily PO administration of ceritinib. The pivotal studies were GLP compliant and the number of animals and species used and duration of study were as recommended in the ICH guideline S9 Nonclinical evaluation of anticancer pharmaceuticals. To investigate the reversibility of effects, studies were conducted in both species with a 4 week recovery (4 week study duration) or 8 week recovery period (3 month study duration).

The highest dose in male rats in the 13 week study resulted in reduced body weight gain, which remained lower than control over the duration of the recovery period. There were no treatment related effects on body weight gain in the 13 week monkey study but the monkeys experienced vomiting at all doses and liquid faeces at the high dose during the treatment period. Rats and monkeys survived through to scheduled sacrifice in all studies, except for one male monkey, which was moribund and euthanised on Day 10 at 100 mg/kg/day in a 2 week pilot study.

Relative exposure

Toxicokinetic analysis indicated that maximum plasma concentrations for ceritinib (T_{max}) were reached between 3 to 10 h post-dose for both species with only slight gender differences. Ceritinib exposure in both rats and monkeys increased with dose. There was only slight accumulation with repeated dosing except for the mid and high doses in the 3 month monkey study where $AUC_{0\text{-}24h}$ on day 73 was 1.5 to 3 fold higher than the Day 1 value. Overall, ceritinib (≤ 30 mg/kg/day; PO) was well tolerated in both rats and monkeys but the exposures were low.

Animal: human exposure ratios were calculated based on plasma the area under the plasma concentration versus time curve from time 0 to 24 h ($AUC_{0\text{-}24h}$) (Table 2). Low relative exposure ratios were achieved at the highest doses in the pivotal repeat dose studies for both species.

Table 2: Relative exposure in pivotal repeat-dose toxicity studies

Species	Study duration [Study no.]	Dose (mg/kg/day)	$AUC_{0\text{-}24h}$^ (ng·h/mL)	Exposure ratio#
Rat (Wistar Hannover)	4 weeks [Study 09700416]	7.5	3135	0.13
		25	14500	0.61
		50	33700	1.4
	3 months [Study	3	1865	0.08
		10	9995	0.42

Species	Study duration [Study no.]	Dose (mg/kg/day)	AUC_{0-24h}^ (ng·h/mL)	Exposure ratio#
	1270164]	30	30350	1.3
Monkey (Cynomolgus)	3 months [Study 1270165]	3	408	0.02
		10	3720	0.16
		30	24450	1.0
Human (Patients)	steady state [Study CLDK378X2101]	[750 mg]	23800	–

= animal: human plasma AUC_{0-24h}; ^ = data are for the sexes combined at the last sampling day.

Major toxicities

Major target organs in both species were bile ducts (including extra hepatic bile duct), biliopancreatic duct, gastrointestinal tract (mainly duodenum), liver and pancreas. Other organs affected were lungs (rat only), mesenteric lymph nodes, thyroid and thymus. Most findings were class effects of tyrosine kinase inhibitors.

- *Bile ducts*: Effects on bile and biliopancreatic ducts were observed in rats at all doses and monkeys at the high dose (30 mg/kg/day). Findings included dilatation, inflammation, vacuolation, erosion, necrosis, and/or hyperplasia. The findings were more severe in rats than in monkeys, and biliopancreatic duct lesions were not reversed after an 8-week recovery period in rats.
- *Gastrointestinal (GI) toxicity*: Findings were limited to the duodenum and were seen in rats at all doses and in monkeys at the high dose. Histological lesions included epithelial inflammation, vacuolation, hyperplasia, and/or necrosis. In monkeys, there were also congestion/haemorrhage, vacuolation and macrophage infiltration, and clinical signs of GIT disturbance such as emesis (all doses) and liquid faeces (high dose). The GIT effects were reversible and only minimal degeneration and vacuolation were seen in one out of 6 male rats (no lesions in female rats or in monkeys) after the recovery period.
- *Liver toxicity*: Minimal to slight necrosis of hepatocytes and minimal subacute peri-cholangiolitis were observed in the preliminary 2-week study at 100 mg/kg/day (AUC 1.8 times the AUC in patients). Hepatic lesions (apart from bile duct findings discussed above) were not apparent in longer term studies at lower doses. Liver weight was slightly increased in rats at 50 mg/kg/day for 2 weeks, and plasma AST and/or ALT slightly increased (< 2 fold) in rats at ≥50 mg/kg/day and monkeys at ≥ 10 mg/kg/day.
- *Effects on pancreas*: Focal acinar atrophy, mixed cell inflammation, and decreased zymogen were observed in rats after 4 weeks of dosing with 50-75 mg/kg/day ceritinib and in the 4-week monkey study at 30 mg/kg/day. No histological findings were evident in longer term (13 weeks) studies in rats or monkeys. Other findings indicative of pancreatic toxicity were increased plasma amylase in the 13-week rat study at 30 mg/kg/day (no change in lipase) and increased lipase in monkeys at 30 mg/kg/day (amylase unchanged). Increased plasma glucose (28-42% at all doses; not dose-related) and insulin levels (2-3 fold at 10 at 30 mg/kg/day) were detected in monkeys, although there was no histological lesion in pancreas islets.

- *Findings in lungs* were alveolar foamy macrophages and macrophage aggregates in rats at ≥25 mg/kg/day, consistent with phospholipidosis. Phospholipidosis was also evident in bile duct epithelia. Increased macrophage aggregates (possibly phospholipidosis) were observed in lymph nodes of rats. These findings were not seen in monkeys. Phospholipidosis is a common effect of cationic amphiphilic agents and was also reported in studies with crizotinib. The clinical relevance of phospholipidosis is uncertain; however, pneumonitis was reported in patients receiving ceritinib or crizotinib.
- *Plasma thyroid hormones* (thyroid stimulating hormone (TSH), T3 and T4) were increased (1.1 to 1.9 fold) in the 13 week rat study at all doses, without changes in organ weight or histological lesions. In monkeys, thyroid weights were decreased in males at all doses in the 4 week study, colloid depletion and small follicles in males at ≥ 10 mg/kg/day. Similar findings were not apparent in the 13 week study at the same doses, although one male had diffuse follicular cell hyperplasia and increased TSH. The clinical relevance of the thyroid findings is uncertain.
- Effects on thymus were relatively minor and findings included lymphoid depletion in the 4 week monkey study at 30 mg/kg/day and decreased thymus weight in the 4-week rat study at 75/50 mg/kg/day, and slight cortical atrophy/lymphocytolysis at 100 mg/kg/day in the 2 week pilot study. However, no thymic changes were observed in the longer term studies in either species.
- Additional findings in rats at 100 mg/kg/day for 2 weeks (1.8 times clinical AUC) were hypocellularity of bone marrow, absence of haematopoiesis of spleen, minimal to moderate focal/multifocal necrosis (cortex/paracortex) and smaller or absence of germinal centre of mesenteric lymph node, and glandular erosion of stomach.

Overall, the toxicological profile and pharmacological effects of ceritinib is comparable with other medicines in this class, such as crizotinib. Since the exposures in the rat and monkey studies were low, many of the reported effects, of which most are reversible after recovery, may occur clinically.

Genotoxicity and carcinogenicity

The potential genotoxicity of ceritinib was assessed in the standard battery of tests in accordance with ICH guidelines[14]. A suitable set of *S. typhimurium* strains were used in the bacterial mutagenicity assay. Concentrations/doses were appropriate.

Ceritinib was not mutagenic in the bacterial reverse mutation assay but significant increases in numerical aberrations (polyploidy) were seen in human peripheral lymphocytes (with or without metabolic activation) in vitro at ≥ 4 µg/mL (with low cytotoxicity) and a small increase (approximately 2.3 fold) in micronuclei in TK6 cells (without metabolic activation) in vitro at ≥ 2.8 µg/mL (approximately 53% cell growth). No structural chromosome aberrations were observed in the human lymphocytes assay. An in vivo bone marrow micronucleus assay in male Wistar rats at up to 2000 mg/kg PO gave negative results. Bone marrow drug exposure was demonstrated in the tissue distribution study in rats (C_{max} and AUC 13 and 28 fold, respectively, higher than the blood drug level), indicating adequate exposure to ceritinib and/or metabolites in the target tissue of the micronucleus assay. Polyploidy is a common finding in chromosome aberration assays *in vitro* and the absence of chromosome structural breakage and a negative *in vivo* micronucleus assay with appropriate exposure would provide sufficient

[14] ICH S2(R1): Guidance on genotoxicity testing and data interpretation for pharmaceuticals intended for human use

assurance of lack of potential for aneuploidy[15]. Thus, ceritinib is considered to have a low risk of genotoxicity in patients.

No carcinogenicity studies were conducted, which is considered acceptable given the intended patient group.[16]

Reproductive toxicity

Fertility and early embryonic development studies were not conducted with ceritinib. This is acceptable for a drug indicated for advanced cancer.[16] There were no abnormal findings in male or female reproductive organs in repeat dose toxicity studies conducted in rats and monkeys for up to 3 months at exposures approximately 1.4 times and equal to, respectively, the human exposure based on AUC. However, based on the pharmacological activities of ceritinib which inhibits IGF-1R at clinically relevant concentrations (IC_{50} 8 nM as compared to the clinical free fraction of C_{max} of approximately 60 nM), ceritinib might affects fertility in patients since IGF-1 deficiency causes infertility in mice.[17]

Embryofetal development studies were performed in rats and rabbits. The studies were GLP compliant with appropriate group sizes and treatment period. However, higher doses could have been tested in rats because of the absence of maternal effects (discussed below). Systemic exposures in both species were below the clinical exposure based on AUC (Table 3).

Placental transfer was demonstrated in both species, although fetal plasma ceritinib concentrations were low. Fetal plasma ceritinib concentrations were 7 to 20 (rat) and 13 to 19 (rabbit) fold lower than maternal plasma concentrations.

Table 3: Relative exposure in reproductive toxicity studies

Species	Study [Study no.]	Dose mg/kg/day	AUC_{0-24h} ng·h/mL	Exposure ratio#
Rat (Wistar)	Embryofetal development [Study 1370073/9000189]	1	142	0.01
		10	2940	0.12
		50	14900	0.63
Rabbit (NZW)	Embryofetal development [Study1370072/9000190]	2	543, 403*	0.02, 0.02
		10	4180, 2340*	0.18, 0.1
		25	18000, 11200*	0.76, 0.47
Human (patients)	Steady state [Study CLDK378X2101]	[750 mg]	23800	–

= animal: human plasma AUC_{0-24h}; * GD 13, 19 data.

[15] ICH guideline S1(R1): Guidance on genotoxicity testing and data interpretation for pharmaceuticals intended for human u

[16] ICH S9: Nonclinical Evaluation for Anticancer Pharmaceuticals

[17] Baker J et al. (1996) Effects of an Igf1 gene null mutation on mouse reproduction. Mol Endocrinol. 10:903-918.
Liu ZZ et al. (1997) Developmental regulation and the role of insulin and insulin receptor in metanephrogenesis. *Proc. Natl. Acad. Sci. USA.* 94: 6758-6763.

In the rat embryofetal development study at doses up to 50 mg/kg/day (animal: human exposure ratio (ER) 0.6), the dams were generally not affected, with only mild decreases in body weight gain at the high dose (gestational body weights comparable), suggesting higher doses could have been administered in the study. The only fetal findings were slightly higher incidences of incomplete ossification of parietal and interparietal bones and wavy ribs at 50 mg/kg/day.

In rabbits, abortions occurred at ≥ 35 mg/kg/day and embryolethality at 50 mg/kg/day in a pilot study. The main rabbit study showed maternal toxicity at 10 and 25 mg/kg/day, manifested as decreased body weight gain. Fetal findings were limited to low incidences of small or malpositioned gallbladder and subclavian retroesophageal cardiac artery at 10 and 25 mg/kg/day and absent gallbladder at 2 mg/kg/day (not at higher doses). The incidence of unossified/incomplete ossification of sternebrae was significantly increased at all doses, although the incidences were not dose-related (42.9%, 51.4% and 42.5% at 2, 10 and 25 mg/kg/day, respectively, compared with 26% in the control group). The incidences of incomplete ossification of other bones (including parietal and hyoid) and other skeletal variations (for example, semi-bipartate thoracic vertebral centrum) were low and only slightly higher than that of the control group.

Because of the low exposures achieved in the animal studies, the potential effects on embryofetal development have not been adequately assessed. As an ALK inhibitor, ceritinib also inhibits other members of the insulin receptor superfamily, such as InsR, IGF-1R and ROS1 (See *Pharmacology* assessment above). Since InsR and IGF-1R play vital roles during early development including embryofetal development and postnatal growth[18] ceritinib is likely to adversely affect embryofetal development and, if excreted in milk, postnatal growth.

Pregnancy category D[19] is appropriate for ceritinib, consistent with the pregnancy classification for another ALK inhibitor, crizotinib and most other tyrosine kinase inhibitors.

There were no studies on peri/postnatal development, and nor were studies on excretion of ceritinib or its metabolites into milk. As discussed above, ceritinib may cause adverse effects in breastfed babies if ceritinib is excreted in milk. Mothers taking ceritinib should stop breast-feeding.

Phototoxicity

Phototoxicity studies were conducted in vitro in the standard 3T3 NRU phototoxicity assay and in a murine local lymph node assay with ultraviolet (UV) A irradiation. The in vitro assay returned photo irritation factor (PIF) values of 8.1 and 5.1 from two assays, indicating ceritinib has phototoxic potential. However, ceritinib was not phototoxic in a murine local lymph node assay by oral administration. Ear and lymph node weights and

[18]Liu JL et al. (2000) Conditional knockout of mouse insulin-like growth factor-1 gene using the Cre/loxP system. Proc Soc Exp Biol Med. 223:344-51.

Liu ZZ et al. (1997) Developmental regulation and the role of insulin and insulin receptor in metanephrogenesis. *Proc. Natl. Acad. Sci. USA.* 94: 6758-6763.

Rother KI & Accili D (2000) Role of insulin receptors and IGF receptors in growth and development. Pediatr. Nephrol. 14: 558-561

Sonnenberg E et al (1991) Transient and locally restricted expression of the ros1i protooncogene during mouse development. EMBO J. 10: 3693-3702.

[19] Category D: Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

lymph node cell counts were unaffected in mice dosed with up to 100 mg/kg/day for 3 days with skin ceritinib concentrations 7 to 15 fold higher than plasma concentrations (plasma C_{max} 2.4 times the clinical C_{max}). Despite the positive results of the in vitro assay and association of ceritinib with melanin, the negative findings in the mouse study suggest ceritinib has a low risk of phototoxicity in patients.

Paediatric use

Ceritinib is not proposed for paediatric use and no specific studies in juvenile animals were submitted. Based on the pharmacological activities discussed above (*Pharmacology*, *Reproductive toxicity*), ceritinib is likely to impair growth and development of children.

Nonclinical summary and conclusions

- The nonclinical dossier was adequate with pivotal studies conducted under GLP conditions and compliant with the relevant ICH S9 guideline on Nonclinical Evaluation for Anti-cancer Pharmaceuticals.
- In vitro primary pharmacology studies demonstrated that ceritinib was most active against ALK among a panel of 36 recombinant human protein kinases. In vitro cell proliferation studies using a variety of cancer cells found that ceritinib inhibited proliferation of cancer cells transfected with fused NPM-ALK or EML4-ALK or ALK activated by fusion with TEL. Ceritinib inhibited proliferation of human lung cancer NSCLC cell lines and the growth of NCI-H2228 cells which carries the EML4-ALK gene fusion.
- In vivo primary pharmacology studies in SCID mice and nude rats showed that administration of ceritinib at clinically relevant concentrations produced a dose-dependent inhibition of H2228 and Karapas299 (expressing EML4-ALK and NPM-ALK, respectively) xenograft growth, with complete or nearly complete tumour regression. Phosphorylation of STAT3 (downstream protein of the ALK signalling pathway) in tumour tissues was dose-dependently inhibited by ceritinib in the mouse Karapas299 xenograft model. Ceritinib was effective in the treatment of crizotinib-resistant tumour.
- No specific secondary pharmacology studies were submitted. However, in vitro assays found that ceritinib inhibited InsR, IGF-1R and ROS1 kinases of the insulin receptor superfamily, with potency around 50 fold (kinase activity inhibition assay) or 3 to 7 fold (cell proliferation assay) less than against ALK.
- Ceritinib inhibited potassium hERG channel activity in human embryonic kidney cells expressing hERG (IC_{50} 04. µM). In vivo monkey studies of cardiovascular effects found that ceritinib (a single PO dose of 100 mg/kg) caused QT/QTc prolongation in 1 out of 4 monkeys. The results indicate a QT prolongation risk in patients. Rat studies found no behavioural changes following a single PO dose of ceritinib (100 mg/kg). A transient increase in respiratory rate (by approximately 20%) was recorded 35-60 min post-dosing but tidal volume and minute volume were unchanged.
- Ceritinib by oral administration had a slow rate of absorption and moderate bioavailability (T_{max} 7-18 h; bioavailability 43-58%) in mice, rats and monkeys. The volume of distribution is large, consistent with high tissue levels of ceritinib/metabolites in a rat tissue distribution study. Ceritinib/metabolites bind to melanin and cross the blood brain barrier. Plasma protein binding is high in all species including humans (95-98%). The distribution of ceritinib to blood cells was higher than in plasma. Ceritinib has a slow clearance and the elimination half-lives in laboratory animals were 12-16 h (compared to approximately 40 h in humans). Unchanged ceritinib is the major species in plasma of rats and monkeys after IV or PO

administration (85-90% of total drug-related components in monkey plasma; no metabolites in rat plasma), similar to humans (82%).

- Ceritinib is cleared by metabolism and biliary excretion. The primary biotransformation pathways of ceritinib included mono-oxygenation, O-dealkylation, S-dealkylation, and N formylation, with secondary pathways including di-oxygenation, glucuronidation, sulfation and dehydrogenation.
- Ceritinib is metabolised predominantly by CYP3A and is also a P-gp substrate, suggesting potential pharmacokinetic interactions with CYP3A and P-gp inhibitors and inducers. It is an inhibitor of CYP3A, CYP2A6 and CYP2C9, and has only weak or no inhibition of other CYPs (including CYP2E1 and CYP2D6). Ceritinib is not an inhibitor of P-gp, BCRP, MRP2 or organic anion/cation transporters, OAT3 and OCT2, and has only weak inhibition of OAT1, OCT1, OATP1B1 and OATP1B3.
- Repeat-dose toxicity studies by the oral route were conducted up to 3 months in Wistar rats and cynomolgus monkeys. Low exposures were achieved in the repeat dose studies (up to 1.4 times the clinical exposure and similar to humans in rats and monkeys, respectively, based on AUC). Major target organs in both species were:
  - Bile ducts/extra hepatic bile duct/biliopancreatic duct; dilatation, inflammation, vacuolation, erosion, necrosis, and/or hyperplasia.
  - Gastrointestinal tract (mainly duodenum); epithelial inflammation, vacuolation, hyperplasia, necrosis, congestion/haemorrhage, vacuolation and macrophage infiltration.
  - Liver; minimal to slight necrosis of hepatocytes and minimal subacute peri cholangiolitis, hepatic lesions, increased liver weight and slight increases in AST and/or ALT.
  - Pancreas; focal acinar atrophy, mixed cell inflammation, decreased zymogen, increased plasma amylase, increased lipase, increased plasma glucose and insulin.
  - Phospholipidosis (rat only) in lungs, lymph nodes and bile duct epithelium.
  - Thyroid; increased plasma TSH, T3 and T4.

Other findings were hypocellularity of bone marrow, absence of haematopoiesis of spleen, focal/multifocal necrosis and small or absence of germinal centre of mesenteric lymph node and glandular erosion of stomach in rats.

- Genotoxicity of ceritinib was adequately assessed by in vitro and in vivo assays. Ceritinib was not mutagenic in the bacterial reverse mutation assay. Nor was it clastogenic in human lymphocytes in vitro or in a bone marrow micronucleus assay in rats in vivo. Ceritinib induced polyploidy in human lymphocytes and a small increase in micronuclei in TK6 cells in vitro. Weight of evidence indicates that ceritinib has a low risk of genotoxicity in patients.
- No carcinogenicity studies were conducted, which is considered acceptable given the intended patient group.
- Fertility and early embryonic development studies were not conducted, which is considered acceptable for a drug indicated for advanced cancer. Repeat dose toxicity studies showed no abnormal findings in male or female reproductive organs. Embryofetal development studies in rats and rabbits at systemic exposures below the clinical exposure (based on AUC) revealed skeletal anomalies (incomplete ossification in both species and wavy ribs in rats) and a slight increase in visceral anomalies in rabbits (absent or malpositioned gallbladder and retro-oesophageal subclavian cardiac artery). Placental transfer was demonstrated in both species although fetal plasma concentrations of ceritinib were low. No studies on peri/postnatal development or studies on excretion of ceritinib or its metabolites into milk.

- An in vitro phototoxicity study in 3T3 NRU cells indicate that ceritinib has phototoxic potential but ceritinib was found not to be phototoxic in a murine local lymph node assay by oral administration, suggesting low phototoxicity potential in patients.

Nonclinical conclusions and recommendation

- The nonclinical dossier was adequate with no major deficiencies.
- Primary pharmacology studies demonstrated the ALK inhibitory activity of ceritinib and activity against crizotinib-resistant tumours, supporting the proposed indication. Other insulin receptor superfamily members, InsR, IGF-1R and ROS1, are also potential targets.
- Safety pharmacology studies indicate that ceritinib may prolong QT intervals in patients.
- Pharmacokinetic profiles of ceritinib in rats and monkeys were sufficiently similar to that in humans. The animal species were appropriate models for the assessment of drug toxicity in humans.
- Ceritinib is a substrate of P-gp and metabolised by CYP3A. It inhibits CYP3A, 2A6 and 2C9 at clinically relevant concentrations. Pharmacokinetic interactions with CYP3A and P-gp inhibitors and inducers and drugs predominantly metabolised by CYP3A, 2A6 or 2C9 are expected to occur in patients.
- Most findings in repeat dose toxicity studies were class effects of tyrosine kinase inhibitors, and are expected to occur in patients.
- Ceritinib has a low risk of genotoxicity in patients.
- Embryofetal development studies in rats and rabbits and the potential inhibition of IGF-1R suggest embryofetal toxicity in patients. Pregnancy category D is considered appropriate. Ceritinib might affect fertility in patients since IGF-1 deficiency causes infertility in mice. Ceritinib may impair growth and development of children.
- There are no nonclinical objections to the registration of ceritinib for the proposed indication.
- Amendments to the draft PI were also recommended but these are beyond the scope of this AusPAR.

V. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

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). Further, lung cancer incidence rates were two fold higher in males compared to females (1,241,601 and 583,100, respectively). In 2011, lung cancer was the most common cause of cancer death for men

and women (8114 deaths overall: 4959 in men; 3155 in woman), accounting for 18.8% of all cancer deaths here in Australia[20].

The two most prevalent sub-types of lung cancer are small cell lung cancer and 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 carcinoma. Adenocarcinoma (40% of lung cancers) is the most common type of lung cancer in the United States (US), and is also the most frequently occurring in non-smokers[21].

NSCLC 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.[22] 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.[23] 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.[22] However neither pemetrexed nor bevacizumab is reimbursed here in Australia for first line setting. 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.[24]

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

[20] Australian Cancer Incidence and Mortality Books

[21] American Cancer Society 2013

[22] NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer Version .2015

Vansteenkiste J et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013;Suppl 6:vi89-98.

[23] Scagliotti GV et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naïve patients with advanced-stage non-small-cell lung cancer. J Clin Oncol 2008;26:3543-51.

Ciuleanu T et al. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomized, double-blind, phase 3 study. Lancet 2009: 374:1432-40.

Ettinger DS et al. Non-small cell lung cancer. J Natl Compr Canc Netw 2010;8:740-801.

Paz-Ares L. Maintenance therapy with pemetrexed plus best supportive care versus placebo plus best supportive care after induction therapy with pemetrexed plus cisplatin for advanced non-squamous non-small-cell lung cancer (PARAMOUNT): a double-blind, phase 3, randomised controlled trial. Lancet Oncol 2012;13:247-55.

[24] Shepherd FA. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol 2000;18:2095-103.

Fossella FV. Randomzied phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX320 Non-Small Cell Lung Cancer Study Group. J Clin Oncol 2000;18:2354-62.

Hanna N et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. J Clin Oncol 2004;22:1589-97.

becoming more appropriate to consider NSCLC as a collection of disease subtypes according to the driving oncogenic aberration, and to select treatment accordingly.[25]

Personalised 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.[26] Several molecular aberrations have been identified in NSCLC, with subsequent development of drugs that target these aberrations. Gefitinib, erlotinib and afatinib for the treatment of NSCLC harbouring epidermal growth factor receptor (EGFR) mutations or overexpression, and crizotinib for the treatment of NSCLC with the ALK fusion translocation oncogenes are examples of this rational targeted approach to treating cancer.[26,27]

Multiple large randomised 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.[28,22] The success of EGFR TKIs highlights the importance of identifying specific NSCLC molecular drivers to appropriately develop targeted agents for treating specific patient populations.

ALK, a receptor tyrosine kinase, was first identified as a fusion protein resulting from chromosomal translocation in the majority of anaplastic large cell lymphoma (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.[29]

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. With an annual incidence of 10,296 lung cancer diagnosis in 2010, up to 720 patients annually could be diagnosed with ALK-positive cancer in Australia.

Patients with ALK-positive NSCLC are associated with specific demographic and clinical features, including never or light smoking history, younger age, and adenocarcinoma histology.[30] In addition, several reports have associated ALK positivity with a more advanced stage at diagnosis and worse prognosis.[4,27] Further, ALK gene rearrangements are largely mutually exclusive with EGFR or KRAS mutations[3], 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

[25] Bang YJ. The potential for crizotinib in non-small cell lung cancer: a perspective review. Ther Adv Med Oncol 2011;3:279-91.
[26] Ma PC. Personalized targeted therapy in advanced non-small cell lung cancer. Cleve Clin J Med 2012;79 Electronic Suppl 1:eS56-60.
[27] Yang P et al. Worse disease-free survival in never-smokers with ALK+ lung adenocarcinoma. J Thorac Oncol 2012;7:90-7.
[28] Gettinger S. A decade of advances in treatment for advanced non-small cell lung cancer. Clin Chest Med 2011;32:839-51.
[29] Soda M et al. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. Nature 2007;448:561-6.
[30] Shaw AT et al. Clinical features and outcome of patients with non-small-cell lung cancer who harbor EML4-ALK. J Clin Oncol 2009;27:4247-53.
Wong DW et al. The EML4-ALK fusion gene is involved in various histologic types of lung cancers from nonsmokers with wild-type EGFR and KRAS. Cancer 2009;115:1723-33.
Rodig SJ et al. Unique clinicopathologic features characterize ALK-rearranged lung adenocarcinoma in the western population. Clin Cancer Res 2009;15:5216-23.

single-arm trials of crizotinib in patients with ALK-positive NSCLC demonstrated impressive activity and with response rates of 50 to 61% and duration of response of 6 to 10 months.[5] Crizotinib (Xalkori) is registered by TGA for the treatment of patients with ALK-positive advanced non-small cell lung cancer and received PBS reimbursement in Australia as of 1 July 2015 under the Managed Entry Scheme for the treatment of adults with stage IIIB or IV non-squamous type of NSCLC harbouring an ALK gene rearrangement in tumour material, defined as 15% (or greater) positive cells by fluorescence in situ hybridisation (FISH) testing.

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 (HR) = 0.49; 95% confidence interval (CI): 0.37–0.64; p<0.001). In addition, crizotinib significantly increased overall response rate over chemotherapy (65% versus 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.[1]

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.[31] Furthermore, not all patients respond to or tolerate crizotinib treatment. These patients have no available effective therapy options. Additionally, brain metastases pose a clinical challenge in NSCLC due to the high overall incidence, and because brain metastases are often the initial site of progression, in particular after crizotinib treatment.[32] Therefore an unmet medical need exists for more potent ALK inhibitors that are highly active in crizotinib-resistant ALK-positive NSCLC.

Patients with metastatic ALK-positive NSCLC do progress after crizotinib therapy and current standard of care is conventional chemotherapy. While the evaluator agrees that there is an unmet need for use of more potent ALK inhibitors that are highly active in ALK-positive NSCLC, it is possibly more important to determine fully the mechanism of crizotinib resistance and see how that influences ceritinib efficacy in that setting.

Guidance

Pre-submission meeting was conducted on 3 December 2014 between TGA and the sponsor, Novartis Pharmaceuticals Australia Pty Ltd and the proposed indication discussed at that time was *Zykadia is indicated for the treatment of patients with locally advanced or metastatic NSCLC that is ALK-positive*.[33]

[31] Katayama R et al. Mechanisms of acquired crizotinib resistance in ALK-rearranged lung cancers. Sci Transl Med 2012;4:120ra17.

Doebele RC et al. Mechanisms of resistance to crizotinib in patients with ALK gene rearranged non-small cell lung cancer. Clin Cancer Res 2012;18:1472-82.

[32] Yang P et al. Worse disease-free survival in never-smokers with ALK+ lung adenocarcinoma. J Thorac Oncol 2012;7:90-7.

Camidge DR et al. Activity and safety of crizotinib in patients with ALK-positive non-small-cell lung cancer: updated results from a phase 1 study. Lancet 2012;13:1011-9.

Camidge DR and Doebele RC. Treating ALK-positive lung cancer – early successes and future challenges. Nature 2012;9:268-77.

[33] TGA guidance at pre-submission meetings is nonbinding and without prejudice.

Contents of the clinical dossier

The clinical dossier documented a full clinical development programme of pharmacology, efficacy and safety studies.

The submission contained the following clinical information:

- 4 clinical pharmacology studies, including four (Studies A2101, A2104, A2105 and A2106) that provided pharmacokinetic (PK) data and no specific studies that provided pharmacodynamic data.
- 1 population PK analyses (based on Studies X2101, X1101, A2201 and A2203).
- Pivotal efficacy/safety studies (Studies X2101, X1101, A2201, A2203) of which Studies X2101 and X1101 also provide PK and pharmacodynamics data
- 2 dose-finding studies (Studies X2101 and X1101).

Paediatric data

The submission did not include paediatric data. Other regulatory bodies found this to be acceptable. The EMA confirmed that ceritinib in the proposed indication falls under the scope of the class waiver on 12 April 2013. Similarly, in the US, ceritinib has an orphan drug designation, and is therefore exempt from the requirements of the Pediatric Research Equity Act.

Given ALK- positive lung cancer occurs in adult population, the evaluator thought it reasonable not to include paediatric data.

Good clinical practice

All the clinical studies in the submission are complied with CPMP/ICH/135/95 Note for Guidance on Good Clinical Practice.

Pharmacokinetics

Studies providing pharmacokinetic data

The studies relating to each pharmacokinetic topic and the location of each study are shown in Table 4 below.

Table 4: Submitted pharmacokinetic studies

PK topic	Subtopic	Study ID	Primary aim
PK in healthy adults	General PK- Single dose (750 mg)	A2105	Human ADME
	- Multi-dose	No studies	
	Bioequivalence† - Single dose	No studies	
	- Multi-dose	No studies	

PK topic	Subtopic	Study ID	Primary aim
	Food effect – 2 x single doses (500 mg)	A2101*	Food effect
PK in special populations	Target population § - Single dose	X2101*	PK parameters and exposure-response relationships
		X1101*	PK in Japanese patients
		X2101	PK parameters
	- Multi-dose	X1101	
		A2201	
		A2203	
	Hepatic impairment	No studies	A2110 ongoing
	Renal impairment	No studies	
	Neonates/infants/children/ adolescents	No studies	
	Elderly	No studies	
Genetic/gender-related PK	Males versus females	No specific studies	
PK interactions	Ketoconazole (2 x single doses; 450 mg)	A2104	DDI (ketoconazole)
	Rifampin (2x single doses; 750 mg)	A2106	DDI (rifampin)
Population PK analyses	Healthy subjects	No studies	
	Target population	X2101	

PK topic	Subtopic	Study ID	Primary aim
		X1101	
		A2201	
		A2203	

* Indicates the primary aim of the study. † Bioequivalence of different formulations. § Subjects who would be eligible to receive the drug if approved for the proposed indication. ADME = absorption, distribution, metabolism and excretion
DDI = drug-drug interaction

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

Evaluator's conclusions on pharmacokinetics

The clinical pharmacology documentation of ceritinib seems to be satisfactory.

Ceritinib PK has not been investigated in patients with mild, moderate and severe hepatic impairment. A study in non-cancer patients with varying degrees of impaired hepatic function is currently ongoing (A2110). Among the patients included in the population PK analysis, 48 had mild pre-existing hepatic impairment. The steady-state AUC_{tau} of ceritinib in these patients was estimated to be similar to that in patients with normal liver function but the analysis is limited since none of the patients included in the population analysis had pre-existing moderate or severe hepatic impairment, as they were excluded from participating in the trials.
In vivo and in vitro data have shown that the concomitant use of CYP3A/P-gp inhibitors can increase the ceritinib plasma concentrations. In fact, results from the ketoconazole study, show that the estimated geometric mean ratios for AUC_{inf} and C_{max} were increased almost 3 fold and 1 fold respectively. Results from a drug-drug interaction (DDI) study with rifampin clearly indicate that strong CYP3A inducer decreases the ceritinib concentrations, leading to reduce both the C_{max} and AUC_{inf} (44% and 70%, respectively). This was addressed appropriately in the PI under 'Interactions with other Medicine'.
Based on in vitro data, ceritinib competitively inhibits the metabolism of CYP3A and CYP2C9 substrates but no clinical studies have been submitted for review. The evaluator understands that an interaction with midazolam (CYP3A4 substrate) as well as with warfarin (CYP2C9) is being performed post-approval (ClinicalTrials.gov Identifier: NCT02422589). Furthermore ceritinib also inhibits CYP2A6 and CYP2E1 at clinically relevant concentrations in the in vitro experiments. The evaluator thinks this has been adequately addressed in the Australian PI but clinical studies have not been conducted. In addition, according to the EU Guideline on Interactions, all important CYPs (as listed in the guideline) should be evaluated for time-dependent inhibition. Such data seems to be lacking for CYP1A2, CYP2C8, CYP2C19, and CYP2D6.

The proposed PI is generally an adequate and accurate summary of the PK presented in the submission. However the following points need further consideration based on the above discussion:

- Given the current lack of specific data in patients with moderately to severely impaired hepatic function, the evaluator thinks it is in the patients best interest to be more conservative in the wording of this issue until hepatic impairment data (Study A2110) becomes available, particularly given that hepatotoxicity was observed in the efficacy-safety study for the target population. Consideration should be made to change the phrasing to '*Ceritinib is not recommended in patients with moderate to severe hepatic impairment*'.

- Ceritinib might induce CYPs regulated by PXR. For some PXR regulated enzymes and transporters (including uridine diphosphate glucuronosyl transferase (UGTs)) the net effect may be induction. In particular, there may be a risk for decreased efficacy of hormonal contraceptives, if UGTs are induced. The evaluator notes that a warning that effectiveness of concomitant administration of oral contraceptives may be reduced with concomitant use of ceritinib was not included in the Australian PI. This is probably important given the young demographics this disease tends to affect.
- The Australian PI does not state the potential effect of gastric acid-reducing agents. Given the prevalence of the use of this class of agents, potential interaction from in vitro data and the lack of human studies, the evaluator thinks it would be reasonable to include this in the PI.

Pharmacodynamics

Studies providing pharmacodynamic data

Table 5 shows the studies relating to each pharmacodynamic topic and the location of each study summary. No specific clinical pharmacodynamics studies have been conducted. Therefore no summaries of the pharmacodynamics studies are presented. Studies below contained report of some pharmacodynamics data for review as a result.

Table 5: Submitted pharmacodynamic studies

PD Topic	Subtopic	Study ID
Primary Pharmacology	Effect on efficacy (ORR)	X2101
		A2201
		A2203
	Effect on safety (hepatotoxicity, hyperglycaemia, QT prolongation, GI related AEs	X2101
		A2201
		A2203

Evaluator's conclusions on pharmacodynamics

The submitted dossier does not contain proper clinical PD studies. In addition, dose investigations presented for ceritinib were limited by few patients. While this is a major limitation, the proposed mechanism of ALK inhibition based on pre-clinical studies and the impressive response of ceritinib in the clinical studies, would justify the use of ceritinib in the proposed indication.

However, further refinement of the target population and understanding the de novo and secondary resistance to ceritinib would benefit the clinical management of ALK-positive NSCLC. The Novartis biomarker programme will hopefully elucidate this clinical issue. The lack of molecular characterisation in the current application is not a significant problem that would prevent approval of use in the crizotinib-resistant setting in NSCLC patients.

Dosage selection for the pivotal studies

Determination of maximum tolerated dose (MTD) has been conducted as part of registration Study X2101. This study was originally designed as a Phase I dose escalation trial for the determination 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 characterise the efficacy, safety and pharmacokinetics (PK) of ceritinib.

The dose-escalation phase included a 3 day single dose PK run-in and the 750 mg daily 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 non-assumable 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 Bayesian Logistic Regression Model (BLRM) assessing the probability of dose-limiting toxicity (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.

- 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 > 400 mg.

Efficacy

Studies providing efficacy data

The Pivotal efficacy/safety Studies X2101, X1101, A2201, A2203 provided efficacy data to support of this application.

Evaluator's conclusions on efficacy

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 of 750g in Study X1101). With regards to patient disposition, a significant proportion of patients are still ongoing 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, although the primary objective has been met, full OS data is not available.

Of the 246 NSCLC patients in the Study X2101, 180 patients (73.2%) who received the first dose of ceritinib 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 so that

patients would have sufficient follow-up for assessment and confirmation of response. The primary efficacy endpoints are overall response rates (ORR) and duration of response (DOR) as assessed by the Investigator per Response Evaluation Criteria In Solid Tumors (RECIST) 1.0[34]. 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 this pivotal efficacy study) should have been considered. However, given ceritinib has a clear mechanism of action where it targets ALK, the evaluator thinks the ORR will likely translate into clinical benefit such as PFS and patient reported outcomes (PRO). This was the case for crizotinib (an ALK-inhibitor that is registered in Australia) where the Phase III trials confirmed the clinical benefit that was hinted by impressive ORR in earlier phase trials. Therefore the evaluator thinks the endpoint of ORR is reasonable at this point. Study A2303 is a Phase III, multi-centre, randomised open-label study of ceritinib versus standard second-line chemotherapy (pemetrexed or docetaxel) in patients previously treated with chemotherapy and crizotinib, and is currently enrolling patients.

Overall, the profile of the patient population in Study X2101 and A2201 largely resembles the population included in the pivotal studies that supported the approval of crizotinib.

It is interesting to note that the primary endpoint of ORR per investigator showed less magnitude of effect in the Phase II study of A2201 (37.1%) than in the Phase I study of X2101 (55.4%) in ALK inhibitor-treated NSCLC patients. Supportive PFS endpoint also showed the same trend. However, patients in both studies appeared to have a similar clinical benefit. The DCR was similarly high in both studies (77.1% in Study A2201 and 74.2% in Study X2101). The differences in the ORR in the two studies may be explained by several factors, including a higher rate of baseline brain metastases (71.4% in A2201 versus 60.1% in X2101) and more advanced disease in Study A2201 than in Study X2101 (median time from diagnosis to first dose of ceritinib of 26.2 months in Study A2201 versus 21.2 months in Study X2101). In addition, different RECIST criteria were used to evaluate ORR in the two studies (RECIST 1.0 in Study X2101 versus RECIST 1.1 in Study A2201), making direct comparison inaccurate.

While investigator determined best overall response (BOR) is subject to bias and therefore questionable as the primary endpoint, the supportive analyses in Study A2201 suggested that overall efficacy results were similar between investigator versus BIRC assessments including ORR, DOR and PFS.

In conclusion, the overall efficacy of ceritinib in the treatment of ALK-positive NSCLC is based on the results of three uncontrolled, open label studies (the extension phase of one Phase I and two Phase II clinical trials). The efficacy of ceritinib in the treatment of ALK-positive NSCLC patients who have had a prior ALK inhibitor (the indication sought) is based on a subgroup of the Phase I trial as well as the A2201 Phase II study. The absence of direct comparative data with other agents such as, chemotherapy in the crizotinib-treated patients is an important limitation. The lack of controlled studies leaves the comparative size of the benefit on PFS, the real effect on patient reported outcomes (PROs) and OS as unknown. However, despite these limitations, the results represent a clinically meaningful value for patients with prior ALK inhibitor treatment for whom there exists an unmet medical need. The efficacy results in the generally heavily pre-treated patients included in the trial are better than would have been expected if treated with conventional chemotherapy only. For example, the estimated ORR for second line chemotherapy was only 20% and a median PFS of 3.0months in the Phase III crizotinib trial (Shaw AT et al, 2013). Therefore there is a favourable benefit risk balance for the proposed indication where patients were previously treated with an ALK inhibitor.

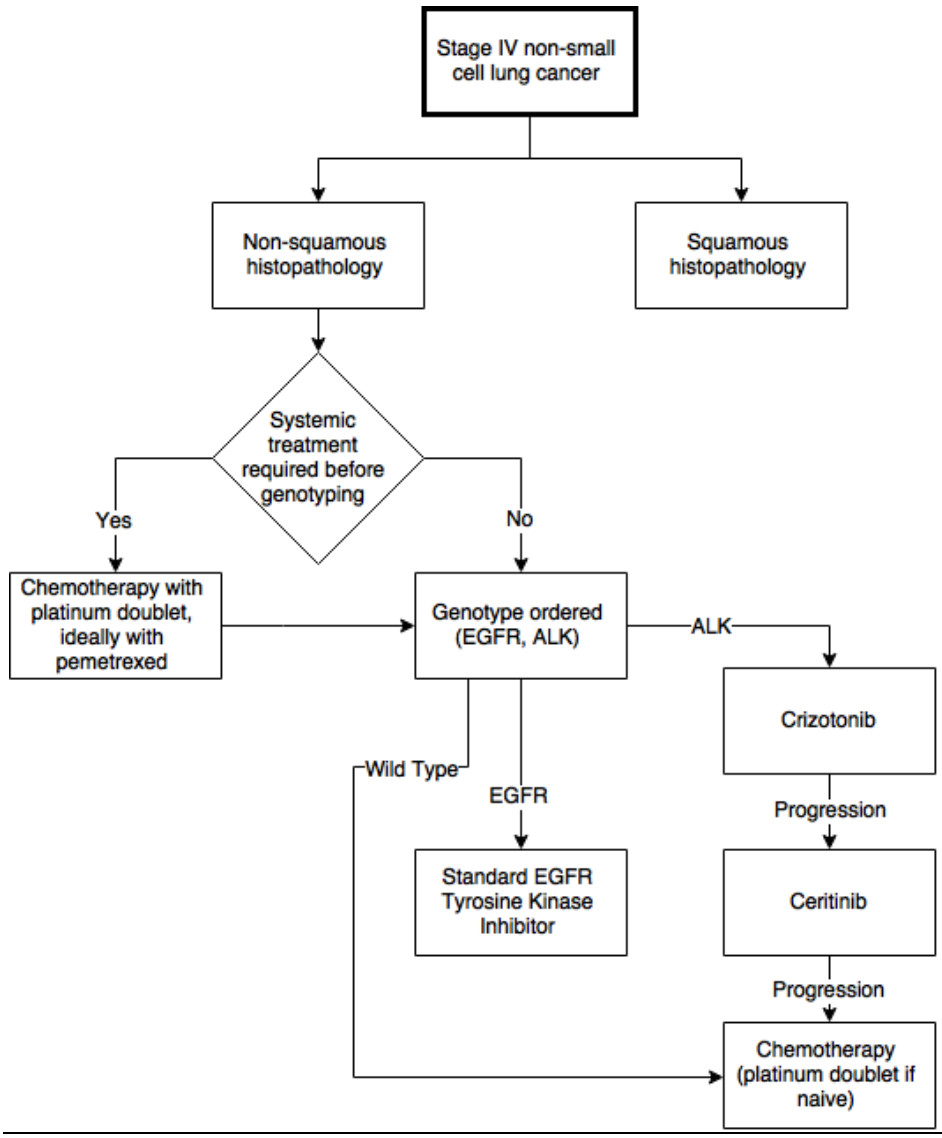
[34] Response Evaluation Criteria In Solid Tumors (RECIST) is a set of published rules that define when tumors in cancer patients improve ('respond'), stay the same ('stabilize'), or worsen ('progress') during treatment.

In contrast, ALK inhibitor naïve patients have access to crizotinib which is registered and reimbursed here in Australia. Consequently, the appropriateness of using a single arm study (with ORR as primary endpoint) to assess efficacy in ALK inhibitor naïve patients is not appropriate in view of the absence of controlled studies with robust endpoints. Moreover, alectinib, another novel ALK inhibitor is being compared with crizotinib in ALK inhibitor naïve patients in a Phase III trial (ALEX study; NCT02075840) and the lack of direct comparison between ceritinib and crizotinib is a deficit in the application. In addition, it is worth mentioning the results from crizotinib Phase III trial where patients were ALK inhibitor naïve but chemotherapy pre-treated.[1] In the trial, 65% of the patients had a PR with approximately 8 months of DOR and 7.7 months of median PFS. While direct cross-trial comparison should not be made, there is no convincing signal, as yet reported, that ceritinib in the ALK-inhibitor naïve patients is superior.

Currently there is insufficient evidence to support a first line indication.

Figure 2 illustrates a suggested Australian algorithm for treatment for ALK-positive NSCLC in 2015, if ceritinib becomes available for use. This obviously may change depending on the outcome of the Phase III randomised trials of alectinib versus crizotinib and ceritinib versus chemotherapy in the first line setting. Understanding in the mechanism of resistance for ALK inhibitors may also assist in the sequential use of different ALK inhibitors.

Figure 2: A suggested Australian algorithm for treatment of ALK-positive NSCLC in 2015 if ceritinib is registered for use



Safety

Studies providing safety data

The following studies provided evaluable safety data: X2101, X1101, A2201 and A2203.

In the pivotal efficacy Study of X2101 safety data was collected but there was no single pivotal study that assessed safety as a primary outcome (see Attachment 2). The designs of the studies have been described in detail in Attachment 2.

Patient exposure

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 750 mg 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 median duration of exposure was 33 weeks (range: 0.3 to 106.1 weeks): 71.6% of patients had been exposed for at least 24 weeks and 25.7% of patients had been exposed for at least 48 weeks. The duration of exposure in the pooled dataset is summarised in the Table 6.

Table 6: Duration of exposure to study drug in the pooled dataset (Safety set)

	X2101	A2201	A2203	X1101	All patients pool
	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
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.

Safety issues with the potential for major regulatory impact

Liver toxicity

There are currently no cases of Hy's law or death due to hepatic failure, although hepatotoxicity AEs were common. A continuing Pharmacovigilance plan is important, particularly given the lack of data in ceritinib use in patients with moderate and severe hepatic impairment.

Cardiovascular safety

There is good clinical evidence of ceritinib prolonging QT interval but there were no deaths or Torsade de Pointes. Warning and recommendation regarding monitoring and dose adjustment is well documented in the draft PI. A Pharmacovigilance plan is in place to monitor this on an ongoing basis.

Interstitial lung disease/Pneumonitis

This is potentially an issue for major regulatory impact. One death was observed attributed to this AE due to ceritinib in the clinical trials and a further patient was captured in the Novartis Global Pharmacovigilance safety database. Recommendation is made regarding monitoring patients for pulmonary symptoms indicative of pneumonitis is made in the draft PI. Ongoing surveillance of this Tyrosine kinase inhibitors (TKI) effect is required.

Serious skin reactions

AEs in 'Skin and subcutaneous tissue disorder' as a system organ class was documented in 189 patients (36%) with very low incidence of Grade 3 to 4 reactions (0.8%). Pruritus and dry skin occurred in 6.7% and 6.5% of patients respectively, with 0.2% and 0% Grade 3 to 4 severity, respectively. Ceritinib does not appear to have significant skin toxicity that would have major regulatory impact.

Postmarketing data

Up to June 2014, there were a total of 20 cases identified and retrieved from the Novartis global pharmacovigilance safety database. Fifteen (15) cases were solicited reports from post-marketing studies [all assessed as related] including 3 serious and 12 non-serious. Five (5) cases of spontaneous reports were identified including 3 serious and 2 non-serious. The majority of the cases had events that either were considered as expected for Zykadia (such as diarrhoea, nausea, vomiting and abdominal pain) or required more information to allow a meaningful assessment.

Evaluator's conclusions on safety

The median duration of exposure to ceritinib 750 mg up to the data cut-off date is the following: 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.

AEs occurred commonly in patients treated with ceritinib at a daily dose of 750 mg in the clinical development programme. Almost all patients (99.8%) experienced an AE, with 73.1% of AEs being graded as 3 to 4. In addition over half of the AEs were suspected to be drug-related. The most common AEs observed across studies were GI disorders, followed by General disorders and administrative site conditions, and Investigations. The most frequently reported Grade 3-4 AEs were increased ALT, increased gamma-glutamyl transferase (GGT), increased AST, fatigue, diarrhoea, nausea and hyperglycaemia. The AEs experienced by patients also tended to be these events were persistent and recurrent, and the AEs requiring dose adjustments or interruptions was also reported for a large proportion of patients (74.9%). Furthermore significant proportion of patients (84.8%) required supportive medications for management of their GI AEs. Despite this, treatment discontinuation was not frequent (8.8%). It is however important to bear in mind that the target population in these studies included heavily pre-treated NSCLC where symptom burden is typically high.

There were no clinically meaningful differences in the safety findings of ceritinib in patients previously treated with ALK inhibitor and ALK inhibitor naïve patients.

Although hepatic enzyme elevations were frequently reported and led to dose adjustments or temporary interruptions, very few patients had to discontinue ceritinib due to hepatic AEs (0.8%). Importantly, no cases of Hy's law or deaths due to hepatic failure have been reported in the ceritinib programme, up to the data cut-off date.

Ceritinib has been associated with interstitial lung disease (ILD)/pneumonitis, a class-effect in some TKIs. A total of 18 cases were detected in all studies (n=525), including one

case of pneumonitis with fatal outcome. There was another case with ceritinib-related ILD/pneumonitis leading to an outcome of death in the Novartis Global Pharmacovigilance safety data.

Cardiac disorders including bradycardia and electrocardiogram (ECG) abnormalities have also been observed during the ceritinib development programme. Taking into consideration that QTc prolongation is a pharmacological class effect and an important safety concern for TKIs (including crizotinib); QTc effect was documented in the studies. QT prolongation AEs were reported in 7.6% of patients (Grade 3-4 in 1.5%), but there were no deaths or cases of Torsades de Pointes. It is interesting to note that Study X2101 showed that increased exposure of ceritinib was associated with increased population-corrected QT (QTcP), indicating a modest QT prolongation effect of ceritinib. This needs clear documentation in the PI and warning regarding drug interaction and monitoring is required.

Other safety concerns identified were: hyperglycemia, increased lipase, visual disorders, bradycardia, neuropathy, increase creatinine levels/renal failure, and oedema.

In conclusion, the available safety findings suggest that, although the AEs seem to be manageable, ceritinib is not particularly well tolerated. This is further supported by the persistent and recurrent nature of the most frequent AEs and the need for dose reduction in majority of patients.

First Round Benefit-Risk Assessment

First round assessment of benefits

The benefits of Zykadia in the proposed usage (in ALK-positive locally advanced or metastatic NSCLC previously treated with an ALK-inhibitor) are:

- Zykadia has an ORR of 37.1% in A2201 and 55.4% in X2101 in patients who were heavily pre-treated, with more than half of the patients having received at least 3 prior regimens including crizotinib. Similarly, the duration of response was similarly long in both studies (median 9.2 months and 7.39 months, respectively).
- Furthermore, the PFS seen in these patients ranged from a median of 5.7 months in Study A2201 to 6.9 months in Study X2101, while preliminary median OS ranged from a median of 14 months in Study A2201 to not being reached in Study X2101. These secondary efficacy measures were immature to draw definitive conclusions.
- While these results came from uncontrolled, open-label clinical trials and the primary endpoint was ORR based on investigator assessment, these ORR rates exceed what is expected with chemotherapy in this setting (ORR of 20% and PFS of 3 months in chemotherapy arm of the Phase III crizotinib trial) and indicates that patients who have progressed on a prior ALK inhibitor would have a high likelihood of responding to ceritinib and therefore derive a clinical benefit.
- Phase III comparative study in ALK-positive NSCLC previously treated with platinum doublet and crizotinib (ceritinib versus chemotherapy) is ongoing[35].
- Consideration should be made to include a warning for decreasing effectiveness of oral contraceptives with concomitant use of Zykadia and the potential effect of gastric acid-reducing agents on Zykadia (subject of an ongoing clinical trial) as discussed in the Pharmacokinetics section.

[35] ClinicalTrials.gov Identifier: NCT01828112

First round assessment of risks

The risks of Zykadia in the proposed usage are:

- The most common adverse events observed across studies (comprising 525 patients exposed to ceritinib 750 mg, with a median duration of treatment of 33 weeks) were GI disorders (nausea, diarrhoea, vomiting and constipation), followed by general disorders and administrative site conditions, and investigations. The most frequently reported Grade 3-4 adverse events were increased ALT, increased GGT, increased AST, fatigue, diarrhoea, nausea and hyperglycaemia.
- Hepatic enzyme elevations were frequently reported and led to dose adjustments or temporary interruptions and discontinuation (only 0.8% of patients). There were no AEs leading to death or cases of Hy's law.
- Interstitial lung disease/pneumonitis has been associated with Zykadia, a class-effect known for some TKIs. A total of 18 cases were detected in the trials presented in the dossier, with one outcome of death.
- Cardiac disorders including QT prolongation and bradycardia were observed. No deaths or Torsades de Pointes were observed. It appears that increased exposure of ceritinib was associated with increased QTc.
- While Zykadia associated AEs appears manageable, Zykadia is not well tolerated. This is supported by the persistent and recurrent nature of the frequent AEs.

First round assessment of benefit-risk balance

The benefit-risk balance of Zykadia, given the proposed usage, is favourable.

Although the true clinical benefit of Zykadia is unknown due to the limitations of immature PFS and OS data and the uncontrolled nature of the clinical trials, the impressive effect of Zykadia on tumour burden in previously heavily pre-treated patients is clinically meaningful in a population with limited options of treatment. From the literature, we know that this degree of ORR is not usually observed in solid tumours including ALK-positive NSCLC after several lines of chemotherapy. In the Phase III crizotinib trial[1], patients treated with chemotherapy in second line have shown an ORR of 20% only and a median PFS of 3.0 months.

Previous experience with crizotinib showed a clear initial response rate translating into true clinical benefit in ALK-positive lung cancer patients in Phase III trials and the evaluator thinks the currently available data could support approval of Zykadia given the similar mechanism of action, provided confirmatory data of the benefit of Zykadia could be provided through the ongoing Phase III clinical trial.

While ceritinib did not seem to be well tolerated based on the data, it was manageable. The high AE rates may also be related to the inherent nature of the target population in the studies, that is heavily pre-treated patients. In view of the likely clinical benefit in an area of unmet needs, the profile of AEs presented is acceptable. In addition the Risk management plan is satisfactory in ongoing monitoring of the safety profile of Zykadia.

First round recommendation regarding authorisation

Based on the clinical data submitted the evaluator recommends that the application for Zykadia be approved.

Second Round Evaluation of clinical data submitted in response to questions

For details of the sponsor's responses and the evaluation of these responses please see Attachment 2.

Second Round Benefit-Risk Assessment

Second round assessment of benefits

The responses to the Clinical questions have not altered the evaluator's initial assessment of benefits (see above fore details).

Second round assessment of risks

The responses to the Clinical S31 questions have not altered my initial assessment of risks (see above fore details).

Second round assessment of benefit-risk balance

The responses to the Clinical questions have not altered the initial assessment of benefit-risk balance. The evaluator continues to believe that the benefit-risk balance of Zykadia, given the proposed usage, is favourable (see above for details).

The evaluator believes the revised changes made to the Australian PI clearly communicate the potential risks and drug interactions to the prescribers. In addition the Risk management plan is satisfactory in ongoing monitoring of the safety profile of Zykadia.

Second round recommendation regarding authorisation

Based on the clinical data originally submitted, as well as the responses to the Clinical questions, the evaluator recommends that the application for Zykadia be approved.

VI. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (EU-RMP (Version: 2.4, dated 27 February 2015) with an Australian Specific Annex (ASA) Version: 1.0, dated 31 March 2015) which was reviewed by the RMP evaluator.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 7.

Table 7: Sponsor's summary of ongoing 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

The sponsor proposes routine pharmacovigilance activities to monitor all the specified safety concerns and missing information. Additional pharmacovigilance activities, in the form of ongoing Phase I clinical trials are proposed to further characterise the missing information: 'Patients with hepatic impairment', 'Concomitant use of ceritinib and CYP3A, CYP2C9, CYP2A6, or CYP2E1 substrates; ceritinib and drugs that may prolong the QT interval' and 'Concomitant use of ceritinib and gastric acid reducing agents such as PPIs'.

Risk minimisation activities

The sponsor concludes that routine risk minimisation activities for all the specified safety concerns and missing information are sufficient, except for the important potential risk: 'Neuropathy' and the missing information: 'Patients with severe cardiac impairment', 'Long-term safety' and 'Concomitant use of ceritinib and gastric acid reducing agents such as PPIs' for which no risk minimisation activities are proposed.

Reconciliation of issues outlined in the RMP report

Table 8 summarises the first round evaluation of the RMP, the sponsor's responses to issues raised by the evaluator and the evaluation of the sponsor's responses.

Table 8: Reconciliation of issues outlined in the RMP Evaluation Report

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
1. Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated section request and/or the Nonclinical and Clinical Evaluation Reports respectively. It is important to ensure that	The sponsor states: *'At this time no specific issues have been raised by the Clinical Evaluator regarding the EU RMP submitted and the Nonclinical*	The nonclinical report have now become available and the sponsor should now adequately address any outstanding issues (see Section 2: 'Comments on the safety specification

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
the information provided in response to these includes a consideration of the relevance for the Risk Management Plan and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.	*Evaluation Report first round is not available at this time'.*	of the RMP'), preferably before this application is approved.
2. Consistent with the US FDA 'Postmarketing Requirements', the important potential risk: 'Toxicity from drug over-exposure when taken with food' should be included as a new safety concern. Consideration must be given as to what pharmacovigilance and risk minimisation activities will be proposed for this new safety concern and only the ASA need be revised accordingly.	The sponsor has provided justification and concluded: *'modeling demonstrates that even if a patient took ceritinib at 750 mg daily with food, the expected increased exposure would not result in a QT prolongation beyond 21.6 ms, indicating a low risk of increased toxicity driven by increased systemic exposure caused by food intake. Therefore, the applicant does not consider that that 'Toxicity from drug over-exposure when taken with food' should be included as a new safety concern'.*	This is acceptable.
3. As previously stated consideration must be given as to what pharmacovigilance activities will be proposed for the new important potential risk: 'Toxicity from drug over-exposure	The sponsor states*: 'As indicated in response to Recommendation 2, the Applicant does not consider that 'Toxicity from*	The sponsor has documented this undertaking in the updated ASA and this is acceptable.

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
when taken with food'. To that end the sponsor should at least include the US FDA required clinical trial to evaluate the systemic exposure and safety of 450 mg Zykadia (ceritinib) taken with a meal and 600 mg Zykadia (ceritinib) taken with a light meal as compared with that of 750 mg Zykadia (ceritinib) taken in the fasted state in metastatic ALK-positive NSCLC patients as an additional pharmacovigilance activity for this new safety concern. Only the ASA need be revised accordingly and it is expected that at least a draft protocol for this study will be attached to the revised ASA.	*drug over-exposure when taken with food' should be included as a new safety concern, therefore no pharmacovigilance activities are proposed. Although Novartis does not propose to add 'Toxicity from drug over-exposure when taken with food' to the summary of ongoing safety concerns at this time, effects on drug exposure due to food interactions will be evaluated in Study A2112 as previously discussed.*	
4. When the US FDA approved the ALK-positive NSCLC indication this approval stated: *'This indication is approved under accelerated approval based on tumor response rate and duration of response. An improvement in survival or disease-related symptoms has not been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials'*. If applicable, it is recommended to the Delegate that similar statements alluding to an absence of efficacy data be included in the Indications section of the Australian PI. Any such change should be adequately	The sponsor has objected to this recommendation and provided justification for their position.	This recommendation remains outstanding for the Delegate's consideration.

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
reflected in the draft consumer medicine information document.		
5. As previously stated consideration must be given as to what risk minimisation activities will be proposed for the new important potential risk: 'Toxicity from drug over-exposure when taken with food'. It is acknowledged that the following routine risk minimisation is already included under the 'Drug-food/drink interactions' subheading and in the Dosage and Administration section of the draft Australian PI respectively: · *The bioavailability of ceritinib is increased in the presence of food depending on the fat content in the meal (see Pharmacokinetics; Absorption). Ceritinib should be taken on an empty stomach. No food should be eaten for at least two hours before and two hours after the dose of ZYKADIA is taken.* · *ZYKADIA should be administered orally once daily at the same time every day. ZYKADIA capsules should be swallowed whole with water. The capsules should not be chewed or crushed. ZYKADIA capsules must be taken on an empty stomach. No food should be eaten for at least two hours before and two hours after the dose of ZYKADIA is taken (see Pharmacokinetics;*	The sponsor has objected to this wording and proposed alternative wording as follows: '*No food should be eaten for at least two hours before and two hours after the dose of ZYKADIA is taken <u>in order to avoid systemic exposure exceeding that of a 750 mg ZYKADIA dose taken in the fasted state, which may increase adverse drug reactions</u>'.*	The sponsor's overall proposed approach to this matter is generally acceptable, although it is recommended to the Delegate that the following text from the corresponding US FDA monograph be included in the Pharmacokinetics; Absorption section of the Australian PI: *'A 600 mg or higher ZYKADIA dose taken with a meal is expected to result in systemic exposure exceeding that of a 750 mg ZYKADIA dose taken in the fasted state, and may increase adverse drug reactions'.* The ASA should be amended accordingly, preferably before this application is approved.

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
Absorption). However, it is recommended to the Delegate that the last identical sentence be strengthened as follows and all these sections of the Australian PI be cross-referenced to each other: *'No food should be eaten for at least two hours before and two hours after the dose of ZYKADIA is taken <u>in order to avoid the serious risk of toxicity from drug over-exposure</u>'.* Any such change should be adequately reflected in the draft consumer medicine information document.		
6. In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the draft product information document be revised as follows: · For the important identified risk: 'Hepatotoxicity', the sentence in the PRECAUTIONS section of the Australian PI: *'Monitor with liver laboratory tests (including ALT, AST, and total bilirubin) prior to the start of treatment and monthly thereafter'* should be amended to: *'Monitor with liver laboratory tests (including ALT, AST, and total bilirubin) prior to the start of treatment, <u>every 2 weeks for the first month of treatment</u> and monthly thereafter'.* This would align with the approved EU SmPC and enhance the safe use of this medicine. · For the important identified risk: 'Hepatotoxicity' and the missing information:	The sponsor has objected to this recommendation and provided justification for their position. The sponsor has concluded: *'Therefore, monthly evaluation of liver laboratory tests is acceptable to follow patients for hepatotoxicity. The AU PI recommendation is based on the US PI, the Canadian Product Monograph, and the Swiss label'.* The sponsor states: *'Novartis acknowledges that the clinical and exposure data in patients with pre-existing moderate to severe hepatic impairment are not currently*	This is acceptable. This is acceptable. This is acceptable. This is acceptable.

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
'Patients with hepatic impairment', the Dosage and Administration section of the Australian PI states: *'Caution should be used in patients with severe renal impairment as there is no experience with ZYKADIA in this population (see Pharmacokinetics; Special Populations)'.* However this internal cross reference states: *'The pharmacokinetics of ceritinib has not been studied in patients with moderate to severe hepatic impairment. A recommended dose has not been determined for patients with moderate to severe hepatic impairment'.* Consequently the cautionary statement should be amended to: *'Ceritinib is not recommended for patients with moderate to severe hepatic impairment'* or words to that effect. This would ensure internal consistency within the Australian PI, align with the approved EU SmPC and enhance the safe use of this medicine. · For the important potential risk: 'Concomitant use of ceritinib and strong CYP3A inhibitors or strong CYP3A inducers', the Dosage and Administration section of the Australian PI may be amended as follows: *'Avoid concurrent use of strong CYP3A inhibitors during treatment with ZYKADIA (see Interactions with other Medicines). If concomitant use of a strong CYP3A inhibitor is unavoidable, reduce the ZYKADIA dose by*	*available, and therefore, agrees that ceritinib should not be recommended in patients with moderate to severe hepatic impairment. The Australian PI Dosage and Administration section [module 1.3.1.2], Precautions section [module 1.3.1.2] and Pharmacodynamics section [module 1.3.1.2] have been amended to align with the EU SmPC language'.* The sponsor states: *'Novartis agrees to include in the DOSAGE AND ADMINISTRATION section of the Australian PI [module 1.3.1.2] the additional information regarding strong CYP3A inhibitors'.* The sponsor states: *'The applicant acknowledged that data regarding the potential interaction of ceritinib with H2-blockers/proton pump inhibitors are not currently available and therefore agrees to add this information in the Australian PI*	

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
approximately one-third, rounded to the nearest multiple of the 150 mg dosage strength. Patients should be carefully monitored for safety. If long-term concomitant treatment with a strong CYP3A inhibitor is necessary and the patient tolerates the reduced dose well, the dose may be increased again with careful monitoring for safety, to avoid potential under-treatment. After discontinuation of a strong CYP3A inhibitor, resume the ZYKADIA dose that was taken prior to initiating the strong CYP3A4 inhibitor'. This would align with the approved EU SmPC and enhance the safe and effective use of this medicine. · For the missing information: 'Concomitant use of ceritinib and gastric acid reducing agents such as PPIs', the following information may be included under the subheading: 'Agents that may decrease ceritinib plasma concentrations' in the Interactions with Other Medicines section of the Australian PI: *'Caution should be exercised with concomitant use of P-gp inducers. 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. A dedicated study to evaluate*	*Interactions section [module 1.3.1.2]'.*	

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
the effect of gastric acid-reducing agents on the bioavailability of ceritinib has not been conducted'. This would align with the approved EU SmPC and enhance the safe use of this medicine.		
7. In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the draft consumer medicine information document be revised to adequately reflect any changes made to the Australian PI as a result of the above recommendations.	The sponsor states: *'Novartis agrees to amend the CMI in line with the PI changes [module 1.3.2]'.*	This is acceptable.

Summary of recommendations

This document seeks to reconcile issues identified in the RMP evaluation report for the above submission with consideration of the following documents:

1. The updated EU-RMP for Ceritinib (Version 2.5, dated 29 April 2015) with an updated ASA (Version 2.0, dated 23 November 2015)
2. Sponsor's response to TGA's request for further information (25 November 2015)
3. Prescription Medicines Authorisation Branch (PMAB) of the TGA Clinical Evaluation Report (CER) for Zykadia (7 October 2015)
4. Scientific Evaluation Branch (SEB) Nonclinical Evaluation Report (NCER) for Zykadia (11 December 2015 & 7 January 2016)

It is considered that the sponsor's response to the TGA's request has not adequately addressed all of the issues identified in the RMP evaluation report.

Outstanding issues

Issues in relation to the RMP

The sponsor was asked to respond to safety considerations raised by the nonclinical and clinical evaluators through the consolidated request for information and/or the nonclinical and clinical evaluation reports, in the context of relevance to the RMP. The sponsor states: *'At this time no specific issues have been raised by the Clinical Evaluator regarding the EU RMP submitted and the Non-Clinical Evaluation Report Round 1 is not available at this time'.* Nevertheless the nonclinical evaluation report has now become available and the sponsor should now adequately address any outstanding issues, preferably before this application is approved.

Consistent with the US FDA 'Postmarketing Requirements', the sponsor was asked to include the important potential risk: 'Toxicity from drug over-exposure when taken with food' as a new safety concern. The sponsor has provided justification and concluded: *'modeling demonstrates that even if a patient took ceritinib at 750 mg daily with food, the*

expected increased exposure would not result in a QT prolongation beyond 21.6 ms, indicating a low risk of increased toxicity driven by increased systemic exposure caused by food intake. Therefore, the applicant does not consider that that 'Toxicity from drug over-exposure when taken with food' should be included as a new safety concern'. Despite this position the effects on drug exposure due to food interactions will be evaluated in Study A2112 being conducted in the USA and the sponsor has provided an undertaking (as documented in the updated ASA) *'to include 'Toxicity from drug over-exposure when taken with food' in the RMP if the results of Study A2112 warrant an amendment to the summary of ongoing safety concerns. Study results from A2112 can be provided to the TGA upon request'.* The sponsor has advised that this study achieved FPFV in April 2015 and a full study report is anticipated on 31 September 2017. Furthermore it was acknowledged that routine risk minimisation was already included under the 'Drug-food/drink interactions' subheading and in the Dosage and Administration section of the draft Australian PI for this safety concern. However, it was recommended to the Delegate that all these sections of the Australian PI be cross-referenced to each other and the following sentence be strengthened as follows:

'No food should be eaten for at least two hours before and two hours after the dose of ZYKADIA is taken in order to avoid the serious risk of toxicity from drug over-exposure'. The sponsor has objected to this wording and proposed alternative wording as follows: '*No food should be eaten for at least two hours before and two hours after the dose of ZYKADIA is taken in order to avoid systemic exposure exceeding that of a 750 mg ZYKADIA dose taken in the fasted state, which may increase adverse drug reactions'.*

The sponsor's overall proposed approach to this matter is generally acceptable although it is recommended to the Delegate that the following text from the corresponding US FDA monograph be included in the Pharmacokinetics; Absorption section of the Australian PI: *'A 600 mg or higher ZYKADIA dose taken with a meal is expected to result in systemic exposure exceeding that of a 750 mg ZYKADIA dose taken in the fasted state, and may increase adverse drug reactions'.* The ASA should be amended accordingly, preferably before this application is approved.

It was recommended to the Delegate that statements alluding to an absence of efficacy data, similar to the corresponding US FDA monograph, be included in the Indications section of the Australian PI. The sponsor has objected to this recommendation and provided justification for their position. Nevertheless this recommendation remains outstanding for the Delegate's consideration.

Advisory Committee on the Safety of Medicines (ACSOM) advice was not sought for this submission.

Key changes to the updated RMP

In their response to the TGA's requests the sponsor provided an updated EU-RMP (Version 2.5, dated 29 April 2015) with an updated ASA (Version 2.0, dated 23 November 2015). Key changes from the versions evaluated in the first round are summarised below:

	Key changes
EU-RMP	· The important identified risk: 'Pancreatitis' has been included as a new safety concern, for which routine pharmacovigilance and routine risk minimisation are proposed.
ASA	· Section 5.2.2: 'Additional studies not part of the Pharmacovigilance Plan of the EU RMP', which references the food effect study (A2112) being conducted in the USA, has been added. · Table 2: 'Details by safety concern of information proposed to be included in the Australia Product Information and EU SmPC and justification for any differences' has been updated to incorporate

	Key changes
	changes requested by the TGA and to align with the EU-RMP. · Table 3: 'Summary of safety specification, pharmacovigilance plan and planned risk minimisation measures in Australia' has been updated to incorporate changes requested by the TGA and to align with the EU-RMP.

Suggested wording for conditions of registration

RMP

Any changes to which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise. At this time no wording can be provided, as it is recommended that an acceptably revised ASA be submitted before this application is approved.

VII. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The quality evaluator had issues still outstanding and the sponsor is requested to comment if these have been resolved (see Questions for Sponsor):

1. Some changes to the Provisional ARTG Records are required.
2. The labels require revision.
3. The capsule dissolution limit should be reviewed by the sponsor (or a tighter limit could be made a condition of registration).

Acceptability of the proposed trade name Zykadia to Kadian morphine sulfate sustained release capsule Mayne Pharma (which are export only).

The Delegate commented that the similarity to, Kadian, the morphine sulphate medicine is noted and is of concern given this could well be used in lung cancer patients. However, this is not marketed in Australia limiting the risk.

The low solubility except in acid is drawn to the attention of the delegate (that is, the potential risk of low bioavailability in achlorhydric patients or if dosed with antacids etc).

The Delegate commented that information is included in the PI regarding this and there is a study of the effect of esomeprazole on ceritinib absorption to be submitted as a Condition of Registration upon completion.

Otherwise registration is recommended with respect to Chemistry, Manufacturing, and Controls (CMC) and bioavailability aspects.

Nonclinical

The non-clinical evaluator had no objections on nonclinical grounds to registration of ceritinib for the proposed indication.

The following conclusions and recommendations were made:

· The nonclinical data dossier was adequate with no major deficiencies.

- Primary pharmacology studies demonstrated the ALK inhibitory activity of ceritinib and activity against crizotinib resistant tumours, supporting the proposed indication. Other insulin receptor superfamily members such as InsR, IGF-1R and ROS1 are also potential targets.
- Safety pharmacology studies indicate that ceritinib may prolong the QT interval in patients.
- Pharmacokinetic profiles of ceritinib in rats and monkeys were sufficiently similar to that in humans. The animal species were appropriate models for the assessment of drug toxicity in humans.
- Ceritinib is a substrate of P-gp and metabolised by CYP3A. It inhibits CYP3A, 2A6 and 2C9 at clinically relevant concentrations. Pharmacokinetic interactions with CYP3A and P-gp inhibitors and inducers and drugs predominantly metabolised by CYP3A, 2A6 or 2C9 are expected to occur in patients.
- Most findings in repeat dose toxicity studies were class effects of tyrosine kinase inhibitors and are expected to occur in patients.
- Ceritinib has a low risk of genotoxicity in patients.
- Embryofetal development studies in rats and rabbits and the potential inhibition of IGF-1R suggest embryofetal toxicity in patients. Pregnancy category D is considered appropriate. Ceritinib might affect fertility in patients, since IGF-1 deficiency causes infertility in mice. Ceritinib may impair growth and development of children.

The nonclinical evaluator noted:

> *'The longest duration of toxicity studies was 13 weeks in rats and monkeys. It is unclear why a rat 26-week study was referenced in the RMP (under Respiratory tract, and Hepatobiliary system and pancreas).'*
>
> *The sponsor stated that a 26-week rat study and a 39-week toxicity study had been conducted but have not been provided for evaluation. No new toxicology findings were identified in these studies. The study reports should be provided to TGA for evaluation in future applications for ceritinib.'*

The Delegate commented that the submission of the 26 and 30 week toxicity study with the next Category application, for evaluation by the TGA is a condition of registration (see Conditions of Registration).

Clinical

The submitted data was evaluated using TGA adopted EMA Guidelines as follows:

- Guideline on the evaluation of anticancer medicinal products in man Points to consider on application with1. Meta-analyses; 2. One pivotal study.

The following references were used:

- European Medicines Agency Public Assessment Record accessed 18 February 2016
- FDA Medical Review and label accessed online 18 February 2016 http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails

Clinical evaluator's recommendation

The clinical evaluator recommended that the application should be approved on the limited evidence available on the grounds of unmet need.

Paediatric data
The submission did not include paediatric data which is acceptable.

Pharmacokinetics/Pharmacodynamics

Summary of PK data

Ceritinib is slowly absorbed and plasma concentrations peaked at approximately 6 to 8 hours in healthy subjects. The terminal half-life ranged from 36 to 48 hours across doses of 450 to 750 mg in healthy subjects.

The geometric median apparent volume of distribution (Vz/F) was 4670 L (range: 2280 to 9100 L) in healthy volunteers receiving a single dose of ceritinib 750 mg, suggesting that ceritinib is extensively distributed.

The geometric mean apparent terminal half-life ranged from 36 to 48 hours across the 450 to 750 mg dose groups in healthy subjects. There was significant inter-individual variability.

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. 91% of ceritinib was found in the faeces suggesting minimal renal clearance and hepatic metabolism +/- biliary excretion.

C_{max} and AUC_{last} increased dose-proportionally across the 50 to 750 mg dose range following a single oral dose; however, pre-dose lowest plasma concentration (C_{trough}) appeared to increase with dose in a greater than-proportional manner following multiple daily doses at steady-state.

Ceritinib demonstrated non-linear PK in patients over time with lower apparent clearance at steady state after daily oral dosing at maximum tolerated dose (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.

Overall, the inter-patient variability in exposure parameter estimates was high in target population also, with coefficients of variation of 93% and 87% for AUC_{last} and C_{max}, respectively, based on a model developed for dose proportionality analysis. Intra-patient C_{trough} variability was also demonstrated.

Pharmacokinetic interactions demonstrated in human studies

Hepatic impairment

A formal study has not been submitted for evaluation and a trial is underway to investigate this and submission is a condition of registration. Hepatotoxicity is a significant toxicity with ceritinib (25% patients had Grade 3-4 elevations in transaminases), therefore the PI contains a statement advising that it is not recommended in patients with pre-existing hepatic impairment. The PI information is contradictory at present and is likely to confuse prescribers due to use of preferred terms that are not in use in routine clinical medicine. See PI changes.

Renal impairment

Renal clearance appears to be low. No studies have been carried out in patients with severe renal impairment. This is stated in the PI.

Gender, race and other factors

While the clearance was reported not to be significantly affected by gender or race, the clinical studies raise uncertainty about the conclusion that race has no effect on adverse

events and therefore whether special dose adjustments are required. Study X1101 in 19 Japanese patients indicated a higher risk of a range of AEs ('drug-induced liver injury' and grade 3 elevation in amylase) across a range of doses and required discontinuation in 2 patients due to 'hepatic injury' (10.5% of population).

Although a small study, the higher rate of severe AEs and discontinuations across a range of doses raises uncertainties about potential ethnic differences and with the limited information available to date, it has not been established satisfactorily that there is no ethnic variation in AEs. Therefore, the following are required:

1. The sponsor is requested to analyse and present the safety including all grade AEs in Asian patients versus non-Asian patients.
2. Increased toxicity in Asian patients needs to be in the RMP as an important potential risk.
3. A study in Phase I/II study in Chinese patients is being undertaken and the sponsor is requested to provide a update on the accrual and likely completion date plus clarify if this was a dose finding study. Depending upon the outcome of Question 1, submission of this study for evaluation may be required as a condition of registration.

The clinical evaluator was concerned that the relationship between AEs and ceritinib exposure might have implications for patients with low body weight receiving the fixed dose.

Influence of food

Results from the food effect Study A2101 in healthy subjects showed that the bioavailability of ceritinib was increased when given with a meal. Compared with the fasted state, a low-fat meal increased mean C_{max} and mean AUC_{inf} of a single oral dose of ceritinib 500 mg by 43% and 58%, respectively, whereas a high-fat meal increased mean C_{max} and mean AUC_{inf} by 41% and 73%, respectively. The upper limit for the effects of a low-fat or high fat meals on AUC_{inf} were 86% increase and more than 2 fold increase. It should be noted that there are significant inter-individual variability in the means. No food should be eaten for at least 2 hours before, and for 2 hours after the dose of ceritinib is taken.

The Delegate commented that no standard deviations for these mean values are presented but wide inter-individual variability in the PK parameters above would suggest there will be significant variation.

Table 9: Summary statistics of ceritinib pharmacokinetic parameters under fasted or fed conditions (Study A2101-PAS)

Parameter[a]	Ceritinib (500 mg), fasted (Treatment A) N=27	Ceritinib (500 mg), low-fat (Treatment B) N=14	Ceritinib (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.

The Delegate commented that currently this information is not presented adequately to reflect its potential critical and indeed, uncertain impact on patient safety; its current location in the PI in 'Method of Administration', is 2.5 pages after the start of the 'Dosage and Administration' section. Information about the timing with food should be included in a Boxed Warning and in a boxed warning at the start of the Consumer Medicine Information (CMI) in appropriately worded language, for the following reasons:

1. The starting dose is associated with substantial toxicities (requiring dose reduction in > 50%), and the severities of the toxicities increase with increasing exposure (including QTc prolongation).
2. No higher doses were tested investigated doses beyond 750 mg due to persistent Grade 2 gastrointestinal toxicities and Grade 3 transaminase elevations.[36] So the safety profile is not known for any potential increase in exposure above the starting dose is unknown. Thus the consequences of food ingestion with the starting dose are unknown and potentially severe.
3. The Delegate notes that this NEJM publication[36] where practitioners may seek PK, safety and efficacy information does not mention the method of administration or potential effect of food.
4. The food study used a 500 mg dose, not the proposed starting dose so the food effect for 750 mg is unknown.
5. Any patient noncompliance, accidental or otherwise, could have severe consequences. The Delegate notes the indication requires previous treatment with crizotinib which can be taken without regard to food, potentially increasing the likelihood of prescriber error, and patient error or noncompliance if not made aware.
6. With AEs of nausea and vomiting in > 80%, patients may experiment with food and dose timing to try and manage this by themselves. They must be made aware not to.
7. Australian oncologists' and institutions' prescribing experience with ceritinib is very limited because:

[36] Shaw AM et al (2014) Ceritinib in ALK-Rearranged Non–Small-Cell Lung Cancer. N Engl J Med 2014; 370:1189-1197.

a. ALK-positive NSCLC is rare (orphan designation granted)

b. Registration is being sought at a very early stage in the development

c. Few Australian sites were involved in the clinical trials presented here. The following is taken from the dossier:

   i. no Australian sites in the Phase II pivotal trial

   ii. 9 Australian patients in the Phase I study from a single trial site

   iii. 3 patients treated in a Phase II study not contributing efficacy information for this application (3 clinicians in 3 registered sites)

This issue is being clarified further somewhat with a study planned to assess the steady-state PK and safety of reduced doses of ceritinib taken with a low-fat meal, as compared with 750 mg ceritinib taken in the fasted state: a randomized food effect study. Submission of this for evaluation is a condition of registration (see Conditions of Registration).

Pharmacokinetic Interactions

The concomitant use of CYP3A/P-gp inhibitors can increase the ceritinib plasma concentrations; the ketoconazole study (CYP3A inhibitor), show that the estimated geometric mean ratios for AUC_{inf} and C_{max} were increased almost 3 fold and 1 fold respectively. Results from the DDI study with rifampin (a CYP3A inducer) clearly indicate that strong CYP3A inducer decreases the ceritinib concentrations, leading to a reduction of both the C_{max} and AUC_{inf} (44% and 70%, respectively).

The Delegate commented that information is clearly stated in the PI regarding this. Dose reduction may be needed for co-administered medications that are predominantly metabolised by CYP3A and CYP2C9.

Ceritinib also inhibits CYP2A6 and CYP2E1 at clinically relevant concentrations. Therefore, ceritinib may have the potential to increase plasma concentrations of co-administered drugs that are predominantly metabolised by these enzymes.

Gastric pH

Ceritinib solubility decreases with increasing gastric pH. Currently there is no information regarding the interaction with pH-elevating agents, such as H2-blockers or proton pump inhibitors. The study investigating the effect of esomeprazole is underway and submission for evaluation is a Condition of Registration. In the interim, the PI provides information to avoid concomitant use where possible.

Pharmacodynamic effects

Mechanism of action

No data on clinical pharmacodynamics were submitted, with a total reliance on nonclinical data to support the mechanism of action. In response to EMA questions (Day 180 Report), the sponsor has indicated that biomarkers to characterise resistance mechanisms to ceritinib and predict response rates were under development but these were not provided for evaluation.

The cut-off used to determine ALK positivity was ≥ 15% based on crizotinib studies. Data provided to the EMA showed response rates above this level by independent and investigator assessment but it did not predict response to therapy; non-responders also had similar levels of detection by FISH or immunohistochemistry.

Other

The EMA report noted that higher exposure to ceritinib was not strongly matched by an increasing ORR. However, increases in toxicities and in particular QTc prolongation were clearly linked with increasing exposure. This risk was apparent in animal studies (see

above). QTc prolongation was noted in 6% of patients in the overall safety population, with 3.3% suspected to be treatment-related.

This information is key, as there is the existing risk which may be further increased with increased exposure if taken with food. QTc prolongation is included in the proposed Boxed Warning.

The sponsor has justified that lack of a Thorough QT/QTC study based on the collection of ECGs along with time-matched ceritinib plasma concentrations in Study X2101 and given the wide ranges of doses studied in this trial (50 to 750 mg), that these data enable a robust characterisation of the ceritinib concentration-QTc relationship. Further data will come from the two Phase II studies (A2201 and A2203) and ongoing Phase III studies (A2303 and A2301), where triplicate ECGSs along with time matched ceritinib plasma concentrations at pre-dose and at various post-dose time-points will be obtained and analysed.

It is unclear whether the triplicate ECGs and matched plasma concentrations are just being undertaken in the Phase III trials. No such data could be located in the Phase II studies. The sponsor is requested to comment on this.

Dose Selection

This was undertaken as part of the Phase I Study X2101, a Phase I dose escalation trial for the determination of the MTD, with a dose-escalation phase (to determine the MTD and RD) and an expansion phase to characterise the efficacy, safety and pharmacokinetics (PK) of ceritinib.

At the time that the MTD was determined, eight Dose Limiting Toxicities (DLTs) had occurred during the first cycle of treatment in six patients:

- 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 claimed 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 >400 mg.

Delegate noted:

1. The substantial toxicities and dose reductions required in the clinical trials do not support that the MTD was established adequately. Furthermore, with increases in AUC when taken with food demonstrated and serious toxicities such as QTc prolongation occurring with increasing exposure.
2. The toxicities, lack of predictive biomarkers, and uncertain improvement of efficacy with higher exposure support that 750 mg may be unnecessarily high as a starting dose.
3. It is noted that most toxicities were manageable with dose reduction (expert comment in response to specific TGA question on this in the presubmission meeting, and the relatively low discontinuation rates support this). The Delegate considers it likely that oncologists, familiar with managing toxicities, will have a low threshold for reducing the dose early and introducing supportive therapies to manage this.

Efficacy

Pivotal study

Study A2201 was Phase II, multicentre, single-arm, open label study of ceritinib in adult patients with locally advanced or metastatic ALK-positive non-small cell lung cancer previously treated with chemotherapy (1-3 prior lines, of which one must have been a platinum doublet), and most recently progressed on or within 30 days of crizotinib.

Primary objective: Overall response rate (ORR) by investigator assessment

The study targeted an ORR of 38%, with <25% considered insufficient activity H0: ORR ≤ 25% was tested versus H1: ORR > 25%, using a one-sided test with α=0.025 based on the exact binomial distribution

Secondary Objectives:

- duration of response (DOR)
- disease control rate (DCR)
- time to response (TTR), overall intracranial response rate
- ORR as assessed by blinded independent review committee (BIRC)
- safety
- progression-free survival (PFS)
- overall survival (OS)

Key inclusion and exclusion criteria:

- Stage IIIb or IV NSCLC that is ALK-positive as detected by FISH in ≥ 15% of tumour cells

The Full Analysis Set (FAS) consisted of all patients who received at least one dose of ceritinib (n=140). All patients received at least one dose.

The demographics were representative, including a median age of 51, half were women, and most had ECOG 0 or 1 performance status. 95% of patients had metastatic disease, including 71% with brain metastases and the median number of prior treatments was 3 (range 2-7).

Results for the primary efficacy outcome

The median duration of follow-up from the start of study drug to last contact date on or prior to the data cut-off date for the 140 patients in the FAS was 7.39 months (range: 0.1 to 14.0 months).

Table 10: Best overall response by investigator assessment (FAS)

	Ceritinib 750 mg N=140		
	n (%)	**95% CI (1)**	**p-value (2)**
Best overall response			
Complete response (CR)	3 (2.1)		
Partial response (PR)	49 (35%)		
Stable disease (SD)	56 (40.0)		
Progressive disease (PD)	19 (13.6)		

	Ceritinib 750 mg N=140		
Unknown (UNK)	13 (9.3)		
Overall response rate (ORR: CR + PR)	52 (37.1)	29.1, 45.7	< 0.001*
Disease control rate (DCR: CR + PR + SD)	108 (77.1)	69.3, 83.8	

N: the total number of patients in FAS. It is the denominator for percentage calculation. n: number of patients who are in the corresponding category. (1) exact binomial 95% confidence interval. (2) p-value associated with exact test of H_0: ORR ≤ 25% versus H_1: ORR > 25% based on exact binomial distribution. * indicates statistical significance (one-sided) at the 0.025 level.

Table 11: Summary efficacy results (ORR, DOR and PFS) by investigator and BIRC assessment

Efficacy Parameter	By investigator assessment	By BIRC assessment
In Full Analysis Set (FAS)	**N=140**	**N=140**
Overall response rate (CR+PR) (1), n (%) [95% CI]	52 (37.1) [29.1, 45.7]	48 (34.3) [26.5, 42.8]
Duration of response (median [95% CI]), months	9.2 [5.6, NE]	9.2 [5.5, NE]
Progression-free survival (median [95% CI]), months	5.7 [5.3, 7.4]	6.1 [5.4, 7.4]
In Per Protocol Set (PPS)	**N=128**	**N=104**
Overall response rate (CR+PR) (1), n (%) [95% CI]	52 (40.6) [32.0, 49.7]	48 (46.2) [36.3, 56.2]

(1) CR, PR confirmed. NE = not estimable.

Investigator assessment, especially in a single arm, open label study is a potential source of bias. There is however, fairly strong concordance between the investigator and independent review committee's assessments. For those with no major protocol deviations and full data for analysis, the ORR results by the BIRC assessment were higher.

Patients with brain metastases

Among the 100 patients (71.4%) with brain metastases, the ORR was 33.0% (95% CI: 23.9, 43.1.). Furthermore in the FAS, 20 out of the 140 patients had brain metastases at baseline considered to be target lesions by the Investigator per the RECIST 1.1 criteria. In these patients, the overall intracranial response rate (OIRR) based on Investigator assessment was 35% (95% CI: 15.4, 59.2). The intracranial DCR (CR+PR+SD) based on Investigator assessment was 80% (95% CI: 56.3, 94.3).

Median survival

The median OS was 14 months (95% CI: 10.3, 14.0). A total of 101 patients (72.1%) were censored for survival including 100 patients who were alive and one patient who was lost to follow-up as of the data cut-off date. Given the majority of patients are alive the OS data is immature and should be interpreted with caution.

It is difficult to interpret the PFS, OS results without a comparator but this is a heavily pretreated population who had recently progressed on crizotinib, with few remaining options. Therefore, the ORR, DCR and duration of response when taken together, represent a clinically meaningful response to this treatment. The high rate of disease control rate for those with brain metastases is also highly relevant.

A significant deficiency of this study is the absence of quality of life data to support these findings. This is especially in light of the substantial toxicities.

Study X2101

This is a first-in-human, Phase I, open label, dose-escalation and expansion study investigating the safety, pharmacokinetics, and anti-tumour activity of oral, once-daily, continuous dosing of ceritinib in adult patients with advanced tumours confirmed to have genetic abnormalities in ALK.

ORR results (reported for those receiving 750 mg dose, with first dose at least 18 weeks prior to cut-off date: 121/163)

Only efficacy outcomes for those 121/163 patients with a prior exposure to crizotinib receiving 750 mg dose at least 18 weeks before the cut-off date are considered. All patients had been previously treated with crizotinib, on which 110 (92%) had experienced disease progression, or much less commonly discontinued due to an adverse event. The investigator ORR was 55.4% (95% CI:46.1, 64.4) with 53.7% having a PR, and 1.7% a CR).

The BIRC assessment identified 118 patients with an ORR of 44.1% (95% CI: 34.9%, 53.5%). Of note, most of these patients (n=108) had PD during treatment with the last prior ALK inhibitor and the ORR in these patients was 46.3% (95% CI: 36.7, 56.2).

Duration of response results

For the population relevant to the indication proposed here, that is 67 patients treated with prior ALK inhibitor with a confirmed PR or CR, the investigator estimated median DOR was 7.39 months (95% CI: 5.42, 10.12). By BIRC assessment, the 52 patients treated with a prior ALK inhibitor with a confirmed PR or CR, the estimated median DOR was 7.06 months (95% CI: 4.80, NE). All these patients had received prior treatment with crizotinib. Of note, most of these patients (n=50) had PD during treatment with the last prior ALK inhibitor and the median DOR in these patients was: 7.06 months (95% CI: 5.52, NE).

PFS

The estimated median PFS was 6.90 months (95% CI: 5.39, 8.67) in patients previously treated with an ALK inhibitor, although there was censoring in 23.4% of patients still alive due to reasons such as commencement of further antineoplastic treatments, withdrawal of consent and so on.

OS

These data are immature, and no conclusions can be drawn due to the non-comparative nature of the study.

The BIRC assessment of ORR was lower but the duration of response was the same for these heavily pretreated patients, made up of a vast majority whose disease no longer responded to crizotinib. The treatment options are very limited and this supports a treatment effect and an option for such patients.

Other studies

Study A2203 recruited patients with no prior ALK-inhibitor treatment and as this does not inform the decision in the population for whom registration is being sought, this was not formally evaluated other than for safety signals. Any submission in the future that might rely upon this study to provide direct evidence of efficacy and safety would require a full evaluation.

- All reference and claims currently in the PI Clinical Trials section must be removed.

Study X1101 was a small dose escalation Phase I study conducted in Japan, involving 19 patients treated in 4 dose cohorts: 300 mg, 450 mg, 600 mg and 750 mg. Efficacy was noted across all dose levels, with the highest ORR and PFS in the 300 mg/day cohort. The small number limit definitive conclusions but together with the safety profile may indicate that Asian patients metabolise the drug differently and/or a lower starting dose should be used in such patients.

The following summary from the dossier raises concerns about safety in this population:

> *'Two DLTs occurred during the first cycle (including the PK run-in period): Grade 3 lipase increased at 600 mg/day, and grade 3 drug-induced liver injury at 750 mg/day. The MTD was determined to be 750 mg/day considering the safety and PK profile of LDK378. Two patients discontinued treatment in this study due to hepatic injury (10.5%).'*

The Delegate commented as follows:

1. These efficacy and safety events further underscore the Delegate's concern that the MTD was not adequately established and that 2/19 patients experiencing a severe event should result in the next lower dose level being selected.
2. It is unclear whether this might be due to ethnic differences in metabolism or just chance, with low numbers in the development program contributing to the low chance of detection. Population PK analyses are not adequate to explore these signals, and therefore, the Delegate considers increased toxicity in Asian patients should be listed as an uncertainty in the PI under ethnic differences until further clarification otherwise, and added to the RMP.
3. The sponsor has been requested to present an analysis of all grades of AEs in Asian patients versus non-Asian patients in the Studies done to date.
4. The Delegate notes that no information is provided regarding an application in Japan; the sponsor is requested to state whether there have been any discussions with PMDA about registration in Japan, and to disclose the outcome of those discussions.

Safety data

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 750 mg, 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 median duration of exposure was 33 weeks (range: 0.3 to 106.1 weeks): 71.6% of patients had been exposed for at least 24 weeks and 25.7% of patients had been exposed for at least 48 weeks. The following studies provided evaluable safety data: Studies X2101, X1101, A2201 and A2203. AEs of particular interest included hepatotoxicity, interstitial lung disease/pneumonitis and QT prolongation, bradycardia, hyperglycaemia and GI toxicity (diarrhoea, nausea and vomiting).

AEs suspected to be study drug related (all grades) were reported in ≥ 25% of the patients in the Study X2101 were: diarrhoea (78.6%), nausea (74%), vomiting (53.3%), ALT increased (31.3%), abdominal pain (26.3%), and fatigue (25.3%). Most of the patients experienced mild-moderate AEs. Grade 3-4 AEs were reported in 168 patients (66%), the most common being elevated ALT (in 21.2% of patients), followed by elevated AST (in 7.5% of patients). Majority of adverse events (95.7%) in patients treated with the proposed dose of 750 mg were assessed as treatment related by the investigators.

Table 12: Integrated summary of adverse drug reactions in the ceritinib 750 mg dose group (Safety set)

Primary System Organ Class Preferred Term	Ceritinib 750 mg, N=525			
	All grades n (%)	Frequency category	Grades 3/4 n (%)	Frequency category
Blood and lymphatic system disorders				
Anemia	60 (11.4)	Very common	17 (3.2)	Common
Metabolism and nutrition disorders				
Decreased appetite	216 (41.1)	Very common	11 (2.1)	Common
Hyperglycemia	41 (7.8)	Common	26 (5.0)	Common
Hypophosphatemia	28 (5.3)	Common	11 (2.1)	Common
Eye disorders				
Vision disorder[m]	39 (7.4)	Common	0	
Cardiac disorders				
Pericarditis[h]	31 (5.9)	Common	16 (3.0)	Common
Bradycardia[e]	10 (1.9)	Common	0	
Respiratory, thoracic and mediastinal disorders				
Pneumonitis[i]	17 (3.2)	Common	10 (1.9)	Common
Gastrointestinal disorders				
Diarrhea	440 (83.8)	Very common	28 (5.3)	Common
Nausea	419 (79.8)	Very common	28 (5.3)	Common
Vomiting	330 (62.9)	Very common	24 (4.6)	Common
Abdominal pain[a]	253 (48.2)	Very common	8 (1.5)	Common
Constipation	132 (25.1)	Very common	3 (0.6)	Uncommon
Esophageal disorder[f]	79 (15.0)	Very common	2 (0.4)	Uncommon
Hepatobiliary disorders				
Abnormal liver function tests[c]	11 (2.1)	Common	8 (1.5)	Common
Hepatotoxicity[d]	3 (0.6)	Uncommon	3 (0.6)	Uncommon
Skin and subcutaneous tissue disorders				
Rash[j]	100 (19.0)	Very common	2 (0.4)	Uncommon
Renal and urinary disorders				
Renal failure[k]	11 (2.1)	Common	1 (0.2)	Uncommon
Renal impairment[l]	7 (1.3)	Common	1 (0.2)	Uncommon
General disorders and administration site conditions				
Fatigue[g]	265 (50.5)	Very common	39 (7.4)	Common
Investigations				
Liver laboratory test abnormalities[b]	265 (50.5)	Very common	153 (29.1)	Very common

Primary System Organ Class Preferred Term	Ceritinib 750 mg, N=525			
	All grades n (%)	Frequency category	Grades 3/4 n (%)	Frequency category
Blood creatinine increased	93 (17.7)	Very common	0	
Electrocardiogram QT prolonged	34 (6.5)	Common	4 (0.8)	Uncommon
Lipase increased	24 (4.6)	Common	16 (3.0)	Common

a Abdominal pain includes PTs of Abdominal Pain, Abdominal Pain Upper, Abdominal Discomfort, Epigastric Discomfort b Liver laboratory test abnormalities includes PTs of Alanine Aminotransferase Increased, Aspartate Aminotransferase Increased, Gamma-Glutamyltransferase Increased, Blood Bilirubin Increased, Transaminases Increased, Hepatic Enzyme Increased, Liver Function Test Abnormal
c Abnormal liver function tests includes PTs of Hepatic Function Abnormal, Hyperbilirubinaemia
d Hepatotoxicity includes PTs of Drug-Induced Liver Injury, Hepatitis Cholestatic, Hepatocellular Injury, Hepatotoxicity
e Bradycardia includes PTs of Bradycardia and Sinus Bradycardia
f Esophageal Disorder includes PTs of Dyspepsia, Gastrooesophageal Reflux Disease, Dysphagia
g Fatigue includes PTs of Fatigue and Asthenia
h Pericarditis includes PTs of Pericardial Effusion and Pericarditis
i Pneumonitis includes PTs of Interstitial Lung Disease (ILD) and Pneumonitis
j Rash includes PTs of Rash, Dermatitis Acneiform, Rash Maculo-Papular
k Renal Failure includes PTs of Renal Failure Acute and Renal Failure
l Renal Impairment includes PTs of Azotaemia and Renal Impairment
m Vision disorder includes PTs of Visual Impairment, Vision Blurred, Photopsia, Vitreous Floaters, Visual Acuity Reduced, Accommodation Disorder, Presbyopia

Deaths

Ceritinib related SAEs were reported in 13.1% of patients. Ceritinib-related SAEs were each reported in < 1% of patients, with the exception of pneumonitis (1.9%), pericarditis (1.5%), nausea (1.1%) and pneumonia (1.0%).

With regards to deaths, a total of 68 on-treatment deaths (13.0%) were reported in the safety set (all patients; n=525). All deaths, with the exception of 3 deaths, were not suspected to be related to study drug. These included:

- One death due to ILD (Study X2101)

- One death due to multi-organ failure that occurred in the context of infection and ischaemic hepatitis (Study X2101)
- One death due to pneumonia (Study A2201).

Currently the PI does not adequately present the risks associated with ceritinib treatment; acceptance of the proposed boxed warning for communication of the risks is required, and the Delegate proposes inclusion of the deaths from ILD (See ILD section below).

Serious Adverse Events

Ceritinib related SAEs were reported in 13.1% of patients. Ceritinib-related SAEs were each reported in <1% of patients, with the exception of pneumonitis (1.9%), pericarditis (1.5%), nausea (1.1%) and pneumonia (1.0%).

Currently the PI does not adequately present the risks associated with ceritinib treatment; acceptance of the proposed boxed warning for communication of the risks is required and the Delegate proposes inclusion of the death from ILD.

Table 13: 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.

Table 14: Summary of adverse events leading to study drug discontinuation for ceritinib 750 mg group (n ≥ 2 in all grades) by preferred term in pooled dataset (n=525), including Study X2101, X1101, A2201 and A2203.

Preferred Term	All patients N=525	
	All grades N (%)	Grade 3/4 N (%)
- Total	46 (8.8%)	37 (7.0%)
Pneumonitis	4 (0.8%)	3 (0.6%)
Interstitial lung disease	2 (0.4%)	1 (0.2%)
Pneumonia aspiration	2 (0.4%)	2 (0.4%)
Respiratory failure	2 (0.4%)	2 (0.4%)
Infection/infestations	7 (1.3%)	7 (1.3%)

Preferred Term	All patients N=525	
Pneumonia	4 (0.8%)	4 (0.8%)
Nausea	3 (0.6%)	1 (0.2%)
Fatigue	2 (0.4%)	2 (0.4%)
General physical health deterioration	2 (0.4%)	2 (0.4%)
Increased AST	2 (0.4%)	1 (0.2%)
Cardiac tamponade	2 (0.4%)	2 (0.4%)
Decreased appetite	2 (0.4%)	1 (0.2%)

The presentation of data by n ≥ 2 in a small dataset, with variable duration of exposure means less common but severe events will not be presented or may not even have been captured, especially as no randomised controlled trials had been completed and presented. Of note, the single case of drug induced liver injury requiring discontinuation in Study X1101 has not been presented, but appears to be captured in the overall figure of 46 discontinuations.

Consistent with the high rate of AEs, dose adjustments (57.8% reported in the European Public Assessment Report (EPAR)) and delays were frequent: 74.9% in the pooled dataset with 49.5% due to a Grade 3-4 AE. The most frequent (any grade, ≥ 5% of patients) AEs requiring dose adjustment or interruption were increased transaminases (ALT 29.0%, AST 15.6%), GI toxicity (nausea 18.7%, vomiting 18.7%, diarrhoea 16.0%), fatigue (6.9%), abdominal pain (6.1%) and decreased appetite (5.3%).

Grade 3-4 AEs requiring dose adjustment or interruption were increased transaminases (ALT 20.6%, AST 6.5%), GI toxicity (diarrhoea 4.4%, nausea 3.8% and vomiting 3.6%), and fatigue (3.0%).

The Delegate agrees with the clinical evaluator that the high rate of dose adjustment indicates that the starting dose is too high. It is unclear why the next dose level down was not used as the starting dose, particularly as so many patients were then reduced to that dose. There are no pharmacodynamic data to support the higher dose and efficacy did not appear to be strongly linked to exposure. The detrimental impact of the gastrointestinal toxicities on quality of life should not be underestimated. The Delegate is concerned that some patients may take ceritinib with food in an attempt to manage the severe nausea, vomiting inadvertently increasing exposure and the risk of other severe AEs. The boxed warning in both the PI and CMI is required to reduce that risk. The relatively low discontinuation rate supports that the AEs are manageable with additional medications or dose modification but also indicates the motivation of the patients with this disease.

Adverse events of special interest

The sponsor identified the following as hepatotoxicity, interstitial lung disease (ILD)/pneumonitis, QT prolongation, bradycardia, hyperglycaemia and GI toxicity. Some of the following summaries are taken from the EMA's EPAR:

Hepatoxicity

> *'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.'*

The Delegate commented that the current wording in the PI may be confusing to clinicians as striking elevations of transaminases are reported, but the term 'hepatotoxicity' has been reserved to be used as a synonym for the most severe outcome of drug-induced liver injury. The Delegate has recommended changes to clarify this, including statement using the words 'drug-induced liver injury' used in the sponsor's own description of the outcome (Study X1101).

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, causing death in one patient.

The clinical evaluator noted an additional death from ILD in Study X2102 (ceritinib + AUY922 combination study), that was assessed as related to study drug (which drug is uncertain).

The Delegate's proposed modified indication specifying monotherapy reflects the lack of evidence regarding the safety in combination; in addition, this death in a trial involving combination treatment warrants a statement in the PI that there is no evidence to support the safety and efficacy of ceritinib in combination with other medicines, and that this should only be undertaken in the context of clinical trials (see PI changes).

QT prolongation and related AEs

The following is taken from the EPAR, together with the table.

> '*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 15: 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]

The higher figure of 7.6% reflects consideration of events likely to be related to QT prolongation, which are largely inferred, as well as actual ECG recording abnormalities. The PI currently reports the ECG findings alone under the heading QT prolongation which is adequate, as this is the means of detection and management.

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.

Delegate noted that with the recommended changes to the PI, this will be adequately conveyed.

Hyperglycaemia (including all preferred terms such as diabetes mellitus etc)

The rates reported in the CER are 11.4% for all grades, with 6.1% of patients experiencing Grade 3-4 AEs in the pooled dataset. 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. 7 patients developed de novo diabetes. The event required dose adjustment or interruption in 2.1% of patients and led to discontinuation in 0.2% (2 patients). The event was serious in 2.3% of patients but there were no deaths. One Grade 4 event developed on Day 77 indicating this is not immediate and ongoing monitoring is clearly important.

Delegate comments:

1. The use of the isolated term hyperglycaemia, when diabetes, glucose abnormal and so on are also listed potentially underrepresents the risk as these are synonymous. The de novo development and to a lesser extent worsening of diabetes, is a major medical AE requiring intensive management and is a significant quality of life issue, and was sufficiently severe to result in discontinuation in 2 patients.
2. The PI needs to reflect the risk by representing this under a heading of hyperglycaemia and diabetes and incorporate appropriate figures. The PI currently states that the rate was below 10% and this needs to be amended.
3. The additional effect of other medications such as corticosteroids, especially with the large number of patients with brain metastases is acknowledged but this can only be clarified with randomized trial data which are awaited.

Gastrointestinal toxicity

The EPAR states the following: GI AEs (that is, 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).

With the recommended changes to the PI, this will be adequately conveyed.

Pancreatic toxicity

Elevations in lipase and amylase were frequent and together with abdominal pain. The PI needs to inform of the frequency in the trials and it is important that this is included in the patient safety card, as this is an unusual toxicity from a cancer therapy, and patients may seek attention out of hours.

Other

Renal impairment, indicated by a rise in creatinine, as well as acute renal failure occurred in 63% patients on ceritinib, with the majority being Grade 1 or 2 and only 1.5% were Grade 3 and none were Grade 4. The renal events were serious in 1.1% of patients, leading to dose modification or delay in 4.8% of patients, discontinuation in 0.2% of patients (one patient due to acute renal failure).

The cause is unclear but may be related to the dehydration secondary to the significant GI toxicity.

No clinically significant haematological abnormalities occurred and those that did were generally easily managed and seldom required dose modification or interruption.

Clinical summary

Efficacy in support of the proposed usage comes from 2 non-randomised, open label studies involving 303 patients who have previously received crizotinib: 163 in Study X2101 and 140 ALK inhibitor pretreated patients in Study A2201.

In these heavily pretreated patients (1-3 prior lines of chemotherapy) and essentially no remaining treatment options, ceritinib had an investigator assessed ORR of 37.1% in A2201 and 55.4% in X2101. The duration of response was similarly long in both studies (median 9.2 months and 7.39 months, respectively). Blinded independent review yielded generally concordant results although was lower for ORR in Study A2201 (44.1% versus 55.4%). Nonetheless, these results suggest strongly that ceritinib is effective after progression on crizotinib and compare favourably with the only ORR reported in an ALK-positive population receiving chemotherapy of 20% ORR (from the randomised Phase III trial randomised trial comparing crizotinib versus single agent chemotherapy in a much less heavily pretreated population). Thus, together with the duration of response, this offers a clinical benefit. The median PFS data support a meaningful delay in progression (6.9 months in Study X2101 to a median of 5.7 months in Study A2201) and OS data are too immature but favourable, but these findings should be interpreted cautiously in the absence of a control arm. Ceritinib appears to have activity in patients with brain metastases, although this requires randomised controlled trial to establish the true clinical benefit. There is a randomised, controlled Phase III clinical trial underway comparing ceritinib with chemotherapy in patients whose disease has progressed on crizotinib, which will provide further evidence of safety and efficacy in this population.

The pooled safety set included 525 patients provided information about the risks with the proposed 750 mg dose. Toxicities are significant, especially the gastrointestinal side effects of nausea, vomiting and diarrhoea which occurred in > 80% and often required dose reduction and/or supportive medications and were likely to cause some of the rises in creatinine/renal failure observed. Other significant adverse events include frequent hepatotoxicity with 2 cases of drug induced liver injury, interstitial lung disease/pneumonitis (including 2 fatalities), pancreatitis, hyperglycaemia, QT prolongation and bradycardia. These were largely manageable with dose reductions and supportive measures but the high rate does suggest very strongly that the maximum tolerated dose was not 750 mg and with efficacy not strongly linked to exposure, a low threshold for managing these with a dose reduction would seem reasonable (and was required in 54%). An additional risk is possible increased exposure and adverse events from an error or noncompliance with the unusual requirement for ceritinib to be taken with no food for 2 hours either side of administration.

Risk management plan

The TGA has reviewed an updated EU-RMP for Ceritinib (Version 2.5, dated 29 April 2015) with an updated ASA (Version 2.0, dated 23 November 2015) but currently the ASA to the EU-RMP does not adequately addresses the outstanding issues and therefore the Branch has not been able to provide a recommended wording as a condition of registration.

The outstanding issues are:

1. Inadequate information and cross-referencing of the risk of taking ceritinib with food versus in a fasting state (see Delegate's proposed PI changes to address this concern)

2. Inclusion of the evidence base on which the decision was made, particularly including the efficacy endpoints. The Delegate shares this concern (see Delegate's proposed Note to the Indication and Condition of Registration that this be marketed) and this is key matter in consideration of any decision to register this product.

A number of recommendations for the RMP have been provided by the RMP evaluator and the sponsor should address these matters in the Pre-Advisory Committee on Prescription Medicines (ACPM) Response and follow up where appropriate with the RMP evaluator.

The Delegate considers that the following risk minimisation activities and pharmacovigilance are required, in addition to those proposed:

1. Wallet-sized safety information card for patient/doctor for presentation to any treating doctor.
2. Boxed warning for adverse events and risk of food increasing exposure.
3. Inclusion of identified potential risk of increased in toxicity in Asian patients
4. Inclusion as potential identified risk of drug errors related to ingestion with food
5. A registry or equivalent to capture efficacy and safety outcomes in patients using this prior to the availability of the CSR for the Phase III study in the same population

Risk-benefit analysis

Delegate's considerations

Registration is being sought at a very early stage of the ceritinib development program for a population where no effective alternative treatments exist, on the grounds of unmet need. The benefit-risk is considered positive for those with essentially no remaining treatment alternatives. The Delegate considers the limited but clinically relevant demonstration of efficacy to date as determined by the early endpoints ORR and DoR is likely to be acceptable to a patient informed about the known significant toxicities as well as the existence of uncertainties about longer term efficacy and other potential adverse events. Clear presentation of the evidence base is important to inform patients prior to making their decision to commence treatment. However, currently the information proposed in the PI and CMI require extensive revision support a treatment decision that is based upon informed consent.

There are uncertainties with approval based on earlier datasets when only non-comparative information is available (treatment in 304 patients to inform efficacy for the proposed usage in two single arms, open label Phase I/II and Phase II trials and 525 patients in total who have received the proposed 750 mg dose including patients who are less heavily pretreated).

The Delegate notes that ceritinib has only received conditional marketing authorisation (or its equivalent) from the EMA, FDA and Health Canada. The Delegate believes that patients in Australia should not be excluded from early access; however, approval is predicated upon a clear communication of the risks in a Boxed Warning, of the early nature of the endpoints supporting registration in a Note to the Indication; both of which must be marketed with any promotional material. In addition, a statement is included in the Clinical Trials section of the proposed PI, but needs rewording. Similarly, the CMI must contain the same information as the boxed warning in language that is appropriately worded for consumers. In addition, it is recommended the sponsor set up a registry to capture better both relevant efficacy and safety outcomes, acknowledging that earlier registration, while providing access, necessarily reduces the information that would otherwise have been captured in clinical trials. This should inform about key efficacy questions such as longer term outcomes, efficacy in patients with brain metastases and in

populations excluded from clinical trials. The sponsor is responsible for setting up a registry (or its equivalent) to ensure this critical information is not lost.

Due to the rarity of this particular cancer, and the early stage of the development program, there is very limited experience of Australian clinicians to date and in institutions in prescribing and monitoring patients on ceritinib (4 clinicians across 4 sites treated 12 patients involved in the clinical trials presented in the dossier). Some of the adverse events are more frequent with ceritinib than crizotinib (for example, hepatotoxicity) and/or severe (for example, gastrointestinal side effects) or new (pancreatitis and hyperglycaemia), so do not represent a 'class effect'. To facilitate management this adverse event profile by both patients and doctors, the Delegate requires the sponsor to prepare a patient safety card as these patients are likely to present to their local practitioner or to Accident and Emergency Departments with adverse events such as bradycardia, pancreatitis and so on as these clinicians would not be expected to be aware of the safety profile of this drug. Oncologists would be familiar with the majority of the adverse events as these occur with other TKIs but the boxed warning will promote awareness of some of the key differences.

Approval of the Delegate's proposed modified indication (which includes a note to the indication) is dependent upon the sponsor's adequate response to the PI changes and acceptance of the Conditions of Registration. The advice of the ACPM is sought as to any other additional risk minimisation activities that would be required to ensure safe use of this medicine.

Data deficiencies/limitations

There are no quality of life data which is a significant limitation given the severity of the adverse events and the palliative treatment intent.

The clinical evaluator noted that the sponsor had presented information from the global pharmacovigilance safety database for 20 adverse events of which just 5 were reported spontaneously, with the remainder coming from postmarketing studies. The majority were expected toxicities of ceritinib or 'required more information to allow a meaningful assessment'. The latter suggests very strongly that for any new event outside of a clinical trial, insufficient information is being gathered to inform whether this might be related to ceritinib. To this end, the Delegate proposes the sponsor considers either a registry or a more effective way to collect information about outcomes for both safety and efficacy for patients using ceritinib until randomised data from the planned Phase III trials are available for evaluation.

Summary of issues

Registration is being sought at an early stage of the development program in a population with no treatment alternatives following disease progression on crizotinib. There are substantial toxicities but overall the benefit risk is considered favourable given the improvement in overall response rate and duration of response on the grounds of unmet need. Verification of a clinical benefit is to follow with submission of a randomised Phase III trial in the same population.

Proposed action

Pre ACPM preliminary assessment

Subject to the extensive PI changes that are required being made (including a Boxed Warning), agreement to the additional risk management strategies and agreement to the Conditions of Registration, the Delegate considers the following modified indication (inclusive of the Note to the Indication) approvable:

Zykadia is indicated as monotherapy for the treatment of adult patients with ALK-positive locally advanced or metastatic non-small cell lung cancer (NSCLC) whose disease has progressed on or who are intolerant of crizotinib.

Note to the Indication: This indication is approved based on tumour response rate and duration of response. An improvement in survival or disease-related symptoms has not been established.

Conditions of registration

The following are proposed as conditions of registration:

1. Implementation of the EU-RMP Version and ASA is a standard condition of registration but no wording can be provided as yet as an updated ASA has not been evaluated by the RMP evaluator.
2. Submission for evaluation [information redacted], the 26 week rat study and a 39 week toxicity study that was referenced in the RMP for this application (under Respiratory tract, and Hepatobiliary system and pancreas).
3. Submission of the following clinical trial(s) [information redacted],which were designed to examine/assess:
    a. Ceritinib in patients with hepatic impairment [information redacted],
    b. The interaction with warfarin and midazolam [information redacted],
    c. The effect of esomeprazole on the PK of ceritinib [information redacted],.
    d. The steady-state PK and safety of reduced doses of ceritinib taken with a low-fat meal, as compared with 750 mg ceritinib taken in the fasted state: a randomized food effect study [information redacted].
    e. Oral ceritinib versus standard chemotherapy in adult patients with ALK-rearranged (ALK-positive) locally advanced or metastatic NSCLC who have been treated previously with one chemotherapy regimen (platinum doublet) and crizotinib ([information redacted] A Phase III multicentre, randomized study)
4. Submit [information redacted],for evaluation as soon as available:
    a. The CSR with the final results of the Phase II single-arm efficacy [information redacted].
    b. The CSR for the Phase I/II study of ceritinib in adult Chinese patients with ALK-rearranged (ALK+) advanced NSCLC previously treated with crizotinib
5. The Note to the Indication must follow the Indication in any promotional material; and the Boxed Warning must be marketed together with the indication and note to the indication in any promotional material.

Request for ACPM advice

The committee is requested to provide advice on any pharmacovigilance activities considered necessary, including requirement for a registry to capture safety and efficacy outcomes in more detail than present routine pharmacovigilance.

Questions for the sponsor

1. The sponsor is requested to clarify the maximum dose tested in the dose escalation phase of Study X2101.
2. It is unclear whether the triplicate ECGs and matched plasma concentrations are just being undertaken in the Phase III trials. No such data could be located in the Phase II studies. The sponsor is requested to comment.

3. The sponsor is requested to present an analysis of all grade adverse events in Asian versus non-Asian patients to inform about concerns identified regarding the adverse event rates in the Study X1101 in Japanese patients.
4. The sponsor is also requested to advise on the accrual status, study design (including whether this is a dose-finding study vs PK study at fixed dose of 750 mg) and likely completion date for the Phase I/II study of ceritinib in adult Chinese patients with ALK-rearranged (ALK+) advanced NSCLC previously treated with crizotinib. Given this directly informs of the concern the Delegate has prompting Question 3, submission of the CSR for evaluation of this as a condition of registration may be required (see *Questions for sponsor, Conditions of Registration*).
5. The Delegate notes that no information is provided regarding an application in Japan; has sponsor approached PMDA about registration in Japan, and if so, what was the outcome of those discussions?
6. What is the current accrual status of the Phase III Study of the same population and anticipated date for the primary analysis and the CSR to be available?
7. The sponsor is requested to present a registry or a more effective way to collect information about outcomes for both safety and efficacy for patients using ceritinib, given the limitations described in the pharmacovigilance to date.

Response from sponsor

This document provides responses to the TGA Delegate's *Overview Questions for the sponsor* for Zykadia ceritinib (LDK378) 150 mg hard capsules, submission PM-2015-00418-1-4.

Question 1

The sponsor is requested to clarify the maximum dose tested in the dose escalation phase of Study X2101.

Sponsor response:

The maximum dose tested in the dose escalation phase of Study X2101 was 750 mg orally once daily under fasting condition.

Question 2

It is unclear whether the triplicate ECGs and matched plasma concentrations are just being undertaken in the Phase III trials. No such data could be located in the Phase II studies. The Sponsor is requested to comment.

Sponsor response

Triplicate ECGs with matched plasma concentrations are collected in the Phase II studies (CLDK378A2201 and CLDK378A2203) and in the Phase III studies.

The details on the ECG collection (and matched PK samples) can be found in both Phase II study protocols. In addition, the results can be found in the CSRs for both Phase II studies in Section 'Change in QTc versus ceritinib PK concentration'.

The Phase III study protocols describe the ECG collection.

Question 3

The sponsor is requested to present an analysis of all grade adverse events in Asian versus non-Asian patients to inform about concerns identified regarding the adverse event rates in the Study X1101 in Japanese patients.

Sponsor response

A subgroup analysis of adverse events (AE) between Asian and non-Asian patients was conducted based on the pooled dataset from patients with ALK-positive malignancies, among whom all but 10 patients had NSCLC, treated with ceritinib 750 mg. Among the 515 NSCLC patients included in the pooled dataset, 214 patients were Asian and 301 were non-Asian . The overall occurrence of adverse events was similar in Asian and non-Asian patients. System organ classes (SOCs) where higher proportions of Asian patients reported events (with ≥ 10% differences relative to non-Asian patients) included: Metabolism and Nutrition Disorders (+ 15.2%) and Skin and Subcutaneous Disorders (+ 11.6%). Non-Asian patients had a higher Psychiatric Disorders SOC than Asian patients (26.6% versus 16.4%). The AE Preferred Terms (PT) where higher proportions of Asian patients reported events (with ≥ 10% differences relative to non-Asian patients) included: decreased appetite (+25.9%), diarrhea (+12%), vomiting (+15.4%) and cough (+12.5%). The differences observed in the frequency of diarrhea may have been influenced by diet. Thus, there were no clinically relevant differences in the safety profile of ceritinib observed between Asian and non-Asian patients.

Hepatic function disorder was the one additional event that was reported with a higher frequency in the Asian population than in the non-Asian population (4.2% in Asian patients versus 0% in non- Asian patients); it is further discussed below.

The 9 Asian patients with hepatic function disorder had elevations of AST and/or ALT; 8 of the 9 cases were without elevations in total bilirubin. None of these 9 patients had any associated AEs with coagulation/bleeding or hepatic encephalopathy. One of these patients had hepatic enzyme elevations reported as an AE under the SOCs of both Investigations and Hepatobiliary Disorders. Except for Patient [information redacted] with hypoalbuminemia, none of the other 8 patients with hepatic function abnormal had any liver protein synthesis abnormalities or symptoms from their abnormal lab values. None of these events were reported as an SAE.

None of the non-Asian patients had hepatic function disorder reported as an AE; the reporting of AST, ALT and TBili elevations in the Asian and non-Asian patients was similar. Given that 8 of the 9 Asian patients had no associated coagulation/bleeding or other serious symptoms of liver dysfunction and only one patient had CTC Grade 1-2 hypoalbuminemia, the sponsor considers the hepatic safety profiles for Asians and non-Asians to be similar.

Question 4

The sponsor is also requested to advise on the accrual status, study design (including whether this is a dose-finding study vs PK study at fixed dose of 750 mg) and likely completion date for the Phase I/II study of ceritinib in adult Chinese patients with ALK-rearranged (ALK+) advanced NSCLC previously treated with crizotinib. Given this directly informs of the concern the Delegate has prompting Question 3 above, submission of the CSR for evaluation of this as a condition of registration may be required (see Questions for sponsor, Conditions of Registration below).

Sponsor response

The study in Chinese patients is a Phase I/II multicenter, open-label, single-arm study of LDK378, administered orally in adult Chinese patients with ALK-rearranged (ALK-positive) advanced non-small cell lung cancer (NSCLC) previously treated with crizotinib. The study was not a dose finding study. The LDK378 dose tested throughout the study (including during the run-in period) was 750 mg orally once daily (fasted). The study includes a Phase I component for the first 15 patients and a Phase II component for all of the patients with continuous dosing. The first 15 patients enrolled had an additional 5 day PK run-in period before the treatment period.

The study enrolled 103 (100 planned) patients in 17 sites in China.

Question 5

The Delegate notes that no information is provided regarding an application in Japan; has the sponsor approached PMDA about registration in Japan, and if so, what was the outcome of those discussions?

Sponsor response:

The JNDA was submitted to the Japanese Health Authority (PMDA) on 24 June 2015. On 26 February 2016, the Drug Committee met to discuss Novartis' application. At the conclusion of the meeting, the Drug Committee endorsed the approval of Zykadia in Japan. Approval is expected in March 2016.

Question 6

What is the current accrual status of the Phase III Study, and anticipated date for the primary analysis and the CSR to be available?

Sponsor response

Per protocol, the primary analysis will be performed when approximately 161 PFS events are confirmed by the blinded independent review committee (BIRC), and when all randomised patients have completed at least 12 weeks of follow-up or have discontinued. The data are currently being cleaned so that the database can be locked.

Question 7

The sponsor is requested to present a registry or a more effective way to collect information about outcomes for both safety and efficacy for patients using ceritinib, given the limitations described in the pharmacovigilance to date.

Sponsor response

Regarding the Delegate's request for a registry or equivalent to capture efficacy and safety outcomes in patients the sponsor believes that the ongoing Phase III clinical trials appear best suited to collect information about outcomes for both safety and efficacy for patients using ceritinib. Furthermore [Zykadia EU PSUR] covering the period from 29 April 2015 to 28 October 2015 is being submitted. The safety and efficacy information about Zykadia® (ceritinib) did not change during the reporting interval and the cumulative experience with the drug remained in accordance with the CDS (v 1.2; 31 March 15) and the Risk Management Plan.

In addition to the Australian patients who participated in the clinical trials in the submitted dossier, Australian patients are also taking part in 2 new clinical trials (Phase II and III) at 5 additional centres. The sponsor considers the limited numbers of patients that can participate may not generate the patient outcomes data TGA have requested. Novartis will submit Phase III Study primary analysis as soon as possible, provide safety label updates in timely manner, submit EU PSUR and EU RMP updates and carry out conditions of registration promptly.

Conditions of registration

The sponsor agrees with the proposed list of conditions of registration.

The Delegate considers that the following risk minimisation activities and pharmacovigilance are required, in addition to those proposed (by the RMP Evaluator):

1. ***Wallet-sized safety information card for patient/doctor for presentation to any treating doctor.***

Sponsor response

In order to emphasise the importance of not taking ceritinib with food, the sponsor agrees to implement a patient/physician wallet card as an additional risk minimisation activity for Australia.

2. Boxed warning for adverse events and risk of food increasing exposure.

Sponsor response

The sponsor agrees with the Delegate's proposal. A Boxed warning for adverse events and risk of food increasing exposure has been included in the product information with few exceptions as discussed in the Response to the Delegate's Proposed Product Information Comment 1.

3. Inclusion of identified potential risk of increased in toxicity in Asian patients

Sponsor response

The sponsor does not agree with the inclusion on an identified potential risk of increased toxicity in Asian patients in the Australian Specific Annex. As indicated in Response to the Delegate's Question 3, the analysis of the adverse event in Asian versus non-Asian patients shows that there is no clinically relevant difference in the safety profile of Asian versus non-Asian patients.

Of note, Zykadia is currently approved in several Asian countries including South Korea (approved on 12 January 2015), Singapore (Approved on 24 April 2015) and Taiwan (Approved on 07 January 2016). The approval in Japan is anticipated in March-2016.

4. Inclusion as potential identified risk of drug errors related to ingestion with food.

Sponsor response

The sponsor acknowledges the Delegate's concerns regarding potential risk of drug errors related to ingestion with food. As mentioned above, the PI describes the pharmacokinetic parameters around taking ceritinib with and without food and recommends taking ceritinib on an empty stomach in the Pharmacokinetic, Interactions with Medicines, Dosage and Administration sections of the PI and the Boxed Warning on page 1 of the PI. In addition, the sponsor agrees to implement a patient/physician wallet card which will emphasize the need to follow the dose and administration instructions.

5. A registry or equivalent to capture efficacy and safety outcomes in patients using this prior to the availability of the CSR for the A2303 study in the same population.

Sponsor response

As indicated in the Response to the Delegate's Question 7, Novartis considers that submission of the Phase III primary analysis CSR would address the TGA's concerns regarding sufficient data to assess safety and efficacy in the proposed indicated population.

Advisory Committee Considerations

Advice from the Advisory Committee on Prescription Medicines (ACPM) was not sought for this application.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Zykadia (ceritinib) 150 mg hard capsule blister pack, indicated for:

> *Zykadia is indicated as monotherapy for the treatment of adult patients with ALK-positive locally advanced or metastatic non-small cell lung cancer (NSCLC) whose disease has progressed on or who are intolerant of crizotinib.*

Note to the Indication: This indication is approved based on tumour response rate and duration of response. An improvement in survival or disease-related symptoms has not been established.

Specific conditions of registration applying to these goods

1. Implement EU-RMP Version 2.5 (dated 29 April2015, DLP 27 June 2014) and Australian-specific annex (AsA) Version 3.0 (dated 11 March 2016), and future updates where TGA approved, as a condition of registration.
2. Submission for evaluation with the next Category I submission, the 26-week rat study and a 39-week toxicity study that was referenced in the RMP for this application (under Respiratory tract, and Hepatobiliary system and pancreas).
3. Submission of the following clinical trial(s) [information redacted] which were designed to examine/assess:
    a. Ceritinib in patients with hepatic impairment [information redacted]
    b. The interaction with warfarin and midazolam [information redacted]
    c. The effect of esomeprazole on the PK of Ceritinib [information redacted]
    d. The steady-state PK and safety of reduced doses of ceritinib taken with a low fat meal, as compared with 750 mg ceritinib taken in the fasted state: a randomized food effect study [information redacted].
    e. Oral ceritinib versus standard chemotherapy in adult patients with ALKrearranged (ALK-positive) locally advanced or metastatic NSCLC who have been treated previously with one chemotherapy regimen (platinum doublet) and crizotinib ([information redacted] A Phase I/II multicentre, randomized study)
4. Submit [information redacted]for evaluation as soon as available:
    a. The CSR with the final results of the Phase II single-arm efficacy study [information redacted].
5. The Note to the Indication must follow the Indication in any promotional material; and the Boxed Warning must be marketed together with the indication and note to the indication in any promotional material.

Attachment 1. Product Information

The PI for Zykadia approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

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