Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Alectinib hydrochloride

Proprietary Product Name: Alecensa

Sponsor: Roche Products Pty Limited

November 2017

TGA Health Safety Regulation

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- 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
(Su)	Suspected
(U)	Unsuspected
[14]-	Radiolabelled (prefix)
µg	Microgram(s)
ADME	Absorption, distribution, metabolism and excretion
AE	Adverse event
AIC	Akaike information criterion
AJCC	American Joint Committee on Cancer
ALCL	Anaplastic large cell lymphoma
ALK	Anaplastic lymphoma kinase
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
alt.	Alternate
AMS	Accelerated mass spectrometry
ARTG	Australian Register of Therapeutic Goods
AST	Aspartate aminotransferase
AUC	Area under the curve (of plasma concentration versus time)
AUC_{0-10}	AUC from time 0 to10 hours post-dose
$AUC_{0-\infty}$	AUC from time 0 post-dose extrapolated to infinity
AUC_{0-last}	AUC from time 0 to last measured time point post-dose
BIRC	Blinded independent review committee
BMI	Body Mass Index
bpm	Beats per minute
Br	Bilirubin

Abbreviation	Meaning
CDOR	CNS Duration of Response
CI	Confidence Interval
Cl	Clearance
C_{max}	Maximum Observed Plasma Concentration
CNS	Central Nervous System
CORR	CNS Objective Response Rate
CPR	CNS progression rate
CR	Complete Response
CSF	Cerebrospinal Fluid
CSR	Clinical Study Report
CT	Computed Tomography Imaging
Ctrough	Minimal Observed Plasma Concentration (Trough Concentration)
CV%	Coefficient Of Variation (%)
DCR	Disease Control Rate
DDI	Drug-Drug Interaction
DIC	Disseminated Intravascular Coagulation
DOR	Duration of Response
DVT	Deep vein thrombosis
ED_{50}	Estimated dose required to have 50% of the maximal effect
EMA	European Medicines Agency (European Union regulator)
FaSSIF	Fasting state simulated intestinal fluid
FDA	Food and Drug Administration (United States of America regulator)
FeSSIF	Fed state simulated intestinal fluid
FISH	Fluorescence In Situ Hybridisation
GAM	Generalised Additive Modelling

Abbreviation	Meaning
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
GI	Gastrointestinal
GLP	Good laboratory practice
GMR	Geometric mean ratio
h	Hours
hERG	Human ether-a-go-go-related gene
HLM	Human liver microsomes
HPLC	High performance liquid chromatography
HR	Hazard ratio
HRQoL	Health-Related Quality of Life
IC_{50}	Concentration at which 50% of maximal inhibition is achieved
IMP	Investigational medicinal product
INR	International Normalised Ratio
IRC	Independent (radiological) review committee
IRR	Independent radiology review
IV	Intravenous
LC/MS-MS	Liquid chromatography/tandem mass spectrometry
LFT	Liver function test
LP	Lumbar puncture
LSC	Liquid scintillation counting
M/P	Metabolite/parent ratio
M1b	Minor metabolite of alectinib, also 'UK'
M4	Major and active metabolite of alectinib, also 'RO5428924'
max	Maximum
MDZ	Midazolam

Abbreviation	Meaning
mg	Milligram(s)
min	Minimum OR minute(s)
MS	Mass spectrometry
ms	Millisecond(s)
msec	Millisecond(s)
MTD	Maximum tolerated dose
N	Number
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
NCE	New Chemical Entity
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
ng	Nanogram(s)
nM	Nanomole/nanomolar
NSCLC	Non-small cell lung cancer
OCT1	Hepatic uptake transporter 'organic cation transporter 1'
OCT2	Renal uptake transporter 'organic cation transporter 2'
ORR	Objective response rate
OS	Overall survival
PBPK	Physiologically-based pharmacokinetic(s)
PD	Progression of Disease
PFS	Progression-free survival
P-gp	P-glycoprotein
PI	Product information
PK	Pharmacokinetic(s)
pKa	Dissociation constant

Abbreviation	Meaning
PO	Per oral
PopPK	Population pharmacokinetic(s)
PPI	Proton-pump inhibitor
PR	Partial response
PV	Pharmacovigilance
QTc	Corrected QT interval
QTcB	QT interval corrected using Bazett's formula
QTcF	QT interval corrected using Fridericia's formula
RANO	Response Assessment in Neuro-Oncology (criteria)
RE	Response evaluable
RECIST	Response Evaluation Criteria in Solid Tumors
RET	Rearranged during Transfection (tyrosine kinase)
RMP	Risk management plan
RO5424802	Alectinib
RO5428924	Major metabolite of alectinib, also 'M4'
RP2D	Recommended Phase II dose
RR	Respiratory rate
SAE	Serious adverse event
SCS	Summary of Clinical Safety
SD	Standard deviation OR Stable Disease
SLS	Sodium lauryl sulfate
TEAE	Treatment-emergent adverse event
TGA	Therapeutic goods administration
Tlast	Time to last measurable plasma concentration
T_{max}	Time at which maximum concentration was reached
TRAE	Treatment-related adverse event

Abbreviation	Meaning
UK	Unknown
ULN	Upper limit of normal
URTI	Upper respiratory tract infection
WBC	White blood cell
WCC	White blood cell count

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Decision:	Approved
Date of decision:	10 March 2017
Date of entry onto ARTG	14 March 2017
Active ingredient(s):	Alectinib hydrochloride
Product name(s):	Alecensa
Sponsor's name and address:	Roche Products Pty Limited PO Box 255 Dee Why NSW 2099
Dose form(s):	Hard capsule
Strength(s):	150 mg
Container(s):	Aluminium - aluminium blisters
Pack size(s):	224 capsules (carton with four sub-cartons of 56 capsules)
Approved therapeutic use:	*Alecensa is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive, locally advanced or metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.* *Note to Indication: This indication is approved based on tumour response rates and duration of response. An improvement in survival or disease-related symptoms has not been established*.
Route(s) of administration:	Oral (PO)
Dosage:	Standard Dosage: The recommended dose of Alecensa is 600 mg (four 150 mg capsules) given orally, twice daily with food (total daily dose of 1200 mg). For further details see Attachment 1 PI.
ARTG number (s):	272115

Product background

This AusPAR describes the application by the sponsor to register alectinib hydrochloride, (as Alecensa) a new chemical entity for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive, locally advanced or metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib. The sponsor proposed the following wording for the indication:

> *Treatment of patients with anaplastic lymphoma kinase (ALK)-positive, locally advanced or metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib*.

The following dosage regimen was proposed by the sponsor:

> *600 mg (Equivalent as free base) PO twice daily until disease progression or unacceptable toxicity*.

Alectinib is a small-molecule and reversible (adenosine triphosphate (ATP) competitive) inhibitor of anaplastic lymphoma kinase (ALK) tyrosine kinase and has the same pharmacological activity as crizotinib (Xalkori) and ceritinib (Zykadia), which have been approved by the TGA for similar indications as sought here (see Table 1 below).

The two major types of lung cancer are small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC; approximately 81% of lung cancers). Six percent of lung cancer rises from other cell types. The World Health Organization (WHO)/International Association for the Study of Lung Cancer (IASLC) histological classification of NSCLC is:

- Squamous cell carcinoma (20% of lung cancers; approximately 25% of NSCLC)
- Adenocarcinoma (38% of lung cancers; approximately 47% of NSCLC)
- Large cell carcinoma (5% of lung cancers; approximately 6% of NSCLC)
- Other (18% of lung cancers; approximately 22% of NSCLC)

Besides histology, influences on choice of initial therapy for advanced disease are:

- extent of disease (for example, number and site of metastases);
- presence of symptoms related to a specific metastatic site;
- presence of driver mutations (for example, EGFR, ALK and ROS11); and
- the patient's overall condition and co-morbidities

Influences on the choice of subsequent therapy for advanced disease are similar. Another factor is choice of prior treatment (that is, the need for non-cross-resistance).

Treatment of advanced NSCLC aims to prolong survival and maintain quality of life, while minimising side effects. Almost all patients with advanced NSCLC eventually develop progressive disease.

Anaplastic lymphoma kinase (ALK) gene rearrangement is found in approximately 4% of all patients with NSCLC (but, for example, in 33% of 'never/light smokers with adenocarcinoma without EGFR mutation'). Shaw writes in Up-To-Date:

> *Tumors that contain the EML4-ALK fusion oncogene or its variants are associated with specific clinical features, including never or light smoking history, younger age, and adenocarcinoma with signet ring or acinar histology. ALK gene arrangements are largely mutually exclusive with epidermal growth factor receptor (EGFR) or KRAS[2] mutations.*

ALK rearrangement has been reported in squamous cell carcinoma, but rarely. National Comprehensive Cancer Network (NCCN) guidelines (NSCLC, v3.2017) suggest ALK testing in SQ NSCLC only in 'never smokers' or in small biopsy specimens or in those specimens with mixed histology.

[1] A receptor tyrosine kinase (encoded by the gene ROS1)
[2] KRAS (K-ras or Ki-ras) is proto-oncogene corresponding to the oncogene first identified in Kirsten rat sarcoma virus[5] and the gene product was first found as a p21 GTPase.

Shaw also notes that ALK gene amplification does not carry the same significance as ALK rearrangement regarding responsiveness to ALK inhibitors.

ALK inhibitors have recently been introduced into practice (Table 1).

Table 1: ALK inhibitors registered in Australia

Drug	Indication	Precautions (selected)	Other
Crizotinib	Xalkori is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC).	Hepatotoxicity ILD (pneumonitis) QT interval prolongation Bradycardia Cardiac Failure Leucopenia GI perforation Visual effects	Registered 2013 Study 1014 showed PFS superiority versus 1L SOC (HR 0.45) but no OS advantage – attributed to crossover; ORR 74% versus 45% Study 1007 showed PFS superiority versus second line (2L) SOC (HR 0.49) but no OS advantage, again attributed to crossover; ORR 65% versus 20% (29% pemetrexed, 7% docetaxel) Also inhibits ROS1
Ceritinib	Zykadia is indicated as monotherapy for the treatment of adult patients with anaplastic lymphoma kinase (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 Indication: This indication is approved based on tumour response rates and duration of response. An improvement in survival or disease –related symptoms has not been established.	Hepatotoxicity ILD / pneumonitis QT interval prolongation Bradycardia GI toxicity Hyperglycaemia Pancreatic toxicity	Registered 2016 Boxed warning notes: QT, ILD, and DILI, GI effects; no data in liver impairment; food effect; only use by qualified physicians. Studies X2101 and A2201 were single arm studies; ORRs were 56% and 37% respectively, 46% and 34% by blinded independent review.
Nivolumab	Opdivo, as monotherapy is indicated for the treatment of locally advanced or metastatic squamous non-small cell lung cancer (NSCLC)	(not listed)	Registered 2016 Boxed warning notes: immune-related adverse reactions (more frequent and

Drug	Indication	Precautions (selected)	Other
	with progression on or after prior chemotherapy. Opdivo, as monotherapy is indicated for the treatment of locally advanced or metastatic non squamous non-small cell lung cancer (NSCLC) with progression on or after prior chemotherapy. In patients with tumour EGFR or ALK genomic aberrations, Opdivo should be used after progression on or after targeted therapy.		more serious in combination with IPI, in melanoma) In Study 057, patients had progressed on a platinum-based doublet AND for ALK translocation an additional line of therapy was allowed. Versus 2L SOC, OS HR was 0.73; PFS HR was 0.92; ORR was 19.2% versus 12.4% (in the overall patient population). According to the AusPAR, patient on 3L therapy did not share in the OS benefit (HR 1.34) and amongst these would be patients who had been treated with an ALK inhibitor (but the analysis of OS HR in ALK positive patients was curtailed by low numbers).

Crizotinib is Pharmaceutical Benefits Scheme (PBS) listed in Australia[3].

Criteria for use are at www.pbs.gov.au/medicine/item/10322G-10323H and include:

- monotherapy use;
- non-squamous (NSQ) NSCLC or not otherwise specified (NOS) NSCLC;
- WHO PS 2 or less; and A
- ALK + by FISH.

Despite high activity, almost all patients develop resistance to crizotinib, usually within the first few years. Shaw writes:

- *In approximately one-third of resistant cases, tumors have acquired a secondary mutation within the ALK tyrosine kinase domain. The most common resistance mutation is the gatekeeper L1196M mutation, followed closely by the G1269A mutation. Other mutations occur at residues 1151, 1152, 1156, 1174, 1202, 1203, and 1206. The G1202R mutation is notable, as it confers high-level resistance to crizotinib as well as to next-generation ALK inhibitors (see below).*
- *A second mechanism of crizotinib resistance is amplification of the ALK fusion gene. This can occur alone or in combination with a secondary resistance mutation.*

[3] www.pbs.gov.au/medicine/item/10323h

– *Finally, a number of alternative or bypass signaling pathways have been shown to mediate crizotinib resistance. These include abnormalities in the epidermal growth factor receptor (EGFR), KIT, and insulin-like growth factor-1 receptor (IGF1R) pathways, and suggest the potential need for combination therapies to overcome resistance.*

Shaw also notes 'frequent CNS relapses' in patients on crizotinib and this is noted by Roche as a reason for poor survival after relapse on crizotinib.

Ceritinib is registered for patients whose disease has progressed on crizotinib and may be available for use (although it is not PBS listed as of 9 December 2015).

Anti-PD-1 monoclonal antibody checkpoint inhibitors are recent additions to the therapeutic landscape. Nivolumab has amongst its indications:

> *Opdivo, as monotherapy is indicated for the treatment of locally advanced or metastatic non squamous non-small cell lung cancer (NSCLC) with progression on or after prior chemotherapy. In patients with tumour EGFR or ALK genomic aberrations, Opdivo should be used after progression on or after targeted therapy.*

Opdivo can be considered a second or later line option after crizotinib treatment. It is unclear whether clinicians would exhaust targeted therapy options and even more traditional chemotherapies before using anti-PD-1 therapies, in patients with ALK positive disease. The AusPAR for nivolumab states in the description of Study 057 '*there are too few subjects with ALK mutations to understand the benefit / risk balance of second-line nivolumab in such subjects*'. NCCN guidelines (NSCLC v3.2017; NSCL-20, 21) suggest targeted therapies take precedence.

Alectinib is a tyrosine kinase inhibitor, active against ALK and Rearranged during Transfection (tyrosine kinase) (RET) and multiple point mutated versions of both proteins. The nonclinical evaluation report also states:

> *Alectinib showed inhibitory kinase activity in vitro against RET, GAK and LTK kinases, L type Ca^{2+} and Cl- (GABA-gated) channels at high concentrations. However, alectinib has not been assessed in cellular assays against these kinases. The clinical relevance is uncertain. Alectinib also showed inhibitory activity against 5-HT, dopamine and norepinephrine uptake transporters at concentrations 7-22 times the clinical C_{max}. While these findings suggest potential neurological effects, no signs of neurotoxicity were evident in safety pharmacology and toxicity studies.*

According to the nonclinical evaluation, alectinib has only weak activity against ROS1. Specificities across different agents are as follows:

Alectinib	ALK, RET
Crizotinib	ALK, ROS1, MET[4], RON[5]
Ceritinib	ALK, ROS1

Regulatory status

The product received its initial registration on the Australian Register of Therapeutic Goods (ARTG) on 14 March 2017.

Alectinib was first approved in Japan on July 4, 2014. Alectinib has received accelerated approval from the FDA based on tumor response rate and duration of response with the following indication:

[4] Mesenchymal-epithelia transition
[5] Recepteur d'Origine Nantais

Alecensa is a kinase inhibitor indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive, metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.

Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial.

Key Precautions in the US PI are: hepatotoxicity; ILD[6] / pneumonitis; bradycardia; severe myalgia and CPK elevation; and embryo-foetal toxicity.

The FDA approval, on 11 December 2015, was conditional on conduct and submission of results of at least one randomised controlled trial (RCT) establishing superiority of alectinib over available therapy in patients with metastatic ALK positive NSCLC (requirement 2995-1). A final report is to be submitted by June 2018. The FDA also required a study in hepatic impairment (requirement 2995-2; final report submission by December 2017).

At the time of the initial Australian submission, Alectinib was not yet approved for use in the European Union (EU). The European Commission granted a conditional marketing authorisation valid throughout the European Union for Alecensa on 16 February 2017.

Product Information

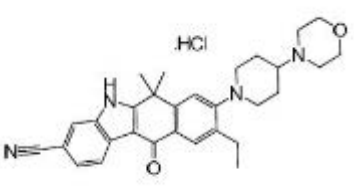
The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Quality findings

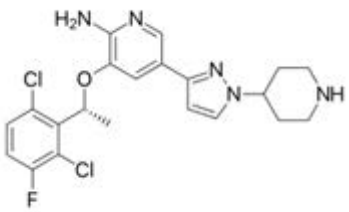
Introduction

Alectinib is an ALK and RET tyrosine kinase inhibitor. The structure is not closely related to other kinase inhibitors but the sponsor's modelling suggests that alectinib can dock in the same binding pocket as crizotinib which is another ALK inhibitor (Pfizer's Xalkori 200 and 250 mg capsules indicated for the treatment of ALK+ advanced non-small cell lung cancer: recommended dose 250 mg twice daily).

Figure 1: Chemical structure of alectinib hydrochloride and crizotinib



Alectinib·hydrochloride



Crizotinib

Drug substance (active ingredient)

Alectinib hydrochloride is a white to yellow white powder. The partition coefficient ($LogP_{octanol/water}$) of alectinib is 1.96, with a dissociation constant (pKa) of 7.05 (very

[6] ILD=interstitial lung disease

slightly basic). Alectinib hydrochloride has low solubility in aqueous buffers across the pH range. Alectinib hydrochloride is produced in a consistent crystalline form which is slightly hygroscopic.

Alectinib is made by chemical synthesis. It has no stereogenic centres and is achiral. Drug substance manufacturing and quality control details are acceptable. The drug substance specification includes water content and particle size limits. The drug substance is stable stored below 30ºC.

Drug product

The sponsor proposes registration of one strength only (150 mg) as immediate-release, hard capsules, with shells made of hypromellose (not gelatine). These are white, size 1, capsules with 'ALE' printed in black ink on the cap and '150 mg' printed in black ink on the body.

Due to the poor solubility of the drug substance, a capsule fill was developed which contains an unusually high level of the surfactant sodium lauryl sulfate (SLS). The fill also contains carmellose calcium, lactose monohydrate, hyprolose and magnesium stearate.

SLS is a gastrointestinal tract irritant. The nonclinical data included some animal studies with varying SLS levels. The sponsor states that SLS is better tolerated when taken with food and Alecensa was administered with meals in the clinical studies. The sponsor also undertook a bioequivalence comparison (Study NP29040) of capsules made with different levels of SLS which is discussed below. The proposed '50% SLS' formulation was used in all Phase II and Phase III clinical studies.

Drug product manufacturing involves wet granulation of the fill mass blend, followed by wet sieving, drying, blending, encapsulation and packaging. Suitable manufacturing controls are applied.

The finished product specification is generally conventional and includes appropriate tests and limits.

The dissolution method was shown to be discriminatory for various formulation and manufacturing parameters including SLS content and source, granulation water and time, exposure to stress storage conditions such as heat and humidity, and morphology of the drug substance.

Capsules are packed in aluminium-aluminium blisters within a 'multipack' of 224 capsules (four separate 56 capsule cartons). Alecensa capsules are stable at 30°C (stored in the original package to protect from light and moisture).

Biopharmaceutics

Alectinib absorption is formulation dependent. The proposed capsule formulation, given as a fed, four capsule 600 mg dose, has moderate absolute bioavailability [36.9% (90% confidence interval (CI) 34 - 40%) in healthy subjects [Study NP28989]. The sponsor attributes this to incomplete absorption given poor solubility and moderate permeability. Absorption is relatively slow, especially with food (time to peak plasma concentration (T_{max}) ranges from 6 to 12 hours fed).

Two low strength capsules (20 and 40 mg) were developed for some early clinical trials. The '50% SLS' 150 mg capsule formulation proposed for registration was used in all Phase II and Phase III studies.

Alectinib is metabolised by cytochrome P450 isozyme CYP3A4. The major metabolite (M4 or RO5468924) shows similar in vitro activity. Alectinib and M4 were the main circulating species in plasma (total about 76% of the total radioactivity).

Study NP28989A was a combined absolute bioavailability study and an ADME (absorption, distribution, metabolism, excretion) study using radiolabelled alectinib under fed conditions in healthy male subjects. The absolute bioavailability part compared single oral doses of the proposed capsules (4 x 150 mg) and a low dose tracer intravenous solution formulated with cyclodextrin administered 3.75 h after the capsules.

The ADME part used a 600 mg dose of an oral suspension formulated only with drug and water. The majority of radioactivity after the suspension dose was excreted in faeces (95.6%-100%) with minimal excretion in urine (0.3%- 0.6%). In faeces, 84% of the dose was excreted as alectinib and 5.8% as M4.These figures may well be slightly different after capsule dosing. The mean elimination half-life for alectinib was 32.5 hours. Alectinib is not a substrate of the efflux transporters p-glycoprotein (P-gp) or Breast Cancer Resistance Protein (BCRP).

Study NP28991 assessed the effect of a high fat, high calorie meal on bioavailability. Plasma profiles are generally conventional. Food has large effect on bioavailability. Absorption is slow, particularly with food (median T_{max} 4 h [range 2 to 8 h] fasting: T_{max} 8 h [range 6 to 12 h] fed). Food markedly increased both peak plasma concentration (C_{max}) and the area under the concentration versus time curve (AUC). Clinical doses were to be taken with food, consistent with PI directions.

Table 2: Plasma exposure in fasted and fed subjects

Analyte	Parameter	Fasted	Fed	Ratio (%)	90% CI Lower	90% CI Upper
RO5424802	$AUC_{0-\infty}$(h*ng/mL)	1790	5230	292	258	329
	AUC_{0-last}(h*ng/mL)	1670	5110	306	269	348
	C_{max} (ng/mL)	95.1	257	270	228	320
RO5468924	$AUC_{0-\infty}$(h*ng/mL)	1030	3390	328	276	389
	AUC_{0-last}(h*ng/mL)	920	3210	349	288	422
	C_{max} (ng/mL)	32.4	122	377	303	468
Geometric means are presented in table						
Fasted: Single 600mg RO5424802 dose given under fasted conditions						
Fed: Single 600mg dose following ingestion of a high fat, high calorie meal						

Study NP29040 was a crossover bioequivalence comparison of single 600-mg oral doses of the proposed 50% SLS capsules and alternative formulations with lower levels of SLS under fasting and fed conditions. This compared formulations with 25% SLS, 12.5% SLS and 3% SLS. SLS has a clear effect of enhancing bioavailability but the 25% SLS formulation was found to be bioequivalent. The sponsor may propose registration of a formulation containing a lower amount of SLS in the future, in place of the 50% SLS formulation.

Quality summary and conclusions

Registration is recommended from a chemistry and quality perspective.

The submission has not been considered by the Pharmaceutical Sub-Committee of the TGA's Advisory Committee on Prescription Medicines (ACM).

III. Nonclinical findings

Introduction

The main body of the nonclinical evaluation report was largely based on the US FDA assessment report which is available in the public domain.

The submitted nonclinical dossier was in general accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline on the nonclinical evaluation of anticancer pharmaceuticals.[7] The overall quality was generally adequate. All pivotal toxicity studies were conducted under Good Laboratory Practice (GLP) conditions using the proposed clinical route (oral (PO)).

Pharmacology

Rationale of drug development

ALK is a tyrosine kinase normally expressed only in certain neuronal cells. A rare subset of patients with NSCLC have tumours that contain a deletion and inversion within chromosome 2p which results in fusion of the N-terminal portion of the protein encoded by the echinoderm microtubule-associated protein-like 4 (EML4) gene with the signalling portion of the ALK receptor tyrosine kinase.[8] This results in the expression of a ligand-independent and constitutively active tyrosine kinase with oncogenic activity. Inhibition of this fusion protein blocks downstream signalling and reduces cell proliferation and inhibits growth of tumours expressing the EML4-ALK fusion protein.

Clinical treatment with crizotinib therapy has generated cancer cells resistant to crizotinib due to secondary mutations in ALK or amplification of ALK fusions[9], acquired alternative signalling pathways such as EGFR, mast/stem cell growth factor receptor (c-KIT), KRAS or unknown mechanisms.[10] In addition, progression in the central nervous system (CNS) was reported to be the primary site of initial treatment failure in 46% of patients with ALK+ NSCLC, treated with crizotinib.[11]

[7] ICH S9: Nonclinical Evaluation For Anticancer Pharmaceuticals

[8] Soda M *et al*. (2007) Identification of the transforming *EML4-ALK* fusion gene in non-small cell lung cancer. *Nature* 448: 561–566.

[9] Doebele R *et al.* (2012) Mechanisms of resistance to crizotinib in patients with ALK gene rearranged non-small cell lung cancer. *Clin Cancer Res* 18:1472-82 and Katayama R *et al.* (2011) Therapeutic strategies to overcome crizotinib resistance in non-small cell lung cancers harboring the fusion oncogene EML4-ALK. *PNAS* 108:7535-40

[10] Doebele R *et al.* (2012) Mechanisms of resistance to crizotinib in patients with ALK gene rearranged non-small cell lung cancer. *Clin Cancer Res* 18:1472-82 and Katayama R *et al.* (2011) Therapeutic strategies to overcome crizotinib resistance in non-small cell lung cancers harboring the fusion oncogene EML4-ALK. *PNAS* 108:7535-40 and Kim S *et al*. (2013) Heterogeneity of Genetic Changes Associated with Acquired Crizotinib Resistance in ALK-Rearranged Lung Cancer. *J Thorac Oncol* 8(4):415-22.

[11] Costa DB *et al.* (2011) CSF concentration of anaplastic lymphoma kinase inhibitor crizotinib. *J Clin Oncol* 29:e443-5 and Chun SG *et al.* (2012) Isolated central nervous system progression on crizotinib. *Cancer Biol Ther* 13(14):1376-83 and Weickhardt AJ *et al.* (2012) Continuation of EGFR/ALK inhibition after local therapy of oligoprogressive disease in EGFR mutant (Mt) and ALK+ non-small cell lung cancer (NSCLC). *J Clin Oncol* **30(suppl)**:ASCO Abstract 7526.

Primary pharmacology

Mechanism of action

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

In vitro studies in cell free assay systems demonstrated that alectinib was most active against ALK (50% inhibitory concentration (IC_{50}) 1.9 nM) and RET (IC_{50} 4.8 nM) and multiple mutants of both these kinases among a panel of 26 recombinant human protein kinases (IC_{50} against most mutants at or below the steady state clinical free fraction C_{max} 15 nM and lowest concentration reached by a drug before the next dose is administered (Ctrough 13 nM[12])). 3D structural analysis indicated ATP competitive kinase inhibition (alectinib interacts at the adenosine triphosphate (ATP) binding site of the ALK enzyme). ALK is a receptor tyrosine kinase of the insulin receptor superfamily. Alectinib has only weak activity against two other receptor tyrosine kinases of the insulin receptor superfamily, InsR (IC_{50} 550 nM) and ROS1 (IC_{50} 3600 nM) and no activity against other kinases. A study with crizotinib and ceritinib showed that crizotinib (IC_{50} 9.0 nM) and ceritinib (IC_{50} 3.1 nM) are only slightly less active against ALK than alectinib but both crizotinib and ceritinib have a different specificity pattern and are not restricted to targeting only ALK and RET at clinically relevant concentrations (alectinib: ALK, RET; crizotinib: ALK, ROS1, MET and RON; ceritinib: ALK, ROS1).

Activity against cancer cell proliferation in vitro

In cell proliferation studies using a variety of cancer cells (human lung cancer NSCLC, lymphoma and neuroblastoma cell lines), alectinib concentration dependently inhibited proliferation of cancer cells harbouring ALK fusion or amplification (that is, ALK fusion proteins EML4-ALK or NPM-ALK, ALK with point mutations or gene amplification) but showed no inhibitory activity in cells carrying the wild type ALK. The IC_{50} value (12 nM) against the human lung cancer NSCLC NCI-H2228 cell line harbouring EML4-ALK in the cell proliferation assay was similar to clinical plasma concentrations at steady state. Alectinib also showed activity against tumour cells harbouring fusion RET proteins (IC_{50} 100-200 nM). Alectinib had no activity against growth of tumour cell lines driven by EGFR, MET or Ras mutations (IC_{50}s ≥ 400 nM).

There was no attempt to directly correlate the anti-proliferative activity (nor anti-tumour activity) of alectinib with inhibition of phosphorylation of ALK and/or downstream signalling proteins. However, alectinib was shown to directly inhibit ALK autophosphorylation and prevent phosphorylation of the downstream STAT3 and AKT signalling molecules in a human NSCLC NCI H2228 lung cancer cell line expressing the EML4-ALK fusion protein (EML4 ALK positive) and human KARPAS-299 anaplastic large cell lymphoma (ALCL) cell line harbouring the NPM-ALK fusion gene. In a human NSCLC xenograft model in mice, an oral dose of 20 mg/kg suppressed intra tumoural ALK phosphorylation.

The main human metabolite, M4, showed inhibitory activity (IC_{50} 1.2 nM) against human recombinant ALK, activity against ALK mutants associated with crizotinib resistance as alectinib and cytotoxic activity against an EML4 ALK fusion-positive (human NSCLC NCI H2228) cell line with an IC_{50} of 37 nM in the same range as alectinib. The kinase selectivity and inhibitory activity of M4 against other kinases, RET and RET mutants, was also very similar to that of alectinib. Since M4 shows a similar profile of activity and potency to alectinib in vitro, it is expected to contribute to clinical efficacy.

[12] Based on mean steady state clinical Cmax 723 ng/mL (1.5 μM) and Ctrough 630 ng/mL (1.3 μM) and 1% unbound fraction at the proposed dose of 600 mg PO twice daily.

Activity in animal cancer models

In vivo studies in severe combined immunodeficiency (SCID) mice showed that alectinib resulted in dose-dependent inhibition of human NSCLC NCI H2228 (expressing EML4-ALK), ALCL Karapas299 (nucleophosmin NPM-ALK) and NB 1 neuroblastoma (ALK gene amplification) SC xenograft growth at oral, well tolerated doses of 2 to 60 mg/kg for 11 days. Partial regression was observed at 6 mg/kg and complete regression at ≥ 20 mg/kg. The anti-tumour effect was maintained with no tumour re-growth for 4 weeks when tested at 20 and 60 mg/kg in the human NSCLC tumour model. However, minimal inhibition was observed with alectinib in the ALK wild-type (A549) human NSCLC tumour model (lacking ALK perturbations). Alectinib was also effective against NSCLC cells expressing CCDC6-RET.

Efficacious doses/exposures were lower than or similar to that anticipated clinically. The C_{max} (21.2 ng/mL) and AUC (296 ng.h/mL) at the nonclinical 50% effective dose (ED_{50}) (0.46 mg/kg/day) against NCI H2228 (NSCLC) tumour growth in SCID mice were considerably below the clinical steady state C_{max} (723 ng/mL) and AUC (16260 ng.h/mL). The intra tumoural (tumour tissue C_{max}) levels of alectinib was not, however, determined.

Activity against crizotinib-resistant tumours

Alectinib also showed inhibitory activity against ALK point mutations (identified in patients treated with crizotinib and associated with acquired crizotinib resistance) in both biochemical kinase panels and BaF3 cell lines expressing mutant proteins (that is, inhibition of cell growth and viability) including L1196M, C1156Y, 1151Tins, L1152R, F1174L, G1202R and G1269A point mutations. In enzyme assays, IC_{50}s values against L1196M and wildtype (WT) ALK were similar, 2.1 and 1.9 nM, respectively. IC_{50}s for other ALK mutations ranged from 0.93 nM (C1156Y) to 41 nM (G1202R). In a comparative cell based study, and L1196M, G1269A and S1206Y mutations were more sensitive to growth inhibition by alectinib (IC_{50} = 16-240 nM) by up to10 fold when compared to crizotinib (IC_{50} = 170-690 μM). However, the activity against ALK mutants relative to ALK (that is, IC_{50} ratio against ALK mutant/ALK) was similar between alectinib and crizotinib in the in vitro enzyme and cellular assays.

In animal cancer models in vivo, alectinib (60 mg/kg) was active against crizotinib-resistant tumours in SCID mice following SC implantation of Ba/F3 cells expressing crizotinib resistant mutations (except G1202R), while crizotinib (100 mg/kg) was ineffective. Alectinib demonstrated significant anti-tumour activity in a mouse human NSCLC tumour model in which xenograft growth had already been maximally suppressed by crizotinib (100 mg/kg). Alectinib dosing (60 mg/kg) for a further 21 days resulted in significant tumour regression, while continued crizotinib dosing maintained tumour size with no further regression. In the same study animals treated with alectinib gained more body weight than crizotinib treated animals.

Activity in models of NSCLC brain metastases

In a brain tumour model of NSCLC brain metastases, alectinib (60 mg/kg) showed significant anti-tumour activity based on survival, bioluminescence imaging and histopathology following intracranial implantation of human NSCLC (NCI-H2228) cancer cells, while crizotinib had no or minimal effects. Notably, alectinib prolonged survival (102.5 days) compared to crizotinib (57 days) and vehicle (39 days). The findings indicate alectinib crosses the blood brain barrier, a finding supported by a rat tissue distribution study indicating distribution and retention in the CNS. Radioactivity detected in the brain was about 30 to 40% of that in blood up to 24 hours following PO dosing. These findings are in accordance with the finding that alectinib is not a substrate of efflux transporters in the blood brain barrier (that is, both p glycoprotein and BCRP).

Anti-tumour activity in combination with other anticancer drugs

Compared to the inhibitory effect of either agent alone, alectinib (3 mg/kg) showed a slight to moderate increase in anti-tumour activity (by 19 to 46%) in NSCLC (NCI H2228) ALK fusion-positive (EML4-ALK) xenograft models in SCID mice when administered in combination with other standard chemotherapeutic agents for NSCLC (cisplatin, paclitaxel, gemcitabine and bevacizumab). The combination therapies were well tolerated with generally no remarkable body weight loss.

Overall, in vivo studies demonstrated that treatment with alectinib in mice produced dose-dependent inhibition of xenograft growth. Alectinib also inhibits growth of crizotinib-resistant tumours and showed anti-tumour activity in the brain. In general, the data support the proposed indication.

Secondary pharmacodynamics

In a screening assay of 450 human kinases and disease related mutants, alectinib at clinically relevant concentrations of 10 nM resulted in ≥ 75% of GAK (cyclin G associated kinase[13]) and LTK (leukocyte receptor tyrosine kinase[14] and >99% at 1000 nM) in addition to kinases (RET, InsR, ROS1) discussed above. Beyond the screening assay, there were no further studies examining potential inhibitory activity of alectinib against LTK or GAK kinases. Alectinib has not been assessed in cellular assays against any of these kinases. Whilst inhibition of LTK and GAK kinases is likely to occur clinically, the clinical relevance of inhibition of these kinases is uncertain.

In vitro assays screening for off-target activity against a panel of 109 receptors, ion channels and transporters (ligand binding studies) and 42 enzymes (activity studies), all at a single high concentration of 10 μM (approximately 700 times the peak clinical plasma free fraction C_{max}), showed > 50% inhibition of about 20 of the receptor, ion channel and transporter targets . These targets included peripheral benzodiazepine receptors, dopamine receptors, muscarinic receptors, neurokinin receptors, serotonin receptors, sigma [σ] receptors, glucocorticoid receptors, urotensin receptors, L type calcium (Ca_{2+}) channels, chloride (Cl^-) channels (GABA-gated) as well as monoamine transporters (serotonin, norepinephrine and dopamine). Alectinib (10 μM) also interacted with 4 of the enzyme targets with > 50% inhibition [Angiotensin converting enzyme 2 (ACE-2)[15]: 80%, Abl kinase[16]: 64%, Ca^{2+}/calmodulin-dependent protein kinase (CaMK2α[17]): 72% and IRK (=insulin receptor (InsR) tyrosine kinase domain 66%; IC_{50} 550 nM in another study)].

Further functional assays showed no effects on muscarinic, neurokinin and urotensin receptors at 1 or 10 μM but demonstrated inhibitory activity against monoamine serotonin (5-HT), dopamine and norepinephrine with IC_{50} values of 100, 260 and 330 nM, respectively, 7, 17 and 22 fold the clinical plasma free fraction C_{max} at steady state). Activity at these 3 monoamine transporters could result in some neurological effects.

[13] GAK: is a serine/threonine kinase. In eukaryotes, the cell cycle is governed by cyclin-dependent protein kinases (CDKs) and GAK is an association partner of CDK5 and cyclin G (a direct transcriptional target of the p53 tumour suppressor gene). GAK has been implicated in viral infection, cancer and Parkinson's disease.

[14] LTK: the exact function and the LTK ligand is not known, but it is closely related to the insulin receptor family of receptor tyrosine kinases (RTKs). Tyrosine-specific phosphorylation activity is involved in diverse pathways leading to cell growth/differentiation.

[15] ACE 2 (different from ACE; ACE hydrolyses angiotensin I (Ang I) to angiotensin II, while ACE2 hydrolyses Ang II to Ang1-7) has direct effects on cardiac function and is expressed predominantly in vascular endothelial cells of the heart and kidneys.

[16] The ABL1 proto-oncogene encodes a cytoplasmic and nuclear protein tyrosine kinase implicated in processes of cell differentiation, cell division, cell adhesion, and stress response.

[17] CaMK2 is a serine/threonine-specific protein kinase involved in many signalling cascades, learning and memory, Ca2+ homeostasis/reuptake in cardiomyocytes, chloride transport in epithelia, positive T-cell selection, CD8 T-cell activation; misregulation is linked to Alzheimer's disease, Angelman syndrome and heart arrhythmia.

However, in vivo safety pharmacology studies investigating effects on the CNS in rats and the repeat-dose toxicity studies in rats and cynomolgus monkeys (≤3 months) showed no signs of CNS effects (discussed below).

Potential inhibitory activity seen at the single high concentration of 10 μM against ACE-2, CaMK2α, L type calcium (Ca^{2+}) channels and chloride (Cl; γ-aminobutyric acid (GABA) gated) channels were not examined any further, ideally at lower, clinically relevant concentrations. Therefore, the clinical relevance of the observed inhibition of the enzymes and ion channels remains equivocal, although the inhibition of L-type Ca^{2+} channel may contribute to the hypotensive effect of alectinib observed in monkeys (see below).

Safety pharmacology

The potential effects of alectinib on cardiovascular, respiratory, gastrointestinal and CNS function were investigated in in vitro assays and in vivo in monkeys and rats. Three of the five in vivo studies were GLP compliant, while the design, conduct and reporting of the remaining studies [assessing gastrointestinal effects and a cardiovascular exploratory study] were adequate to reveal any treatment-related effects.

Alectinib inhibited potassium (K^+) hERG channel activity in human embryonic kidney cells stably expressing hERG with an IC_{50} of 450 nM. The IC_{50} is 30 times higher than the anticipated free fraction clinical C_{max} 15 nM (approximately 7 ng/mL), suggesting low potential for QT prolongation in patients. In cynomolgus monkeys, only slight hypotension (approximately 10 mmHg) was observed after a single oral dose of 20 or 60 mg/kg alectinib (C_{max} was about 700 ng/mL derived from toxicokinetic data from 2 week monkey toxicity study). There was no evidence of QT prolongation in monkeys. No significant cardiovascular effects were seen at lower doses (≤15 mg/kg; the 4 hour post dose plasma drug concentration was 279 ng/mL, approximately 0.4 times the clinical C_{max}). However, reductions in heart rate in both sexes (7-12%) at 12 mg/kg/day in the last week of the study were seen in the 13 week monkey study (C_{max} approximately 0.4 times the clinical C_{max}). The nonclinical study findings indicate some potential for minor cardiovascular effects, that is, bradycardia and possibly hypotension in patients.

Alectinib (free base) caused vasodilation in pre contracted rat aortic rings in vitro, with IC_{50} of 168 nM and IC20 of 15.3 nM. Alectinib also inhibited the Cav1.2 current (which plays a dominant role in vascular smooth muscle contraction) in Chinese hamster cells expressing the human L-type Ca^{2+} channel (20% inhibitory concentration (IC20): 203 nM, IC_{50}: 461 nM) and also inhibited the L-type Ca_{2+} channel (approximately 90% inhibition at 10 μM) in the receptor, ion channel and enzyme screening study (see above). The in vitro study findings explain to some extent hypotension observed in the in vivo study in telemetered monkeys.

No behavioural changes were observed in a rat modified Irwin test following a single oral dose of alectinib up to 300 mg/kg (plasma C_{max} 1770 ng/mL, approximately 2.5 times the clinical C_{max}). Similarly, there were no adverse effects of alectinib (3 300 mg/kg) on respiratory or gastrointestinal function in rats. No signs of neurological toxicity or effects on respiration were observed in repeat dose toxicity studies. Alectinib is not expected to cause effects on vital functions of the central nervous, gastrointestinal and respiratory systems in patients.

Pharmacokinetics

An in vitro study in a human epithelial cell line (Caco-2) culture indicated moderate permeability of alectinib through the intestinal membrane (1.88×10^{-6} cm/sec). Following oral dosing, absorption was slow to moderate with peak plasma levels of alectinib seen 2 9 h after dosing in rats and Cynomolgus monkeys, comparable to the T_{max} (4 to 6 h) in

human subjects. Oral bioavailability was high in rats (approximately 88%) and moderate in monkeys (approximately 50%); both higher than in human subjects (37%). Absorption of alectinib appeared to become saturated at 27 mg/kg in rats and at 20 mg/kg in monkeys. Exposures in female rats were generally slightly higher (up to 2 times) than in male rats, while there were no clear sex related differences in exposure in monkeys. AUC values increased by up to 2 times in rats following repeated doses but there was no consistent evidence of accumulation in monkeys. The elimination half-life was long in monkeys (8 to 10 h), longer in rats (13 to 32 h) and humans (32.5 h). Plasma clearance was slower in rats and monkeys (6 to 13 mL/min/kg) than in humans (81.9 mL/min/kg). Steady state volume of distribution (Vss) was high in all animal species (9 13 L/kg in rats, 5 L/kg in monkeys) and humans (6.4 L/kg), indicating extensive tissue distribution and consistent with rat tissue distribution study results (discussed below).

Plasma protein binding by alectinib was high and independent of concentration (0.1 to 10 µg/mL) in the plasma of mice, rats, monkeys and humans (>99% in all species). Alectinib was highly bound to human serum albumin (97%), with very low binding to α1-acid glycoprotein (<5%). Plasma protein binding by the major metabolite, M4, was also high and similar in rat, monkey and human plasma (>99% at all concentrations, 0.2 – 2 µg/mL). There was a high degree of distribution of alectinib and the M4 metabolite into red blood cells. In vitro blood distribution assays showed blood/plasma concentration ratios of alectinib of 2.1 (rat), 3.7 (monkey) and 2.8 (human) at 0.1-1 µg/mL. Binding to blood cells was saturated at above 1 µg/mL with blood/plasma concentration ratios of 1.4 (rat), 1.7 (monkey) and 1.3 (human) at 10 µg/mL. Blood/plasma concentration ratios of M4 were approximately 2.5 (rat and human) and 2.2 (monkey) at 0.3 to 2 µg/mL.

Quantitative whole-body autoradiography of pigmented and albino rats following oral dosing with radiolabelled (^{14}C) alectinib showed rapid and wide tissue distribution with tissue radioactivity levels higher than in the plasma. High levels of radioactivity were seen in the uveal tract, Harderian gland, adrenal, thyroid, pituitary, heart muscle, lung and spleen. Some of these organs (adrenal and pituitary) were target organs for toxicity with alectinib. Radioactivity in pigmented skin was not markedly different (<2-fold) from that of skin not pigmented. In both pigmented and non-pigmented rats, highest levels of radioactivity were reported in the uvea, possibly due to a high degree of binding to melanin. Penetration into CNS tissues (that is, across the blood-brain barrier) was observed, with radioactivity in the cerebrum, cerebellum, and spinal cord at levels of 30-40% of that of blood up to 24 hours following PO dosing. Elimination from tissues was slow, with radioactivity still detectable in many tissues (for example, uvea, adrenal, lung and Harderian gland) 21 days after dosing.

Alectinib is cleared by metabolism and biliary excretion. At least 10 metabolites were identified across species. Metabolites were formed by morpholine ring opening (M4), morpholine ring opening and subsequent oxidation (M1), morpholine ring hydroxylation (M5) and morpholine ring opening and subsequent dealkylation (M6). Additional metabolites which were all detected at low or trace levels in hepatocytes from rats, monkeys and humans were M3, M5, M7, M8, M9 and M10. M4 was the major metabolite in rats and humans in vivo (no metabolism study in monkeys) and/or in hepatocyte (mouse, rat, monkey and human) incubations in vitro. CYP3A4 was identified as the isoenzyme responsible for the formation of M4 and subsequent oxidation of M4 to M6. All human metabolites (M1, M4, M6) detected in vivo were found in animals in vivo or in vitro. Thus, there were no unique human metabolites that were not observed in either of the key nonclinical species used in toxicity testing (M1, M4 and M6 were detected in rats and monkeys in pharmacokinetics or toxicity studies and in rat and monkey hepatocyte incubations in vitro).

M4 is a pharmacologically active metabolite (see discussion above under Primary pharmacology). The plasma C_{max} and AUC of M4 in patients at the clinical dose of 600 mg

were both approximately 37% of the C_{max} and AUC values of alectinib. While the M4 metabolite was produced at low levels in the pivotal toxicity studies in Cynomolgus monkeys (about 25 % of parent) and rats (2-5% of parent) at the highest dose, unchanged alectinib is the major species in plasma of both rats and humans after PO administration (70-90% of total drug-related components in plasma; no metabolism study in monkeys). Unchanged alectinib was also the major component in faeces (80-90% in rats and humans; not investigated in monkeys), although M4 was the major component in bile (rat, about 10%).

Excretion of alectinib and/or its metabolites was predominantly via the faeces in both rats and human subjects (> 95% by 168 h), with 0.5% of the dose excreted in urine. Alectinib was the main drug-related species in the faeces of rats and humans (80-90%), with M4 also a significant component in the faeces of rats (0-24 h: 22%; 24-48 h: 39%) and humans (6%). Significant biliary excretion was seen following IV dosing in bile duct-cannulated rats (42.5% of the dose as metabolites with M4 the most abundant, that is, 10% of the dose; unchanged drug, 1.3%), with minimal enterohepatic recirculation.

Overall, the pharmacokinetic profile of alectinib was qualitatively similar in rats, Cynomolgus monkeys and humans to support the choice of animal species for toxicity studies for the assessment of drug toxicity in humans.

Pharmacokinetic drug interactions

CYP inhibition/induction

Alectinib showed weak competitive inhibition of CYP2C8 (IC_{50} 3.87-6.81 µM; Ki 1.98 µM), and alectinib and the M4 metabolite showed weak time-dependent inhibition of CYP3A4 (KI >60 and >369 µM, K_{inact} 0.0624 and 0.0620 min^{-1} for alectinib and M4, respectively; IC_{50} after 30 min pre incubation: 6.07-7.46 µM for alectinib and > 10 µM [48% inhibition at 10 µM] for M4). There was no significant inhibition against CYP1A2, CYP2B6, CYP2C9, CYP2C19 and CYP2D6 by alectinib and M4 at up to 10 µM or against CYP2C8 by M4. The IC_{50} or KI were >250 fold higher than the clinical free fraction C_{max}. Alectinib is unlikely to increase plasma concentrations of drugs that are predominantly metabolised by CYP3A4 or CYP2C8 or other CYP enzymes.

In vitro assays with human hepatocytes from 3 donors showed weak induction of CYP1A2 up to 2 fold induction of enzyme activity/mRNA expression) and slight induction of CYP3A4 and CYP2B6 (CYP3A4: up to 2 fold and mRNA levels up to 4 fold; CYP2B6: activity/mRNA levels both increased up to 3 fold) by alectinib at the nominal test concentration of 1 µM (measured concentration 76-153 nM at the start of exposure and 11-36 nM at the end of exposure). There was no significant induction at 0.1 µM (measured concentrations approximately 40 nM at the start and <2 nM at the end of exposure). The text concentration of 10 µM resulted in 99.6% protein binding. The low concentrations measured in the incubation suggest adsorption to test equipment and possibly metabolism of alectinib during incubation. While the results would indicate further in vitro studies, it was noted that clinical studies in patients with multiple dosing showed no effects on the exposure to midazolam, a CYP3A substrate.

CYP3A4 is the major CYP isoenzyme (≥ 80%) in the metabolism of alectinib and M4. Therefore, inhibitors or inducers of CYP3A enzymes could alter the systemic exposure to alectinib and M4.

Membrane Transporters

In vitro transporter studies showed that alectinib was not a substrate of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), organic anion-transporting polypeptide (OATP) 1B1 and OATP1B3. There was no active uptake of alectinib by human hepatocytes

in vitro. Therefore inhibitors of these transporters are not expected to alter the disposition of alectinib.

M4 is a substrate of P-gp (efflux ratio approximately 11 at 0.3 μM in the Caco-2 cell assay) but not of BCRP, OATP1B1 or OATP1B3. There was no active uptake of M4 by human hepatocytes in vitro. Co-medication with P gp inhibitors may increase M4 exposure in patients.

Alectinib and M4 were inhibitors of P-gp, BCRP and the hepatic biliary salt export pump (BSEP) at supra clinical concentrations (respective IC_{50}: 1.13, 0.103 and 0.912 μM for alectinib; 4.68, 2.64 and 22 μM for M4). IC_{50} values for P-gp, and BSEP inhibition for alectinib and M4 greatly exceeded (by > 60 fold) the mean free clinical plasma C_{max} but the IC_{50} for alectinib against BCRP is only approximately 7 times the mean clinical free C_{max} and the IC_{50} value for alectinib against P-gp is approximately 0.2% of the estimated intestinal concentration of alectinib (497 μM[18]). Alectinib may increase the plasma concentrations of co administered drugs that are substrates of P glycoprotein and/or BCRP.

Alectinib did not significantly inhibit (M4 not tested) the hepatic uptake transporters OATP1B1 and OATP1B3, showing only weak inhibition at the highest concentration of alectinib (3 and 23 % inhibition, respectively at 3 μM, 200 times the free clinical plasma C_{max}), which is not considered clinically relevant. Similarly, alectinib (M4 not tested) did not inhibit the organic anion/cation renal transporters OAT1, OAT3 and OCT2 at 3 μM. Alectinib and M4 also did not inhibit the MRP2 efflux transporter at 3 μM and 70 μM, respectively. Alectinib is not expected to alter the disposition of co-administered drugs that are substrates of these transporters.

In conclusion, alectinib and M4 do not undergo human active hepatic uptake and alectinib is not expected to alter exposures to CYP450 substrates. However, pharmacokinetic drug interactions involving P-gp and BCRP transporters are predicted based on alectinib and M4 inhibition of intestinal P-gp/BCRP following a therapeutic dose and M4 as a substrate of P-gp. CYP3A4 is the major enzyme in the metabolism of alectinib and M4, suggesting potential interactions with CYP3A inhibitors or inducers. However, in clinical studies, a strong CYP3A4 inducer (rifampicin) and an inhibitor (posaconazole) had minor impacts on the exposures of alectinib and its major active metabolite M4.

Toxicology

Acute toxicity

Studies specifically designed as single dose toxicity studies were not submitted. The maximum non-lethal dose in rats in a repeat dose toxicity study where the animals survived for at least the first 2 weeks was 60 mg/kg/day (maximum dose tested). The maximum non-lethal dose in monkeys in a repeat dose study where the animals survived for at least the first 2 weeks is 20 mg/kg/day, indicating a moderate order of acute toxicity by the clinical (PO) route.

In a 2 week preliminary (non-GLP) toxicity study in monkeys, a single female (one of two animals) in the high dose group (60 mg/kg/day; n=1/sex/group) was sacrificed moribund on Day 13 after deterioration due to gut abnormalities, including retention of gastrointestinal (GI) tract contents and dilatation. These effects were considered dose limiting. Toxicokinetic data in monkeys provided evidence of systemic exposure. In the surviving male at 60 mg/kg/day, the $AUC_{0\text{-}24h}$ and C_{max} on Day 14 were 9820 ng·h/mL and 568 ng/mL, respectively. Exposures were 60% and 79% of the clinical AUC_{24h} at steady

[18] Based on the clinical dose of 600 mg and intestinal volume of 0.25 L.

state and C_{max} (16260 h·ng/mL and 723 ng/mL), respectively at the recommended starting clinical dose of 1200 mg/day (600 mg twice a day (bd)). Exposure to a high local concentration of alectinib could have contributed to the gastrointestinal tract findings in monkeys.

Repeat-dose toxicity

GLP-compliant repeat-dose oral toxicity studies of up to 13 weeks were conducted in rats and cynomolgus monkeys. Dosing was by the intended clinical route (PO) in all studies. The use of both genders in the studies, the group sizes used and the duration of the pivotal studies are considered acceptable and according to ICH guidelines S9[7] and M3[19]. To investigate the reversibility of effects, studies were conducted in both species with a 4 (4 week dosing duration) or 8 week recovery period (13 week dosing duration).

Rats and monkeys are considered appropriate species for toxicity testing as discussed in the pharmacokinetics section. Cynomolgus monkeys have been used previously to assess the toxicity of ALK receptor tyrosine kinase inhibitors (crizotinib and ceritinib) and are considered an acceptable choice as the non-rodent species.

Dosing in the pivotal 13 week rat study was limited by toxicity including short and crushed teeth and reductions in body weights (16 to 22%) at the high dose (27 mg/kg/day). The maximum dose in the 13 week study in monkeys (12 mg/kg/day) resulted in no overt signs or effects on body weight gain. Higher doses could have been administered. However, clear toxicity was evident at 12 mg/kg/day and in the 4 week GLP study at 15 mg/kg/day, and 60 mg/kg/day in the preliminary 2 week study was lethal.

The dosage regimen in the animal studies does not fully replicate the clinical situation. Dosing in all studies was only once daily, whereas dosing clinically is intended to be twice daily. However, the mean plasma C_{trough} at the highest dose of 27 mg/kg/day in the pivotal 13 week rat (mean 985 [male] and 1285 [female] ng/mL) were 1.6 to 2.0 fold higher than the mean clinical C_{trough} at steady state (630 ng/mL). This suggests rats were exposed to the drug at a clinically-relevant level for the duration of the study. The mean C_{trough} level (males: 204 and females: 191 ng/mL) at the highest dose in the 13 week monkey study was only 32% for males and 30% for females of the corresponding clinical value.

Relative exposure

Exposure ratios have been calculated based on steady state plasma $AUC_{0\text{-}24h}$ (that is, animal: human plasma $AUC_{0-24\,h}$). The AUC data in rats and monkeys is the mean of male and female values on the last sampling occasion. Exposures were generally subclinical in monkeys (about half the clinical plasma AUC at the high dose), while exposures of only up to 2.5 times the clinical exposure were achieved in rats (Table 3).

Table 3: Relative exposure (exposure ration or ER) in repeat-dose toxicity studies

Species	Study duration Study no.	Dose mg/kg/day	Alectinib		M4	
			AUC_{0-24h}^ ng·h/mL	**ER #**	**AUC_{0-24h}^ ng·h/mL**	**ER #**
Rat RccHan:WIS	4 weeks Study	6	11620	0.7	_	_
		20	35650	2.2	_	_

[19] ICH M3 Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals

Species	Study duration	Dose mg/kg/da	Alectinib		M4	
T	1054084	60	40050	2.5	_	_
	13 weeks Study 1053940	3	6775	0.42	_	_
		9	22200	1.4	_	_
		27	38200	2.3	1445	0.24
Monkey Cynomolgus	4 weeks Study 1054085	1.7	1230	0.08	_	_
		5	3190	0.2	_	_
		15	6535	0.4	_	_
	13 weeks Study 1053944	1.3	962	0.06	_	_
		4	3210	0.20	_	_
		12	6990	0.43	1710	0.28
Human patients	Human Phase I/II Studies NP28761 & NP28673	1200 mg/day (600 mg BID)	16260*	–	6120*	–

(#): Animal:human plasma AUC_{0-24h}; ^ data are for the sexes combined at the last sampling occasion ; (-) = Not determined; (*): The human $AUC_{SS,\ 24h}$ value is twice the arithmetic mean $AUC_{SS,12h}$ (8130 ng·h/mL) from population PK analysis of Phase I/II studies NP28761 and NP28673 (2.7.2 Summary of Clinical Pharmacology Studies, Table 15);

Rats and monkeys do not produce significant amounts of the main human metabolite, M4, which is a significant metabolite in human plasma (approximately 37% of the parent based on AUC). Exposures to the M4 metabolite were subclinical in both rats and monkeys (less than half the clinical plasma AUC) (Table 3). The animal/human exposure ratios based on total active moieties (alectinib and M4) are lower than the ratios based on alectinib alone (data not shown). However, the submitted toxicity studies were considered sufficient to assess the safety of the M4 metabolite.

Major toxicities

Major target organs/systems for toxicity (mostly minimal to mild in severity) were the gastrointestinal tract, erythropoiesis, haemostasis, liver and bile ducts, lungs and pancreas in both species and bone in rats only. In general, the toxicity profile showed similarity to other ALK receptor tyrosine kinases (such as crizotinib and ceritinib). Additional major organs for toxicity not seen with crizotinib and ceritinib included the adrenal gland, male reproductive organs in both species and teeth in rats only. The treatment related alterations had recovered or had mostly shown a tendency to recover by the end of the 4 and 8 week recovery periods in the 4 and 13 week repeat-dose toxicity studies, respectively. Given the low exposure margins, the toxicities below should all be considered as toxicologically and clinically relevant unless noted otherwise.

Gastrointestinal (GI) tract

GI tract findings were observed in both rats and monkeys and were considered dose-limiting in the monkey due to constipation at high oral doses of 60 mg/kg/day. In the monkey, macroscopic findings included dilation of caecum, colon and ileum at 60 mg/kg/day, whilst in rats, presence of blood in the large intestine and mucosal haemorrhage of ileum were observed at 27 mg/kg/day. Histological findings in the rat at ≥ 9 mg/kg/day included degeneration of glandular stomach epithelium, hypertrophy of glandular stomach mucosal epithelium, erosion of stomach mucosa, macrophage/inflammatory cell infiltration along the length of the digestive tract mucosa and disarrangement/desquamation of mucosal epithelium in the small intestine.

Extension of proliferative zone of gastric and intestinal mucosa was present in rats and monkeys at ≥ 9 and ≥ 4 mg/kg/day, respectively.

Hepatobiliary system

Liver findings were evident in both species with clinical chemistry findings and macroscopic and/or microscopic correlates in the rat at ≥ 3 mg/kg/day and in monkeys at ≥ 4 mg/kg/day. Clinical chemistry changes (minimal to mild increases in cholesterol, triglyceride, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), hepatic alkaline phosphatase (ALP), direct bilirubin and α2 globulin and decreases in albumin) correlated with macroscopic (enlarged liver and increased liver weights) and microscopic findings in the liver. Histological findings included hepatocyte enlargement, focal lymphocyte cell infiltration, swelling/yellow brown pigmentation of sinusoidal cells and single cell/focal necrosis of hepatocytes. Findings also included bile duct proliferation and degeneration /necrosis /vacuolation of bile duct epithelium in rats at ≥ 3 mg/kg/day and in monkeys at ≥ 4 mg/kg/day. Inflammatory cell infiltration of Glisson's sheath was observed in monkeys at 12 mg/kg/day. Decreased plasma total protein and albumin, increased α1 and α2 globulin and total cholesterol were also reported in pregnant rabbits dosed with alectinib.

Lungs and trachea

In rats at ≥ 6 mg/kg/day (4 and 13 week studies) and monkeys at 12 mg/kg/day (13 week study), microscopic and/or macroscopic findings were observed in the respiratory system. Macroscopic findings were brownish and reddish patches on the lung (monkey) and increased lung weights (rat and monkey). Microscopic findings included minimal alveolus haemorrhage (monkey), perivascular hemosiderin pigmented macrophage accumulation (monkey) and foamy macrophage infiltration in alveoli (rat; phospholipidosis as observed in studies with crizotinib and ceritinib). In the trachea, microscopic findings in rats (4 and 13 week studies) at ≥ 20 mg/kg/day included inflammatory cell infiltration in the lamina propria, disarrangement of mucosal epithelium and multinucleated giant cells in the lamina propria.

Adrenal gland

Treatment related microscopic findings of cortical hypertrophy (reticular and fascicular zones) and changes in lipid droplets in fascicular cells of the adrenal gland in most of the repeat-dose toxicity studies was observed in rats at ≥ 3 mg/kg/day and monkeys at ≥ 4 mg/kg/day. These findings correlated with high levels of ^{14}C-alectinib found in the adrenal glands of rats in a tissue distribution study. Adrenal gland weights were increased in rats in 4 week and 13 week repeat-dose toxicity studies at ≥ 20 mg/kg/day. Treatment related findings of decreased lipid droplets in fascicular cells of the adrenal cortex and cortical hypertrophy in animals could also be a finding possibly associated, to some extent, with stress accompanying other drug-induced changes in the animals.

Effects on haematopoiesis and haemostasis

Treatment related alterations in cells were observed in both species at ≥ 3 and ≥ 4 mg/kg/day in rats and monkeys, respectively. Findings included increases in reticulocytes, mild decreases in haemoglobin, haematocrit and/or red blood cells, abnormal red blood cell morphology including anisocytosis and poikilocytosis (burr cells, fragmented red cells) and polychromatic and immature erythrocytes. The mild anaemia was probably due to a direct effect of alectinib on red blood cells (RBC) or haemorrhage since bone marrow smears showed no abnormalities except for decreased haemotopoietic cells in a single monkey at 60 mg/kg/day. Haemosiderin deposition and erythrophagy occurred in mesenteric lymph nodes of rats. As a compensatory response to anaemia, increased extramedullary haemotopoiesis was seen in spleen.

Slight increases in white blood cells (WBC), neutrophils, monocytes, lymphocytes and large unstained cells were seen in rats and to a lesser extent, monkeys. The increases in WBC and differentials might be related to inflammation in the gastrointestinal tract (GIT) and other tissues and/or direct haematopoietic effects of alectinib. Increased neutrophils in bone marrow were seen in the 4 week rat study at ≥ 20 mg/kg/day. Similar haematological findings (red and white blood cells) were also reported in pregnant rabbits treated with alectinib.

Prolongation of clotting time or increases in activated partial thromboplastin time (APTT) (males: ≥ 3 g/kg/day; females: 27 mg/kg/day) and partial thromboplastin time (males: 27 mg/kg/day) were observed in rats in the 13 week study. Consistent with prolonged clotting times, blackish faeces, presence of blood in the large intestine (dark-red gelatinous material, presumably blood in cecum and colon) and ileal haemorrhage (in the mucosa of the ileum) were seen at the high dose (27 mg/kg/day) in the 13 week study in rats. Blackish stools were also seen in monkeys in the 4 week study at ≥ 5 mg/kg/day (from Day 7). Haemorrhage could not be explained by significant increases in blood platelet counts and large platelets in rats and occasionally in monkeys. Increased mature megakaryocytes and megakaryocytic emperipolesis in bone marrow and increased mature megakaryocytes in spleen were observed in rats at ≥ 20 mg/kg/day in the 4 week study. It is possible that platelet function were compromised by alectinib treatment. Increased megakaryocytes, megakaryocytic emperipolesis and increased neutrophils in bone marrow and blood, and increased mature megakaryocytes in spleen suggest stimulation of the production of these cells by alectinib.

Lymphoid tissues

Mild decreases in lymphocytes in spleen, thymus and lymph nodes were observed in rats after 4 or 13 weeks of treatment at ≥ 9 mg/kg/day, with the thymus also having increased tingible body macrophages, of which the clinical significance is unknown.

Pancreas

In a 4 week study in rats, there were findings of minimal increases of apoptotic bodies in acinar cells (≥ 20 mg/kg/day). In the 2 week study in monkeys (≥ 20 mg/kg/day), there were findings of decreased zymogen granules in acinar cells/irregular shaped islets whilst in the 13 week monkey study (at 12 mg/kg/day), there was minimal focal capsule fibrosis in a single monkey.

Kidneys

Increased kidney weights were recorded in rats at > 9 mg/kg/day and in male monkeys at > 4 mg/kg/day in the 13-week studies. Histological lesions, described as yellow brown pigmentation in proximal tubules, were only detected in rats at 27 mg/kg/day. There was a slight increase in blood urea nitrogen in rats at 27 mg/kg/day in the 13 week study but serum creatinine was slightly decreased. Increased urine volume was reported in male rats at ≥ 3 mg/kg/day and in male and female monkeys at ≥ 4 mg/kg/day. Urinary sodium excretion was also increased in monkeys. Short term studies showed no signals of renal effects. The risk of renal toxicity in patients is expected to be low.

Eyes

There was a single finding of minimal to slight thinning of the corneal epithelium in rats in the 4 week dose range study at ≥ 3 mg/kg/day with no other ocular toxicity seen in either species in other studies, suggesting low clinical relevance. No ocular abnormalities were observed by ophthalmological examination in rats and monkeys. No specialised nonclinical studies were carried out to investigate some of the ocular toxicities/vision disturbances seen in the clinical trials (also seen with crizotinib and ceritinib).

Skin

Thickening of epidermis (minimal to slight in severity) was observed in the 13 week rat study at 27 mg/kg/day and in one female in the 4 week study at 60 mg/kg/day. There were no effects on the skin in monkeys.

Effects on teeth and bones

Effects on growing incisor teeth in rats were only seen in the 13 week study at the high dose of 27 mg/kg/day. Findings included discolouration (whitened)/crushed teeth or short lower teeth and disarrangement/degeneration/necrosis of ameloblast and dilatation of capillary at the papillary/odontoblast layers (mainly in the middle region where enamel is produced).

Effects of decreased trabecular bone in the femur and/or sternum with increased osteoclast activity in the metaphysis (femur) on growing bones in rats was seen in the 4 and 13 week studies at the high dose levels of 60 mg/kg/day and 27 mg/kg/day, respectively. The findings were also seen in the 4 week dose range study at the high dose level of 30 mg/kg/day. The increased osteoclast activity correlated with increases in serum bone ALP (≥ 6 mg/kg/day) and inorganic phosphorus (≥ 27 mg/kg/day). Whilst exposure at the high dose in the 4 and 13 week repeat-dose toxicity studies were similar (about 2.5 times the anticipated clinical $AUC_{0-24\,h}$), extension of the dosing period resulted in both higher incidence and severity of the histopathological findings.

The effects on growing teeth and bones in rats were not seen in monkeys and are consequently not considered to be a clinically relevant to adult patients. However, the effects are relevant to children.

Reproductive organs

In the 13 week studies, treatment related effects were observed on reproductive organs in a small number of males of both species. In rats, findings at 27 mg/kg/day included reduced size of the prostate gland and seminal vesicles, and histological findings of slight seminal vesicle and prostate atrophy in one rat and minimal prostate atrophy in another rat. Testes weights were increased at 20 mg/kg/day in the 4 week study and at 27 mg/kg/day in the 13 week study with no histological abnormalities. Similarly, in monkeys reduced weight of the prostate gland and microscopic findings in the epididymis (minimal focal unilateral lymphocyte cell infiltration) of one male at 4 mg/kg/day and one at 12 mg/kg/day and testes (minimal focal fibrosis/unilateral fibrosis of the interstitium) one male at 12 mg/kg/day were observed. High levels of ^{14}C-alectinib were detected in these tissues in rats in the tissue distribution study. In females, treatment related findings in reproductive organs observed in the 13 week studies were limited to minimal mammary gland atrophy at the high dose in rats (27 mg/kg/day) and decreased ovarian weights at ≥ 4 mg/kg/day in monkeys. Reproductive organ findings in the 4 week studies were observed in a single rat at 60 mg/kg/day after recovery and included small testes and epididymides, decreased spermatogenic cells in testes and epididymides, and vacuolation of glandular epithelium of the prostate (minimal to mild in severity). Treatment relationship of the above findings is uncertain because of the low incidence and nature of the findings (unilateral findings in male monkeys).

Other findings

Effects on the pituitary gland (minimal, reversible) were seen in the 4 week (≥ 20 mg/kg/day) and 13 week (27 mg/kg/day) repeat-dose toxicity studies in rats only (decrease in absolute organ weight and anterior pituitary cell atrophy/increased apoptotic bodies and mitotic figure). Parathyroid cysts were observed in monkeys at 12 mg/kg/day in the 13 week study. The toxicological and clinical relevance of these findings is unclear.

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

Genotoxicity

The genotoxicity of alectinib was assessed in a standard battery of genotoxicity studies according to the appropriate guideline.[20] The studies were appropriately conducted and validated. Alectinib did not induce gene mutation in a bacterial assay. In Chinese hamster lung cells in vitro, alectinib did not increase structural chromosome aberrations but caused an increase in polyploidy in the presence of metabolic activation (4% at 10 µg/mL compared to 0% for the concurrent vehicle control). It also increased micronucleus formation in human lymphoblastoid TK6 cells in vitro at ≥ 2.7 µg/mL without metabolic activation (no tests with metabolic activation) and in two micronucleus studies in rats at oral doses ≥ 500 mg/kg (C_{max} 4.2 times the steady state clinical C_{max}), with no significant increase at 200 mg/kg (C_{max} 2.6 times the steady state clinical C_{max}). Fluorescence in situ hybridization (FISH) analysis in the in vitro human lymphoblastoid TK6 cell assay and in one of the in vivo micronucleus assays in rats showed that alectinib is an aneugen. Aneugenicity has also been reported for crizotinib and ceritinib.

Carcinogenicity

No carcinogenicity studies were submitted which is acceptable for a pharmaceutical for the treatment of advanced cancer.[21]

Reproductive toxicity

There are no fertility, early embryo development and pre/post-natal development studies, which is acceptable.[21] Embryofetal development studies were conducted in rats and rabbits, which were dosed with 3, 9 or 27 mg/kg/day alectinib during the period of organogenesis (gestational day (GD) 7–17 in rats and GD 6-18 in rabbits). The studies were GLP compliant, but they were preliminary dose range finding studies with only 6 animals per group.

Toxicokinetic data were obtained from pregnant rats and rabbits in the embryofetal development studies. The systemic exposures to alectinib are compared with the clinical exposure in the table below. Plasma M4 concentrations were not determined. A maternal-fetal distribution study in pregnant rats showed that alectinib and/or metabolites readily cross the placenta as indicated by levels of drug-related materials in fetal tissues similar to that in maternal blood.

Table 4: Relative exposure in embryofetal development studies

Species	Dose mg/kg/day	C_{max} ng/mL	AUC_{0-24h} ng·h/mL	Exposure ratio#	
				C_{max}	**AUC**
Rat (RccHan:WIST) [Study 1055407]	3	827	13850	1.1	0.9
	9	2135	40600	3	2.5
	27	3590	66400	5	4.1

[20] ICH S2 Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use

[21] ICH S9 Nonclinical evaluation for Anticancer Pharmaceuticals

Species	Dose mg/kg/da	C_{max}	AUC_{0-}	Exposure ratio#	
Rabbit (NZW) [Study 1055408]	3	163	2950	0.2	0.2
	9	385	6650	0.5	0.4
	27	2090	43200	2.9	2.7
Human*	1200 mg/day	723	16260	-	–

animal/human plasma C_{max} and AUC_{0-24h}; * human steady state C_{max} and AUC from population PK analysis of Phase I/II studies NP28761 and NP28673

Findings on male reproductive organs were observed in a small number of animals in rats and monkeys. As discussed above under Repeat dose toxicity, relationship of the findings to alectinib treatment is uncertain.

Alectinib caused embryofetal loss and fetal abnormalities in both species. In rats, total litter loss occurred in all dams at 27 mg/kg/day. In the 9 mg/kg/day group were decreased fetal weights, increased incidences of visceral and skeletal anomalies (dilated ureter, thymic cord, small ventricle, thin ventricle wall and decreased number of sacral and caudal vertebrae) were observed. Maternal toxicity was observed at 9 and 27 mg/kg/day (decreased body weight at both doses and decreased food consumption at the high dose). Necropsy showed red focus in the stomach and dark read mesenteric lymph node in dams dosed with 27 mg/kg/day. No maternal or embryofetal effects were observed at 3 mg/kg/day.

Pregnant rabbits dosed with 27 mg/kg/day alectinib had increases in post-implantation loss and dead fetuses, and decreases in litter size, viable fetuses, placental weight and fetal weight. The number of live fetuses was also slightly decreased in the 9 mg/kg/day group. Visceral malformation (retro-oesophageal subclavian) and skeletal variations (an increase in full supernumerary fibs and a corresponding decrease in short supernumerary ribs) were higher in the 27 mg/kg/day group than the control group. In addition, the incidence of supernumerary lumbar vertebra was increased in the 9 and 27 mg/kg/day groups. Maternal toxicity (decreased body weight, food consumption and faeces) was observed at 27mg/kg/day. Haematology and clinical chemistry analyses revealed microcytic anaemia (decreases in erythrocyte counts, haemoglobin, haematocrit and mean corpuscular volume, but increased mean corpuscular haemoglobin concentration), thrombocytopenia, neutrophilia, decreased eosinophil and basophil counts, decreased total protein and albumin, increased α1 and α2 globulin, increased total cholesterol, glucose and creatinine, and decreased calcium and chloride in the high dose group. There were no maternal and embryofetal effects at 3 mg/kg/day.

The animal studies suggest embryofetal toxicity in patients at the proposed clinical dose. Appropriate precautionary statements are proposed in the draft PI.

Pregnancy classification

The sponsor has proposed Pregnancy Category X[22]. As discussed above, alectinib caused embryofetal lethality in rats and rabbits, visceral and skeletal anomalies (dilated ureter, thymic cord, small ventricle, thin ventricle wall and decreased number of sacral and caudal vertebrae) in rats, and visceral malformation (retro-oesophageal subclavian) and skeletal variations (increase in full supernumerary fibs and decrease in short supernumerary ribs) in rabbits. The other two ALK inhibitors, crizotinib and ceritinib with similar embryofetal

[22] Category X: Drugs which have such a high risk of causing permanent damage to the fetus that they should not be used in pregnancy or when there is a possibility of pregnancy.

toxicity at exposures below the clinical exposure, have a Pregnancy category D[23]. Pregnancy Category D is recommended for alectinib.

Phototoxicity

Alectinib absorbs light in the 200 to 400 nm wavelength range. An in vitro 3T3 NRU assay using cultured Balb/c 3T3 mouse fibroblast cells with ultraviolet (UV) A irradiation returned a photo irritation factor (PIF) value of 94.8, indicating phototoxic activity. A tissue distribution study in pigmented rats showed distribution to both pigmented and non-pigmented skin. Therefore, phototoxic reactions on sun exposed skin may occur during clinical use.

Excipient sodium lauryl sulfate (SLS)

SLS is a common excipient in oral pharmaceutical products but the concentration of SLS in the alectinib formulation is many folds higher than the levels present in approved pharmaceutical products.

SLS is present in the clinical formulation at 50% (weight/weight (w/w) SLS to alectinib). Nonclinical toxicology studies were conducted with formulations of alectinib which did not contain SLS. A 4 week bridging toxicity study was carried out in rats to compare the toxicity of alectinib formulations with and without SLS at a single dose level of 20 mg/kg/day alectinib and 10 mg/kg/day of SLS. The addition of 50% SLS to the formulation did not significantly alter the toxicity and pharmacokinetics of alectinib. No new toxicities were observed with the addition of 50% SLS. No toxicity was observed in the SLS group (without alectinib). The toxicity profile of the formulation containing 50% SLS and toxicokinetics were consistent with an earlier 4 week toxicity study without SLS in the testing formulation.

The main safety issue with SLS is local irritation to the skin, eye or GIT (gavage only, not by dietary feeding). The liver is the target organ of systemic toxicity. The No observable adverse effect level (NOAEL) is 90 mg/kg/day for GIT effects by oral gavage and approximately 100 mg/kg/day for systemic toxicity based on studies of 28 days, 3 months and 2 years by gavage and dietary dosing with SLS or sodium alkyl (C12-15) sulphates.

For local irritation effects to the GIT, a risk assessment based on dose expressed in mg/kg gave a safety margin of 15 (NOAEL 90 mg/kg compared to clinical dose of 300 mg or 6 mg/kg for a 50 kg person). Thus, SLS in the clinical alectinib formulation is not expected to cause local irritation of the GIT in patients.

For systemic effects, the daily human exposure to SLS is 600 mg/day (12 mg/kg/day for a 50 kg person, equivalent to 396 mg/m^2/day), which is only slightly below the NOAEL established in animal toxicity studies (600 mg/m^2/day), with a safety margin of 1.5. For excipients with no therapeutic benefit, a much higher safety margin is desirable. However, given the proposed indication of treating patients with advanced cancer, the small safety margin for SLS is acceptable. The use of a different excipient may have been preferable.

Paediatric use

There were no toxicity studies in juvenile animals. In repeat dose toxicity studies in rats, adverse effects on the growing teeth and bones were observed at alectinib doses resulting in exposures (based on AUC) approximately 2 times those in adult patients given 600 mg twice daily. Findings included discoloured/crushed/shorter teeth with

[23] 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.

disarrangement/degeneration/necrosis of ameloblasts, disarrangement of odontoblasts and capillary dilatation, and decreased trabecular bone with increased osteoclast activity. Increased plasma ALP of the bone isoform was observed at alectinib doses resulting exposures similar to the clinical exposure. It is recommended that precautionary statements be included in the Australian PI.

Nonclinical summary and conclusions

- The submitted nonclinical dossier was in accordance with the relevant guideline[21] on the nonclinical evaluation of anticancer pharmaceuticals. Consistent with this guideline, no carcinogenicity and only limited reproductive toxicity studies were conducted. The overall quality of the nonclinical dossier was adequate. All pivotal safety related studies were GLP compliant. The sponsor considered the role of the M4 metabolite in pharmacological and toxicological studies. The lack of metabolism and protein binding data in rabbits, which is used in the investigation of embryofetal effects, is a deficiency.
- In vitro primary pharmacology studies demonstrated alectinib was most active against ALK and RET and multiple point mutations of both at clinically relevant concentrations. In vitro cell proliferation studies using a variety of cancer cells showed alectinib inhibited proliferation of cancer cells (irrespective of cancer type) with ALK perturbations (ALK EML4 ALK or NPM-ALK fusion proteins, ALK point mutations or gene amplifications). Alectinib inhibited proliferation of human lung cancer NSCLC cell lines and the growth of NCI H2228 cells, which carry the EML4 ALK gene fusion. Efficacious concentrations were within clinical plasma levels. Alectinib inhibited ALK autophosphorylation and phosphorylation of downstream STAT3 and AKT signalling molecules in separate in vitro and in vivo studies.
- The main human metabolite, M4 was pharmacologically active in vitro, with a similar potency to alectinib. Due to high abundance, it is expected to contribute to in vivo pharmacological activity.
- In mouse xenograft tumour models, alectinib showed dose-dependent anti-tumour activity in 1) ALK fusion-positive (EML4-ALK or NPM-ALK) SC implanted human NSCLC (NCI-H2228), anaplastic large cell lymphoma (ALCL, KARPAS-299) and neuroblastoma (NB 1; ALK gene amplification); 2) NSCLC with ALK mutations resistant to crizotinib; and 3) intra-cranial NSCLC models for brain metastases (crizotinib did not show activity in the last model). Efficacious doses/exposures were similar to or slightly greater than that anticipated clinically.
- Alectinib showed inhibitory kinase activity in vitro against RET, GAK and LTK kinases, L type Ca^{2+} and Cl^- (GABA gated) channels at high concentrations. However, alectinib has not been assessed in cellular assays against these kinases. The clinical relevance is uncertain. Alectinib also showed inhibitory activity against 5-HT, dopamine and norepinephrine uptake transporters at concentrations 7-22 times the clinical C_{max}. While these findings suggest potential neurological effects, no signs of neurotoxicity were evident in safety pharmacology and toxicity studies.
- Safety pharmacology studies assessed effects on the cardiovascular, respiratory, gastrointestinal and central nervous systems. No adverse effects were seen on CNS, respiratory or gastrointestinal function in rats. In vitro, alectinib inhibited L-type Ca^{2+} Cav1 .2 currents and vasodilation of rat aortic rings at clinically relevant concentrations. A slight decrease in blood pressure (10 mmHg) was seen in monkeys at clinically relevant exposures. Decreased heart rate was recorded in monkeys after repeated dosing. Significant inhibition of hERG K+ channel tail currents was also

observed at relative exposures of 30 fold the free clinical C_{max} but QT prolongation was not observed in monkeys. Minor hypotension and bradycardia may occur in patients.

- Oral bioavailability was high in rats (88%) and moderate in monkeys (50%), higher than in human subjects (37%). The volume of distribution is large, consistent with high tissue levels (including blood cells) of alectinib/metabolites in rat tissue distribution studies. Alectinib/metabolites cross the blood brain barrier and bind to melanin (very high level in uveal tract). Plasma protein binding is high in all species including humans (>99%). Distribution of alectinib to blood cells was higher than in plasma.
- The main metabolic pathway of alectinib involves the formation of the oxidative metabolites (M4 and M6) contributing to 40 50% of total hepatic alectinib metabolism by CYP3A4. Unchanged alectinib was the dominant circulating species (up to 90%) and the main drug related species in the faeces of rats and humans (80 to 90%). M4 is the predominant metabolite in plasma (in vivo) and hepatocytes (in vitro) of humans, rats and monkeys. M4 is further converted to M6 by CYP3A4. All human metabolites (M1, M4 and M6) detected in vivo were found in animals in vivo or in vitro. The M4 metabolite was a major metabolite in human plasma (approximately 37% of parent based on AUC) with M4 present at lower levels in plasma of rats (2 to 5% of parent) and Cynomolgus monkeys (approximately 25% of parent) as detected at the high dose in the 13 week toxicity studies.
- Excretion of alectinib and/or its metabolites was predominantly via the faeces in rats and humans (> 95% of the administered dose), with minimal enterohepatic recirculation. Biliary excretion (mostly as M4) was demonstrated in rats. Excretion of drug-related material in urine was <0.5%.
- At greater than normal (supra-clinical) concentrations, alectinib was a weak to moderate inhibitor of CYP3A4 (time dependent only) and CYP2C8 (competitive) and a slight inducer of CYP3A4 and 2B6 expression. Alectinib is not expected to alter the exposure of co administered drugs that are CYP450 substrates. Since alectinib and M4 are metabolised by CYP3A4, CYP3A4 inhibitors/ inducers could alter the systemic exposure to alectinib and M4.
- At the proposed clinical dose, alectinib may inhibit intestinal P-glycoprotein (P-gp) and BCRP, and may increase the exposure of co-administered drugs that are substrates of these transporters. M4 is a substrate of P-gp. Since there is signification biliary excretion of M4 (in rats), strong P-gp inhibitors may increase exposure to M4 in patients. No clinically-relevant inhibition by alectinib and/or M4 was seen on CYP1A2, 2B6, 2C9, 2C19 or 2D6 enzymes or on the OATP1B1, OATP1B3, OAT1, OAT3, OCT2, BSEP and MRP2 transporters in vitro.
- Alectinib had a low to moderate order of acute oral toxicity in rats and monkeys.
- Repeat-dose toxicity studies by the oral route were conducted up to 13 weeks in rats and cynomolgus monkeys. Low exposures were achieved in the repeat dose studies (up to 2.5 times and 0.4 times in rats and monkeys, respectively, the clinical exposure based on AUC). Similarly, in rats and monkeys only low exposures were achieved for the M4 metabolite of about 20% to 30% the clinical exposure at the high dose (based on AUC).
- Toxicity findings of clinical-relevance included:
  - *GIT*: degeneration glandular epithelium (stomach); extension of proliferative zone in mucosa; dilation of large intestine (monkey); ileal haemorrhage (rat)

- *Lungs and trachea*: alveolar haemorrhage (monkey); foamy macrophage infiltration in alveoli and inflammatory cell infiltration in lamina propria in trachea (rat)
- *Adrenal gland*: cortical hypertrophy/changes in lipid droplets in fascicular cells
- *Liver*: increased liver weights/enlarged liver; slight increases in cholesterol, AST, ALT, ALP, alpha2 globulin; hepatocyte enlargement, lymphocyte cell infiltration, swelling/yellow brown pigmentation of sinusoidal cells and single cell/focal necrosis of hepatocytes
- *Bile ducts*: proliferation and degeneration /necrosis /vacuolation of bile duct epithelium
- *Erythrocytes and coagulation*: mild anaemia, poikilocytosis; increases in PT/APTT (rats); increased platelet counts (no changes indicative of myelosuppression)
- *Pancreas*: apoptotic bodies/decreased zymogen granules in acinar cells; irregular islets
- *Eyes*: slight thinning of corneal epithelium (rat only)
- *Skeletal system* (rat only): decreased trabecular bone; increased osteoclast activity; discoloration/crushed/short incisor teeth with microscopic findings

· Alectinib was not mutagenic or clastogenic. It is aneugenic and induced numerical chromosome aberrations in vitro and micronuclei in bone marrow cells in rats. No carcinogenicity studies were conducted which is considered acceptable.

· Reproductive toxicity studies examined only effects on embryofetal development toxicity in rats and rabbits in preliminary studies. Maternal doses of alectinib equivalent to 2.7 times the recommended human dose of 600 mg twice daily (based on AUC), caused embryo-fetal loss (miscarriage), visceral malformation and skeletal variations in pregnant rabbits. The same equivalent dose given to pregnant rats (4 times the clinical AUC) resulted in total litter loss. Alectinib at 9 mg/kg/day (2.5 times the clinical AUC) caused small fetuses with retarded ossification and minor abnormalities of the organs.

· An in vitro phototoxicity study (3T3 NRU assay) showed alectinib has phototoxic potential.

Nonclinical Conclusions and Recommendation

· The nonclinical dossier was adequate with no major deficiencies.

· The primary pharmacology studies demonstrated the ALK and RET inhibitory activity of alectinib and activity against crizotinib-resistant tumours, supporting the proposed indication.

· Safety pharmacology and toxicity studies indicate there is a slight clinical risk of hypotension and/or bradycardia. Inhibitory activity at monoamine uptake transporters could result in neurological effects in some patients.

· Most findings in repeat dose toxicity studies (mostly minimal to mild in severity) were class effects of tyrosine kinase inhibitors and are expected to occur in patients.

· Effects on growing teeth (crushed/short incisor teeth) and bones (decreased trabecular bone) in rats are relevant to the paediatric population. An appropriate precautionary statement is proposed for the draft Product Information PI.

- Phototoxicity was seen in a nonclinical cytotoxicity assay. There is a clinical risk of phototoxicity to patients.
- The nonclinical studies predicted embryofetal toxicity in patients at the proposed clinical dose. The sponsor has proposed Pregnancy Category X. However, Pregnancy Category D is recommended for alectinib (see discussion above).
- Provided the above effects are appropriately addressed in the risk management plan and adequately monitored or managed during clinical use, there are no nonclinical objections to the registration of alectinib for the proposed indication.
- The RMP and draft PI were commented on by the nonclinical evaluator but the detail of this is beyond the scope of this AusPAR.

IV. 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

Information on the condition being treated

The sponsor has provided an introduction to the condition being treated:

> Lung cancer (ICD10 C33-C34) is the fifth most commonly diagnosed invasive cancer in Australia and causes more deaths than any other cancer in both males and females. In 2012 there were 8,137 deaths from lung cancer in Australia and in 2011 10,511 new cases were diagnosed. Despite the fact that there are a number of treatments currently available for patients with NSCLC, most have limited effectiveness in the advanced stages of the disease, and therefore the prognosis for these patients remains poor.
>
> Recent progress in the identification of genetic mutations or chromosomal rearrangements in epidermal growth factor receptor (EGFR), Kirsten rat sarcoma viral oncogene homolog (KRAS), mesenchymal-epithelial transition factor (MET), and other genes has provided new opportunities to use targeted therapeutic agents for the treatment of NSCLC.

The clinical overview of this submission contains a definition of 'ALK+' as '*tumors harboring a rearranged ALK gene/fusion protein*'. This definition is accepted.

Current treatment options

UpToDate provides comprehensive clinical guidelines around treatment options for advanced (Stage 4) NSCLC. Initial systemic therapy for patients with advanced NSCLC depends on whether a driver mutation, such as ALK re-arrangement, is identified (Figure 2). For patients whose tumour contains a driver mutation, specific inhibitors are recommended as first-line treatment.

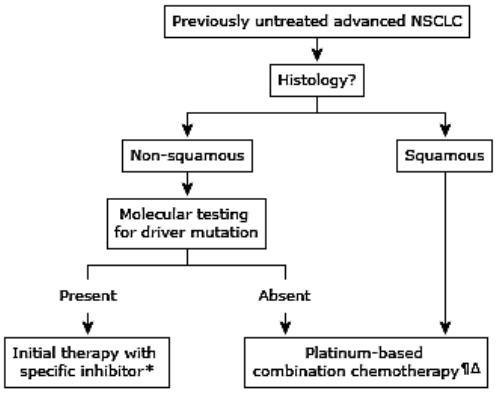
First line therapy

In the case of ALK+ tumours, the first-line specific inhibitor is crizotinib (Xalkori).[24]

Crizotinib is a small molecule ALK, cMET and ROS1 inhibitor, and is the current standard of care first line therapy for the treatment of locally advanced or metastatic ALK+ NSCLC.[25]

Conditional approval for crizotinib in the US was initially based on data from 255 patients with ALK+ NSCLC, enrolled in two single-arm trials, with response rates of 50% and 61%. Common adverse events with crizotinib use include 'mild transient visual disorders, mild gastrointestinal toxicities, fatigue, rare alanine transaminase elevations, and even rarer pneumonitis (1.6%).'[26]

Figure 2: Initial systemic therapy for patients with advanced non-small cell lung cancer.



NSCLC: non-small cell lung cancer; EGFR: epidermal growth factor receptor; ALK: anaplastic lymphoma kinase.
* Targetable mutations for which inhibitors are currently indicated for initial therapy include EGFR (erlotinib, gefitinib, afatinib), ALK (crizotinib), ROS1 (crizotinib), BRAF V600E, and MET exon 14 skipping mutation. Inhibitors for other mutations may be available in a clinical trial setting.
¶ Therapy generally consists of four to six cycles of a platinum-based combination, which may be supplemented by bevacizumab in patients with non-squamous histology. For patients responding or with stable disease after initial chemotherapy, maintenance therapy may prolong progression-free and overall survival.
Δ If a targetable mutation is identified after initiation of chemotherapy, subsequent management should integrate use of an appropriate inhibitor.

Subsequent confirmatory Phase III trials compared crizotinib to standard chemotherapy.

The current application for alectinib is based on early data without a control arm. The chemotherapy overall response rates of 20% in NSCLC seen in the crizotinib Phase III trials provide a useful point of comparison for the response with alectinib, in the absence of an actual control arm.

[24] Shaw et al., 2016. UpToDate topic: Anaplastic lymphoma kinase (ALK) fusion oncogene positive non-small cell lung cancer. Available at: http://www.uptodate.com/contents/anaplastic-lymphoma-kinase-alk-fusion-oncogene-positive-non-small-cell-lung-cancer

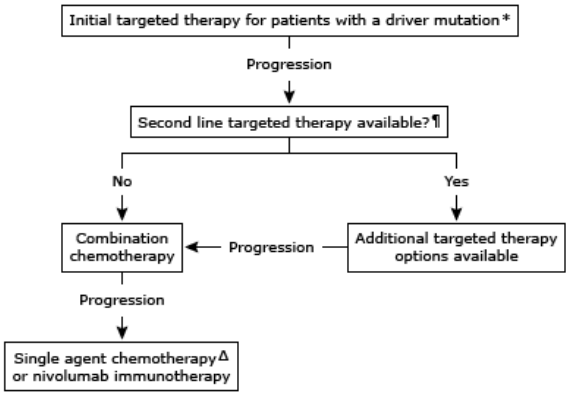
[25] Chan BA and Hughes BGM. Targeted therapy for non-small cell lung cancer: current standards and the promise of the future. Transl Lung Cancer Res. 2015 Feb; 4(1): 36–54. doi: 10.3978/j.issn.2218-6751.2014.05.01

[26] 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

Second-line therapy

If a patient with an ALK+ tumour did not receive crizotinib as a first-line treatment then crizotinib targeted treatment is indicated as the second- line therapy.[27] If a first-line targeted treatment fails then second-line targeted agents are indicated where available, followed by combination chemotherapy and then single-agent chemotherapy (Figure 3).

Figure 3: Second line therapy



NSCLC: non-small cell lung cancer; EGFR: epidermal growth factor receptor; ALK: anaplastic lymphoma kinase.
* Targetable mutations include EGFR, ALK, ROS1. Other mutations may be appropriate for protocol inclusion.
¶ Where available or by clinical trial protocol.
Δ With a non-cross resistant agent not included in the original regimen. Ramucirumab may be combined with docetaxel in this setting, although benefits are limited and its use may be associated with increased toxicity.

The only other ALK-targeted therapy approved in Australia at the time of review is ceritinib, another small molecule inhibitor. It is described in UpToDate as follows[28]:

> Ceritinib is a second generation TK inhibitor of ALK that is approximately 20 times more potent than crizotinib. Ceritinib is indicated for patients who are resistant to or unable to tolerate crizotinib. Preclinical studies suggested that ceritinib had significant activity against cells that were either sensitive or resistant to crizotinib, including resistant tumors with the most common L1196M and G1269A resistance mutations.
>
> After the maximum tolerated dose was established in the Phase I study, ceritinib was studied in a dose expansion cohort of NSCLC patients with the ALK rearrangement. Results from that expansion cohort were updated at the 2014 ASCO meeting:

- A total of 246 patients with ALK positive NSCLC were treated with ceritinib. Of these patients, 163 had previously been treated with an ALK inhibitor and 83 were ALK inhibitor naïve.
- The objective response rate was 58 percent overall, 55 percent in those with prior crizotinib treatment and 66 percent in ALK inhibitor naïve patients. The median duration of response was 10 months in the entire cohort and 7.4 months in those with prior crizotinib treatment. The median progression-free survival for the entire cohort

[27] 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
[28] UpToDate infographic on initial systemic therapy for patients with advanced non-small cell lung cancer. Available at: http://www.uptodate.com/contents/image?imageKey=ONC%2F100108
[28] FDA Division Director Summary Review for NDA 208434. Dated December 9, 2015. Accessed 10/06/2016.

was 8.2 months, including 6.9 months for those previously treated with an ALK inhibitor and not estimable (lower bound of 95% CI 8.3 months) for those who had not previously received an ALK inhibitor.

Two Phase III trials are currently recruiting patients with ALK+ NSCLC, one in which ceritinib is being compared with single-agent chemotherapy after progression on a platinum-based doublet and on crizotinib (NCT01828112) and the other as first line treatment compared with a platinum-based doublet (NCT01828099).

Ceritinib has received accelerated approval by the FDA for patients who have progressed on or are intolerant of crizotinib. Because it was not full approval, the need was considered still unmet in this group of patients when a new drug application for alectinib was submitted and alectinib subsequently also received accelerated approval from the FDA in the same population.

Ceritinib (Zykadia) was not registered in Australia at the time the current application for alectinib was submitted. However, approval has since been granted (31 March 2016) for a similar indication to that which received accelerated approval in the USA:

> *Zykadia is indicated as monotherapy for the treatment of adult patients with anaplastic lymphoma kinase (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 Indication: This indication is approved based on tumour response rates and duration of response. An improvement in survival or disease –related symptoms has not been established.*

However, as ceritinib is not PBS listed, the need for medical therapy (other than second-line chemotherapy) in patients in whom disease progression has been seen after crizotinib therapy remains unmet.

Clinical rationale

The sponsor's cover letter for the current application summarises the population in which the sponsor states that alectinib has a potential treatment role supported by the currently available evidence. They state:

> The ALK-fusion protein is an appropriate target for the treatment of patients with NSCLC harbouring ALK gene rearrangements as demonstrated with crizotinib (Xalkori® Product Information) and ceritinib (Zykadia™ SmPC) both of which have received marketing authorization in ALK+ NSCLC in Europe and the United States (US). In Australia, crizotinib is indicated, 'for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive advanced NSCLC.
>
> Although substantial benefit has been observed with crizotinib therapy, relapse remains the norm and survival after relapse is poor.[29] This is believed to be due to three main reasons:
>
> § Development of acquired resistance because of secondary mutations in ALK or amplification of ALK fusions[30],
>
> § Development of acquired resistance driven by alternative signalling pathways such as EGFR, mast/stem cell growth factor receptor (c-KIT), KRAS or due to unknown mechanisms [31]

[29] Solomon B, Wilner KD, Shaw AT et al. Current Status of Targeted Therapy for Anaplastic Lymphoma Kinase–Rearranged Non–Small Cell Lung Cancer. Clin Pharmacol Ther. 2014; 95(1):15-23.
[30] Summary Review for NDA 208434. Dated December 9, 2015. Accessed 10/06/2016.

§ Progression of disease in the central nervous system (CNS), which has been reported to be the primary site of initial treatment failure in 46% of patients with ALK+ NSCLC treated with crizotinib.[32]

The sponsor notes in the introduction to the study report for Phase I/II Study NP-28761 that a high incidence of brain or CNS relapse is:

> …consistent with the fact that crizotinib cannot cross the blood–brain barrier and the level of crizotinib in CSF is significantly lower than that in serum.

The sponsor's cover letter continues:

> There remains an unmet need following disease progression on crizotinib for an effective, well-tolerated ALK inhibitor with proven activity against ALK resistance mutations, as well as a proven CNS activity. In this context, Roche believes that the consistent efficacy demonstrated by Alecensa in the two pivotal Phase I/II studies (NP28761 and NP28673), both overall and specifically in the CNS, together with the well-tolerated and manageable safety profile, represents a significant advance over currently available treatment options in this population and supports the application to register Alecensa in this setting.

Guidance

The specific requirements from the TGA given in pre submission guidance were:

· Inclusion of the 90 day updated safety report in the dossier.

This has been undertaken and the report was provided by the sponsor.

· Inclusion of further information in the dossier outlining the rationale for a capsule being chosen as the optimal formulation for development.

The sponsor states that this has been done.

Whether the Risk Management Plan (RMP) advice has also been incorporated will be reviewed by the RMP section.

Evaluator's commentary on the background information

For patients with ALK+ NSCLC who have progressed on or are intolerant to crizotinib, treatment options are limited to ceritinib, which appears to have significant safety concerns or chemotherapy with a lower response rate. In this context, alectinib may meet unmet need or provide a viable alternative treatment, provided the safety and efficacy profile is similar to or compares favourably to that of ceritinib.

---

[31] Roche Media Release. July 4 2014. Japan becomes first country to approve Roche's alectinib for people with a specific form of advanced lung cancer." Accessed 27/04/2016 at: http://www.roche.com/media/store/releases/med-cor-2014-07-04.htm

McKeage K. Alectinib: a review of its use in advanced ALK-rearranged non-small cell lung cancer. Drugs. 2015 Jan;75(1):75-82. doi: 10.1007/s40265-014-0329-y. Abstract accessed 27/04/2016 at: http://link.springer.com/article/10.1007%2Fs40265-014-0329-y

Kim S, Kim TM, Kim DW, et al. Heterogeneity of Genetic Changes Associated with Acquired Crizotinib Resistance in ALK-Rearranged Lung Cancer. J Thorac Oncol 2013;8(4):415-22.

[32]Costa DB, Kobayashi S, Pandya SS, et al. CSF concentration of the anaplastic lymphoma kinase inhibitor *crizotinib. J Clin Oncol 2011;29:e443-5.*

Chun SG, Choe KS, Iyenger P et al. Isolated central nervous system progression on crizotinib. Cancer Biol Ther. 2012;13(14):1376-83.

Weickhardt AJ, Scheier B, Burke JM, et al. Continuation of EGFR/ALK inhibition after local therapy of oligoprogressive disease in EGFR mutant (Mt) and ALK+ non-small cell lung cancer (NSCLC). J Clin Oncol 2012;30(suppl):ASCO Abstract 7526.

Results from the Phase III trials are expected to provide further insight into the safety profile of alectinib and direct comparison of its efficacy to that of crizotinib.

The sponsor was asked when they expect that the data from the two Phase III trials (ALEX and J-ALEX) will be reported on (see Clinical question 15).

Contents of the clinical dossier

Scope of the clinical dossier

- 11 biopharmaceutics studies establishing the methodologies employed in the clinical studies and bioequivalence of an alternative, lower SLS formulation (still in development).
- Clinical pharmacology studies providing PK, PD and safety data:
  - One Phase I dedicated PK study.
  - Three Phase I drug-drug interaction (DDI) studies (CYP3A inhibition, CYP3A induction, effect of food and inhibition of gastric pH).
- Pivotal efficacy/safety and dose-finding studies
  - No Phase III studies available
  - Two pivotal Phase I/II studies (NP28673 and NP28761)
- Population PK (popPK) analyses.
  - 3 population PK analyses, including an exposure-efficacy and safety (dose-finding) analysis, carried out using data from both of the pivotal studies.
- Other efficacy/safety studies
  - Phase I/II trial from Japan, which supported registration in Japan and provides supportive PK, efficacy and safety data and guided dose-finding in the two subsequent pivotal Phase I/II studies
    - The report is provided in an English translation with separate PK analyses for both alectinib and its metabolites.
- Other reports such as pooled analyses, meta-analyses, periodic safety update reports PSURs), integrated analyses across more than one study: efficacy, safety, resistance.
  - A 90 day safety report, encompassing data from both of the English language ongoing Phase I/II trials.
  - A QT report based on pooled data from the two pivotal Phase I/II studies. As agreed with the EMA during their pre-submission process, rather than a dedicated QT study, thorough QT assessments were conducted in these Phase I/II pivotal trials.
- Literature references.
  - 107 references are listed including:
    - Foreign labelling (PI from Japan) ‘alecensa pi’

Submitted biopharmaceutic studies are summarised in Attachment 2.

Paediatric data

No paediatric data was included with this submission. Toxicology data regarding developmental toxicity is referred to in the US label.

Good clinical practice

The clinical study reports for both of the pivotal Phase I/II trials (NP28673 and NP28761) contain detailed assurances of compliance with ICH E6 guideline for Good Clinical Practice (another name for the CPMP/ICH/135/95 guideline referred to by the TGA in their 'Note for guidance on good clinical practice'.

For more details see Attachment 2.

Pharmacokinetics

Pharmacokinetics studies submitted are listed in the table below.

Table 5: Studies providing pharmacokinetic data

PK topic	Subtopic	Study ID	*
PK in healthy adults	General PK - Single dose	NP28989	*
	- Multi-dose	N/A	
	Bioequivalence † - Single dose	NP29040	*
	- Multi-dose	N/A	
PK in special populations	Target population § - Single dose	NP28673	
	- Multi-dose	NP28673 NP28761	* *
	Hepatic impairment (mild)	POPPK-1064536	
	Renal impairment (mild to moderate)	POPPK-1064536	
	Neonates/infants/children/adolescents	N/A	
	Elderly	POPPK-1064536	
	Asian patients, similar to target population but crizotinib-naïve, multi-dose.	AF-001JP	*
Genetic/ gender related PK	Males versus females	POPPK-1064536	
	Other genetic variable	POPPK-1064536	
Food effect	In healthy adults	NP28991	*
	In target population	*NP28761*	

PK topic	Subtopic	Study ID	*
	In crizotinib-naïve with ALK+ NSCLC	*AF-001JP (Japan)*	
PK interactions	Posaconazole (CYP3A inhibitor) – healthy subjects	NP28990	*
	Rifampin (CYP3A inducer) – healthy subjects	NP29042	*
	Esomeprazole (PPI) healthy subjects	NP28991	*
	Midazolam *in ALK+ NSCLC patients*	NP28673 (substudy)	*
Population PK analyses	Healthy subjects	N/A	
	Target population	PK1064595 (GastroPlus™)	
		PBPK 1064597 (SimCYP®)	
		POPPK-1064536	

* Indicates the primary PK aim of the study.
† Bioequivalence of different formulations.
§ Subjects who would be eligible to receive the drug if approved for the proposed indication.

Evaluator's conclusions on pharmacokinetics

Alectinib pharmacokinetics has been adequately profiled, including direct clinical studies in healthy volunteers, studies of population PK data from clinical trials and physiologically based PK modelling of the same data, directed by nonclinical data. Alectinib PK shows moderate inter-individual variability.

The solubility of alectinib appears to most influence its bioavailability and this is changed most significantly by SLS content of the formulation (higher SLS giving more exposure) and dosing relativity to food intake (higher exposure with fed state intake).The factor most influential on alectinib exposure for an individual is body weight (lower exposure with higher weight). PK does not seem to be affected by sex, age, race or gender, mild to moderate renal impairment or mild hepatic impairment.

No CYP3A4 related DDIs are expected. Physiologically based pharmacokinetic (PBPK) modelling predicts no CYP2C8 DDIs are expected. Interaction with CYP3A inhibitors or inducers is not expected to be clinically relevant and gastric acid-lowering medications should not have a clinically significant effect.

The fact that major metabolite M4 is a substrate of P-gp may have relevance to efficacy in the CNS and may confound the conclusions drawn from PK calculations that have relied on total molar concentration of both alectinib and M4 due to their similar potency. See clinical question 1 in Attachment 2.

Alternative PI text regarding PK information is proposed for clarity.

Pharmacodynamics

Studies providing pharmacodynamic data

No specific pharmacodynamics studies have been submitted. Pharmacodynamic information is provided principally by population PK analysis of the pivotal efficacy studies and is supported by non-clinical pharmacodynamics data. Exposure-safety and exposure-efficacy analyses were performed as part of the popPK study.

Evaluator's conclusions on pharmacodynamics

The pharmacodynamics data from nonclinical studies and the population PK report support that alectinib should show efficacy in treating cancer patients with ALK+ tumours and with CNS disease.

The reliance on nonclinical data and population PK analyses of data in assessing pharmacodynamics is appropriate due to the nature of the disease, as a pharmacodynamics effect on a neoplasm cannot be studied clinically in the absence of a neoplasm.

Dosage selection for the pivotal studies

The 600 mg twice daily (bid) dose is well supported by the evidence.

For further details see Attachment 2.

Efficacy

Studies providing efficacy data

The application for registration of alectinib relies on efficacy evidence from Phase I/II clinical trial data:

- NP28673:
  - An open-label, non-randomized, multicenter Phase I/II trial of RO5424802 given orally to non-small cell lung cancer patients who have ALK mutation and who have failed crizotinib treatment.'
  - Pivotal Phase I/II trial (global) 138 patients enrolled
- NP28761:
  - NP28761/AF-002JG – a Phase I/II Study of the ALK Inhibitor CH5424802/RO5424802 in Patients with ALK-Rearranged Non-Small Cell Lung Cancer Previously Treated with Crizotinib'
  - Pivotal Phase I/II trial (USA and Canada) 135 enrolled
- AF001-JP:
  - Phase I/II Study of CH5424802 in Patients with Non-small Cell Lung Cancer Harboring the ALK Fusion Gene
  - First-in man study (Japan)
  - The Phase I/II trial on which registration was based in Japan
  - Consisted of a dose-escalation phase followed by a safety and efficacy at recommended dose phase.

– A supporting trial for the purposes of this study as the exclusion criteria included prior use of ALK-inhibitors

Evaluator's conclusions on efficacy

Evidence for efficacy of alectinib in the treatment of ALK positive NSCLC to date is available from two pivotal Phase I/II studies (in patients with ALK positive NSCLC who have failed crizotinib therapy) and one supporting Phase I/I study (in patients with ALK positive NSCLC who are crizotinib naïve).

There is reasonable external validity to these studies as the target population in Australia can be expected to be similar to those enrolled in the study. Screening failures were seen at a rate of 21% and 26% in Studies NP28673 and NP28761 respectively. Data is not present for children, patients with severe hepatic impairment, pregnant or breastfeeding women or patients who are less high functioning (with higher ECOG scores), as they have not been represented in the clinical studies so far.

The optimal dose range appears to have been established on the basis of dose limiting toxicities (DLT) seen in Phase I of Study NP28761 and is supported by the exposure-efficacy analyses in popPK studies. Subgroups requiring dose adjustment for efficacy reasons and predictors of positive or negative responses have not been identified, as subgroup analyses were underpowered and therefore can only be considered exploratory.

Whether the study population represented the population in the proposed indication in two aspects was specifically considered by the FDA in their assessments:

· There were 2 patients with locally advanced, rather than metastatic disease.

· There were 5 patients who were intolerant to, rather than had progressed on crizotinib.

Inclusion of 'intolerant to' in the Australian indication is considered reasonable. Whether the pooling of Stage IIIB and Stage IV patients is appropriate, and whether inclusion of 'locally advanced' in the indication is acceptable is unclear. See clinical question 13 in Attachment 2.

The magnitude of the primary treatment effect has been measured using a widely used, well-validated set of radiological diagnostic criteria (RECIST) for treatment-response in solid tumours, with assessments made by the investigator and reviewed by an independent radiological review committee (IRC) for the final analysis. The Statistical Analysis Plan for Study NP28673 states the following:

> The results of the investigator review of radiographs will still be used to determine whether or not patients should be enrolled and remain on study. IRC review will only be used in the final analysis. All decisions during the study will be based on a local investigator read.

The primary outcome was overall response rate (ORR), with a predetermined lower clinical significance bound of 35%, as agreed with the FDA. The reason for selection of this bound is not explicitly stated in the dossier, only that this is 'considered to be clinically relevant.' See Clinical question 5 in Attachment 2.

One would estimate this might relate to the only other treatment options available to patients with ALK+ NSCLC after failure of crizotinib (other than palliative radiotherapy and supportive treatment): ceritinib or cytotoxic chemotherapy. Second-line platinum-based chemotherapy achieves an ORR of around 20% (95% CI 14%-26%) in ALK+, crizotinib-naïve NSCLC patients. Ceritinib was initially assessed by blinded IRC in the pivotal registration studies to achieve an ORR of 44% (95% CI 36% - 52%) in ALK+ crizotinib pretreated patients. However, subsequently published data from the Phase II

ASCEND-2 study of ceritinib found the ORR in this group to be 38.6% (95% CI 30.5-47.2%).

The FDA statistical review for the alectinib new drug application in the US states that the size of the population studied was adequate to identify a clinically relevant response by rejecting a null hypothesis of ORR=35%.40

The alectinib efficacy results can be summarised as follows:

- There has been one complete response recorded in each of the pivotal trials and the remaining responses have all been partial.
- The primary endpoint was ORR as assessed by the IRC in the response evaluable (RE) population:
  - ORR in study NP28761: 47.8% (95% CI 35.6% - 60.2%)
  - ORR in study NP28673: 49.2% (95% CI 40.0% - 58.4%)

These response rates both were significant within the pre-determined bounds and were very consistent with each other.

  - ORR in study NP28673 (updated): 50.0% (95% CI 40.8% - 59.1%)

Updated efficacy analysis was performed for Study NP28673 (IRC-assessed endpoints only) with a data cut-off date of 8 January 2015.

- In Study NP28673, a co-primary endpoint was considered of ORR in the subset of ALK+ NSCLC patients who have failed crizotinib therapy: those who were also chemotherapy pre-treated. In this subgroup, the ORR was 43.8% (95% CI 33.6% - 54.3%)
  - Although this co-primary endpoint didn't reach statistical significance according to the pre-determined bound, the result still is likely to be of clinical significance given the ORRs for second-line chemotherapy in this population. This finding also does not invalidate the first primary endpoint.
- The secondary endpoint was ORR as assessed by the investigator in the response evaluable (RE) population:
  - Investigator-assessed ORR in Study NP28761: 46.0% (95% CI 35.2% - 57.0%)
  - Investigator-assessed ORR in Study NP28673: 47.8% (95% CI 39.3% - 56.5%)

These response rates both were significant within the pre-determined bounds and were very consistent with each other and with the IRC-assessed ORR result.

- The key CNS endpoint was CNS ORR (CORR), assessed by IRC, in patients with measurable CNS lesions at baseline RECIST v1.1:
  - CORR in study NP28761: 68.8% (95% CI 41.3% - 89.0%)
  - CORR in study NP28673: 55.9% (95% CI 37.9% - 72.8%)
  - CORR in study NP28673 (updated): 60.8% (95% CI 46.1% - 74.2%)

These results don't show as close a consistency as those seen for ORR but are still concordant.

- Concordance between the IRC and investigator-assessed best overall response (BOR) in Studies NP28673 and NP28761 were 72% and 74% respectively for the patients that were assessed by both sets of assessors to have measurable lesions at baseline. In the context of very consistent results despite the 25% discordance, this likely reflects the independence of the assessments, including choice of baseline lesion.

Results from Study AF-001JP are supportive of those in the pivotal studies, but were carried out in a crizotinib naïve population. In this study the IRC-assessed response rate in patients who had progressed on at least one line of chemotherapy (Phase II) was 93.5% (95% CI 82.1% - 98.6%) and all patients had a reduction of their target lesions of at least 30%.

During the FDA's consideration of this application, an updated data cut-off date of 8 January 2015 was agreed upon, providing an additional 4 months of follow up to the efficacy results for NP28673. Due to the discordance between results based on differences in analysis set definitions and cut-off dates, the FDA statistical reviewer re-calculated the efficacy results for Studies NP28673 and NP28761, using the later cut-off date and the AT population rather than RE.40 The FDA statistical reviewer's conclusions were that:

> Trial NP28673 had ORR of 44% (95% confidence interval [CI]: 36%, 53%), consisting of 61 (44%) PRs. This trial had ORR-PC of 39% (95% CI: 30%, 49%). The CORR with baseline measurable lesions was 57% (95% CI: 39%, 74%).
>
> Trial NP28761 had ORR of 38% (95% CI: 28%, 49%). The CORR with baseline measurable lesions was 69% (95% CI: 41%, 89%). Fifty one CNS patients with baseline measurable lesion in Trials NP28761 and NP28673 had ORR of 61% (95% CI: 46%, 74%), consisting of 9 (18%) CRs and 22 (43%) PRs.
>
> Without control arm, statistical inference cannot be drawn from this trial.

If adhering to the predefined 35% significance cut-off criterion, the ORR point estimates in both trials still met this but the lower 95% CI bound for the ORR found in NP28761 fell below this mark.

The primary endpoints of the two pivotal alectinib studies, despite the lack of a control arm and the small study population, suggest that it is effective against metastatic ALK+ NSCLC in patients who have failed crizotinib therapy. Previously determined rates of response to other treatment options (see above) provide some point of comparison in the absence of a formal control arm, which was not possible to have due to the ethics of allocating patients to a known ineffective treatment.

The use of a blinded, IRC in duplication of radiological assessment of disease response, concordance between the IRC and the investigator-assessed results, as well as the concordance between results of the two pivotal studies, gives additional credence to the findings.

Time-dependent endpoints for the pivotal studies are not yet mature and so upper confidence interval bounds cannot yet be determined. Estimates based on interim analyses gave median point estimates for duration of response in NP28761 (as at October 2014) of 7.5 months and in NP28673 (as at January 2015) of 11.2 months. Time-to-event based outcomes will require further follow up before they can be meaningfully interpreted. Longer-term efficacy data is expected in the near future: a Phase III trial, the 'ALEX' study with progression free survival (PFS) as the primary endpoint is currently underway.

Although overall survival data is not yet mature and response rates are lower if measured in the as-treated population rather than the response evaluable population (discussed further in Attachment 2), evidence of alectinib efficacy is consistent in the response rates across analyses, and the magnitude of ORR for alectinib is in keeping with rates seen with crizotinib and ceritinib, and higher than those seen with chemotherapy in similar populations.

With regard to disease control rate (DCR), this information has not been included in the FDA label, as[33]:

> DCR was not a measure of clinical benefit as the treatment effect could not be discerned in a single arm trial as compared to the natural history of CNS metastases in ALK+ NSCLC.
>
> …it was unclear how DCR leads to patient benefit, in contrast to partial responses (PR) or complete responses (CR) where reduction in tumor size may be linked to a reduction in tumor-related symptoms.

DCR is a weaker endpoint than ORR in the context of a single arm, open label trial and it is agreed that inclusion of this data in product documentation is not appropriate. The PI has been amended appropriately. Waterfall plots showing change in lesion size have also removed from the proposed PI as these are redundant in repeating the primary efficacy outcome given that all responses were partial and do not provide any insight into whether the findings were correlated with symptomatic relief.

Finally, it is noted that around 65% of patients had at least one treatment with radiation therapy prior to study which is not surprising as it is part of the standard of care. 47% of patients had previous radiotherapy to the brain. Whether this had an effect on the efficacy outcomes was explored by the FDA statistical reviewer by subgroup analysis who found that previous CNS radiation therapy did not affect efficacy outcomes in the CNS.

Overall, the efficacy results support the intended indication for the target population. In this group of patients where there is unmet need; in a context where all other treatment options have failed or are not available or tolerated; this evidence is supportive of registration. Similarly, the evidence of activity in CNS disease, coupled with biological plausibility for such effects, supports usage in patients where progression of disease on crizotinib has occurred in the CNS.

Safety

Studies providing safety data

Not applicable. There are no clinical trials that assessed safety as the sole primary outcome for alectinib.

Pivotal and/or main efficacy studies

- NP2867)
- NP28761

Other efficacy studies

- AF-001-JP

Studies with evaluable safety data: dose finding and pharmacology

- NP28989 – PK/PD in healthy volunteers
- NP28990 - posaconazole (CYP3A inhibitor)
- NP28991 - food and esomeprazole
- NP29040 - bioequivalence SLS

[33] Lindquist M (2008) Vigibase, the WHO Global ICSR Database System: Basic Facts. Drug Information Journal 42: 409–19

· NP29042 - rifampin (CYP3A4 inducer)

Patient exposure

The most recent safety and exposure data comes from the 90 Day Safety Report, with a data cut-off date of 27 April 2015. Information from this and from the CSRs for all of the clinical pharmacology studies, pivotal and supporting efficacy studies has been summarised in Table 6 to describe exposure, although dose changes and dose intensity are not reflected in this table. In the pivotal trials (including the midazolam substudy [15 patients] and the 600 mg cohort of Phase I of Study NP28761 [13 patients]), there were a total of 253 patients exposed to alectinib at the recommended dose of 600 mg bd, with a median duration of exposure of 40.6 weeks (range 0.1-114 weeks) up to the cut-off date.

Table 6: Exposure to alectinib in clinical studies according to dose and duration (as at the cut off for the 90 day safety report: 27 April 2015, data sourced from 90 day safety report and CSR for NP28761) (wks=weeks).

Study type/indication		Number of people exposed at any dose	Number of people exposed at proposed dose (600 mg BD)			
			> 24 wks	> 36 wks	> 52 wks	Any duration
Clinical pharmacology studies						
NP28989		6	-	-	-	6
NP28990		23	-	-	-	0
NP28991		42	-	-	-	42
NP29040		97	-	-	-	97
NP29042		24	-	-	-	24
(pharmacology studies subtotals)		*192*	-	-	-	*169*
Pivotal phase I/II trials						
NP28673	phase II	138	102	86	67	138
	midazolam substudy	15	18	14	0	15
NP28761	phase I	47			7	13
	phase II	87	57	46	26	87
(pivotal studies subtotals)		*287*	*177*	*146*	*100*	*253*
Supporting phase I/II trials						
AF001JP		70	-	-	-	0
(supporting studies subtotal)		*(70)*	-	-	-	*(0)*

Study type/indication	Number of people exposed at any dose	Number of people exposed at proposed dose (600 mg BD)			
		> 24 wks	> 36 wks	> 52 wks	Any duration
TOTAL ALL STUDIES	**549**	**177**	**146**	**100**	**442**

The characteristics of the safety population were summarised from the 90 day safety report by the FDA medical reviewer, as shown in Table 7. The FDA reviewer commented that although the quality of the submission was adequate for review and the data was representative of the US population, there was not sufficient numbers of people older than 65 to determine whether alectinib safety was different in this group compared to younger patients. This evaluator agrees and suggests similar comment in the Australian PI.

The 90-day Safety Update report also contains an updated exposure table including dose intensity, which is reproduced in Table 8. The extent of exposure in supporting efficacy Study AF-001JP (in which the standard dose was 300 mg bd) is summarised in Table 9.

Table 7: Characteristics of the safety population and their baseline disease, as outlined in the FDA medical review of alectinib

Patient Characteristic	N=253
Age (years)	
Mean (SD)	52.6 (11.3)
Median (Range)	53.0 (27-81)
≥65 years (%)	36 (14.2%)
Race*	
White (%)	186 (73.5%)
Asian (%)	46 (18.2%)
Other (%)	17 (6.7%)
Gender	
Female (%)	138 (54.5%)
Male (%)	115 (45.5%)
ECOG Performance Status	
0 (%)	88 (34.8%)
1 (%)	142 (56.1%)
2 (%)	23 (9.1%)
Smoking Status	
Non-smoker (%)	171 (67.6%)
Past smoker (%)	78 (30.8%)
Active smoker (%)	4 (1.6%)
*Race reported as "Unknown" for 4 patients	
Disease Characteristic	N=253
Stage	
IIIB (%)	3 (1.2%)
IV (%)	250 (98.8%)
Histology	
Adenocarcinoma (%)	242 (95.6%)
Squamous cell (%)	1 (0.4%)
Other* (%)	10 (4.0%)
CNS Metastases	
CNS metastases at baseline	135 (53.4%)
Prior Systemic Therapy	
Prior platinum-based chemotherapy	(75%)
>2 prior regimens (including crizotinib)	135 (53.3%)
>4 prior regimens (including crizotinib)	61 (24.1%)
Prior Radiotherapy	
Any radiotherapy for NSCLC	159 (62.8%)
Radiation therapy for brain metastasis	119 (47.0%)
Prior Crizotinib	
Time on crizotinib, median (days) (range)	372 (1-1822)
Time since last dose, median (days) (range)	15 (7-733)
ORR with crizotinib	115 (45.5%)
PD as best response to crizotinib	58 (22.9%)
Discontinued for reason other than PD	2 (0.8%)
*Other includes adenosquamous, large cell, and poorly differentiated SD, standard deviation; ORR, objective response rate; PD, progressive disease	

Table 8: Patient exposure summary as at 27 April 2015

	Group 1 NP28761 Phase II		Group 2 NP28673 Phase II		Group 3 NP28761 Phase I and II, NP28673 Phase II and MDZ	
	SCS n=87 (%)	Safety Update n=87 (%)	SCS n=138 (%)	Safety Update n=138 (%)	SCS n=253 (%)	Safety Update n=253 (%)
Treatment Duration (Weeks)						
Mean (SD)	22.2 (11.7)	36.2 (21.0)	27.3 (11.3)	45.7 (24.9)	25.6 (14.9)	42.0 (25.0)
Median	19.6	39.6	27.1	51.6	26.1	40.6
Min–Max	3.00–59.4	3.00–85.9	2.40–53.0	2.40–89.0	0.100–87.6	0.100–114
Dose Intensity (%)						
Mean (SD)	92.9 (13.1)	91.9 (13.7)	96.5 (8.59)	96.1 (8.98)	95.5 (10.7)	95.0 (11.2)
Median	99.4	98.6	100	99.7	99.8	99.6
Min–Max	24.1–100	15.5–100	42.9–100	42.9–100	24.1–134	15.5–138
Number of Doses						
Mean (SD)	303 (165.2)	495 (292.5)	375 (160.8)	630 (350.1)	352 (207.8)	578
Median	270	540	377	709	352	564
Min–Max	14.0–832	10.0–1200	34–742	34–1250	1–1210	1–1580
Total Cumulative Dose (mg)						
Mean (SD)	174685 (97618)	281743 (170728)	223190 (96933)	372787 (209225)	208179 (130120)	339745 (215246)
Median	155400	275250	225000	397575	207600	333600
Min–Max	8400–498600	5400–720600	19800–445200	19800–747600	600–982800	600–1315800
Days Not Dosed						
Mean (SD)	4 (7)	6 (9)	3 (8)	4 (9)	4 (7)	5 (9)
Median	0	1	0	0	0	0
Min–Max	0–31	0–43	0–55	0–55	0–55	0–55
Days Not Dosed						
No day without a dose	50 (58)	40 (46)	95 (69)	83 (60)	165 (65)	141 (56)

AE = adverse event; MDZ = midazolam; SAE = serious adverse event; SCS = Summary of Clinical Safety; SD = standard deviation.

Table 9: Summary of extent of exposure in study AF-001JP

	CH5424802 600 MG (N=46)	CH5424802 600 MG+ Step1 Cohort6+8 (N=58)
Cumulative Duration of Administration [month]		
Mean	13.2	14.0
Std Dev	5.19	5.30
Median	14.4	14.7
Min-Max	0-20	0-23
n	46	58
Cumulative Duration [month]		
Mean	13.6	14.5
Std Dev	5.14	5.26
Median	14.8	15.8
Min-Max	1-20	1-24
n	46	58
Cumulative Duration of Dose Interruption Caused by AE [day]		
Mean	13.6	12.5
Std Dev	19.97	19.61
Median	7.0	4.5
Min-Max	0-76	0-76
n	46	58
Cumulative Dose [mg]		
Mean	240170.9	254292.4
Std Dev	94817.76	95245.00
Median	262020.0	267750.0
Min-Max	5700-359700	5700-423900
n	46	58

Postmarketing data

Alectinib at the recommended dose has only been registered in the US since December 2015, so the available post-market safety data is limited. Alectinib has been registered in Japan since the middle of 2014 but at half the proposed dosage for registration in Australia and for a different indication: *for the treatment of 'ALK fusion gene-positive unresectable, recurrent or advanced non-small cell lung cancer*. The post-market section in the 90 Day Safety Update Report states that:

> …as of 3 January 2015, no regulatory actions were undertaken for safety reasons by the regulatory authorities or the Marketing Authorization Holder in Japan (Chugai Pharmaceuticals Co Ltd for alectinib 300 mg BID). A review of the post-marketing data did not reveal any new, pertinent safety information for alectinib.
>
> …As of 3 January 2015, an estimated 634 patients have received 300 mg bid alectinib in the post-marketing setting in Japan.

The serious post-marketing case list from Japan includes

- 3 patients with gastrointestinal perforations:
  - 'gastrointestinal perforation' and 'sepsis' [fatal]
  - 'rectal perforation', 'constipation' and 'haemorrhagic shock'
  - 'intestinal perforation', 'ileus of intestine' and 'constipation'
- 2 patients with ileus, including the patient with perforation and constipation, above
- 14 cases of interstitial lung disease:
  - One drug-induced Pneumonia'
  - Eleven cases of 'Interstitial Pneumonia
  - One Drug-Induced Interstitial Pneumonia
  - One 'Idiopathic Interstitial Pneumonia'

- A case of myalgia in conjunction with increased blood CPK 5 days post commencing alectinib
- A case of erythema multiforme 38 days post commencing alectinib in a setting of multiple concurrent medications: zetia, lansoprazole, lac-b, tsumura goshajinkigan, trazenta, glimepiride, novorapid, lantus, risperidone, desyrel, decadron, glycereb loxoprofen and ipragliflozin.

Interstitial lung disease is reported in the post-market setting in Japan at a rate of 2.2% according to these data.

Cases of intestinal perforation are also of interest/concern. Of note, the Australian PI for crizotinib contains a precaution regarding gastrointestinal perforation. See comments at the end of this section.

The FDA Medical review of alectinib for registration (application number 208434Orig1s000) states:

> The most recent Development Safety Update Report (DSUR) for alectinib, covering the reporting interval from 4 Jun 2014 to 3 Jun 2015, states that post-marketing data that became available from Japan during the reporting interval did not reveal any new, pertinent safety information. During the reporting interval, no safety-related amendments were made to the Japanese label for alectinib or to Chugai's risk management plan for alectinib based on the post-marketing data.

To complement the study data and generate safety related hypotheses to compare to the known safety issues with alectinib, a search of the WHO global individual case safety report (ICSR) database, VigiBase, was conducted on July 5, 2016. Although the WHO Uppsala Monitoring Centre (UMC) has provided the data, it is important to note that the information extracted from the database and the results and conclusions drawn in this document do not represent the opinion of the World Health Organization, the Uppsala Monitoring Centre or National Centres but are those of the author.

The drugs recorded on the reports have been coded according to the WHO Drug Dictionary Enhanced and MedDRA adverse reaction terminology version 19.0, in keeping with the dictionary used in the dossier by the sponsor (though the sponsor used earlier MedDRA versions 16.1 to 18.0, depending on the most recent version available at the time of study data collection). A variety of sources contribute information to the reports in VigiBase and it should be noted that the likelihood of a suspect event being drug-related is also variable.

The search extract of VigiBase [from entry commencement in November 2000] to July 2016 contained 140 unique ICSRs: 4 from the Americas, 102 from Asia (primarily Japan) and 34 from Europe, all with initial database entry dates between April 2014 and April 2016. Males and females accounted for 49.3% of the reports respectively, with 1.4% of reports not having recorded gender. Patient age was in keeping with an ALK+ NSCLC population (see Figure 4). The MedDRA system organ class (SOC) distribution of reports in the Vigibase extract is illustrated in Figure 5.

Figure 4: Age distribution of reports in a VigiBase extract of 140 reports pertaining to alectinib.

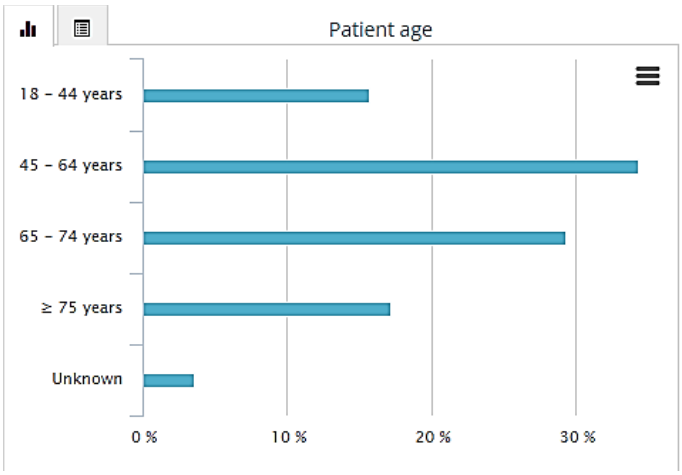
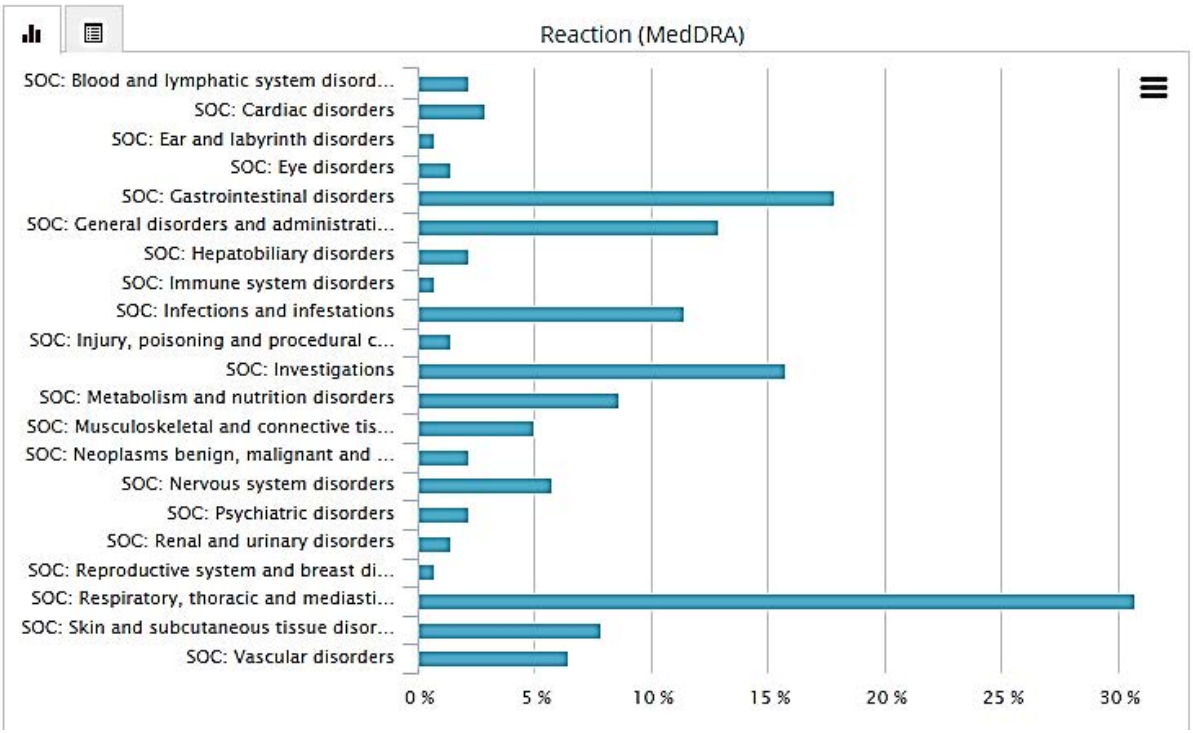


Figure 5: MedDRA SOC distribution of reports in a VigiBase extract of 140 reports pertaining to alectinib.



A measure called the IC (information component) was developed by the UMC as a measure of disproportionality, calculated as follows:

IC = log2 ((Nobserved + 0.5)/(Nexpected + 0.5))

where Nexpected = (Ndrug * Nreaction) / Ntotal

- Nexpected: the number of case reports expected for the drug-reaction combination
- Nobserved: the actual number of case reports for the drug-reaction combination
- Ndrug: the number of case reports for the drug, regardless of reactions
- Nreaction: the number of case reports for the reaction, regardless of drug

The lower 95% credibility interval of the IC is the IC025 and a positive IC025 value is the traditional statistical basis for signal detection at UMC (see Attachment 2 for details). Generally these event terms reflect the safety data seen in the clinical studies.

Given the limitations of these data extracts, the only signal for which a true association can be really predicted is interstitial lung disease (ILD). However, the presence of a rhabdomyolysis case recorded to have a positive dechallenge and rechallenge is noted. This case occurred in June 2015 and involved a patient in Germany. It was reported by a physician and entered into the database in October 2015 with a recorded positive dechallenge, followed by a positive rechallenge. The case details are not available on the VigiBase website.

Given the post-market data available in the safety update report and in Vigibase, can the sponsor please provide an updated post-market incidence estimate for ILD with alectinib use, case analyses for all reported cases of intestinal perforation and a safety signal analysis for rhabdomyolysis? See Clinical question 12 in Attachment 2.

Safety issues with the potential for major regulatory impact

See Attachment 2 section 8.5 Evaluation of issues with possible regulatory impact.

Evaluator's conclusions on safety

The safety profile of alectinib has not been studied in a Phase III trial but instead relies on data from two pivotal Phase I/II trials, as has become increasingly common in oncology drug development. The total number of subjects from the target population exposed to alectinib at the recommended dose (600 mg bd) is 253 patients, of whom just over half had CNS metastases at baseline and 100 have been exposed to alectinib for over a year. The median duration of exposure across all 253 subjects as at 27 April 2015 is 40.6 weeks, with a median total cumulative dose of 333600 mg. Although the safety database is limited in size, the study population is a fair representation of the intended population (albeit the least unwell few percent that meet enrolment criteria). The safety evaluation of this product is therefore limited but given the lack of alternative therapies for this life-threatening disease is acceptable for the purposes of this evaluation.

The safety profile of alectinib overall, based on this evaluation, is reasonable. No particular risk factors were noted for adverse events, the most common of which were fatigue, oedema, constipation and myalgia.

The adverse reactions that have been identified for alectinib based on the assessment of data from clinical trials, nonclinical data, mechanism of action, and causal relationship are summarised in Attachment 2 and include gastrointestinal toxicity (constipation, nausea, diarrhoea and vomiting), oedema, myalgia and CPK elevation, rash, photosensitivity, hepatotoxicity (indicated by elevation of AST, ALT and bilirubin), anaemia, bradycardia and interstitial lung disease. The incidence of all of these reactions has shown small proportional increases between the data cut-off dates for the SCS and the 90-Day Safety Update Report.

Of patients taking the recommended dose of 600 mg bid in the pivotal studies, 5.9% permanently discontinued due to adverse events and the majority of these that were not fatalities were related to signs of hepatotoxicity on investigations.

There have been seven deaths (2.8%) that were not due to disease progression. Within these cases, there is no clear pattern of risk although the two deaths that were considered by the investigator to be possibly related to alectinib were a case of intestinal perforation and a case of haemorrhage, presumed to be intraabdominal. The presence of an additional fatal case and two other cases of gastrointestinal perforation in the post-market data from Japan as well as the high incidence of constipation as an adverse event suggests that this is

a signal which warrants further attention (see Clinical question 12 in Attachment 2). One death is not properly explained as no detail of the death has been provided, although what is available suggests death due to disease progression.

Safety issues of potential regulatory importance which should receive specific attention in the Precautions section of the PI include hepatotoxicity, interstitial lung disease, bradycardia and myalgia and CPK elevation. Myalgia and CPK have not yet been included in the PI under Precautions.

Given the incidence of photosensitivity despite participants being advised to protect themselves from UV exposure in the clinical studies and the nonclinical evidence for phototoxicity this should also be included as a Precaution.

Regarding use in pregnancy: pregnancy and breastfeeding should be avoided during treatment with alectinib and for 1 week following the final dose. Pregnant women considering use of alectinib should be advised of the potential foetal risk and males with female partners of reproductive potential should be advised to use highly effective contraception during treatment with alectinib and for 3 months following the final dose.

There are no particular intrinsic or extrinsic risk factors that have been identified for dosing. Variability in exposure with dose time relative to food and body weight is not expected to affect exposure to a significant extent and dose modification or specific timing advice is not indicated. There are no specific safety concerns related to overdose/abuse/withdrawal, off label use or impairment of mental ability/ability to drive or off-label use.

There is currently no long-term safety data available. The sponsor states in the clinical overview that enrolment in the Phase I/II trials is complete and follow up is ongoing. Ongoing safety data will also be available from the two ongoing Phase III trials comparing alectinib head to head with crizotinib. One of these, the Japanese J-ALEX trial was recommended for early cessation as its endpoints had been met early. The other, the ALEX study, was initiated in July 2014, recruiting globally except in Japan and will compare alectinib 600 mg bid versus crizotinib in treatment-naïve ALK+ advanced or metastatic NSCLC patients.

Long term safety issues are therefore currently unknown, and short-term safety issues are those listed above. Most adverse events have shown reversibility; including bradycardia and elevation of hepatic transaminases. The exception to this rule is ILD which has not been documented to have been reversible in one case but has been reported to show positive dechallenge in 20 of the 27 cases lodged in VigiBase (see Attachment 2 Clinical question 12).

Post-marketing experience remains limited but existing post-marketing data is generally in agreement with the clinical trial data. A single case of rhabdomyolysis with a positive rechallenge has been reported in Germany (see Attachment 2 Clinical question 12).

The safety assessment program is suboptimal in terms of population exposure but is sufficient to support registration given the treatment of unmet need, existing preclinical data and global experience with other ALK inhibitors such as crizotinib and more recently, ceritinib.

First Round Benefit-Risk Assessment

Table 10: First round assessment of benefits

Indication	
Benefits	**Strengths and Uncertainties**
Alectinib has shown efficacy in treating patients with ALK-positive NSCLC who have progressed on or were intolerant to crizotinib therapy. The primary outcome of efficacy, ORR, is an accepted clinical trial surrogate endpoint for accelerated approval of NSCLC medicines according to FDA guidance[34] as long as the treatment effect size is large and responses durable, because this is then reasonably likely to predict clinical benefit. The same guidance states that in conjunction with proven improvements in tumour related symptoms, ORR can support regular registration in the US. The treatment effect size has been demonstrated to be reasonably large for alectinib in this population with otherwise limited treatment options – see below – and the durability of the effect is supported by the preliminary PFS results, although OS is yet to be demonstrated.	These efficacy rates are based on updated January 2015 data. Evidence supporting efficacy is present but limited, being available from only two Phase I/II studies and a supporting study in crizotinib-naïve patients. More mature data, including that from the Phase III studies (currently underway) would be required before the efficacy could be directly compared to current earlier-line therapies. Time-to-event outcomes, particularly overall survival, are immature. If Phase III studies indicate that there is no overall survival benefit and direct clinical benefit cannot be demonstrated (as opposed to surrogate markers), then a reconsideration of the risk-benefit balance of treatment with alectinib would need to be undertaken.
In a Phase I/II study (NP28673) of 138 such patients: · Partial responses were seen in 61 patients, giving an objective response rate (ORR) of 44% (95% CI: 36% - 53%) in the IRC RE population. · The ORR in a subset of patients pre-treated with chemotherapy was 39% (95% CI: 30% - 49%) in the IRC RE population. · The ORR in CNS disease that was measurable at baseline (CORR) (n=35)35 was 57% (95% CI: 39% - 74%). · In the investigator RE population, the ORR was higher than in the IRC RE population: 49.2% (95% CI 40.0% - 58.4%) · The investigator-assessed ORR in the IRC RE population at cut-off date Jan 8 2015 was consistent with the above: 50.0% (95% CI 40.8% - 59.1%), with estimates of PFS (median 8.9 months) and DOR (median 11.2 months) available.	· 16 (12%) of the 138 patients did not have measurable disease at baseline according to IRC and were not included in their response-evaluable (RE) population. The decision not to include these patients was not pre-specified in the SAP which suggested that inclusion in the RE would be determined by baseline measurability as determined by the investigator (none of the 138 patients were said to have unmeasurable baseline disease by their determination). · RE population inclusion by determination of baseline did not match who was measuring the final outcome for the investigator-assessed ORR (see Clinical question 8). · Consistency was seen between endpoints.

[34] US Department of Health and Human Services Food and Drug Administration. FDA Guidance for Industry: Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics. Available at http://www.fda.gov/downloads/Drugs/.../Guidances/UCM259421.pdf Accessed 27/07/2016.
[35] Derived from Table 22 of summary-clin-efficacy-nsclc and the statement in the clinical overview that the number of patients with measurable CNS lesions at baseline increased from 50 to 51 when the updated NP28673 data (as at Jan 2015) was included.

Indication	
Benefits	**Strengths and Uncertainties**
In a second Phase I/II study (NP28761) of 87 such patients: · Partial responses were seen in 33 patients, giving an objective response rate (ORR) of 38% (95% CI: 28% - 49%). · The ORR in CNS disease that was measurable at baseline (CORR) (n=16) was 69% (95% CI: 41% - 89%). · In the IRC RE population, the ORR was higher than in the investigator RE population: 47.8% (95% CI 35.6%-60.2%) · The investigator-assessed ORR in the IRC RE population was consistent with the above: 46.0% (95% CI 35.2% - 57.0%)	· 18 (21%) of the 87 patients did not have measurable disease at baseline according to IRC and were not included in their response-evaluable (RE) population. The decision not to include these patients was not pre-specified in the SAP as above. · RE population inclusion by determination of baseline did not match who was measuring the final outcome for the investigator-assessed ORR (see Clinical question 8). · Consistency was seen between endpoints.
Fifty one CNS patients with baseline measurable lesion in both of the pivotal studies combined had CORR of 61% (95% CI: 46%, 74%), consisting of 9 (18%) CRs and 22 (43%) PRs. In the total population (n=135) of patients with CNS lesions at baseline according to IRC (whether measurable or not) the CORR was lower, at 38.5% (95% CI 30.3% - 47.3%). This is because if a CNS lesion wasn't measurable at baseline, it would have to achieve a CR to be counted towards the ORR (as per RECIST criteria). There were 29 CRs seen in CNS lesions (both measurable and unmeasurable), a rate of 21.5%. Median CDOR was 10.3 months (95% CI: 7.6, 11.2 months) for all patients with CNS metastases and 9.1 months (95% CI: 5.8 months, upper bound not estimable) for patients with measurable CNS lesions.	· Data regarding CNS efficacy was pooled from both studies due to small sample size. There were differences in schedules of assessment between the pivotal studies that limit interpretability. · Patients in whom a CNS response was demonstrated included both patients with measurable and/or not measurable CNS lesions at baseline, and patients with no prior CNS radiation. · FDA exploratory statistical analysis found that 'CNS responses were observed in both patients who had and had not received prior CNS radiation, and CNS duration of response was similar across these subgroups'. · There were a number of major protocol violations that may have affected results (see Clinical question 9).
Study AF-001JP supports the results of the pivotal studies in that it showed alectinib to have efficacy in ALK positive NSCLC, of whom the target population for the purposes of registration in Australia are a subset.	· The response rates seen in AF-001JP were much higher but this trial was carried out in crizotinib-naïve patients. Data from a Phase III trial directly comparing crizotinib to alectinib in the ALK positive NSCLC population should be available in the future as the trial is underway (J-ALEX trial).

Table 11: First round assessment of risks

Risks	Strengths and Uncertainties
The most common adverse events seen with alectinib use at the recommended dose were constipation (32%), fatigue (26%), peripheral edema (24%), and myalgia (21%). SAEs were observed in 16% of patients. The most common Grade 3 or 4 AEs were blood CPK increased (3%), dyspnea (3%), ALT increased (3%), and AST increased (2%). Rates of AEs leading to study drug withdrawal, interruption and dose reduction were 5%, 23% and 10% respectively. Treatment-emergent adverse events occurring very commonly (≥ 10%) at any grade or ≥ 2% (Grade 3-4) of patients treated with alectinib in the pivotal studies were as follows:	The current safety profile of alectinib is defined by a group of 253 subjects from the target population exposed to alectinib at the recommended dose (600 mg bd) of whom just over half had CNS metastases at baseline. One hundred subjects have been exposed to alectinib for a year or longer. The median duration of exposure across all 253 subjects as at 27 April 2015 is 40.6 weeks, with a median total cumulative dose of 333600 mg. External validity of the data is good as the study population are reasonably representative of the intended target population and likely treatment settings, that is, under oncology specialist supervision. Current data is limited by both sample size and lack of control arm for comparison. Duration of exposure is comparable to durations in the crizotinib PI [23 and 43 weeks for two different trials] and ceritinib PI [33 weeks]. There is also no data for patients with severe renal impairment, although this is not a concern given the negligible renal clearance. There is no data in moderate to severe hepatic impairment, which is of probable concern given the observed risk of hepatotoxicity. Further safety information will need to be gathered during ongoing Phase III studies to improve safety knowledge. The submission of Phase III data helping to clarify the safety/efficacy profile of alectinib subsequently should be made a condition of registration. Due to the limited safety dataset, post-market safety monitoring is of elevated importance. Existing therapies provide some insight into expected safety profile with ALK inhibitors however; targeted therapies can be unpredictable in their off-target effects. Off-label use may be expected to possibly occur in patients with other cancers who have ALK+ tumours but no specific safety risk is expected. Generally the safety profile appears more tolerable than ceritinib and comparable to crizotinib however this is limited by the size of the dataset.

Adverse events (MedDRA)	Alecensa (N=253)	
System Organ Class	All Grades (%)	Grade 3-5* (%)
Fatigue a	43	1.2
Constipation	34	0
Oedema b	32	0.8
Myalgia c	29	1.2
Cough	19	0
Rash d	18	0.4
Nausea	18	0
Headache	17	0.8
Diarrhoea	16	1.2
Dyspnoea	16	3.6
Vomiting	12	0.4
Back pain	12	0
Increased weight	11	0.4
Vision disorder f	10	0

*Per Common Terminology Criteria for Adverse Events (CTCAE) version 4.0

[a] Includes fatigue and asthenia.

[b] Includes peripheral edema, edema, generalised edema, eyelid edema, and periorbital edema.

[c] Includes myalgia and musculoskeletal pain.

[d] Includes rash, maculopapular rash, acneiform dermatitis, erythema, generalized rash, papular rash, pruritic rash, and macular rash.

Risks	Strengths and Uncertainties
[f] Includes blurred vision, vitreous floaters, visual impairment, reduced visual acuity, asthenopia, and diplopia. Safety issues with alectinib appear to be: Gastrointestinal toxicity (constipation , nausea, diarrhoea and vomiting) with possible gastrointestinal perforation [0.4%] (see Clinical question 12) Interstitial lung disease [0.4% in trials, 2.2% in postmarket] (possibly irreversible see Clinical question 12) Hepatotoxicity (indicated by elevation of AST, ALT and bilirubin) [Grade 3 ALT rises in 4.8%, and AST in 3.6%] Myalgia and CPK elevation [4.6% grade 3+], possibly rhabdomyolysis (postmarket report – see Clinical question 12) Bradycardia – nonserious [7.5%] Peripheral oedema Photosensitivity [9.9%] and rash Embryofetal harm Other treatment-emergent events that should be listed in the PI as there is no control data to inform whether these can be attributed to alectinib use are: Anaemia, leukopenia, lymphopenia Elevation of blood creatinine, alkaline phosphatase and glucose Low blood sodium, potassium, phosphate and calcium Fatigue, headache Cough, dyspnoea Weight increase Back pain Vision disorder	
No dose-response relationship was seen with any adverse events on popPK analysis. The adverse events that occurred in clinical trials are generally able to be monitored for and have generally been manageable by dose reductions as described in the PI. The consequence of discontinuation of treatment is essentially the same as the risk of not treating – the options for therapy after this are limited to conventional chemotherapy (with a lower response rate), palliative radiotherapy and supportive therapies. The adverse event profile of alectinib is generally comparable to the other two ALK-targeted therapies crizotinib and ceritinib, particularly with regard to ILD (incidences of	

Risks	Strengths and Uncertainties
2% and 3.2% respectively) and hepatotoxicity (Grade 3 ALT elevation incidences of 11% and 25% respectively). Two cases of DILI [0.4%] were seen in ceritinib trials. Exceptions include: Ceritinib has significantly more severe and frequent gastrointestinal toxicity (Grade 3-4 diarrhoea, nausea and vomiting occurred in 5.3%, 5.3% and 4.6% of patients, respectively). It also caused hyperglycaemia that required dose reduction and showed pancreatic toxicity, and Grade 3 hepatic transaminase increase was much more common. Ceritinib and crizotinib both cause QT interval prolongation where alectinib does not Ceritinib and crizotinib are both P-gp substrates and unlikely to persist in the CNS There have been fatal cases of ILD with ceritinib There have been fatal cases of hepatotoxicity with crizotinib Myalgia and CPK elevation are not described in the PI for ceritinib or crizotinib.	
Of all the deaths not due to disease progression, two were considered by the investigator to be related to alectinib: one event of haemorrhage (presumed retroperitoneal) and one of intestinal perforation. Although these do not present a clear signal, gastrointestinal perforation and bleeding should be considered an important potential risk. A second case of fatal gastrointestinal perforation in addition to two other non-fatal cases, have been reported in the post-market in Japan. These require further attention (see Clinical question 12).	

First round assessment of benefit-risk balance

ALK+ locally advanced or metastatic NSCLC is a life-threatening condition associated with poor survival. The current first-line therapy for this population is a targeted ALK inhibitor, crizotinib. The target population for this submission are patients for whom crizotinib is not/no longer effective or not tolerated.

A second ALK inhibitor, ceritinib, was recently approved for treatment of this same target population on the basis of an ORR of 44% with median DOR of 7.4 months. Ceritinib is not currently supplied in Australia, however, and has an inferior safety profile to crizotinib (with dose reductions and permanent discontinuations due to adverse events occurring in around 60% and 10% of patients, respectively). Australian patients who have progressed on or are intolerant to crizotinib therefore have only one remaining treatment option:

second line chemotherapy in conjunction with supportive therapy and palliative radiotherapy.

Platinum-based chemotherapy has demonstrated ORRs of 15%-32% in unselected NSCLC and 45% in ALK+ NSCLC12 when used first-line. Second-line chemotherapy (pemetrexed or docetaxel) in patients who have already received platinum-based chemotherapy demonstrated an ORR of 20%.[36] These therapies are also associated with the usual toxicities linked with chemotherapy.

Therefore there remains an unmet need in Australia for medical treatment for patients with metastatic ALK+ NSCLC who have progressed on crizotinib.

In two early phase, single-arm trials conducted in a total of 253 patients with metastatic or locally advanced ALK+ NSCLC who had progressed on or were intolerant to crizotinib, alectinib therapy at a dose of 600 mg bid (taken after meals) led to a response in over a third of patients (44% in one trial and 38% in the other). The confidence intervals around these findings indicated that the rate of response in this population to alectinib therapy is likely to be higher than the response rate seen with second-line chemotherapy and in keeping with the response rate seen with ceritinib. Alectinib therefore could provide another treatment option in this population with a different safety profile to existing therapies (regardless of the availability of ceritinib).

The safety profile of alectinib is somewhat similar to crizotinib, with the principle features being interstitial lung disease, mild hepatotoxicity with rare events of drug induced liver injury (DILI), gastrointestinal toxicity (mainly constipation but possibly rarely intestinal perforation), embryofetal toxicity (Pregnancy category D), mild, reversible bradycardia and low red and white cell counts. Unlike crizotinib and ceritinib, the potential for drug-drug interactions is likely to be very low and no QT prolongation was seen. Unique to alectinib are clinical photosensitivity and frequent elevations of CPK and/or myalgia, although no cases consistent with rhabdomyolysis have been seen in trials. A post-market case has been reported which requires further investigation.

In addition to the differing safety profile, alectinib is different to crizotinib and ceritinib in that it is not a substrate of CNS efflux transporters P-gp. Metastasis to the CNS has been reported to be the primary site of initial treatment failure in 46% of patients with ALK+ NSCLC treated with crizotinib. Pooled data from the two pivotal trials demonstrated an ORR of 61% in patients who had a baseline measurable disease and 41% in all patients with any CNS lesions.

The response rates seen in the two submitted alectinib trials in conjunction with early data on PFS are surrogate markers that are likely to be correlated with clinical benefit in this population. However, whether overall survival or clinical outcomes are improved is yet to be demonstrated. Further uncertainty is introduced by the small population treated in the submitted pivotal trials as well as a number of questions raised throughout the dossier (Clinical questions Attachment 2) which must be addressed before registration can be recommended. Additional data on safety and efficacy is expected to be available in the near future as the data in the two pivotal studies matures and as ongoing Phase III trials of alectinib in both crizotinib-naïve (J-ALEX) and crizotinib pre-treated (ALEX) studies continue to progress.

The submitted data does not suggest that the benefit-risk balance of alectinib should be expected to be different in any particular subset of patients within the target population although no evidence is available in patients with moderate to severe hepatic impairment.

The unmet need for treatment in this population of patients is indisputable as the alternatives are limited by loss or lack of efficacy, toxicity and inaccessibility, and the

[36] UpToDate clinical reference site. Available at: www.uptodate.com

condition is life-threatening. The efficacy and safety of alectinib has been demonstrated by the sponsor sufficiently for registration to be supported, however, confirmatory data from Phase III trials, a note to the indication, addressing of outstanding clinical questions and modification of the proposed PI, Consumer Medicine Information (CMI) and Risk Management Plan (RMP) should all be conditions of registration.

The benefit-risk balance of alectinib, for the proposed usage, is favourable providing the conditions recommended are adopted.

First Round Recommendation Regarding Authorisation

Approval of Alecensa (alectinib) is recommended for the treatment of patients with ALK+ locally advanced or metastatic NSCLC who have progressed on or are intolerant to crizotinib, subject to:

- Satisfactory responses to the clinical questions outlined (see Attachment 2).
- Modification of the PI and CMI to ensure that it meets the requirements specified in the pre-submission meeting, that is, that 'the limitation of the data set is expected to be clearly made transparent to physicians and public.'
- Particularly, inclusion of a note to the indication regarding the surrogate nature of the efficacy data and a requirement that this note to the indication must accompany the indication in all reproductions and publications of any kind, including marketing.
- Further modifications of the PI and CMI if required based on the responses to clinical questions.
- Subsequent submission to the TGA of data from Phase III trials to confirm overall survival benefit and clinically meaningful benefit, with recognition that failure to show overall survival benefit or clinically meaningful benefit to patients would necessitate reconsideration of the overall benefit-risk balance of the product.
- Subsequent submission to the TGA of the findings of studies addressing the uncertain risk-benefit balance in patients with moderate to severe hepatic impairment.

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

In addition to the issues discussed under the first-round assessment of benefits:

- Dosing under fed conditions probably increases tolerability in relation to reducing the nauseating effects of SLS.
- M4 efflux by P-gp is not likely to decrease CNS efficacy enough that the extent of metabolism of alectinib to M4 would significantly affect overall CNS efficacy. This is supported by additional sensitivity analyses.
- Exclusion of PK data points appears reasonable and consistent.

- The use of corticosteroids in the study is not likely to have significantly changed efficacy outcomes.
- An ORR of 35% is a significant lower threshold based on alternative therapies for this group (second line chemoradiation). The lower limit of confidence intervals around ORRs in both the IRC and investigator assessed ORR endpoints were higher than 10 to 20% which is the historical comparator being used. Phase III data is required to confirm efficacy relative to best care.
- Exploratory CNS efficacy measurement was not likely affected greatly by the temporal separation of CNS sampling and serum sampling (which occurred in two of eight cases).
- A discordance review confirms that the IRC assessments of measurable baseline disease were discordant based on differential interpretation of images, and gives clear reasons for differing opinions. Analysis of efficacy (according to investigator) in the subgroup considered not to have measurable baseline disease by the IRC confirms that this group showed similar distributions of efficacy results to the overall study population.
- The use of corticosteroids in the study is not likely to have significantly changed CNS efficacy outcomes. Amended sensitivity analyses are supportive of this.
- Benefits to Stage IIIB patients who are not candidates for curative combined chemoradiotherapy can probably be predicted to be the same as the benefits to patients with Stage IV disease; however this point requires Delegate consideration.

Second round assessment of risks

In addition to the issues discussed under the first-round assessment of risks:

- The higher rate of low grade hepatic adverse events in Japanese trial AF-001JP is not likely to be significant.
- Assay bias is not likely to have affected the results of electrocardiogram (ECG) analysis showing no correlation between plasma concentration of alectinib and QTc.[37] This is supported by repeat analysis using adjusted values.
- Signal investigation regarding ILD suggests its incidence in the post-market is similar to that seen in the clinical studies as a collective. No specific susceptibility trend was seen on demographic analysis.
- Insufficient evidence of an association between alectinib use and gastrointestinal perforation is present in signal analysis to warrant confirmation of this signal. PI inclusion is not appropriate at this point.
- Severe myalgia and CPK elevation are a confirmed potential risk of alectinib and have been appropriately included in the PI under Precautions with appropriate dose modification instructions under Dosage and Administration.
- Risks to Stage IIIB patients who are not candidates for curative combined chemoradiotherapy can probably be predicted to be the same as the benefits to patients with Stage IV disease however this point requires Delegate consideration.
- Missed dose instructions are in keeping with appropriate risk management.

[37] 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. A lengthened QT interval (QTc) is a marker for the potential of ventricular tachyarrhythmias like torsades de pointes and a risk factor for sudden death.

- Additional safety data has been submitted by the sponsor and they propose to update rates of adverse events in the PI to match the updated data. This is accepted.

Second round assessment of benefit-risk balance

Following on from the benefit-risk balance assessment described in the first round evaluation, satisfactory responses to the Clinical questions have been received.

The response rates seen in the pivotal trials for alectinib, including the uncertainty around these rates, support its efficacy compared to the only other alternatives available to this population (second-line chemotherapy and ceritinib). The safety profile of alectinib is different to the alternatives and arguably better. In addition to the differing safety profile, alectinib shows surrogate evidence of CNS efficacy.

The small population studied in the pivotal trials and the surrogate nature of efficacy endpoints do introduce uncertainty and overall survival or direct evidence of clinical benefit has not yet been clearly shown. There is, however, indisputable unmet need for treatment in this population of patients, as survival remains poor and treatment alternatives are limited by loss or lack of efficacy, toxicity and inaccessibility. The efficacy and safety of alectinib has been demonstrated by the sponsor sufficiently for registration to be supported, however, confirmatory data from Phase III trials and hepatic safety study should be conditions of registration.

The benefit-risk balance of alectinib, for the proposed usage, remains favourable as per the first round evaluation, subject to the conditions recommended in the first round evaluation.

Second round recommendation regarding authorisation

Approval of Alecensa (alectinib) is recommended *for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive, metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib*.

Whether the indication should be amended to include locally advanced disease, plus or minus specification that this must be in the situation where a patient is not amenable to curative combined modality therapy should be considered by the Delegate. Alternative wording of the indication may be for example:

> *…for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive, locally advanced or metastatic non-small cell lung cancer (NSCLC) who are not candidates for curative chemoradiotherapy, and have progressed on or are intolerant to crizotinib.*

Conditions of approval should include:

- The note to the indication (regarding the surrogate nature of the efficacy data) must accompany the indication in all reproductions and publications of any kind, including marketing.
- The CMI currently does not sufficiently reflect the PI and should be modified to include a lay warning of the same nature.
- Data from Phase III trials to confirm overall survival benefit and clinically meaningful benefit must be submitted to the TGA when available. The timeframe within which this data should be required should be the end of 2017, in keeping with the predicted availability of a clinical report for the ALEX trial (third quarter of 2017). The sponsor must recognise that failure to show overall survival benefit or clinically meaningful benefit to patients would necessitate reconsideration of the overall benefit-risk balance of the product.

- The findings of studies addressing the risk-benefit balance in patients with moderate to severe hepatic impairment must be submitted to the TGA when available.

V. Pharmacovigilance findings

Risk management plan

Evaluation summary

- Roche Products Pty Ltd has submitted EU-RMP version 1 (17 August 2015; Data Lock Point (DLP) 31 August 2015) and ASA version 1 (March 2016) in support of this application. In its response to the first round RMP evaluation, the sponsor submitted EU RMP version 1.1 (dated 6 July 2016; DLP 4 July 2016) and ASA version 1.1 (dated October 2016).
- The proposed Summary of Safety Concerns and their associated risk monitoring and mitigation strategies are summarised below (Table 12), with the changes made in version 1.1 of the EU RMP highlighted and indicated as strikethrough (deletions) and bolding (additions).

Table 12: Summary of ongoing safety concerns

R=routine and A=additional

Summary of safety concerns[38]		Pharmacovigilance		Risk Minimisation	
		R	A	R	A
Important identified risks	Interstitial lung disease/pneumonitis	ü	ü	ü	–
	~~Increases in specific liver Enzymes (Bilirubin and hepatic transaminase elevations)~~ Hepatotoxicity	ü	ü	ü	–
	Photosensitivity	ü	ü	ü	–
	Bradycardia	ü	ü	ü	–
	Severe myalgia and CPK elevations	ü	ü	ü	–
Important potential risks	Embryo-fetal toxicity	ü	–	ü	–

[38] *Routine risk minimisation activities* may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:
- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Summary of safety concerns[38]		Pharmacovigilance		Risk Minimisation	
Missing information	Long-term safety	ü	ü	ü	–
	Treatment in pregnant and lactating women	ü	–	ü	–
	Treatment in patients with moderate or severe liver impairment	ü	ü	ü	–
	Treatment in patients with severe renal impairment	ü	–	ü	–

- Risk minimisation activities are restricted to routine measures of product information, consumer medicine information and product labelling.
- Study NP29783 is an additional pharmacovigilance study in the EU-RMP and is also proposed for Australia for the safety concern 'Treatment in patients with moderate or severe liver impairment'.
- The pharmacovigilance activity of 'data collection in study BO28984' is not an additional requirement in the EU-RMP. This pharmacovigilance activity has been added to the ASA as an outcome following the Pre-Submission meeting held with TGA and will address the following safety concerns: interstitial lung disease/pneumonitis; hepatotoxicity; severe myalgia and CPK elevations; photosensitivity; bradycardia and long term safety.

New and outstanding recommendations second round evaluation

There are no outstanding recommendations from the first round RMP evaluation.

From the second round clinical evaluation:

The sponsor should consider and provide a response to the clinical evaluator's recommendation regarding the provision of a wallet sized patient information card as an additional risk minimisation activity.

Wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system. The suggested wording is:

> Implement EU-RMP (version 1.1, dated 6 July 2016; DLP 4 July 2016) with Australian Specific Annex (version 1.1, dated October 2016) and any future updates as a condition of registration.

VI. Overall conclusion and risk/benefit assessment

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

Quality

No significant issues were identified and approval was recommended from a chemistry and quality perspective.

Nonclinical

There were no objections to registration of alectinib for the proposed indication.

There were interesting suggestions of CNS activity for alectinib in nonclinical settings and evidence was discussed that alectinib crosses the intact blood-brain barrier.

The evaluator described nonclinical evidence about interactions:

… alectinib and M4 do not undergo human active hepatic uptake and alectinib is not expected to alter exposures to CYP450 substrates. However, pharmacokinetic drug interactions involving P-gp and BCRP transporters are predicted based on alectinib and M4 inhibition of intestinal P-gp/BCRP following a therapeutic dose and M4 as a substrate of P-gp. CYP3A4 is the major enzyme in the metabolism of alectinib and M4, suggested potential interactions with CYP3A inhibitors or inducers. However, in clinical studies, a strong CYP3A4 inducer (rifampicin) and an inhibitor (posaconazole) had minor impacts on the exposures of alectinib and its major active metabolite, M4.

Of note regarding toxicity:

In general, the toxicity profile showed similarity to other ALK receptor tyrosine kinases (eg, crizotinib and ceritinib). Additional major organs for toxicity not seen with crizotinib and ceritinib included the adrenal gland, male reproductive organs in both species and teeth in rats only.

Phototoxicity on sun-exposed skin was predicted based on an in vitro assay.

Special mention was made of the excipient sodium lauryl sulphate, SLS: '*The concentration of SLS in the alectinib formulation is many folds higher than the levels present in approved pharmaceutical products.*' However, it was concluded that SLS in the formulation '*is not expected to cause local irritation of the GIT*'. There was a small safety margin for systemic effects of SLS (predicted to be hepatic effects). In conclusion, the evaluator considered the small margin acceptable but encouraged Roche to seek an alternative excipient to replace SLS.

Pregnancy category

The sponsor initially proposed Category X. Category D was recommended for alectinib by the evaluator who noted:

…alectinib caused embryofetal lethality in rats and rabbits, visceral and skeletal anomalies (dilated ureter, thymic cord, small ventricle, thin ventricle wall and decreased number of sacral and caudal vertebrae) in rats, and visceral malformation (retro-oesophageal subclavian) and skeletal variations (increase in full supernumerary fibs and decrease in short supernumerary ribs) in rabbits. The other two ALK inhibitors, crizotinib and ceritinib with similar embryofetal toxicity at exposures below the clinical exposure, have a pregnancy category D.

The sponsor has revised its proposal to Category D.

Clinical

The clinical evaluator writes:

Approval of Alecensa (alectinib) is recommended for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive, metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.

Whether the indication should be amended to include locally advanced disease, plus or minus specification that this must be in the situation where a patient is not amenable to curative combined modality therapy, should be considered by the Delegate…

Conditions of registration were also suggested, including a note to the indication (which had already been proposed by the sponsor).

Pharmacology

Pharmacology data are well described in the clinical evaluation (see Attachment 2). Key issues include:

- Low solubility, requiring inclusion of SLS in the formulation; SLS is a known GI irritant (non-clinical data did not point to a major role of SLS in alectinib's GI toxicity.
- A food effect; with 2 to 4 fold increased alectinib bioavailability with administration after a meal, at least after a single dose.
- An apparent affinity for blood cells.
- Metabolism mediated in part by CYP3A4; no dedicated study in patients with hepatic impairment, although one is planned. Studies of alectinib's interaction with posaconazole and rifampin are consistent with the prominent role of CYP3A4 in metabolism.
- The main human metabolite M4 is active and expected to contribute to in vivo pharmacological activity. It is also a P-gp substrate.
- Higher clearance / lower exposure with increasing body weight (justification for a fixed dose detailed in Attachment 2).
- Possibly higher exposure in Japanese subjects, confounded by lower weight in those subjects.

The Delegate agrees with the clinical evaluator that PK has been adequately profiled. It is noted that '*interaction with CYP3A inhibitors or inducers is not expected to be clinically relevant*' but there is some basis to explore the relevance of higher alectinib AUC with strong inhibition, and lower AUC with induction (or at the least to adequately communicate in the PI the DDI study outcomes).

Efficacy

Study NP28673 and Study NP28761 in patients who had progressed on crizotinib were considered pivotal. The first-in-human study AF001-JP in crizotinib-naïve patients, using a lower dose, in Japanese subjects, was considered supportive. The Phase III Japanese study J-ALEX was supplied in summary form and used a 300 mg bid dose and is therefore not considered pivotal.

The sponsor has provided substantially updated efficacy data for the two pivotal studies in a Clinical Overview Addendum (not a Clinical Study Report). The clinical evaluator argues that given the early nature of data in this submission, prescribers should have access to the updated data. The Delegate agrees. However, the formally evaluated (initially reported) outcomes are described below, except where there are significant differences (for example, in duration of response (DoR) and overall survival (OS) outcomes).

The sponsor's response explaining accuracy of figures in the proposed PI related to these updated data is acknowledged.

Study NP28673

Study NP28673 was a single arm study. Patients had progressed on crizotinib. Alectinib 600 mg bid was used. 138 patients were treated; the 37 screen failures were often due to symptomatic brain or leptomeningeal metastases, screening outside the window and Eastern Cooperative Oncology Group (ECOG) performance score >2[39].

Data cut-off for the primary analysis was 17 August 2014, although an 8 January 2015 cut-off was also referenced. Mean duration of follow-up was 30 weeks (range, 2-53). (In the Clinical Overview Addendum, the cut-off was 1 February 2016, with mean duration of follow-up of 17.6 months, that is, 76 weeks which is considerably longer.)

Mean age was 51.5 years (range 22-79 years); 56% were female; 26% were Asian and 67% Caucasian; 70% were non-smokers. 98.6% were Stage IV on enrolment, and 1.4% were Stage IIIB; 96.4% had adenocarcinoma (the few others had adenosquamous or large cell histology); 3/114 were EGFR mutation positive; fluorescence in situ hybridization (FISH) was used in 88% for ALK status testing; median time from diagnosis to first study treatment was 106 weeks (range 15-493 weeks).

As well as having previously used crizotinib, 77% had received a platinum-based therapy; 71% had received an antimetabolite, typically pemetrexed. Median time on crizotinib was 12 months (range 0.03 to 47 months) and median time since last dose of crizotinib until start of alectinib was 15 days (range 7 to 676). 54% had a PR and 22% had stable disease as best response to crizotinib.

Although 138 patients were treated, the sponsor considered that n=16 did not have measurable disease at baseline according to the independent review committee (IRC) so only 122 patients were included in the IRC response evaluable population. However, these 16 did have measurable disease according to the investigator (or else they could not have enrolled; an inclusion criterion was presence of measurable disease).

ORR was 49.2% (95% CI 40.0-58.4%) by independent radiology review (IRC) in n=122 patients in the IRC response evaluable population, and 43.8% (95% CI 33.6-54.3%) in those who had earlier received chemotherapy (these were co-primary outcomes). The clinical evaluation (Attachment 2) summarises ORR by subgroup, with no major variations observed. Median duration of response was 11.2 months using the data cut-off of 8 January 2015. PFS and OS outcomes were immature; estimated median PFS was 7.5 months based on 61 events in 138 patients, while estimated median OS was 12 months, again considered unreliable given only 17% of subjects had died.

In the sponsor's Clinical Overview Addendum, ORR was similar but median duration of response was updated to 15.2 months. Median OS was estimated to be 26 months.

ECOG Performance Status

Developed by the Eastern Cooperative Oncology Group, Robert L. Comis, MD, Group Chair.*

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

*Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5:649-655.

39 *Am J Clin Oncol.* 1982;5:649-655.

34 had measurable CNS disease at baseline and of these, 56% had a CNS response. CNS response rate in those with either measurable (n=34) or non-measurable (n=49) CNS lesions at baseline was 38.6%.

Study NP28761

This was a single arm study. Patients had progressed on crizotinib (inclusions and exclusions were as per Study NP28673). The focus here is on patients treated with an initial 600 mg bid dose, though there was a dose escalation phase. In Phase II, 87 patients were enrolled (the 38 screening failures were most commonly due to inadequate renal function, negative ALK and brain or leptomeningeal metastases that were symptomatic or required treatment).

The data cut-off date for primary analysis was 24 October 2014. This provided a mean duration of follow-up of 23.2 weeks (range, 5-59 weeks). The cut-off in the sponsor's Clinical Overview Addendum was 22 January 2016 (mean follow-up, 14.1 months = 61 weeks).

In the 87 Phase II patients, mean age was 54 years (range 29-79 years); 55% were female; 84% were Caucasian; 62% were non-smokers. 96.6% had metastatic disease; 1 had Stage IIIB and 2 had recurrent disease. 94.3% had adenocarcinoma; n=5 had other histologies (including one with squamous cell carcinoma).

All had received crizotinib; 70% had also received a platinum-based chemotherapy and 58% had received pemetrexed; 73% had received 3+ regimens for metastatic disease before this study. Median time on crizotinib was 12 months (range, 0.5-53 months) and median time since last dose until alectinib was 15 days. Best outcome on crizotinib was CR in one case, PR in 32%, SD in 25% and PD in 31%.

ORR was 47.8% (95% CI 35.6-60.2%) as assessed by IRC in the response evaluable population (n=69). All responses were partial. ORR was 46% as assessed by the investigator in the investigator RE population (n=87). Results in tested subgroups were broadly similar, although those with ECOG PS = 0 did better than those with PS = 1-2[39] (ORR 64% versus 33-40%), and 'never smokers' did better than past smokers (56% versus 36%). Given higher exposure with lower body weight, it is notable that lighter subjects (weight < median) did better than heavier subjects (54% versus 41%), though the difference was not pronounced, and in NP28673 this subgroup was not reported. Median duration of response was 7.5 months. There was no indication of any large change in health-related quality of life, based on symptom assessment. Median PFS was 8.5 months; 6 month OS rate was 86%; median OS was not attained, only 14% of patients having died.

In the sponsor's Clinical Overview Addendum, the ORR was similar but the median duration of response was now 14.9 months. Median OS was estimated to be 22.7 months.

16 had measurable CNS lesions at baseline and CNS response rate here was 69%, falling to 46% based on Response Assessment in Neuro-Oncology Criteria (RANO) (not RECIST) criteria, and to 38.5% by RECIST across the n=52 with measurable or non-measurable CNS lesions.

Study AF001-JP

This supportive study was in crizotinib naïve NSCLC patients but used 300 mg bid (primarily) and was conducted in Japan. In n=46 patients, IRC-evaluated ORR was high at 93.5% and there were 7 CRs.

Study J-ALEX (JO28928)

Results of a pre-planned interim analysis of this Phase III study were included in the sponsor's Clinical Overview Addendum. The evaluator writes: '*new efficacy data and data from the J-ALEX trial are not appropriate for inclusion in the current PI during the current submission process, but are supportive of registration.*'

J-ALEX was an open-label, randomised Phase III study of alectinib versus crizotinib in ALK inhibitor –naïve subjects from Japan who may have received one prior line of chemotherapy for ALK positive NSCLC. Below is a snapshot of outcomes, which seem promising. However, J-ALEX, as with AF001JP, used a dose of 300 mg bd. The sponsor notes that results in the crizotinib arm are comparable to those in Study PROFILE 1014 for crizotinib (a global study), supporting extrapolation from the Japanese population but differences in dosing detract from generalisability.

Snapshot of data from J-ALEX

J-ALEX was an open label, randomised Phase III study of alectinib versus crizotinib in ALK inhibitor naïve subjects from Japan who may have received up to 1 prior chemotherapy treatment for ALK positive NSCLC. At the pre-planned interim analysis, 50% of PFS events had occurred. Median duration of follow-up was 12 months in each arm. There were n=104 in the crizotinib arm and n=103 in the alectinib arm (intent-to-treat (ITT) population). Patients were generally older than in NP28673 and NP28761, with a median age of 60-61 years across arms. Virtually all patients had adenocarcinoma; about a quarter of patients had recurrence rather than metastatic disease; 36% of patients had 1 previous line of chemotherapy. 28% (crizotinib) versus 14% (alectinib) had brain metastases at baseline, according to IRF assessment.

There were some fairly stark differences across arms in disposition (Table 13).

Table 13: Patients withdrawn from treatment by any reason

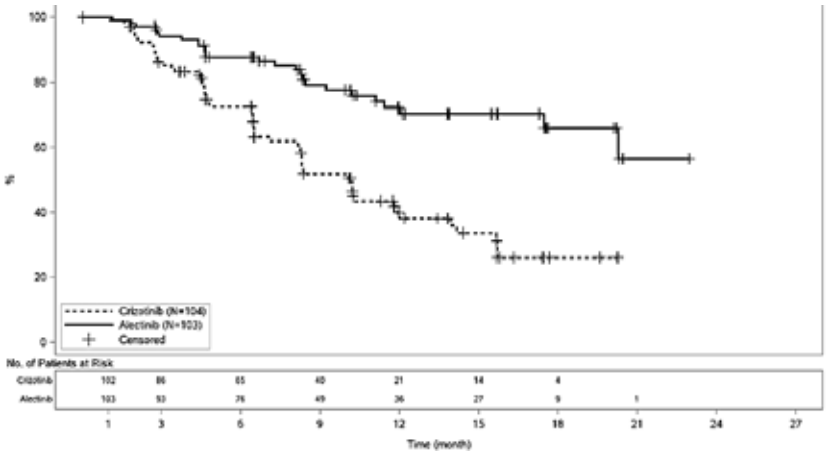
Patients Withdrawn from Treatment by Any Reason
Protocol: JO28928
Analysis: Intention to Treat

Status	Crizotinib (N=104)	Alectinib (N=103)
Discontinued treatment	61 (58.7%)	24 (23.3%)
ADVERSE EVENT	21 (20.2%)	9 (8.7%)
LACK OF EFFICACY	32 (30.8%)	14 (13.6%)
WITHDRAWAL BY SUBJECT	4 (3.8%)	0
OTHER	4 (3.8%)	1 (1.0%)

Percentages are based on N in the column headings.

PFS based on IRF evaluation was significantly longer in the alectinib arm than the crizotinib arm (HR 0.34, 95% CI 0.17-0.71; median PFS not estimated for alectinib, 10.2 months for crizotinib) (Figure 6).

Figure 6: Kaplan-Meier Progression free survival (ITT)



PFS did not vary much in first line (1L) versus second line (2L) patients and varied modestly in Stage IIIB/IV (PFS HR 0.31) versus recurrent (PFS HR 0.49) patients.

Despite an imbalance in baseline CNS metastases, there were interesting outcomes for PFS in this regard: PFS HR in patients with baseline brain metastasis was 0.08 (95% CI 0.01-0.61), and in patients without baseline brain metastasis, 0.39 (95% CI 0.23-0.64).

ORR (IRF) was higher for alectinib patients (91.6% versus 78.9%).

However, OS data are immature:

Only 2 patients in the crizotinib arm (1.9%) and 7 patients in the alectinib arm (6.8%) had died at the data cut off. All these patients died due to disease progression.

The following table from the sponsor's Clinical Overview Addendum summarises safety.

Table 14: Summary of safety findings

	Crizotinib (N=104)	Alectinib (N=103)
Total number of patients with at least one adverse event	104 (100.0%)	100 (97.1%)
Total number of events	1278	590
Total number of deaths	2 (1.9%)	7 (6.8%)
Total number of patients withdrawn from study due to an AE	59 (56.7%)	24 (23.3%)
Total number of patients with at least one		
AE with fatal outcome	0	0
Serious AE	27 (26.0%)	15 (14.6%)
Serious AE leading to withdrawal from treatment	12 (11.5%)	7 (6.8%)
Related Serious AE	24 (23.1%)	10 (9.7%)
AE leading to withdrawal from treatment	21 (20.2%)	9 (8.7%)
Related AE	104 (100.0%)	91 (88.3%)
Related AE leading to withdrawal from treatment	21 (20.2%)	9 (8.7%)
Grade 3,4,5 AE	54 (51.9%)	27 (26.2%)
AE leading to dose interruption	63 (60.6%)	25 (24.3%)
Medical concepts: patients with		
Interstitial Lung Disease	8 (7.7%)	8 (7.8%)
Hepatic function disorder	45 (43.3%)	22 (21.4%)
Haematopoietic Leukopenia	20 (19.2%)	10 (9.7%)
Bradycardia	23 (22.1%)	11 (10.7%)
QT Prolongation	15 (14.4%)	4 (3.9%)
Visual Disorders	78 (75.0%)	9 (8.7%)
Gastrointestinal Perforation	1 (1.0%)	0
Thromboembolism	5 (4.8%)	2 (1.9%)
Photosensitivity	23 (22.1%)	19 (18.4%)
Neuropathy	8 (7.7%)	6 (5.8%)
Oedema	24 (23.1%)	11 (10.7%)
Renal Cyst	3 (2.9%)	0
Cardiac failure	22 (21.2%)	11 (10.7%)
Severe Myalgia and Creatine Phosphokinase Elevation	21 (20.2%)	36 (35.0%)

Percentages are based on N in the column headings.
Investigator text for AEs encoded using MedDRA version 16.1.
Multiple occurrences of the same AE in one individual are counted only once except for 'Total number of events' row in which multiple occurrences of the same AE are counted separately.

Common AEs also differed by treatment as shown in the table below.

Table 15: Common adverse events

MedDRA System Organ Class MedDRA Preferred Term	Crizotinib (N=104)	Alectinib (N=103)
Nausea	77 (74.0%)	11 (10.7%)
Diarrhoea	76 (73.1%)	9 (8.7%)
Vomiting	60 (57.7%)	6 (5.8%)
Visual impairment	57 (54.8%)	1 (1.0%)
Dysgeusia	54 (51.9%)	19 (18.4%)
Constipation	46 (44.2%)	36 (35.0%)
Alanine aminotransferase increased	33 (31.7%)	9 (8.7%)
Aspartate aminotransferase increased	32 (30.8%)	11 (10.7%)
Nasopharyngitis	24 (23.1%)	21 (20.4%)
Pyrexia	21 (20.2%)	10 (9.7%)
Decreased appetite	21 (20.2%)	1 (1.0%)

Percentages are based on N in the column headings.
Investigator text for AEs encoded using MedDRA version 16.1.
Multiple occurrences of the same AE in one individual are counted only once.

Of interest, the evaluator states that a preliminary view of the J-ALEX data suggest alectinib has:

> *…a lower rate than crizotinib for most adverse events, significant exceptions being CPK elevation and severe myalgia (35% alectinib versus 20% crizotinib) and ILD (6% alectinib versus 5% crizotinib). Very significant differences in the rates of nausea and vomiting are noted, with rates of 11% and 6% (respectively) in the*

alectinib arm (n=103) compared to 74% and 58% with the crizotinib comparator (n=104).

Safety

The safety analyses considered by the evaluator include ECG report 1060441 and 90 day safety update RO5424802. The latter with a cut-off date of 27 April 2015. The clinical evaluator emphasised this report. Notably, the proportion in each pivotal study that had died by that date rose: in NP28673, from 17.4% to 31.9%; in NP28761, from 13.8% to 27.6%.

Exposure

Exposure is clearly described in Attachment 2. Of note:

In the pivotal trials (including the midazolam substudy [15 patients] and the 600 mg cohort of Phase I of Study NP28761 [13 patients]), there were a total of 253 patients exposed to alectinib at the recommended dose of 600 mg bd, with a median duration of exposure of 40.6 weeks (range 0.1-114 weeks) up to the cut-off date.

90 day safety report 'Group 3' (n=253)

In this key group, Grade 3-5 AEs were experienced in 34% of patients; serious AEs were reported in 19.4% (and alectinib-related SAEs in 5.5%); AEs leading to discontinuation were reported in 5.9%.

Selected adverse effects

Constipation

This was a prominent AE, reported in 33 to 36% in pivotal studies whereas diarrhoea was reported in 10 to 18%.

Intestinal perforation was reported. In one case a fatality which was considered drug-related (see also the three patients with GI perforations noted in the post-market setting in Attachment 2).

The sponsor argues that '*estimated incidence of GI perforation did not exceed the incidence that was expected in patients with metastatic lung cancer*'. It appears from examination that in none of the 9 cases under discussion was there a history of GI metastases. A commonality was history of diverticulitis or diverticulosis, often overlapping with systemic corticosteroid use (both known risk factors for perforation). In the setting of a drug associated with constipation, perforation has not been ruled out as a rare drug-induced toxicity.

Question 2 for sponsor

Did any of the 9 patients with intestinal perforation under discussion have documented GI metastases at the site of or distal to the perforation?

Fatigue

This was a prominent AE, reported in 26 to 30% (along with asthenia in 18%) in pivotal studies.

Peripheral oedema

This was a prominent AE, reported in 22-25% in pivotal studies. Weight gain was also observed; potentially these two events are related.

Question 3 for sponsor

Is a particular mechanism implicated in alectinib related oedema?

Myalgia and CPK elevation

This was a prominent AE, reported in 22 to 23% in pivotal studies; muscular AEs or creatine phosphokinase (CPK) elevation were reported in 56%.

In NP28761, CPK elevation was reported in 21% but in only 3% in NP28673.

Given the co-occurrence of myalgia and CPK elevation, alectinib must be considered to have the potential to cause rhabdomyolysis until proven otherwise.

Question 4 for sponsor

It is noted that of 90 patients with muscular AEs, 29 had concomitantly increased CPK. Did any of these patients have worsening renal function after onset of CPK elevation? Also, was there any interaction with other drugs known to cause myalgia or myositis?

Rash and photosensitivity

Rash (5-12%) and photosensitivity (9-10%) were reported in pivotal studies. No erythema multiforme, SJS, DRESS or TEN cases were seen.

Liver function

A summary of findings is included on Attachment 2. While no cases of hepatic failure were identified, one case of drug-induced liver injury is described.

In NP28673, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) increases were seen in 10 to 12% of subjects; in NP28761, ALT and AST increases were 18 to 21%. Increased blood bilirubin was also common (7-9%); and was reported in 30 to 35% in Step 2 of AF-001JP. There were 3 reports of hyperbilirubinaemia as an SAE (amongst n=253) in the 90 day safety update.

Anaemia

Alectinib and the M4 metabolite are distributed into red blood cells. The nonclinical evaluator states in a description of toxicity findings:

> *Findings included increases in reticulocytes, mild decreases in haemoglobin, haemocrit and/or red blood cells, abnormal red blood cell morphology including anisocytosis and poikilocytosis (burr cells, fragmented red cells), and polychromatic and immature erythrocytes. The mild anaemia was probably due to a direct effect of alectinib on RBC or haemorrhage since bone marrow smears showed no abnormalities except for decreased haemotopoietic cells in a single monkey at 60 mg/kg/day…*

In pivotal studies, anaemia was commonly reported (14%).

Question 5 for sponsor

Is there evidence establishing that alectinib can cause red cell destruction? Did any patients have anaemia and signs of haemolysis, for example, LDH, haptoglobin changes? Could any (indirect) bilirubin elevation be attributed to haemolysis?

Bradycardia

Alectinib causes bradycardia with a median decrease of 11.6 beats per minute (bpm) at Week 2. Symptomatic events were relatively uncommon but falls in conjunction with dizziness were reported.

Questions 6 and 7 for sponsor

Please confirm that none of the patients who fell after dizziness hurt themselves or if there were injuries arising in this way, please explain why such events were not considered serious in the context of a drug that causes bradycardia.

Was there any indication of additive or synergistic effects on heart rate in subjects concomitantly taking medicines known to slow heart rate, for example, beta blockers?

Vision disorders

17% reported vision disorders which included reduced acuity. The only 'severe' AE was retinal detachment which was not considered drug-related.

Pneumonitis

Though pneumonitis was not prominent in clinical studies, it is a known class effect and there were 14 reports of interstitial lung disease in Japanese patients in the post-market setting. This AE is assessed in a signal analysis (see Attachment 2), with 44 Japanese cases (1.6% of 2679 patients exposed) and 4 cases in the USA (0.6% of 651 patients exposed). In J-ALEX and ALEX, cases were identified although no fatalities were reported. In clinical trials, compared to post-marketing use, treatment discontinuation was more likely when pneumonitis was diagnosed.

Risk Management Plan evaluation

There were no objections to registration from the RMP evaluator.

Recommended condition of registration

The following should be a condition of registration:

- Implement EU-RMP (version 1.1, dated 6 July 2016; DLP 4 July 2016) with Australian Specific Annex (version 1.1, dated October 2016) and any future updates as a condition of registration.

The Delegate agrees with the clinical evaluator that a patient information card would be useful, given that alectinib belongs to a fairly novel class of agents and that it appears to have distinct toxicities (for example, more myalgia and CPK elevation than crizotinib, based on early data from J-ALEX).

Risk-benefit analysis

Delegate's considerations

Issues

Efficacy

Standard of care in ALK positive NSCLC on progression with (or intolerance to) crizotinib

Ceritinib is registered but is not PBS listed so it is not a well-established standard of care in Australia. Nivolumab was recently approved for use in 2L NSCLC but evidence for efficacy in ALK+ disease is limited and it too is not PBS-listed for this use (as of 19 December 2016). Therefore, if platinum-based doublet therapy has not been trialled in a given patient, that may be considered standard of care or pemetrexed (since most patients have adenocarcinoma histology). Palliative radiotherapy and/or supportive care are other options.

Question 1 for ACM

The ACM is asked to comment on 'standard of care' approaches in Australia for patients with ALK+ NSCLC who have failed (or are intolerant to) crizotinib.

General comments about efficacy

Pivotal studies for alectinib were NP28673 and NP28761. These were single arm studies using objective response rate as the primary endpoint. This suggests the need for clear communication with clinicians and patients about the evidence base supporting approval. The sponsor proposes to include an explanatory note as part of the indication:

> *This indication is approved based on tumour response rates and duration of response. An improvement in survival or disease-related symptoms has not been established.*

Updated outcomes using a first quarter 2016 data cut-off support the view that ORR, in this case, will translate into a meaningful survival benefit, though it is difficult to gauge a survival benefit over standard of care when standard of care is not clearly defined and when cross-study comparison is required.

Study BO28984 (ALEX) will provide more robust evidence of alectinib's efficacy and safety in ALK+ NSCLC patients, although ALEX is designed to support use as an earlier line of therapy (1L targeted therapy).

In the absence of a conditional approval pathway, standard approval based on the 'totality of evidence' in the sponsor's dossier is considered preferable to awaiting outcomes from ALEX.

Question 2 for ACM

Does the ACM support registration of alectinib based on evidence from single-arm studies where overall response rate was the primary efficacy endpoint (or at least, based on the totality of evidence presented here)?

Safety

General comments about safety

Toxicity appears manageable, although some common AEs have the potential to impact on quality of life (for example, constipation, fatigue, myalgia and photosensitivity). A few specific issues are worth drawing to the committee's attention:

- In the setting of a drug associated with constipation, perforation has not been ruled out as a rare drug-induced toxicity.
- Given the co-occurrence of myalgia and CPK elevation, alectinib must be considered to have the potential to cause rhabdomyolysis until proven otherwise.
- Symptomatic bradycardia was uncommon but falls in conjunction with dizziness were reported.

Early data from J-ALEX do not raise concerns that alectinib has worse toxicity than crizotinib. The generalisability of J-ALEX is discussed below.

Question 3 for ACM

Does the ACM consider safety of alectinib in the proposed use is sufficiently well characterised and communicated in the PI?

Planned or ongoing studies

The sponsor has stated:

> The Phase III global Study BO28984 (ALEX) completed recruitment of patients in January 2016. The primary analysis is expected to occur in Q2 2017 when the required number of progression-free survival events is achieved and the Clinical Study Report is expected to become available in Q3 2017.

According to clinicaltrials.gov, ALEX is a Phase III study randomising patients with advanced or recurrent (Stage IIIB not amenable for multimodality treatment) or metastatic (Stage IV) NSCLC that is ALK positive to either 600 mg bid alectinib, or 250 mg bid crizotinib; the primary endpoint is investigator-assessed PFS.

It should be a condition of approval that the TGA is kept informed about any major changes to the estimated clinical study report (CSR) availability date, and that the CSR is included in Category 1 submissions to the TGA when interim and final analyses are written up. The same recommendation is made for J-ALEX.

Clinicaltrials.gov also lists NCT02838420, a trial of 600 mg bid alectinib versus 250 mg bid crizotinib in Asian patients with treatment-naïve ALK+ advanced NSCLC.

Question 8 for sponsor

Please provide a status update for NCT02838420, and a CSR availability date.

Study NP29783 will provide information about use in patients with moderate or severe liver impairment.

Overall risk-benefit and indication

The currently proposed indication is:

> *Alecensa is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive, locally advanced or metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.*
>
> *Note to Indication: This indication is approved based on tumour response rates and duration of response. An improvement in survival or disease-related symptoms has not been established.*

NSCLC other than adenocarcinoma

The proposed indication endorses use in patients with any histology, although the large majority of patients in pivotal studies had adenocarcinoma.

Question 9 for sponsor

Although only a few patients in pivotal studies had non-adenocarcinoma NSCLC, it is relevant to understand individual responses. Please list these patients' efficacy outcomes, so inadequate efficacy in non-adenocarcinoma patients can be ruled out.

Locally advanced disease

This is discussed in Attachment 2. Almost all patients in pivotal studies had metastatic disease. The US indication is limited to metastatic disease. However, a quarter of patients in J-ALEX had 'only' locally recurrent disease and alectinib seemed to offer an overall advantage versus crizotinib in that particular trial, that is, efficacy is not limited to metastatic disease. The Delegate's preliminary view is that an indication encompassing locally advanced disease is appropriate but the ACM's advice will be influential.

Question 4 for ACM

Should the indication include patients with locally advanced disease, or only those with metastatic (Stage IV) disease?

Patients intolerant to crizotinib

Refer to discussion in Attachment 2. Given the suggestion of a different toxicity profile compared to crizotinib (from J-ALEX; see Snap-shot above), it is reasonable to allow use of alectinib in patients who are intolerant to crizotinib.

Line of therapy in patients with CNS lesions

J-ALEX data suggested good outcomes for alectinib in patients with CNS lesions versus crizotinib. In patients with CNS lesions at baseline, PFS HR was 0.08 (95% CI 0.01-0.61). One approach would be to endorse first-line use of alectinib in patients with baseline CNS metastases, at least if lesions were asymptomatic. However:

- The sponsor has not requested any such indication.
- Second-line use itself is supported only by early, uncontrolled data.
- The CSR for J-ALEX has not been presented for evaluation; only a top-level summary of the study was submitted, within a Clinical Overview Addendum (after the first round evaluation round). For example, it is unclear how quickly alectinib exerts its effects, and it is also unclear whether in J-ALEX patients with symptomatic CNS lesions were studied. Many relevant details are unavailable.
- J-ALEX was in a Japanese population and dosing was 300 mg bid (half the dose proposed for registration here). The sponsor notes that 600 mg bid dosing in non-Japanese results in exposures only about 32 to 39% above those attained in Japanese patients on 300 mg bd.
- The J-ALEX outcomes are impressive, for example, in terms of ORR and PFS but are not accompanied by mature OS outcomes (at this stage, 7% of alectinib subjects versus 2% of crizotinib had died, all ostensibly due to disease progression).
- The limited information about comparative safety in J-ALEX also pointed to a better safety profile with alectinib versus crizotinib, but similar caveats apply to the interpretation of these data.
- There was an imbalance despite randomisation in the number of patients in J-ALEX with baseline brain metastases, which at the very least reduces sample size in the alectinib arm (and may make meaningful imbalances in prognostic factors in this subgroup more likely).
- The sponsor notes similarity in crizotinib PFS outcomes in J-ALEX relative to crizotinib Study 1014 and argues that this suggests Japanese ethnicity does not confound assessment. However, it is difficult to escape the view that Japanese patients do better on alectinib than patients elsewhere. For example, in AF001-JP, again using 300 mg bid in Japanese patients, results were highly impressive with an ORR of 93.5% including 7 CRs. Such ORRs including CRs were not seen in Studies NP28673 and NP28761.
- The Phase III ALEX study will read out around the third quarter of 2017 and a CSR for the study will be available 1-2 quarters later.

Notably, Shaw and Solomon in Up-To-Date favour the use of alectinib in patients with newly diagnosed, ALK+ NSCLC who present with CNS disease.

Question 5 to ACM

Should consideration be given to indicating use in patients with asymptomatic CNS lesions who have not previously received treatment for advanced NSCLC? Or, is it appropriate to await robust characterisation of efficacy versus crizotinib in patients with CNS lesions?

Question 10 to sponsor

In J-ALEX, median age was 60-61 years, higher than in NP28673 and NP28761. Are the characteristics of ALK positive NSCLC in Japan considered similar to those in Australia and Western populations? Are there known demographic, genetic (for example, EML4-ALK variant) or pathobiological differences in ALK+ NSCLC between Japanese and other populations? Are responses to traditional chemotherapies comparable across these regions in ALK positive patients?

Summary of issues

In NSCLC patients with ALK mutant tumours (approximately 4% of unselected NSCLC patients), crizotinib is PBS-funded for Stage IIIB or Stage IV NSCLC. Resistance to crizotinib generally develops within a few years. The sponsor of alectinib has studied use in NSCLC patients with ALK mutant tumours who have progressed on crizotinib but head-to-head studies against crizotinib are underway.

Pivotal studies for alectinib were NP28673 and NP28761. These were single arm studies using objective response rate as the primary endpoint. This suggests the need for clear communication with clinicians and patients about the evidence base supporting approval. The sponsor proposes to include an explanatory note as part of the indication:

> *This indication is approved based on tumour response rates and duration of response. An improvement in survival or disease-related symptoms has not been established.*

Updated outcomes using a first quarter 2016 data cut-off support the view that ORR, in this case, will translate into a meaningful survival benefit, though it is difficult to gauge a survival benefit *over standard of care* when standard of care is not clearly defined and when cross-study comparison is required.

Study BO28984 ('ALEX') will provide more robust evidence of alectinib's efficacy and safety in ALK+ NSCLC, though ALEX is designed to support the use of alectinib as 1L targeted therapy. In the absence of a conditional approval pathway, standard approval based on the 'totality of evidence' in the dossier is considered preferable to awaiting outcomes from ALEX.

The sponsor emphasises potential for activity of alectinib against CNS lesions and the argument for CNS activity is backed up by preliminary but promising data from a study allowing comparison with crizotinib (J-ALEX – presented in summary form and using a dose *half* that proposed for use in Australia).

Toxicity appears manageable, although some common AEs have the potential to impact on quality of life (for example, constipation, fatigue, myalgia and photosensitivity).

Details about indication wording (for example, relating to locally advanced disease, use in NSCLC other than adenocarcinoma, and use in patients intolerant to crizotinib) are also reviewed below but the currently proposed wording is generally acceptable.

Proposed action

The Delegate's preliminary view is that alectinib can be registered for the proposed indication:

> *Alecensa is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive, locally advanced or metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.*
>
> *Note to Indication: This indication is approved based on tumour response rates and duration of response. An improvement in survival or disease-related symptoms has not been established.*

For Studies ALEX, J-ALEX and NP29783, it will be a condition of registration that the TGA is kept informed about any major changes to the estimated CSR availability dates and that there is a Category 1 submission when each pre-planned analysis (interim analyses and the final analysis) is available for review in CSR format.

Request for ACPM advice

The committee is requested to provide advice on the following specific issues:

1. *The ACM is asked to comment on 'standard of care' approaches in Australia for patients with ALK+ NSCLC who have failed (or are intolerant to) crizotinib.*
2. *Does the ACM support registration of alectinib based on evidence from single-arm studies where overall response rate was the primary efficacy endpoint (or at least, based on the totality of evidence presented here)?*
3. *Does the ACM consider safety of alectinib in the proposed use is sufficiently well characterised and communicated in the PI?*
4. *Should the indication include patients with locally advanced disease, or only those with metastatic (Stage IV) disease?*
5. *Should consideration be given to indicating use in patients with asymptomatic CNS lesions who have not previously received treatment for advanced NSCLC? Or, is it appropriate to await robust characterisation of efficacy versus crizotinib in patients with CNS lesions, in the ALEX study?*
6. *The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application. Pre ACM preliminary assessment*

Response from Sponsor

Sponsor's comment on the Delegate's proposed action and advice sought

The sponsor's comments on aspects of the Delegate's Overview (DO) and responses to questions addressed to the sponsor are summarised below.

Registration based on single-arm studies where overall response rate is the primary endpoint

In Australia, second generation ALK inhibitors are not yet readily accessible to patients. Therefore, treatment options after crizotinib failure are limited and mostly include cytotoxic chemotherapy, palliative radiotherapy, or supportive care.[40] Current chemotherapy options in this setting include pemetrexed and docetaxel.[40] Nonetheless, as shown in PROFILE 1007[41] these agents have very poor efficacy in second-line (ORR of 20% and PFS of 3 months) and the same is expected in third-line. In addition, control of CNS disease remains an important issue in the treatment of ALK+ NSCLC patients, with progression in the CNS occurring in up to 46% of patients treated with crizotinib.

Ceritinib has been registered in Australia based on Phase II data for treatment of ALK+ patients that failed crizotinib treatment but it is not currently reimbursed and access to patients is limited. In addition, while ceritinib has shown clinical benefit in this population with 44% ORR by IRC assessment and median DOR of approximately 7 months[42] its tolerability remains an issue with dose modifications (interruption and/or reduction) reported in 71% of patients[43] dose reductions reported in approximately 60% of patients,

[40] Reck M, Popat S, Reinmuth N, De Ruysscher D, Kerr KM, Peters S; ESMO Guidelines Working Group. Metastatic non-small-cell lung cancer (NSCLC): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2014;25 Suppl 3:iii27-39.
[41] Shaw AT, Kim DW, Nakagawa K, et al. Crizotinib versus chemotherapy in advanced ALKpositive lung cancer. N Engl J Med. 2013;368(25):2385-94.
[42] Zykadia™ (ceritinib) Summary of Product Characteristics
[43] Zykadia™ (ceritinib) FDA (CDER) Medical Review

and discontinuation of therapy occurring in approximately 10% of patients.[44] The safety concerns with ceritinib are sufficient to warrant a boxed warning in Australia.[45]

Additionally, restrictions on concomitant use of ceritinib with a number of medications including the need for avoidance (strong CYP3A inducers) or dose reduction (strong CYP3A inhibitors) further reflects the need for additional therapeutic options.

Similar to crizotinib, ceritinib has been shown to be a P-gp substrate[42] which could impact its ability to cross the blood-brain barrier. Data have been presented on the activity of ceritinib in the CNS in patients previously treated with crizotinib.[46] In total, 75 patients had CNS metastases at baseline (28 measurable and 47 non-measurable). Of these, 14 patients (10 with measurable CNS lesions and 4 with non-measurable CNS lesions, respectively) achieved a response (18.6%) including CR in the 4 patients with non-measurable lesions. Of the 28 patients with measurable lesions at baseline, 10 achieved a CNS PR (35.7%), while none achieved a CR. In Study X2101, of the 100 NSCLC patients treated with ceritinib 750 mg who had progressive disease, 77 had received prior crizotinib and 32 (42%) of these progressed in the CNS (in 26 [34%] CNS was the only site of progression). According to the FDA Medical Review, relapse in the CNS as primary site of disease during ceritinib treatment is relatively common especially in patients previously treated with crizotinib.[43]

Overall, these data suggest that the activity of ceritinib in the CNS is limited.

Therefore, there still remains an unmet need for an effective and well tolerated ALK inhibitor with proven CNS activity. In both Phase II pivotal studies, which were conducted independently of each other, alectinib demonstrated highly consistent, statistically significant and clinically meaningful efficacy in the crizotinib-failed patient population, including notable CNS benefit as exemplified by a high rate of CNS CRs in patients with measurable and/or non-measurable lesions, including patients with no prior CNS radiation. At the time of the updated analyses[47]:

- ORR as assessed by the IRC was 52.2%; 95% CI [39.7%, 64.6%]) in Study NP28761 and 50.8%; 95% CI [41.6%, 59.9%] in NP28673 (RE population)
- Median duration of response was 14.9 months in NP28761 and 15.2 months in NP28673
- In the pooled efficacy population of 50 patients with measurable CNS lesions at baseline, 32 patients achieved a response (64.0%; 95% CI: 49.2%, 77.1%) as assessed by the IRC

Of the 32 responders, 11 patients (22%) achieved a CR.

- The CNS DCR (number of patients achieving a CNS BOR of CR, PR or SD lasting at least 5 weeks) assessed by the IRC was 90% (95% CI: 78.2%, 96.7%).

This is of significant clinical importance given the lack of effective therapies for patients with CNS metastases and the associated morbidity, both because of the involvement of the brain and because of treatments required for disease control (corticosteroids, surgery, and radiation).

[44] Zykadia™ (ceritinib) European public assessment report (EPAR) and Zykadia™ (ceritinib) Summary of Product Characteristics
[45] Zykadia™ (ceritinib) Australian Product Information
[46] Kim DW, Mehra R, Tan DS, et al. Activity and safety of ceritinib in patients with ALKrearranged non-small-cell lung cancer (ASCEND-1): updated results from the multicentre, open-label, phase 1 trial. Lancet Oncol 2016;17:452–63.
[47] Clinical Overview Addendum submitted with Section 31 response: data cut-offs of 22 January 2016 for NP28761 and 01 February 2016 for NP28673

In conclusion, the benefit observed, together with the relatively well tolerated and manageable safety profile and minimal drug-drug interactions demonstrate that alectinib represents a significant advance over currently available treatment options in this setting.

Inclusion of patients with locally advanced disease (LAD)

As for other ALK inhibitors already registered in Australia (crizotinib and ceritinib), the patients with locally advanced disease (LAD) proposed to be included in the alectinib indication are those not amenable to combined modality treatment (chemoradiation). This is in line with protocol inclusion criteria for both pivotal alectinib Phase I/II Studies (that is, unresectable and not a candidate for chemoradiation treatment) resulting in relatively small numbers of such patients enrolled, although in a similar range to that seen in other ALK inhibitor studies.[48]

The Delegate notes that the US indication for alectinib is limited to metastatic disease. This reflects a consistent FDA position concerning ALK inhibitors and the US indications for crizotinib and ceritinib are similarly limited to metastatic disease.

Although their disease is not considered metastatic, patients with locally advanced (LAD) not amenable to chemoradiation are treated in the same way as those with metastatic disease (NCCN guidelines) as there is no other treatment option with potential to prolong survival. The benefit/risk ratio for these patients is expected to be similar to Stage IV patients since their ALK+ NSCLC is expected to benefit equally from alectinib and there is no reason to believe that the safety profile should be any different (given that the medicine's safety profile in this setting is mainly dependent on its mechanism of action and not on the status of the disease itself).

The alectinib Phase II studies enrolled 3 patients with LAD, 2 of who achieved a PR. The safety profile observed in these 3 patients was consistent with that observed in the overall population, with most AEs of Grade 1 or 2 in severity, non-serious, unrelated to study drug and not resulting in dose modifications or interruptions. These data suggest that patients with ALK+ LAD not amenable to chemoradiation can experience clinically meaningful benefit when treated with alectinib.

In conclusion, including patients with LAD in the indication is consistent with current treatment guidelines as well as with the studied population. In addition, inclusion of these patients in the indication would be consistent with the indication for other registered ALK inhibitors in Australia. Demographic information from the ALK inhibitor trials indicate that only a small proportion of locally advanced NSCLC is not amendable to multi-modality treatment with curative intent, however it is important ALK inhibitors remain a treatment option for these patients.

TGA Proposal for Patient Information Card (PIC)

The sponsor currently has no plans to introduce a Patient Information Card (PIC) for Alecensa in NSCLC and this has not been raised as an issue by other regulatory authorities where the product is approved or by the Committee for Medicinal Products for Human Use (CHMP) when recommending approval of alectinib in the EU. This approach is guided by principles outlined in the relevant EU guideline[49] requiring that additional risk minimisation measures be proportionate taking account of the risk-benefit profile of the product and the efforts required to implement them. The Delegate's rationale for a Patient information card (PIC) refers to the novelty of the agent and distinct toxicities, for

[48] Zykadia™ (ceritinib) Canadian Product Monograph and Crinò L, Ahn M-J, De Marinis F, et al. Multicenter Phase II Study of Whole-Body and
Intracranial Activity With Ceritinib in Patients With ALK-Rearranged Non–Small-Cell Lung Cancer Previously Treated With Chemotherapy and Crizotinib: Results From ASCEND-2. J Clin Oncol 2016;34:2866-73

[49] EMA/204715/2012 Guideline on Good Pharmacovigilance Practices (GVP)

example, myalgia and CPK elevation compared with crizotinib in the preliminary J-ALEX data. However, novelty and differences in toxicity profile per se are not determinants of the need for additional risk minimisation according to GVP guidelines adopted by the TGA. This is evidenced by the fact that the first agent in this class, crizotinib, has not been required to provide a PIC.

Specifically with respect to the J-ALEX data summarised in the Snapshot above (*Snapshot of data from J-ALEX*), only myalgia and CPK elevation were reported with noticeably higher rates for alectinib, whereas for most other events the reporting rates were higher for crizotinib, for example, hepatic function disorder (43.3% versus 21.4%), bradycardia (22.1% versus 10.7%), QT prolongation (14.4% versus 3.9%), vision disorders (75.0% versus 8.7%) and cardiac failure (21.2% versus 10.7%). It should also be noted that there are considerable practical difficulties in distributing a PIC which is relevant to only a very small proportion of patients seen by oncologists, resulting in an unreasonable minimisation burden balance (per the guidelines). Therapeutic area consistency and practical considerations have been acknowledged by the TGA's advisory committee for not requiring PICs for other products.[50]

Severe Myalgia and CPK Elevations is an Identified Risk in the Alecensa RMP and the sponsor acknowledges the importance of risk minimisation '*to reduce the incidence of severe myalgia and CPK elevations by informing patients about signs and symptoms and informing physicians about severe myalgia and CPK elevations, as well as by providing appropriate monitoring and dose modifications instructions in the labeling'*.[51] As requested by the Delegate, the Alecensa Consumer Medicine Information (CMI) has been strengthened with regard to information about severe myalgia and CPK elevations and this is considered to be the most appropriate way to communicate with the patient about this risk.

Furthermore in the PI, physicians are advised to solicit patient reporting of unexplained muscle pain, tenderness, or weakness and to test CPK every fortnight for a month and then as clinically indicated. Guidance on dosage modification for CPK elevations > 5 times at the upper limit of normal (UL) is provided in the PI. These measures are considered adequate and sufficient to address this risk.

Responses to questions addressed to the sponsor

1. *What clinical/nonclinical data support alectinib's use in patients with ALK G1202R mutation and other mutations suspected to confer resistance on next generation ALK inhibitors?*

ALK resistance mutations to crizotinib can be overcome by second generation ALK inhibitors. Alectinib is active against most crizotinib resistant mutations.[52] Pre-clinical cell line experiments on known crizotinib resistance mutations have been demonstrated to be sensitive to second-generation ALK inhibitors.[52,53] Case reports from patients with ALK mutations which respond to second generation ALK inhibitors provide clinical evidence that patients with ALK mutations can benefit from ALK TKI's. For example, Ou et al. reported a patient with an ALK F1174V resistant mutation after progression from crizotinib responded to alectinib for 18 months.[54] Another case report shows that

[50] Minutes for 263rd ADEC Meeting for ACTEMRA (tocilizumab) and 269th ACPM Meeting for MABTHERA (rituximab)
[51] ALECENSA RMP, Part V
[52] Bayliss et al. Molecular mechanisms that underpin EML4-ALK driven cancers and their response to targeted drugs. Cell Mol Life Sci. 2016;73(6):1209-24.
[53] Fontana et al., Activity of second-generation ALK inhibitors against crizotinib-resistant mutants in an NPM-ALK model compared to EML4-ALK.Cancer Med. 2015; 4(7): 953–965.
[54] Ou et al. LK F1174V mutation confers sensitivity while ALK I1171 mutation confers resistance to alectinib. The importance of serial biopsy post progression. Lung Cancer 2016;91:70–72

treatment with alectinib was able to overcome resistance to ceritinib mediated by ALK G1123S, though the duration of the response achieved with alectinib is unknown at present.[55]

On the other hand there are ALK mutations which may not be sensitive to second generation ALK inhibitors. ALK G1202R has been found to be highly resistant (>10-fold increased IC_{50} compared to wild type) to second generation ALK inhibitors in ALK G1202R mutated cell lines.[53,56] Additionally, several cases with resistance to second-generation ALK inhibitors associated with G1202R have been reported from the clinic.[57] Another ALK mutation ALK I1171S has been associated with acquired resistance to alectinib in a case report by Ou et al.[54] The ALK I1171 mutation may arise during alectinib treatment.

For most ALK mutations which may confer resistance to second generation ALK inhibitors only very limited or no clinical evidence is available to date. The resistance potential of these ALK mutations is solely based on cell line results and their resistance potential is judged by IC_{50} values derived from these cell line experiments. Preclinical data and very limited data from case reports are not sufficient to draw final conclusions with regards to the clinical benefit that patients with these ALK mutations may obtain from alectinib. Additionally, ALK mutations only represent one fusion gene or activation of alternative bypass pathways.[52] These resistance mechanisms might not be exclusive and may coexist in the same patient, and therefore observed resistance to an ALK TKI may not be fully explained by the detection of a potential ALK resistance mutation.

2. *Did any of the 9 patients with intestinal perforation under discussion have documented GI metastases at the site of or distal to the perforation?*

None of the 9 patients had documented GI metastases at the site of or distal to the perforation at the time of the GI perforation event although examinations to identify metastases at the site at the time of the AE onset were not reported for the majority of cases. However, for 8 of the 9 patients one or multiple metastases were documented prior to alectinib treatment start. As risk factor for AER 1505873 the investigator stated that the possibility of GI metastasis could not be ruled out, while in the remainder of the 7 cases the sites of metastasis were outside the GI tract.

Based on nonclinical data with alectinib showing no findings of GI perforation as well as on the clinical cases that have all occurred in patients with general GI perforation risk factors (for example, older age; concurrent conditions of ileus, diverticulosis or bacterial caused appendicitis; or concomitant systemic corticosteroids) and which had an estimated incidence rate not exceeding that expected in patients with metastatic lung cancer, there is no conclusive evidence of association between gastrointestinal perforation and alectinib treatment.

3. *Is a particular mechanism implicated in alectinib-related oedema?*

The mechanism implicated in alectinib related oedema is unknown.

The Delegate assessed peripheral oedema as a prominent AE potentially related with weight gain. An analysis of the onset of oedema events and weight gain in NP28673 and NP28761 (cut-off date 1 February 2016 and 22 January 2016, respectively) was conducted. A total of 104 patients reported AEs of weight gain and/or oedema. Of the 15

[55] Toyokawa et al. Identification of a Novel ALK G1123S Mutation in a Patient with ALKrearranged Non-small-cell Lung Cancer Exhibiting Resistance to Ceritinib. J of Thorac Oncology 2015:10(7):e55-7.
[56] Katayama et al. Mechanisms of acquired crizotinib resistance in ALK-rearranged lung Cancers. Sci Transl Med. 2012 Feb 8;4(120):120ra17.
[57] Ignatius Ou et al. Next-generation sequencing reveals a Novel NSCLC ALK F1174V mutation and confirms ALK G1202R mutation confers high-level resistance to alectinib (CH5424802/RO5424802) in ALK-rearranged NSCLC patients who progressed on crizotinib. J Thorac Oncol. 2014; 9:549–53 and Friboulet et al. The ALK inhibitor ceritinib overcomes crizotinib resistance in non-small cell lung cancer. Cancer Discov 2014;4(6):662-73.

patients reporting both weight increase and oedema, only 5 patients had an onset day of oedema close to the onset day of weight increase. The result suggests that there is no temporal relationship between the occurrence of oedema and weight gain. The sponsor therefore considers oedema and weight gain to be two different clinical entities observed during alectinib treatment.

4. *It is noted that of 90 patients with muscular AEs, 29 had concomitantly increased CPK. Did any of these patients have worsening renal function after onset of CPK elevation? Also, was there any interaction with other drugs known to cause myalgia or myositis?*

Of the patients with concomitant muscular AEs and increased CPK, one patient had renal failure (serious) and two patients (including the one who had renal failure) had increased creatinine (both non-serious) reported after onset of elevated CPK. One increased creatinine AE was of Grade 1 (G1) intensity, the other was of Grade 4 intensity in the same patient with renal failure of Grade 4 (G4) intensity. A summary of the case with the Grade 4 events is provided below.

> Medical history included kidney stones. Concurrent conditions included diabetes, hypertension and renal insufficiency. Concomitant medications included insulin, furosemide, metoprolol, dabigatran and dexamethasone. It was reported that prior chemotherapy was stopped due to rising renal function tests caused by a combination of diabetes, hypertension, bevacizumab and pemetrexed.
>
> On study Day 17 the patient's blood CPK increased (Grade 1, not serious). The AE lasted 374 days and resolved. Alectinib dose was not changed due to the event. On study Day 25, creatinine was elevated (G4, not serious). On study day 44, renal failure was diagnosed (G4, serious). Renal biopsy revealed acute tubular injury with extensive oxalate crystal deposition, suggesting a hyperoxaluric state. Isolated urate tophus in medulla, suggesting previous or current hyperuricaemia, mild immunoglobulin (Ig) A nephropathy, thin glomerular basement membranes suggesting inherited abnormality of basement membrane collagens. Moderate chronic changes of the parenchyma included: global glomerulosclerosis, tubular atrophy, interstitial fibrosis, arterial and arteriolar sclerosis moderate to severe. Treatment with alectinib was temporarily discontinued and restarted 2 months later. The outcome of the event was reported as not resolved. The investigator assessed the event of renal failure as unrelated to alectinib but related to history of renal stones and family history of oxalate uropathy.

With regards to co-medication, no patients with concomitant statins (drugs known to cause myalgia or myositis) treatment were identified. The mechanism by which alectinib causes myalgia is not known, nor is it for statins. Also no formal studies have been done to elucidate a potential mechanism of interaction between other drugs known to cause myalgia or myositis and alectinib.

5. *Is there evidence establishing that alectinib can cause red cell destruction? Did any patients have anaemia and signs of haemolysis, for example, LDH, haptoglobin changes? Could any (indirect) bilirubin elevation be attributed to haemolysis?*

Poikilocytosis (that is, fragmentation) of red blood cells has been observed in the toxicity studies with alectinib in rat, rabbit and cynomolgus monkey at clinical relevant exposure levels.[58] However, the changes on the erythroid system were considered to be of little toxicological significance because they were very slight (0.94 to 1.3-fold versus baseline), considered reversible, and were not exacerbated by prolonged treatment. In addition, conjugated bilirubin increases were identified, indicating hepatobiliary cause rather than haemolysis in the blood vessels. While markers of haemolysis, for example, LDH and

[58] Alecensa (alectinib) Category 1 Application, CTD module 2.6.6, section 9.2

haptoglobin, have not been routinely monitored in clinical trials with alectinib, haemolysis has not been reported with alectinib in clinical trials or from post market use.

Based on the above considerations, an association between haemolysis and anemia or bilirubin elevations has not been established.

6. *Please confirm that none of the patients who fell after dizziness got hurt, or if there were injuries arising in this way, please explain why such events were not considered serious in the context of a drug that causes bradycardia.*

Falls were reported for 9 patients in NP28673 and NP28761, all were non-serious. All events were assessed as not related to alectinib by the investigators. There were no cases of falls coinciding with dizziness or bradycardia events. One patient with brain metastases and a medical history of stereotactic surgery experienced a 3 day episode of dizziness starting at treatment Day 34 and a fall 11 days after resolution of dizziness. Considering the separation of these events by 11 days, the sponsor assessed the fall as not related to the dizziness AE. The CNS metastatic disease in this patient may have contributed to both the dizziness and the fall. No bradycardia AE was reported for this patient. No injuries related to falls were reported for these 9 patients.

7. *Was there any indication of additive or synergistic effects on heart rate in subjects concomitantly taking medicines known to slow heart rate, for example, beta blockers?*

No formal analysis on the additive or synergistic effects of alectinib and other drugs that lower heart rate has been done. In the Phase II clinical trials, no bradycardia effect was identified in patients concomitantly taking for example beta blockers. Nevertheless the PI recommends evaluation of concomitant medications known to cause bradycardia, as well as anti-hypertensive medications, in the case of symptomatic or life-threatening bradycardia. If such contributing medications are identified, they should be discontinued or their dose adjusted based on the healthcare provider's judgment.

8. *Please provide a status update for NCT02838420 and a CSR availability date.*

The Study YO29449 (NCT02838420) is ongoing.

9. *Although only a few patients in pivotal studies had non-adenocarcinoma NSCLC, it is relevant to understand individual responses. Please list these patients' efficacy outcomes, so inadequate efficacy in non-adenocarcinoma patients can be ruled out.*

A total of 6 patients were enrolled in the Phase II studies with non-adenocarcinoma histology (3 in NP28761 and 3 in NP28673). A table summarising the BOR by investigator (INV) and IRC and where applicable, the CNS BOR by IRC achieved with alectinib in these patients is presented below.[47] Despite the small number size, evidence of clinical benefit is observed.

Table 16: BOR by investigator and IRC

Study	Carcinoma Histology *	Overall Disease by INV		Overall Disease by IRC		CNS by IRC	
		BOR	DOR	BOR	DOR	BOR	DOR
NP28761	Poorly Differen.	PD		PD		PD	
NP28761	Squamous	NE		PR	17.3m	NA	

Study	Carcinoma Histology *	Overall Disease by INV		Overall Disease by IRC		CNS by IRC	
		BOR	DOR	BOR	DOR	BOR	DOR
NP28761	Large Cell	PD		SD		NA	
NP28673	Large Cell	PR	19.4m	SD		CR	19.3m
NP28673	Large Cell	PR	22.4m	PD		SD	
NP28673	Large Cell	SD		SD		CR	10.2m

Data cut-offs of 22 January 2016 for NP28761 and 01 February 2016 for NP28673; NA=Not Applicable (patient did not have CNS disease at baseline); NE=Not Estimable; DOR in months
* Patients with adenosquamous histology (classified as adenocarcinoma) are not included (n=4)

10. *In J-ALEX, median age was 60-61 years, higher than in NP28673 and NP28761. Are the characteristics of ALK positive NSCLC in Japan considered similar to those in Australia and Western populations? Are there known demographic, genetic (for example, EML4-ALK variant) or pathobiological differences in ALK+ NSCLC between Japanese and other populations? Are responses to traditional chemotherapies comparable across these regions in ALK+ patients?*

Baseline characteristics of patients enrolled in J-ALEX are broadly comparable to those observed in NP28761 and NP28673. In both Japanese and Western patients, ALK+ disease tends to be more frequent in females patients with a history of never or former smoking and with a younger age.

Although the median age in J-ALEX was higher compared to the Phase II studies, it was still lower than that observed in the general Japanese and Western NSCLC population.[59]

To further compare the J-ALEX study population to the ALK+ NSCLC Western population, key demographic and clinical characteristics of patients enrolled in J-ALEX were compared to epidemiology data in Western and Asian populations extracted from literature search and the largest real-world oncology data source.[60] This analysis showed that the baseline demographic (median age around 60, more females than males, good performance status, most frequently never smokers) and disease characteristics (adenocarcinoma as the most frequent histological type) of the Japanese ALK+ patients in J-ALEX are comparable to those of the global ALK+ population.

The Delegate has observed that it appears that 'Japanese patients do better on alectinib than patients elsewhere' based on results in AF001-JP compared to NP28673 and NP2876. However, it is important to note that, similar to J-ALEX, AF001-JP was conducted in crizotinib naïve patients. Therefore, the efficacy observed in this population is expected to

[59] Kawaguchi et al. Japanese Ethnicity Compared with Caucasian Ethnicity and Never-Smoking Status Are Independent Favorable Prognostic Factors for Overall Survival in Non-small Cell Lung Cancer: A Collaborative Epidemiologic Study of the National Hospital Organization Study Group for Lung Cancer (NHSGLC) in Japan and a Southern California Regional Cancer Registry Databases. Journal of Thoracic Oncology 2010;5(7):1001–10.
[60] Flatiron Health Inc's electronic health record database

be of a greater magnitude compared to the global Phase II studies conducted in crizotinib-failed patients.

11. Please clarify why 'leukopenia' should be treated differently from other laboratory parameter abnormalities with regard to presentation in the PI?

All the parameters identified to have abnormalities in >20% of patients are based on shift tables. However a full assessment of clinical meaningfulness of the data requires also the consideration of the change from baseline pattern. As such, for all treatment emergent (TE) laboratory abnormalities, shifts and also changes from baseline pattern have been assessed in order to determine inclusion in the table. If there were clinically meaningful changes, these have been included into the table of TE laboratory abnormalities. For leukopenia, no clinically meaningful changes in median values over time have been observed. Changes in leukopenia shift data were driven by scattered elevation primarily occurring during clinical follow up of the patient. Since leukopenia abnormalities were assessed as not clinically meaningful, these are not proposed for inclusion in the table.

Advisory Committee Considerations

The ACM, taking into account the submitted evidence of efficacy, safety and quality, are of the opinion that there is an overall positive benefit–risk profile for Alecensa capsules containing 150 mg of alectinib for the indication**;**

> *Alecensa is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive, locally advanced or metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.*
>
> *Note to Indication: This indication is approved based on tumour response rates and duration of response. An improvement in survival or disease-related symptoms has not been established.*

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACM proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI) and specifically advised on the inclusion of the following:

· Precaution statements to include gastrointestinal (GI) perforation and bradycardia as adverse effects.

Specific Advice

The ACM advised the following in response to the Delegate's specific questions on this submission:

12. The ACM is asked to comment on 'standard of care' approaches in Australia for patients with ALK+ NSCLC who have failed (or are intolerant to) crizotinib.

The ACM noted that crizotinib is approved for treatment of ALK positive advance NSCLC.

However, the current second line (2L) option is chemotherapy for those patients who have developed resistance to crizotinib or immunotherapy (considered more inferior). Furthermore, ceritinib is available (for an unknown period of time) as an option via the manufacturer's Compassionate Access Program. Nivolumab can also be considered in the 2L or 3L setting after progression on crizotinib and chemotherapy. Apart from ceritinib, none of these treatments is considered optimal.

13. Does the ACM support registration of alectinib based on evidence from single-arm studies where overall response rate was the primary efficacy endpoint (or at least, based on the totality of evidence presented here)?

The ACM noted that the indication is based upon overall response rates and duration of response. The ACM advised that despite the limited data these are sufficient with a caveat pertaining to level of evidence and survival data. The ACM noted the absence of viable options for ALK+ NSCLC patients in the 2L setting. It should be clearly communicated to clinicians and patients that no improvement in overall survival has yet been established.

14. *Does the ACM consider safety of alectinib in the proposed use is sufficiently well characterised and communicated in the PI*?

The ACM advised that the safety of alectinib in the proposed use is generally adequately covered; however the PI should include GI perforation and bradycardia in the Precaution section. The ACM noted GI perforation was a known side-effect of crizotinib.

Bradycardia was also reported in the clinical trials and both crizotinib and ceritinib can cause this AE. Myalgia/CPK elevation should also be a Precaution as single case of rhabdomyolysis, the extreme extension of this AE, has been reported and should be included as a rare AE (similar to statins).

15. Should the indication include patients with locally advanced disease, or only those with metastatic (Stage IV) disease?

The ACM noted that the data were limited to metastatic disease but was of the view that a broader definition would be reasonable. The ACM advised that in view of rare subset of population (ALK+ NSCLC) the indication could reasonably be extended to stage 3B NSCLC).

16. Should consideration be given to indicating use in patients with asymptomatic CNS lesions who have not previously received treatment for advanced NSCLC? Or, is it appropriate to await robust characterisation of efficacy versus crizotinib in patients with CNS lesions, in the ALEX study?

ACM noted that the data supported excellent efficacy for CNS disease; however the data were immature. The ACM advised that it is appropriate to wait for robust characterisation of efficacy compared to crizotinib in patients with CNS lesions, in the currently on-going ALEX study.

The ACM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Following the consideration of the application by the ACM, the TGA Delegate confirmed that no further changes were required to the PI, that is, the PI version sent with the pre-ACM response was acceptable, and the sponsor's rationale for not providing a Patient Information Card was also accepted. Based on a review of quality, safety and efficacy, TGA approved the registration of Alecensa (alectinib) 150mg hard capsule for oral administration, indicated for:

> *Alecensa is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive, locally advanced or metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.*
>
> *Note to Indication: This indication is approved based on tumour response rates 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. The Alecensa Risk Management Plan (RMP), (version 1.1, dated 6 July 2016: DLP 4 July 2016), with Australian Specific Annex (version 1.1, dated October 2016) and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
2. Submit as soon as practicable, as Category 1 submission/s the Clinical Study Reports that describe planned interim and final analyses for the following studies:
   - § BO28984 (ALEX)
   - § J-ALEX
   - § NP29783

Attachment 1. Product Information

The PI for Alecensa 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

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