



Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Crizotinib

Proprietary Product Name: Xalkori

Sponsor: Pfizer Australia Pty Ltd

June 2013
March 2014

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- An AusPAR is a static document, in that it will provide 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.

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List of the most common abbreviations used in this AusPAR

Abbreviation	Meaning
AE	Adverse event
ALCL	Anaplastic large cell lymphoma
ALK	Anaplastic lymphoma kinase
ALT	Alanine transaminase
AST	Aspartate transaminase
AUC	Area under concentration-time curve
AUC _{inf}	Area under the plasma concentration-time profile from time zero to infinity
AUC _τ	Area under plasma concentration-time profile from time zero to time τ , the dosing interval
BID	Twice daily
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CR	Complete response
C _{max}	Maximum plasma concentration
C _{trough}	Trough (predose) concentration
CSR	Clinical study report
CTA	Clinical trial assay
CTCAE	Common Terminology Criteria for Adverse Events
CTD	Common Technical Document
CV	Coefficient of variation
CYP	Cytochrome P450
DLT	Dose-limiting toxicity
DR	Duration of response

Abbreviation	Meaning
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EML4	Echinoderm microtubule-associated protein-like 4
EORTC-QLQ-C30	European Organization for Research and Treatment Quality of Life Questionnaire – Core 30
EORTC-QLQ-LC13	European Organization for Research and Treatment Quality of Life Questionnaire – Lung Cancer 13
EQ-5D	EuroQol-5D
EU	European Union
FDA	Food and Drug Administration
FISH	Fluorescence in situ hybridization
GCP	Good Clinical Practice
HGFR	Hepatocyte growth factor receptor
HRQoL	Health-Related Quality of Life
ICH	International Conference on Harmonization
IHC	Immunohistochemistry
MedDRA	Medical Dictionary for Regulatory Activities
Ms	Millisecond
MTD	Maximum tolerated dose
N, n	Number of subjects
NDA	New Drug Application
NPM	Nucleophosmin

Abbreviation	Meaning
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease <i>or</i> Pharmacodynamic
PET	Positron emission tomography
PCR	Polymerase chain reaction
RT-PCR	Reverse transcriptase polymerase chain reaction
RACE-PCR	Rapid amplification of cDNA ends-polymerase chain reaction
PFS	Progression-free survival
PK	Pharmacokinetic
PRO	Patient-reported outcome
PR	Partial response
PT	Preferred term (MedDRA)
QD	Once daily
QTc	QT interval corrected
QTcB	QT interval corrected – Bazett’s conversion
QTcF	QT interval corrected – Fridericia’s conversion
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase II dose
RTK	Receptor tyrosine kinase
SAE	Serious adverse event
SCE	Summary of Clinical Efficacy
SCP S	Summary of Clinical Pharmacology Studies
SCS	Summary of Clinical Safety

Abbreviation	Meaning
SD	Stable disease
SOC	System organ class
TKI	Tyrosine kinase inhibitor
T _{max}	Time of maximum plasma concentration
ULN	Upper limit of normal (range)
US	United States
VSAQ	Visual Symptom Assessment Questionnaire
WHO	World Health Organization

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	New Chemical Entity
<i>Initial TGA decision:</i>	Rejected
<i>TGA review decision¹:</i>	Rejected
<i>AAT² Decision Outcome:</i>	Approved ³
<i>Date of initial TGA decision:</i>	15 August 2012
<i>Date of TGA review decision:</i>	20 December 2013
<i>Date of AAT² decision:</i>	24 September 2013
<i>Active ingredient:</i>	Crizotinib
<i>Product name:</i>	Xalkori
<i>Sponsor's name and address:</i>	Pfizer Australia Pty Ltd 38-42 Wharf Road West Ryde NSW 2114
<i>Dose form:</i>	Capsule
<i>Strengths:</i>	200 mg and 250 mg
<i>Containers:</i>	High-density polyethylene (HDPE) bottles and Polyvinyl chloride (PVC)/Aluminium (Al) blisters
<i>Pack sizes:</i>	60 capsules
<i>Approved therapeutic use:</i>	<i>Xalkor is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK) - positive advanced non-small cell lung cancer (NSCLC).</i>
<i>Route of administration:</i>	Oral (PO)
<i>Dosage:</i>	Maximum daily dose: 500 mg Maximum single dose: 250 mg
<i>ARTG numbers:</i>	190966, 190965, 190964, 190963

¹ The initial Delegate's decision was reviewed in accordance with s.60(4) of the *Therapeutic Goods Act 1989*. For further details see the *Final Outcome* section of this AusPAR.

² AAT=Administrative Appeals Tribunal

³ The sponsor appealed to the Administrative Appeals Tribunal for review of the TGA's decision not to register Xalkori. Under section 42C of the *Administrative Appeals Tribunal Act 1975*, where the parties in a matter before the Administrative Appeals Tribunal reach an agreement about the matter, the Tribunal, if it considers it appropriate to do so, may make a decision in accordance with such an agreement. The TGA and the sponsor reached an agreement about the registration of Xalkori and the Administrative Appeals Tribunal made a decision in accordance with this agreement. The AAT set aside the decision not to register Xalkori and substituted a decision to approve the registration of Xalkori under subsection 25(1) of the *Therapeutic Goods Act 1989*. For further details see the *Final Outcome* section of this AusPAR.

Product background

Pfizer Australia Pty Ltd has applied to register the new chemical entity, crizotinib (Xalkori), as an oral treatment for patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC);

“The treatment of patients with anaplastic lymphoma kinase (ALK)- positive advanced non-small cell lung cancer (NSCLC)”.

The proposal is for first (or subsequent) line use in the advanced NSCLC setting, The proposed dose is 250 mg orally (PO) twice daily, with or without food, with treatment continuing as long as the patient is deriving clinical benefit from the therapy.

Crizotinib is a new chemical entity in Australia. For this submission and indication, crizotinib is an orphan drug. (The sponsor estimates prevalence of ALK-positive NSCLC to be <340 in Australia as of 2011.)

While there are no registered treatments in Australia for ALK-positive advanced NSCLC, multiple products are approved for the broader condition “advanced NSCLC” (summarised below). The sponsor’s claim of “unmet medical need” is only valid in the sense that the safety and efficacy of these treatments for advanced NSCLC can be improved.

Drug details and approved NSCLC indication

Generic	Trade name	Sponsor	Approved NSCLC indication
First-line			
Pemetrexed disodium	Alimta	Eli Lilly	ALIMTA in combination with cisplatin is indicated for initial treatment of patients with locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology .
Gemcitabine	various	various	Treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC)
Vinorelbine	various	various	First line treatment for advanced non-small cell lung cancer, as a single agent or in combination
<i>Etoposide</i>	<i>various</i>	<i>various</i>	<i>No formal indication in NSCLC (but mentioned in NSW Cancer Institute’s EviQ)</i>
Paclitaxel	various	various	Treatment of non-small cell lung cancer (NSCLC)
Docetaxel	various	various	Indicated for the treatment of patients with locally advanced or metastatic non small cell lung cancer, including those who have failed platinum-based

Generic	Trade name	Sponsor	Approved NSCLC indication
			chemotherapy.
<i>Cisplatin</i>	<i>various</i>	<i>various</i>	<i>No formal indication in NSCLC (but mentioned in EviQ and referred to in other products' indications)</i>
<i>Carboplatin</i>	<i>various</i>	<i>various</i>	<i>No formal indication in NSCLC (but mentioned in EviQ and referred to in other products' indications)</i>
Bevacizumab	Avastin	Roche	AVASTIN (bevacizumab), in combination with carboplatin and paclitaxel, is indicated for first-line treatment of patients with unresectable advanced, metastatic or recurrent, non-squamous , non-small cell lung cancer. (Not mentioned in EviQ)
Erlotinib	Tarceva	Roche	Maintenance therapy in patients with locally advanced or metastatic non small cell lung cancer (NSCLC) who have not progressed on first line chemotherapy. Efficacy is influenced by tumour characteristics (see CLINICAL TRIALS).
Gefitinib	Iressa	AstraZeneca	Treatment of patients with locally advanced or metastatic Non Small Cell Lung Cancer (NSCLC) whose tumours express activating mutations of the EGFR tyrosine kinase** <i>** may therefore be a generally different subset of NSCLC than the ALK-positive subset</i>
Crizotinib	Xalkori	Pfizer	Proposed by sponsor: treatment of patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC)
Second-line			
Pemetrexed disodium	Alimta	Eli Lilly	ALIMTA as monotherapy is indicated for the treatment of

Generic	Trade name	Sponsor	Approved NSCLC indication
			patients with locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology after prior platinum-based chemotherapy. <i>There is also a first-line indication.</i>
Docetaxel	various	various	TAXOTERE is indicated for the treatment of patients with locally advanced or metastatic non small cell lung cancer, including those who have failed platinum-based chemotherapy. <i>There is also a first-line indication.</i>
Erlotinib	Tarceva	Roche	Treatment of patients with locally advanced or metastatic NSCLC after failure or prior chemotherapy. <i>There is also a first-line (maintenance) indication.</i>

Targets and mechanism of action

Crizotinib is a small molecule (450.34 Daltons) initially developed as a hepatocyte growth factor receptor (HGFR; c-Met) tyrosine kinase inhibitor. Crizotinib inhibits various other enzymes, notably wild-type anaplastic lymphoma kinase (ALK) receptor tyrosine kinase and its oncogenic variants (expressed after ALK fusion events and selected ALK mutations).

ALK positive NSCLC

The EML4-ALK fusion gene is an oncogenic driver in a fraction of patients with NSCLC. Soda et al (2007)⁴ described this subset as distinct from the activating EGFR-positive subset of NSCLC. Co-expression with HER2 or KRAS mutations is “extremely rare”. Multiple fusion variants of EML4-ALK are described. The resultant expressed tyrosine kinase is ligand-independent and constitutively active. Rarely identified fusion partners for ALK include TFG and KIF5B. The nucleophosmin-ALK fusion gene has also been described, in anaplastic large cell lymphoma. ALK positivity is independent of the fusion partner.

The prevalence of ALK gene rearrangement in NSCLC is on average 3.8%, ranging from 0.4% to 13.4% across series.⁵ In unselected Caucasian NSCLC patients, 12/447 (2.7%)

⁴Soda M, Takada S, Takeuchi K, et al. A mouse model for EML4-ALK-positive lung cancer. Proc Natl Acad Sci USA 2008; 105: 19893-97.

⁵Solomon B. ALK gene arrangements: A new therapeutic target in a molecularly defined subset of non-small cell lung cancer. J Thorac Oncol 2009; 4: 1450-1454.

were ALK positive.⁶ ALK fusion genes have been identified mainly in adenocarcinoma subtypes (40% of NSCLC) but have also been found in squamous cell subtypes.

NSCLC makes up 80% of lung cancers. At diagnosis, 70% of subjects have inoperable disease (locally advanced or confirmed metastatic disease).

Relevant EU guidelines

The TGA has adopted the European Union (EU) Guideline on the Evaluation of Anticancer Medicinal Products in Man⁷ and its Appendices 1 and 2.

Overseas status

Related submissions

This is the first Australian submission to register a medicine specifically for the treatment of patients with ALK-positive advanced NSCLC. The sponsor is seeking registration of crizotinib for first-line treatment of this condition. However, as outlined above in Section 2.1 there are a number of drugs registered in Australia for the first-line treatment of advanced NSCLC, generally in combination with platinum based chemotherapy.

Regulatory status

Xalkori has been approved for ALK-positive NSCLC in at least 65 countries.

European Union (EU)

Crizotinib was approved for marketing in Europe on 23.10.2013. The approved indication is:

- Xalkori is indicated for the treatment of adults with previously treated anaplastic lymphoma kinase (ALK)-positive advanced non small cell lung cancer (NSCLC).

USA

Xalkori was approved by the FDA in August 2011. Since then, the PI has been updated in February 2012 with a Precaution regarding hepatotoxicity. The FDA-approved indication (in the US Product Information updated 24.2.2012) was, verbatim:

Xalkori is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test.

This indication is based on response rate. There are no data available demonstrating improvement in patient reported outcomes or survival with Xalkori.

The US approval is for first-line therapy. Approval was via the “Accelerated Approval” regulation which allows earlier approval of drugs to treat serious diseases that fill an unmet need, based on a surrogate endpoint. Approval is conditional on verification of clinical benefit via post-market trials.

⁶Varella-Garcia M, Schulte AP, Wolf HJ et al. Chromosomal aneusomy in sputum as detected by fluorescence in situ hybridization (FISH) predicts lung cancer incidence. *Cancer Prev Res* 2010; 3: 447-53.

⁷EMEA/EWP/205/95 Rev 3 Corr Guideline on the evaluation of anticancer medicinal products in man

Canada.

Crizotinib was approved for marketing in Canada on 10.5.2012 with a disclaimer:

- Xalkori (crizotinib), indicated as monotherapy for use in patients with anaplastic lymphoma kinase (ALK)-positive advanced (not amenable to curative therapy) or metastatic non-small cell lung cancer (NSCLC), has been issued marketing authorization with conditions, pending the results of studies to verify its clinical benefit⁸. Patients should be advised of the nature of the authorisation.

The following table summarises the International regulatory status of Xalkori.

Table 1. International regulatory status of Xalkori

Country	Approval Date	Approved Indication
Canada	25 April 2012	Xalkori (crizotinib) is indicated as monotherapy for use in patients with anaplastic lymphoma kinase (ALK)-positive advanced (not amenable to curative therapy) or metastatic non-small cell lung cancer (NSCLC).
Switzerland	5 March 2012	Treatment of previously treated locally advanced or metastatic anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC)
USA	26 August 2011	Treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test.
EU	23 October 2012	Treatment of adults with previously treated anaplastic lymphoma kinase (ALK)-positive advanced non small cell lung cancer (NSCLC).

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent Product Information please refer to the TGA website at <<http://www.tga.gov.au/hp/information-medicines-pi.htm>>.

II. Quality findings

There are no monographs available for the drug substance or drug product.

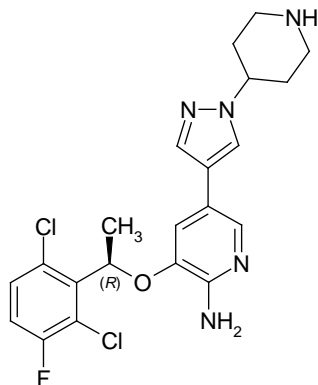
Crizotinib received orphan designation for this indication and the application has been treated with priority. Thus initial questions were raised informally on completion of the chemistry evaluation.

⁸ A notice of compliance with conditions is a form of market approval granted to a product on the basis of **promising** evidence of clinical effectiveness following review of the submission by Health Canada. "Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame" (Xalkori Product Monograph, downloaded from <<http://webprod3.hc-sc.gc.ca/dpd-bdpp/info.do?lang=eng&code=86999>> 11.6.2012).

Drug substance (active ingredient)

Crizotinib is a synthetic drug; the structure is shown below. Crizotinib is chiral, with one asymmetric centre; the *R* enantiomer is used. Structurally, it is not closely related to registered tyrosine kinase inhibitors.

Crizotinib chemical structure



Crizotinib is basic. It is soluble in aqueous acid but its solubility is lower at higher pH.

The particle size of the drug substance is controlled although the limits are relatively coarse. These limits give capsules with satisfactorily *in vitro* dissolution.

Limits for some impurities in the drug substance have been tightened and the specification was considered acceptable. The drug substance is stable.

Drug product

The product will be formulated in gelatin capsules, which will be available in 200 mg and 250 mg strengths under the trade name Xalkori. The capsules will be presented in bottles or Polyvinyl chloride (PVC)/Aluminium (Al) blisters (both as 60 capsule packs). The two strengths are in slightly different size capsules with different colours (white/pink or pink/pink) and have their respective strengths printed on them (as 'CRZ 200' or 'CRZ 250').

The capsule fill is made with conventional pharmaceutical excipients. The fill is manufactured using a conventional process.

No degradation of drug in the capsule has been seen. Stability data have been submitted that support a shelf-life for the product of 24 months, when stored below 30°C.

Biopharmaceutics

Crizotinib has low solubility at some physiologically relevant pHs (see above) and low to moderate permeability in Caco-2 cell monolayers. Nevertheless, Pfizer claims that absorption is not primarily limited by dissolution of the drug from the capsules. It is possible that bioavailability will be lower for achlorhydric patients or if concomitantly dosed with antacids etc.

Following a single oral (fasted) dose, crizotinib is absorbed fairly slowly, with a median time to maximum plasma concentration (T_{max}) of 4 to 6 hours. Plasma profiles are conventional. The mean volume of distribution was 1772 L, indicating extensive uptake of the drug into tissues.

Crizotinib is a substrate of CYP3A4 and 3A5 enzymes. Metabolism is complex, occurring *via* oxidation of the piperidine ring to a lactam, and also *via* *O*-dealkylation, with

subsequent conjugation as sulfates and glucuronides. *In vitro* studies using human liver microsomes have shown that crizotinib is a time-dependent inhibitor of CYP3A. Metabolites are considered less active or inactive.

Studies using radiolabelled crizotinib have shown approximately 63% and 22% elimination *via* urine and faeces, respectively. Unchanged crizotinib accounted for approximately 53% and 2.3% of the administered dose in faeces and urine, respectively. The terminal elimination half-life of crizotinib is approximately 42 hours following single oral doses.

Formulations

In clinical development the first formulation was a 'powder in a capsule', literally just drug (50 and 100 mg) in hard gelatin capsules; these were used in pivotal Study A8081001. Immediate release 50 and 100 mg tablets were developed for subsequent trials, and were also used in the pivotal Study A8081001, as well as bioequivalence and drug interaction studies. Higher dose tablets were not developed because of manufacturing problems related to the stickiness of the drug substance. The 200 and 250 mg "formulated capsules" ('FC' in the submission), as proposed for registration, were then developed as the commercial dosage form.

The application is supported by the ongoing, pivotal efficacy study, A8081001, together with supportive data from Study A8081005. Patients in Study A8081001 variously received both 'powder in capsule' and tablet doses. Patients in Study A8081005 received tablet doses.

Three bioavailability studies were submitted as part of this submission:

Study A8081010 This was a single dose, fasting, crossover, absolute bioavailability study in 14 healthy volunteers comparing a 1x50 + 2x100 mg crizotinib tablet dose with a 50 mg intravenous 2 h infusion. The oral bioavailability of the tablets was approximately 43%. Differences in metabolite profiles suggest that there is some gastrointestinal pre-systemic metabolism.

Study A8081011 This was a four-way crossover bioavailability study in 36 healthy volunteers providing:

- a bioequivalence comparison of 1x250 mg proposed capsules versus [1x50 + 2x100 mg] tablets versus [1x50+2x100 mg] 'powder in capsule' all fasting
- a study of the effect of food on the proposed 250 mg capsules.

The study A8081011 showed bioequivalence between the proposed capsules and both the 'powder in capsule' and tablet formulations used in clinical trials.

A small food effect on crizotinib absorption was observed: a high fat meal prior to dosing resulted in a 14% reduction in crizotinib exposure (Area under concentration-time curve (AUC)) and peak plasma concentration (C_{max}).

Study A8081008 This was a two-way crossover bioavailability study in 24 healthy volunteers comparing 250 mg crizotinib doses given as a 'powder in capsule' and as tablets [1x50 + 2x100 mg]. These formulations, both used in clinical trials, were bioequivalent.

Advisory committee considerations

This application was considered at the 144th (2012/2) meeting of the Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines:

- The PSC noted that crizotinib absorption is likely to be significantly reduced in achlorhydric patients and that there were limited data on interactions with medicines raising gastric pH.
- The Product Information should be amended to include effect on heart rate.

The PSC otherwise considered that there should be no objection to registration on pharmaceutical and biopharmaceutical grounds.

Quality summary and conclusions

Registration was recommended with respect to chemistry, quality control and biopharmaceutical aspects.

III. Nonclinical findings

Introduction

The submitted nonclinical dossier was in general accordance with the ICH (Topic S9) guideline on the Nonclinical evaluation for anticancer pharmaceuticals.⁹ The overall quality was generally adequate. All pivotal toxicity studies were conducted under Good Laboratory Practice (GLP) conditions using the proposed clinical route (PO).

“ALK-positive” is assumed to be EML4-ALK fusion protein positive for the purpose of this assessment.

Pharmacology

Rationale and mechanism of action

ALK encodes 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.⁴ This results in the expression of a ligand-independent and constitutively active tyrosine kinase with oncogenic activity. Crizotinib was initially developed as a c-Met (HGFR) inhibitor but during a general kinase screen was found to inhibit EML4-ALK oncogenic kinases. Inhibition of this fusion protein is intended to inhibit downstream signalling and reduce cell proliferation and inhibit tumour growth.

Primary pharmacology

Activity against EML4-ALK

Crizotinib was assessed for inhibitory activity against a number of kinases. Most relevant to the current indication is the efficacy of crizotinib against the EML4-ALK fusion oncogenic variants. In biochemical assays, crizotinib inhibited the catalytic activity of wild-type ALK (equilibrium rate constant (K_i) 0.50 nM) while in cellular kinase assays, crizotinib inhibited the autophosphorylation of the oncogenic variants EML4-ALK V1, V2, V3a and V3b in a panel of human NSCLC cell lines and cells engineered to express them. The 50% effective concentration (EC₅₀) values (27-74 nM) were similar or marginally below the free clinical trough plasma levels (~50 nM). In a cell-based functional assay,

⁹ EMEA/CHMP/ICH/646107/2008 Note for guidance on nonclinical evaluation for anticancer pharmaceuticals

crizotinib inhibited EML4-ALK V1 dependent cell proliferation and induced apoptosis in a human NSCLC cell line. The EC₅₀ values were similar to or below the free plasma fraction of crizotinib expected clinically, thus supporting the proposed indication.

In vivo, significant tumour growth inhibition (>70%) was seen in nu/nu mice bearing xenografts of EML4-ALK positive human NSCLC cells treated with ≥100 mg/kg/day PO crizotinib for up to 17 days. Partial regression (≥30% reduction in initial tumour volume) was seen in 4/21 mice treated with 200 mg/kg/day PO crizotinib for up to 17 days. Tumour growth inhibition correlated with a dose-dependent inhibition of phosphorylated EML4-ALK and downstream signalling pathways (STAT3, ERK1/2, Akt and PLCγ). Following 14 days of treatment at 200 mg/kg/day PO, there was a significant reduction in proliferating tumour cells (based on Ki67 positivity) and an induction of apoptosis (based on activated caspase-3 levels).

Based on studies in other tumour models, near complete inhibition (>90%) for the duration of the administration schedule would be required for a therapeutic benefit. PK/PD modelling indicated an EC₅₀ of 233–287 ng/mL for inhibition of EML4-ALK phosphorylation and tumour growth inhibition. As the clinical plasma trough levels 242–319 ng/mL are expected to be similar to the EC₅₀ for tumour growth inhibition, and inhibition is expected for the duration of the treatment period, the animal studies support the proposed clinical dose for the proposed indication.

Crizotinib treatment also resulted in a significant reduction in ALK levels and a dose-dependent induction of Akt levels, possibly as a result of feedback effects. There was also a dose-dependent increase in phosphorylated EGFR levels and a decrease in total EGFR levels, the reason for which is unknown. The implications of these effects during long-term crizotinib treatment are unknown.

The main human metabolites, crizotinib lactam diastereomer 1 and 2 (code PF-06270079 and PF-06270080, respectively), had some inhibitory activity against ALK kinase and inhibited phosphorylation by oncogenic EML4-ALK variants in cellular kinase assays. The inhibitory activity of the lactam diastereomer 1 was 5–7 times less potent than the parent drug, while the activity of the lactam diastereomer 2 was 3–5 times less potent than the parent drug. As the lactam constituted only ~17% of the pharmacologically-active material in human plasma and the activity was only ~20% of crizotinib, the lactam diastereomers are not expected to contribute significantly to the *in vivo* pharmacological activity.

No inhibitory activity was seen for two additional metabolites, O-dealkyl crizotinib lactam or O-desalkyl crizotinib, against ALK or EML4-ALK in either the enzyme or cell based assays (Ki >2000 nM in the enzyme assay and EC₅₀ >10,000 nM in the cell based assay). Therefore these metabolites are also not expected to contribute to the pharmacological activity during clinical use.

Resistance

No studies were submitted in the nonclinical dossier to assess potential resistance development to crizotinib. Resistance has been reported in patients receiving crizotinib. Some patients had developed secondary mutations in the tyrosine kinase domain of ALK, had increased ALK copy number, had an increase in the abundance of EGFR mutations or developed a KRAS mutation. The mechanism of resistance in some patients could not be

elucidated.¹⁰ While some mutations in EML4-ALK (namely L1196M and F1174L) confer resistance to crizotinib, these enzymes may still be sensitive to other ALK inhibitors.¹¹

Activity in other tumour models

Crizotinib was assessed for efficacy in other tumour models. Another ALK fusion protein, NPM-ALK, is found in a subset of non-Hodgkin's lymphoma (ALCL). Crizotinib inhibited the constitutive ALK phosphorylation of this fusion protein and demonstrated significant anti-tumour activity in mice bearing human NPM-ALK lymphoma xenografts. Crizotinib was originally developed as a c-Met/HGFR inhibitor. *In vitro*, crizotinib inhibited c-Met/HGFR phosphorylation, while anti-tumour efficacy was demonstrated in mice bearing human xenografts with dysregulated c-Met/HGFR activity (such as gastric carcinoma, glioblastoma and prostate carcinoma). Crizotinib had similar potency, both *in vitro* and *in vivo*, against NPM-ALK positive lymphomas and cells with dysregulated c-Met/HGFR signalling, as it had against EML4-ALK expressing cells.

Secondary pharmacodynamics

Activity against other kinases

Crizotinib was assessed for inhibitory activity against at least 100 human kinases in cell-based assays. As mentioned in the previous section, crizotinib inhibited c-Met/HGFR at clinically relevant concentrations (50% inhibitory concentration (IC₅₀) 5–112 nM compared to peak clinical free plasma levels ~100 nM). Inhibition was also seen at RON kinase and, based on an IC₅₀ of 190–300 nM, is likely to occur clinically. Some inhibition of Axl, Tie-2, TrkA and TrkB may occur clinically (IC₅₀ 294–580 nM). Crizotinib also had significant inhibitory activity at Abl, IRK and Lck, but based on high IC₅₀ values (1000–3000 nM), is unlikely to be clinically relevant. No significant activity was seen at the other ~95 kinases.

Activity at other targets

Crizotinib was assessed for inhibitory activity against a panel of 66 receptors, enzymes and ion channels at concentrations up to 10 nM (~100 times peak clinical free plasma levels). Clinically relevant activity was seen at the adrenergic α_{1A} receptor (antagonist), histamine H₁ receptor, serotonin 5-HT_{2B} (agonist) and 5-HT_{4e} receptors (antagonist), and calcium and sodium channels (K_i values 1.6–230 nM). Activity at these receptors could result in some neurological effects. Although, as there was limited penetration of the blood-brain barrier (cerebrospinal fluid (CSF) levels 3.4% of plasma exposure in rats), these effects may not be seen consistently during clinical use but may be seen in circumstances or patients that have higher central nervous system (CNS) exposure. Some activity was seen at the muscarinic M₁, M₂ and M₃ receptors, dopamine and serotonin 5-HT transporters, and serotonin 5-HT_{1B}, 5-HT_{2A} and 5-HT₇ receptors, but the K_i values (>600 nM) indicate these activities are unlikely to be clinically relevant.

Safety pharmacology

Specialised safety pharmacology studies covered the central nervous, cardiovascular and respiratory systems. Two of the three *in vivo* studies were GLP-compliant, while the design, conduct and reporting of the remaining study (assessing cardiovascular effects) were adequate to reveal any treatment related effects. *In vitro*, crizotinib inhibited the

¹⁰Doebele, R.C., A.B. Pilling, D.L. Aisner, T.G. Kutateladze, A.T. Le, A.J. Weickhardt, K.L. Kondo, D.J. Linderman, L.E. Heasley, W.A. Franklin, M. Varella-Garcia and D.R. Camidge. (2012) Mechanisms of resistance to crizotinib in patients with ALK gene rearranged non-small cell lung cancer. *Clin. Cancer Res.* 18: 1–11.

¹¹Heuckmann, J.M., M. Hölzel, M.L. Sos, S. Heynck, H. Balke-Want, M. Koker, M. Peifer, J. Weiss, C.M. Lovly, C. Grütter, D. Rauh, W. Pao and R.K. Thomas. (2011) ALK mutations conferring differential resistance to structurally diverse ALK inhibitors. *Clin. Cancer Res.* 17: 7394–7401.

neuronal Nav1.1 sodium channel (IC_{50} 0.85 nM; 9 times the clinical plasma C_{max} of ~ 0.1 μ M [free fraction]). Reduced locomotor activity was seen in rats treated with ≥ 75 mg/kg PO (exposure ratio at the C_{max} [ER_{Cmax}] 2.5). The No observable effect level (NOEL) was 10 mg/kg PO (ER_{Cmax} 0.2). There were no drug related effects on neuromuscular or reflex parameters. Decreased respiratory rate, probably related to CNS effects (decreased activity), was seen in rats treated with 500 mg/kg PO crizotinib, (ER_{Cmax} 5; ER_{Cmax} 2.5 at the NOEL 75 mg/kg). Due to the low exposure margins, CNS and respiratory depression may be seen clinically. Inhibition of the Nav1.1 sodium channel as well as the receptors above may indicate seizure potential in individuals that have a compromised blood-brain barrier, or in the event of co-administration with a P-glycoprotein inhibitor.

Crizotinib showed a concentration-dependent inhibition of hERG K^+ tail current (IC_{50} 1.1 nM), inhibition of cardiac L-type calcium channels in guinea pig ventricular myocytes and rat aorta (IC_{50} 14.6 nM and 0.83 nM, respectively) and inhibition of the cardiac Nav1.5 sodium channel (IC_{50} 1.56 nM). The IC_{50} values for hERG K^+ , L-type calcium channels and cardiac Nav1.5 sodium channels were 10 times peak free clinical plasma levels. Reduced action potential duration, consistent with inhibition of calcium channels, was seen in dog Purkinje fibres at 10 nM crizotinib (NOEL 1 nM; approximately 10 times clinical peak plasma levels). Decreased heart rate and increased QRS, PR and QT intervals were seen in dogs treated with crizotinib by intravenous (IV) infusion (plasma concentrations ~ 2000 ng/mL). The prolonged PR and QRS intervals are consistent with Nav1.5 sodium channel inhibition.¹² The exposure at the no effect level (C_{max} 557 ng/mL) was similar to the clinical exposure. In repeat-dose toxicity studies in dogs (at ≥ 5 mg/kg/day PO) QTc interval prolongation (compared to pretreatment values) was consistently seen during the treatment period. The trough levels of crizotinib were ≥ 58 ng/mL (~ 0.2 times the clinical C_{trough} levels at steady state, ~ 300 ng/mL). These data, along with *in vitro* findings, suggest the potential for QT interval¹³ prolongation and other cardiac abnormalities (prolonged PR interval and bradycardia) during clinical use.

Pharmacokinetics

Following oral dosing, the rate of absorption was moderate and similar across animals (mice, rats, dogs and monkeys) and humans (T_{max} generally 4–7 h). Oral bioavailability was low to moderate in rats, dogs, monkeys and humans (26–66%). Exposure (AUC) to crizotinib was generally dose proportional in mice, rats and dogs. Exposure was consistently higher (~ 2 times) in male rats compared to their female counterparts, probably related to greater metabolism to the lactam and the sulfate conjugate of crizotinib and biliary excretion in the latter sex. There were no significant sex differences in dogs or monkeys. The elimination half-life was moderate in rats, dogs and monkeys (8–17 h) and slightly longer in humans (42 h). Clearance was similar in rats, monkeys and humans (29–47 mL/min/kg) and slower in dogs (9–13 mL/min/kg). Hepatic clearance values were similar to *in vivo* blood clearances for rats, dogs, monkeys and humans. No significant accumulation was seen with repeat dosing to rats and dogs.

The main human metabolite, crizotinib lactam (both diastereomers) was also a prominent metabolite in rats but not detected in the plasma of dogs, although this metabolite was formed in trace amounts in dog hepatocytes. *In vivo* metabolism studies were not conducted in monkeys but the lactam was produced *in vitro* in monkey hepatocytes. Peak plasma levels of the lactam occurred at a similar time to crizotinib in both rats and humans, suggesting significant first-pass metabolism. Consistent with this, exposure to the

¹²Erdemli, G., A.M. Kim, H. Ju, C. Springer, R.C. Penland and P.K. Hoffmann. (2012) Cardiac safety implications of hNAV1.5 blockade and a framework for pre-clinical evaluation. *Frontiers Pharmacol.* 3: 1–9.

¹³QT interval: 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. A prolonged QT interval is a risk factor for ventricular tachyarrhythmias and sudden death.

lactam in human subjects was higher following oral dosing compared to IV dosing (Clinical Study A8081010). In rats, exposure to the lactam was 9–16% that of crizotinib. Exposure to the lactam in human subjects was ~24% that of the parent drug after a single dose. In both rats and humans, exposure to diastereomer 1 was consistently ~2 times higher than exposure to diastereomer 2.

Plasma protein binding of crizotinib was moderate to high and, on average, similar in rabbit, monkey and human samples (90–93%) and higher in mouse, rat and dog samples (94–96%). No clear concentration-dependent trends were evident. Plasma protein binding appeared to be largely due to albumin in human samples. Protein binding of the lactam metabolite was also high in rat and human plasma (97–99% in rats and 93–95% in humans). The extent of binding by both diastereomers was similar. Crizotinib distributed largely equally in blood cells and plasma in mouse, rat, dog and human samples. The volume of distribution was greater than the total body water in mice, rats, dogs, monkeys and humans. Consistent with this, tissue exposure to radioactivity was generally 20–40 times higher than in blood following oral administration of radiolabelled (¹⁴C)-crizotinib to rats. Aside from organs of excretion (liver and kidney), the adrenals, pituitary and preputial glands, spleen and eye and associated tissues (lacrimal gland, uveal tract and Harderian gland) had high levels of radioactivity. The high level of exposure in pigmented tissues (skin and eye) suggests some affinity for melanin. Exposures in the eye and uveal tract were >1000 times those in blood and elimination from these tissues was very slow (half life ($t_{1/2}$) >500 h). Significant radioactivity in bile was suggestive of biliary excretion, consistent with the findings of the rat excretion study (see below).

Metabolism of crizotinib involved oxidation of the piperidine ring to form crizotinib lactam and other metabolites, O-dealkylation, loss of the piperidine ring and conjugation (sulfation and/or glucuronidation) of crizotinib and its metabolites. Unchanged drug was the predominant drug related circulating species in rats, dogs and human subjects. Crizotinib lactam was a significant metabolite in the plasma of rats and humans, but not detected in dogs. Five minor human metabolites (<10% of total drug related substances) were not detected in the animal species (rat and dog) used in toxicity studies. These minor metabolites included O-dealkylated crizotinib lactam (M4, in faeces), sulfate conjugate of O-dealkylated crizotinib (M3, in plasma, urine and faeces) and hydroxylated/glucuronidated O-desalkylated crizotinib (M5, in urine), hydroxylated O-dealkylated crizotinib lactam (M6, in faeces) and a cysteine conjugate of O-desalkylated crizotinib lactam (M9, in urine). Most of these metabolites were detected at low levels in human urine and/or faeces with only one (sulfate conjugate of O-dealkylated crizotinib) in plasma. Nonclinical characterisation of these metabolites is not warranted¹⁴. Other minor human metabolites were formed in rats.

In vitro studies indicated a role for CYP3A4/5 in the formation of both crizotinib lactam and O-dealkylated crizotinib. There was only a minor contribution by CYP2C8, 2C19 and 2D6. The lactam was only observed in microsome incubations when liver cytosol was added, suggesting a role for a factor or enzyme in the fraction. The identity of this factor was not determined but was suggested by the sponsor to be aldehyde oxidase. The identity of enzymes involved in the conjugation reactions was not determined.

Excretion of drug related material was predominantly *via* the faeces in rats, dogs and humans (62–87% of the administered dose). Biliary excretion was demonstrated in rats. Unchanged drug was the dominant species in faeces, although biliary excretion was predominantly of glucuronide and sulfate conjugates. The extent of biliary excretion appeared to be greater in female rats compared to their male counterparts, probably as a

¹⁴ICH harmonised tripartite guideline: Guidance on nonclinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals M3(R2). 2009.

result of the greater formation of sulfated crizotinib in this sex. Drug related material was detected in the vomit/emesis of dogs.

Pharmacokinetic drug interactions

Crizotinib is metabolised to crizotinib lactam by CYP3A4/5, undergoing significant first pass metabolism, and it is also a substrate of P-glycoprotein. Therefore, inhibitors or inducers of CYP3A enzymes and/or P-glycoprotein could alter the plasma kinetics of crizotinib. Co-administration with a P-glycoprotein inhibitor could indicate a higher risk for CNS effects, such as seizures, due to greater CNS exposure to crizotinib (see above). Crizotinib is not a substrate of BCRP.

No significant inhibition of CYP1A2, 2C8, 2C19 or 2D6 was seen with crizotinib concentrations up to 30 μM (27 times the peak clinical plasma levels). Only weak inhibition of CYP2B6 and CYP2C9 was seen, with IC_{50} 22–23 μM (~20 times the peak clinical plasma levels) and is unlikely to be clinically relevant. Crizotinib demonstrated time-dependent inhibition of CYP3A activity with a maximal rate of enzyme inactivation (k_{inact}) of 0.11 min^{-1} and concentration of inhibitor associated with 50% of maximal enzyme inactivation rate (K_i) of 3.0 μM . The IC_{50} values in assays with 30 min preincubation were 0.41–0.78 μM .

There was no significant induction of CYP1A2 activity or messenger ribonucleic acid (mRNA) levels (up to 7 μM), but significant induction of CYP2B6, 2C8, 2C9 and 3A4 was observed. The no effect concentration was 0.5 μM for CYP2C9 and 2B6, 0.25 μM for 3A4, and <0.25 μM for CYP2C8 (less than or equal to the clinical C_{max}). Although induction of CYP2B6 and 3A4 expression occurred, crizotinib is also an inhibitor of these two isoforms, and no net effect on CYP3A4 activity was observed *in vitro*, suggesting CYP3A4 induction is unlikely to be clinically relevant. The sponsor states a similar study is currently in progress to assess the net effect on CYP2B6 activity. Therefore, no firm conclusions as to the clinical relevance of CYP2B6 induction can be made. The sponsor provided an argument based on mathematical modelling to suggest the CYP2C8 and CYP2C9 induction is not likely to be clinically relevant. However, this modelling contained several caveats and the sponsor acknowledges *in vitro-in vivo* correlations for non 3A CYP enzymes has not been established. Therefore, crizotinib induction of CYP2C8 and 2C9 needs to be considered as clinically relevant until adequate *in vivo* data are presented to suggest otherwise.

There was no clinically relevant inhibition of the hepatic transporters, hOATP1B1 and hOATP1B3 (IC_{50} 44–48 μM ; 40–44 times the peak clinical plasma levels) or BCRP (up to 27 times the peak clinical plasma levels).

Crizotinib was shown to be an inhibitor of P-glycoprotein (IC_{50} 5.8 μM). While the IC_{50} values are only marginally above peak clinical plasma levels (2.7–5 times), they are well below the maximum expected concentration in the intestinal lumen (2221 μM ¹⁵). Therefore, crizotinib is likely to increase the plasma exposure of substrates of CYP3A and P-glycoprotein.

Toxicology

Repeat-dose toxicity

GLP-compliant repeat dose toxicity studies of up to 3 months duration were conducted in rats and dogs. Non-GLP studies of 28 days duration in female mice and Cynomolgus monkeys (both sexes) were also submitted. Dosing was by the intended clinical route (PO)

¹⁵Based on a 250 mg dose in 250 mL (EMA guideline on the Investigation of Drug Interactions).

in all studies. The use of both sexes, the group sizes used and the duration of the pivotal studies are considered acceptable, according to ICH S9⁹. The highest doses used resulted in reduced body weight gain or body weight loss in rodents and monkeys, and gastrointestinal disturbances (vomiting and diarrhoea) in dogs, suggesting the maximum tolerated dose was achieved. For an anti-cancer drug, high relative exposures (based on AUC) were achieved at the highest doses (26 in mice and 8–12 in the other animal species; Table 2). However, these maximum relative exposures are somewhat lower when taking into account species differences in free fraction; ER_{AUC} based on the free fractions at the highest doses were 10 in mice and monkeys and 4–6 in rats and dogs. Exposure ratios quoted below are based on the total rather than the free fraction.

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 C_{min} levels at the highest doses in the pivotal 3 month rat and dog studies were 2-4 fold higher than the clinical C_{trough} levels, suggesting animals were exposed to the drug at a clinically relevant level for the duration of the study.

Table 2. Relative exposure in repeat-dose toxicity studies

Species	Study; Treatment duration	Dose (mg/kg/day) PO	Crizotinib				Crizotinib lactam	
			AUC _{0-24h} (µg.h/mL)	C _{max} (ng/mL)	ER _{AUC}	ER _{C_{max}}	AUC _{0-24h} (µg.h/mL)	ER _{AUC}
Mouse (C57Bl6)	04HGF003 28 days	40	18.2	1510	4	3	–	–
		200	108	9410	26	20	–	–
Rat (SD)	04HGF004 7 days	50 (♂/♀)	13/5.9	900/510	3/1	1.9/1.1	–	–
		150 (♂/♀)	31/17	1900/1400	7/4	4/3	–	–
	05137 1 month	10 (♂/♀)	2.2/1.1	250/220	1/0.2	0.5/0.5	–	–
		50 (♂/♀)	13.5/8.4	1040/880	3/2	2/2	–	–
		150 (♂/♀)	41.6/14.4	3240/1290	10/3.5	7/3	–	–
	09GR347 3 months [pivotal]	10 (♂/♀)	3.75/1.06	343/120	0.9/0.3	0.7/0.3	–	–
		30 (♂)	14.3	1290	3	2.7	1.81	1.8
		50 (♀)	10.1	813	2	2	3.34	3.3
		100 (♂)	37.6	2090	9	4.4	5.41	5.4
		250 (♀)	32.7	2090	8	4	5.07	5.1

Species	Study; Treatme	Dose (mg/kg/ day) PO	Crizotinib				Crizotinib lactam	
			Plasma C _{max}	Plasma AUC ₀₋₂₄	Urine C _{max}	Urine AUC ₀₋₂₄	Urine C _{max}	Urine AUC ₀₋₂₄
Dog (Beagle)	05162 1 month	1	1.35	87	0.3	0.2	–	–
		6	7.85	523	2	1	–	–
		20	36.1	2224	9	4.7	–	–
	09GR346 3 months [pivotal]	1	1.25	81	0.3	0.2	–	–
		5	8.89	545	2	1	–	–
		25	34.7	1820	8	3.8	–	–
Monkey (Cynom ol-gus)	3584 28 days	50	49	2645	12	6	–	–
Human	A8081001 & A8081005 Steady state	250 mg bid	4.16	478	–	–	1.0 ^a	–

^aestimated based on the lactam exposure being 24% of the exposure to the parent; –=not determined or not relevant

Major toxicities

The major target organs for crizotinib were the liver, gastrointestinal tract, bone marrow, heart and ocular tissue with some effects also observed in lymphoid organs in rats. Vacuolation and the presence of foamy macrophages were also seen in multiple tissues of treated rats.

Hepatotoxicity

Drug related, reversible elevations in liver enzyme levels (alanine transaminase (ALT), aspartate transaminase (AST) and occasionally gamma glutamyl transpeptidase (GGT) or alkaline phosphatase (ALP)) were seen in all species used in the toxicity studies and single cell necrosis and bile duct vacuolation and hyperplasia in rats. Mice treated with ≥ 40 mg/kg/day PO crizotinib (exposure ratio based on AUC [ER_{AUC}] 4) for 28 days had 30–44% higher levels of AST and ALT. Levels of liver enzymes in treated rats (≥ 10 mg/kg/day in males and ≥ 150 mg/kg/day in females; ER_{AUC} 0.9 and 3.5, respectively), dogs (≥ 25 mg/kg/day in males; ER_{AUC} 8) and monkeys (50 mg/kg/day; ER_{AUC} 12) were 2–6 times (ALT) and 1.3–4 times (AST) the level seen in concurrent controls. The elevation in liver enzymes was sometimes associated with increased liver weights, but no histopathological correlates were seen in any species except for a one-month study in rats with a crizotinib containing higher levels of impurities, in which bile duct vacuolation and hyperplasia and single cell necrosis in the liver were observed in male rats at 50 mg/kg/day (ER_{AUC} 4). Although there were no obvious hepatic lesions in other studies, given the magnitude of the increase in liver enzymes in all species and histopathology in rats, there is a concern for potential hepatic injury.¹⁶ The NOEL for an elevation in ALT levels (a marker for liver

¹⁶Boone, L., D. Meyer, D. Cusik, D. Ennulat, A. Provencher Bollinger, N. Everds, V. Meador, G. Elliott, D. Honor, D. Bounous and H. Jordan. (2005) Selection and interpretation of clinical pathology indicators of hepatic injury in preclinical studies. Vet. Clin. Pathol. 34: 182–188.

injury) in female rats was 50 mg/kg/day PO and in dogs was 5 mg/kg/day PO (ER_{AUC} 2 for both). A NOEL was not established in mice, Cynomolgus monkeys and male rats. The consistency of this finding across species and across studies with exposures at the NOEL marginally above the clinical exposure, indicate hepatic toxicity with elevated ALT, AST and possibly GGT levels, is likely during clinical use. Crizotinib inhibits c-Met (HGFR) at clinically relevant concentrations. HGFR signalling plays a role in liver regeneration and studies in conditional c-Met knockout mice indicate inhibition of this signalling pathway delays healing after liver injury, thereby enhancing liver damage by increasing apoptosis/necrosis of hepatocytes.^{17, 18} Therefore, greater hepatotoxicity may be expected with concomitant use of drugs that cause any form of liver injury.

Gastrointestinal disturbances

Vomiting and/or diarrhoea were seen in rats (≥ 150 mg/kg/day for 7 days; ER_{AUC} at least 4), dogs (≥ 5 mg/kg/day; ER_{AUC} 2) and Cynomolgus monkeys (50 mg/kg/day; ER_{AUC} 12). In dogs, vomiting generally occurred 1–2 h post-dose and the incidence and frequency decreased during study duration, suggesting some adaptability. Drug related material was detected in the vomit. Ulceration, hyperkeratosis, inflammation and hyperplasia were seen in the stomach of rats treated with 500 mg/kg/day PO crizotinib (a lethal dose). In the pivotal study, a dilated ileum was seen in a number of rats treated with the highest doses (ER_{AUC} 8–9). Multifocal mucosal erosions and ulcerations were seen in the caecum of the premature decedent in the monkey study. In monkeys, hypophosphataemia correlated with the observed gastrointestinal disturbances. Exposure (AUC) at the NOEL for gastrointestinal findings in rats and dogs was 2 and 0.3, respectively, times the clinical exposure. A NOEL was not established in monkeys. Overall, the studies indicate gastrointestinal disturbances (vomiting and diarrhoea) may be seen in patients taking crizotinib.

Bone marrow toxicity

Mild to moderate bone marrow hypocellularity was consistently seen in rats at ≥ 150 mg/kg/day PO (ER_{AUC} 10) and monkeys at 50 mg/kg/day PO (ER_{AUC} 12). Myeloid cell debris was seen in the bone of rats treated with ≥ 30 mg/kg/day (ER_{AUC} 3) with myeloid/erythroid necrosis seen at the higher dose of 2000 mg/kg/day for 2 days. The bone marrow hypocellularity in rats, dogs and monkeys and decreased percentage of erythroid cells in rats corresponded with decreased peripheral red cell parameters and reticulocytes in all species. Exposure at the NOEL for effects on red cell parameters was 2–3 and 0.3 times the clinical exposure in rats and dogs, respectively. A NOEL was not established in monkeys. These bone marrow effects are likely related to the pharmacological action of crizotinib on c-Met, which has a role in the proliferation of myeloid and erythroid progenitor cells in the bone marrow.^{19,20} Minimal to moderate decreases in bone formation were seen in immature male rats treated with 150 mg/kg/day PO crizotinib (ER_{AUC} 10). The findings indicate a risk for anaemia and possibly other cytopaenias in patients and a risk for an inhibitory effect on growing bones, which may have significance in a paediatric population. All bone marrow effects were reversible upon cessation of treatment.

¹⁷Nakamura, T., K. Sakai, T. Nakamura and K. Matsumoto. (2011) Hepatocyte growth factor twenty years on: Much more than a growth factor. *J. Gastroent. Hepatol.* 26: 188–202.

¹⁸Huh, C.-G., V.M. Factor, A. S nshez, K. Uchida, E.A. Conner and S.S. Thorgeirsson. (2004) Hepatocyte growth factor/c-met signaling pathway is required for efficient liver regeneration and repair. *Proc. Natl. Acad. Sci. USA* 101: 4477–4482.

¹⁹Kmieciak, T.E., J.R. Keller, E. Rosen and G.F. Vande Woude. (1992) Hepatocyte growth factor is a synergistic factor for the growth of hematopoietic progenitor cells. *Blood* 80: 2454–2457.

²⁰Ikehara, S. (1996) Role of hepatocyte growth factor in hemopoiesis. *Leukemia Lymphoma* 23: 297–303.

Ocular toxicity

In the tissue distribution study, a significant amount of drug related material was seen in the eye and associated tissue with exposures >1000 times those in blood. Elimination of drug related material from this tissue was also very slow ($t_{1/2}$ >500 h). Opacity was seen in the eye of 1 mouse treated with 200 mg/kg/day PO crizotinib (ER_{AUC} 26). No drug related effects were detected during ophthalmological examinations in rats treated with >100 mg/kg/day PO or dogs treated with 25 mg/kg/day PO crizotinib for up to 3 months (ER_{AUC} 8–10). As visual disturbances were seen in clinical trials with crizotinib, a specialised study was conducted in male pigmented rats treated with 100 mg/kg/day PO crizotinib for 4 weeks, to assess effects on electroretinogram measurements. A significant reduction in the rate of retinal dark adaptation was seen, indicating some impairment of visual function. Crizotinib levels in the vitreous humour were 0.63 times those in the plasma.

Phospholipidosis

Cellular vacuolation and foamy macrophages were seen in multiple organs (pituitary, GI tract, prostate, bile duct, lungs and mesenteric lymph node) of rats treated for 3 months with crizotinib (≥ 30 mg/kg/day in males and at 250 mg/kg/day in females; ER_{AUC} ≥ 3) and vacuolated lymphocytes in the 1 month study in male rats at 150 mg/kg/day (ER_{AUC} 10). Transmission electron microscopy and ultrastructural analyses suggested these findings were consistent with phospholipidosis, probably as a result of the cationic amphiphilic chemical nature of crizotinib. The vacuolation/presence of foamy macrophages was generally reversible after a 2 month treatment-free period, although prostatic vacuolation was still seen in 1 out of 5 males. Phospholipidosis was not seen in other animal species (mice, dogs and monkeys), but the studies in mice and monkeys were of short duration (28 days) and not GLP-compliant. In dogs, the maximum exposure in the pivotal 3 month study without evidence of phospholipidosis was 8 times the anticipated clinical exposure. It is uncertain if phospholipidosis in animals is predictive for humans and it is also uncertain if it is merely an adaptive response or has toxicological implications.^{21, 22, 23} Given the uncertainty with regard to toxicity and the occurrence at low exposures (NOEL 10 mg/kg/day for males and 50 mg/kg/day for females; ER_{AUC} 1–2), the clinical relevance of phospholipidosis in rats cannot be dismissed. It is unclear whether pneumonitis occurred in patients was associated with phospholipidosis, but the rapid development of pneumonitis (after around 12 days of treatment) in patients is not concordant with phospholipidosis (histiocytosis) induction in rats, which was seen after 3 months of treatment but not after dosing for one month.

Heart

Increased absolute and/or bodyweight-relative heart weights were seen in rats treated with 150 mg/kg/day PO crizotinib for 1 month (ER_{AUC} 3.5) and female dogs treated with ≥ 5 mg/kg/day PO crizotinib for 3 months (ER_{AUC} 2). No significant effects on heart weight were seen in mice and organ weights were not reported in the monkey study. The cardiomegaly may be related to the inhibitory effects of crizotinib on the sodium, potassium and/or calcium channels in cardiac tissue. These data indicate a risk for hypertrophic cardiomyopathy during clinical use. In the pivotal 3 month rat study and the 1 month study with a crizotinib containing higher impurities, there was an increase in the incidence and severity of myonecrosis/myofibrosis in males treated with ≥ 30 mg/kg/day PO crizotinib for 3 months (ER_{AUC} 3) and 50 mg/kg/day for one month (ER_{AUC} 4). No microscopic changes were seen in the heart of treated female rats or dogs after 3 months

²¹Reasor, M.J., K.L. Hastings and R.G. Ulrich. (2006) Drug induced phospholipidosis: issues and future directions. *Expet. Opin. Drug Saf.* 5: 567–583.

²²Reasor, M.J., K.L. Hastings and R.G. Ulrich. (2006) Drug induced phospholipidosis: issues and future directions. *Expet. Opin. Drug Saf.* 5: 567–583.

²³Alakoskela, J.-M., P. Vitovič and P.K.J. Kinnunen. (2009) Screening for the drug-phospholipid interaction: correlation to phospholipidosis. *ChemMedChem* 4: 1224–1251.

(longest studies). After a 2 month treatment-free period, myofibrosis was seen in male rats that had previously received 100 mg/kg/day crizotinib. The sponsor claimed that these cardiac lesions were an exacerbation of murine progressive cardiomyopathy, for which there is no human correlate. However, compelling evidence for a lack of clinical relevance was not provided. Given the low exposures (ER_{AUC} 0.9 at the NOEL in male rats), a lack of sufficiently long studies in other species to suggest this is a “species-specific” effect combined with the other known cardiovascular effects of the drug, these cardiac lesions must be considered clinically relevant until sufficient evidence is provided to suggest otherwise.

Other effects

An increase in inflammatory cells (neutrophils, eosinophils and monocytes) was seen in treated rats (≥ 100 mg/kg/day PO; ER_{AUC} 8–9), dogs (25 mg/kg/day PO; ER_{AUC} 8) and monkeys (50 mg/kg/day; ER_{AUC} 12). Haematology analyses were not conducted in the mouse study. The exposure at the NOEL for this finding in both rats and dogs is estimated to be ~2 times the clinical AUC. A NOEL was not established in monkeys. The reason for the increase in inflammatory cells is unclear.

In the studies of up to 1 month duration in male rats, lymphoid depletion was seen in the thymus, spleen, mesenteric lymph node and/or gastrointestinal associated lymphoid tissue (GALT) at doses ≥ 50 mg/kg/day PO crizotinib (ER_{AUC} 3). These findings were not seen in the 3 month rat study or in any other species and are of uncertain clinical relevance.

Genotoxicity and carcinogenicity

The potential genotoxicity of crizotinib was assessed in the standard battery of tests. A suitable set of *S. typhimurium* and *E. coli* strains were used in the bacterial mutagenicity assay and animals of both sexes were used in at least one of the *in vivo* micronucleus assays. The conduct of the studies was in accordance with ICH guidelines (ICH S2(R1): *Guidance on genotoxicity testing and data interpretation for pharmaceuticals intended for human use*). Concentrations/doses were appropriate. Crizotinib was not mutagenic in the bacterial assay but an increase in both numerical and structural aberrations was seen in human peripheral lymphocytes in the *in vitro* chromosomal aberration assay, while positive results were seen in both *in vitro* and *in vivo* micronucleus tests. Kinetochore staining in the *in vitro* assay confirmed crizotinib was aneugenic. The sponsor claimed the increase in structural aberrations was secondary to the aneugenicity of crizotinib. However, the number of micronuclei staining positive for kinetochores was only moderate (67–84% compared to 98% in the control) and only a single sample per concentration was tested, limiting the power of the study. Therefore, based on a lack of robust data to suggest otherwise, crizotinib is considered to be both clastogenic and aneugenic.

Rat S9 fractions²⁴ were used for metabolic activation in the *in vitro* assays and the rat was the chosen species in the *in vivo* micronucleus study. While not all circulating human metabolites are formed in rats or by rat S9 fractions (see *Pharmacokinetics*), the main human metabolite, crizotinib lactam, was also a major metabolite in rats.

No carcinogenicity studies were conducted, which is considered acceptable given the intended patient group (ICH S9: *Nonclinical Evaluation for Anticancer Pharmaceuticals*).

Reproductive toxicity

Reproductive toxicity studies were restricted to effects on embryofetal development in rats and rabbits, which is considered acceptable considering the intended indication and

²⁴Rat liver S9 fraction is used to mimic the mammalian metabolic conditions so that the mutagenic potential of metabolites formed by a parent molecule in the hepatic system can be assessed. Some compounds, like benzo[*a*]pyrene, are not mutagenic themselves but their metabolic products are mutagenic.

patient group (ICH S9: *Nonclinical Evaluation for Anticancer Pharmaceuticals*)⁹. Nevertheless, findings in the rat repeat-dose toxicity studies (prostate and seminal vesicle atrophy and minimal degeneration of pachytene spermatocytes in the testes in males at ≥ 50 mg/kg/day [NOEL 10 mg/kg/day; ER_{AUC} 1] and single cell necrosis in the ovary of females treated with 500 mg/kg/day [NOEL 150 mg/kg/day; ER_{AUC} 4], combined with its aneugenic activity indicate crizotinib may have effects on fertility.

No studies were conducted to assess placental transfer of crizotinib or its metabolites. In the pivotal embryofetal development studies, adequate animal numbers were used and the treatment periods were appropriate for that type of study and the species chosen. Maximum exposures achieved were generally low, reaching up to 5 times and 3 times the clinical exposure in rats and rabbits, respectively (Table 3). The maximum tolerated dose was clearly achieved in rats based on suppression of body weight gain, and the high dose in the pivotal rabbit study was chosen based on signs of toxicity at ≥ 75 mg/kg/day in the pilot study. Nonetheless, the low tested exposures, particularly in rabbits, and the lack of metabolism data in rabbits suggest the embryofetal toxicity potential of crizotinib in humans might not have been fully assessed by the animal studies.

Table 3. Relative exposure in embryofetal toxicity studies

Species	Study	Dose (mg/kg/day PO)	AUC _{0-24h} (µg.h/mL)	Exposure ratio [#]
Rat (SD)	Embryofetal development (Study 10GR072)	10	0.67	0.16
		50	5.0	1.2
		200	20.8	5
Rabbit (NZW)	Embryofetal development (Study 10GR073)	10	0.57	0.14
		25	2.7	0.65
		60	12.6	3
Human	A8081001 & A8081005 Steady state	250 mg bid	4.16	–

[#] = animal:human plasma AUC_{0-24h}

Reduced fetal weights were seen in both species at the highest doses (exposure at the NOEL 1.2 and 0.65 times the clinical AUC in rats and rabbits, respectively), suggesting crizotinib has the potential to retard fetal growth. An increased incidence of skeletal variations was seen in rats, but only in the context of maternotoxicity, while no significant treatment related fetal variations or malformations were seen in rabbits. Crizotinib has pharmacological activity against c-Met and RON kinase, both of which play a role in embryofetal development. Loss of either c-Met or RON kinase has been shown to be embryolethal in mice.^{25, 26} The stage in which *in utero* deaths occurred would not have been assessed in the submitted embryofetal toxicity studies and therefore an effect of crizotinib on early embryonic development and survival has not been adequately assessed. Furthermore, crizotinib is aneugenic which could result in an increase in the number of resorptions in the first trimester. Based on the potential for crizotinib to have adverse effects on embryofetal development, placement in Pregnancy Category D²⁷ is appropriate.

No studies have been conducted to assess excretion of crizotinib or its metabolites into milk and the effects on peri/postnatal development have not been assessed. This is considered acceptable given the intended indication and patient group (ICH S9: *Nonclinical Evaluation for Anticancer Pharmaceuticals*)⁹; however, several findings in the submitted pharmacology and toxicology studies indicate a risk for adverse effects in the postnatal and juvenile periods (see *Paediatric use*).

Paediatric use

No dedicated juvenile animal studies have been conducted. In the 1 month repeat-dose toxicity study in rats, where treatment was initiated during an immature stage (age 7 weeks), a minimal to moderate decrease in bone formation was seen in males treated with 150 mg/kg/day PO crizotinib (ER_{AUC} 10). This is consistent with pharmacological inhibition of c-Met, which has a role in bone formation (see *Repeat-dose toxicity*). This finding indicates a risk for growth retardation in the paediatric population. *In vitro*, crizotinib inhibited the neuronal Nav1.1 sodium channel as well as numerous other neuroactive receptors. Furthermore, wild-type ALK for which crizotinib has inhibitory activity towards, plays an important role in neurodevelopment and neurogenesis.^{28, 29} This indicates a risk of seizures and other adverse CNS effects in young individuals who do not have a fully formed blood-brain barrier.

Local tolerance

Crizotinib was identified to have haemolytic potential at >0.25 mg/mL in human and rabbit blood. Crizotinib in sodium acetate buffer at pH 4.4 caused concentration-dependent irritation when administered perivascularly to rabbit ears. Mild local irritation was observed following IV injection, and the effects were only marginally greater than the dosing vehicle. The concentrations of crizotinib resulting in haemolysis far exceed the

²⁵ Bladt, F., D. Riethmacher, S. Isenmann, A. Aguzzi and C. Birchmeier. (1995) Essential role for the c-met receptor in the migration of myogenic precursor cells into the limb bud. *Nature* 376: 768–771.

²⁶ Muraoka, R.S., W.Y. Sun, M.C. Colbert, S.E. Waltz, D.P. Witte, J.L. Degen and S.J. Friezner Degen. (1999) The RON/STK receptor tyrosine kinase is essential for peri-implantation development in the mouse. *J. Clin. Invest.* 103: 1277–1285.

²⁷ Pregnancy 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.

²⁸ Bilsland, J.G., A. Wheeldon, A. Mead, P. Znamensky, S. Almond, K.A. Waters, M. Thakur, V. Beaumont, T.P. Bonnert, R. Heavens, P. Whiting, G. McAllister and I. Munoz-Sanjuan. (2008) Behavioral and neurochemical alterations in mice deficient in anaplastic lymphoma kinase suggest therapeutic potential for psychiatric indications. *Neuropsychopharmacol.* 33: 685–700.

²⁹ Weiss, J.B., C. Xue, T. Benice, L. Xue, S.W. Morris and J. Raber. (2012) Anaplastic lymphoma kinase and leukocyte tyrosine kinase: functions and genetic interactions in learning, memory and adult neurogenesis. *Pharmacol. Biochem. Behav.* 100: 566–574.

clinical C_{\max} (0.5 µg/mL) and these findings are not considered a concern for the current indication.

Phototoxicity

Crizotinib absorbs light in the 290–700 nm range with a maximum molar extinction coefficient of 6815 M⁻¹cm⁻¹ at 322 nm and was shown to be probably phototoxic *in vitro* to cultured cells. In the tissue distribution study, crizotinib had some affinity to melanin with exposures in pigmented skin >100 times those in blood. Therefore, phototoxic reactions on sun-exposed skin may be possible during clinical use.

Impurities

Four impurities in the drug substance were specified at limits above the ICH qualification threshold. Two of these were considered qualified at the proposed limits by the submitted data. The remaining two impurities were not considered qualified at the proposed limits. This has been referred to the quality evaluator.

Nonclinical summary and conclusions

- The submitted nonclinical dossier was in general accordance with the ICH guideline on the nonclinical evaluation of anticancer pharmaceuticals. The overall quality was generally adequate.
- Crizotinib inhibited EML4-ALK kinase activity, resulting in inhibition of downstream signalling with a subsequent inhibition of cell proliferation and an induction of apoptosis in *in vitro* and/or *in vivo* models of human (EML4-ALK-positive) NSCLC. Significant tumour growth inhibition was seen in mice bearing xenografts of EML4-ALK positive human NSCLC. The efficacious doses/concentrations were at or below that anticipated clinically, thus supporting the proposed clinical use. The main human metabolite, crizotinib lactam, was also pharmacologically-active, but due to its lower potency and relatively low abundance, is not expected to contribute significantly to the *in vivo* pharmacological activity.
- Crizotinib had similar activity in models of other cancers (NPM-ALK positive non-Hodgkin's lymphoma and tumour cells with dysregulated c-Met/HGFR activity). Inhibitory activity was seen against c-Met/HGFR, RON kinase and 4 other kinases at clinically relevant concentrations. In a screen against a panel of 66 receptors, enzymes and ion channels, clinically relevant activity was seen at the adrenergic α1A receptor, histamine H1 receptor, serotonin 5-HT2B and 5-HT4e receptors, and calcium and sodium channels. Some neurological effects may be seen clinically.
- Safety pharmacology studies covered the CNS, cardiovascular and respiratory systems. Decreased respiratory rate and reduced activity were seen in rats at low exposure margins and may be seen clinically. Inhibition of the neuronal Nav1.1 sodium channel indicates a risk for seizures in individuals that have a compromised blood-brain barrier or in the event of co-administration with a P-glycoprotein (P-gp) inhibitor. *In vitro*, crizotinib inhibited hERG K⁺, cardiac L-type calcium channels and the Nav1.5 sodium channel at clinically relevant concentrations. These ion channel effects manifested as prolonged QT(c), PR and QRS intervals in electrocardiograms (ECGs) from treated dogs. Bradycardia was also observed. As the *in vitro* and *in vivo* cardiovascular findings occurred at clinically relevant concentrations/doses, QT prolongation as well as other serious cardiac and haemodynamic abnormalities (prolonged PR interval and bradycardia) may be seen during clinical use.
- Following oral dosing, the rate of absorption was moderate and similar across animals and humans. Bioavailability was low to moderate in all species (26–66%), with significant first-pass metabolism to the lactam seen in rats and human subjects.

Plasma protein binding of crizotinib was moderate to high in animal and human samples. The volume of distribution was greater than the total body water in mice, rats, dogs, monkeys and humans and tissue exposure to radioactivity was generally 20–40 times higher than in blood following oral administration of ¹⁴C-crizotinib to rats. Exposures in the eye and uveal tract were >1000 times those in blood and elimination from these tissues was very slow ($t_{1/2}$ >500 h). Metabolism of crizotinib involved oxidation of the piperidine ring to form crizotinib lactam and other metabolites, O-dealkylation, loss of the piperidine ring and conjugation (sulfation and/or glucuronidation) of crizotinib and its metabolites. CYP3A4/5 had a prominent role in the formation of both crizotinib lactam and O-dealkylated crizotinib. Excretion of drug related material was predominantly via the faeces in rats, dogs and humans (62–87% of the administered dose). Biliary excretion of mostly sulfate or glucuronide conjugates was demonstrated in rats.

- Inhibitors or inducers of CYP3A4/5 and/or P-gp may affect crizotinib plasma exposure and P-gp inhibitors may increase the potential for adverse CNS effects. In vitro studies showed that crizotinib is an inhibitor of CYP3A and P-gp. Crizotinib is likely to increase the plasma exposure of substrates of CYP3A or P-gp. No clinically relevant inhibitory activity was seen on CYP1A2, 2B6, 2C8, 2C9, 2C19 or 2D6 enzymes or on the hOATP1B1, hOATP1B3 and BCRP transporters. Crizotinib was an inducer of CYP2C8 and CYP2C9 expression at clinically relevant concentrations.
- GLP-compliant repeat-dose toxicity studies by the oral route were conducted in rats and dogs and were of up to 3 months duration. Non-GLP studies of 28 days duration in female mice and Cynomolgus monkeys (both sexes) were also submitted. Animals were dosed to the maximum tolerated dose (MTD) with exposures 8 to 26 times the anticipated clinical AUC. The major target organs for crizotinib were the liver (reversible increases in ALT, AST and occasionally GGT or ALP, bile duct vacuolation and hyperplasia, and single cell necrosis), gastrointestinal tract (vomiting and diarrhoea, and microscopic changes in the GI tract), bone marrow (hypocellularity with secondary haematological effects such as anaemia), heart (cardiomegaly and myonecrosis/fibrosis) and ocular tissue (some impairment of retinal function) with some effects also observed in lymphoid organs in rats. Histopathological findings consistent with phospholipidosis were also seen in multiple tissues of treated rats.
- Crizotinib was not mutagenic in the bacterial assay but an increase in both numerical and structural aberrations was seen in human peripheral lymphocytes in the in vitro chromosomal aberration assay, while positive results were seen in both in vitro and in vivo micronucleus tests. Kinetochore staining in the in vitro assay confirmed crizotinib was aneugenic. Clastogenic potential cannot be dismissed. No carcinogenicity studies were conducted, which is considered acceptable.
- Studies on reproductive toxicity were limited to embryofetal developmental studies conducted in rats and rabbits. Maximum exposures achieved were generally low, reaching up to 5 times and 3 times the clinical exposure in rats and rabbits, respectively. Reduced fetal weights were seen in both species at the highest doses (exposure at the NOEL 1.2 and 0.65 times the clinical AUC in rats and rabbits, respectively), suggesting crizotinib has the potential to retard fetal growth. There was no evidence of teratogenicity; however, based on its pharmacological activity and its observed aneugenicity, adverse embryofetal effects may be predicted.
- No dedicated juvenile animal studies have been conducted. Decreased bone formation in immature rats indicates a risk for growth retardation in the paediatric population. Inhibition of the neuronal Nav1.1 sodium channel indicates a risk of seizures and other adverse CNS effects in young individuals who do not have a fully formed blood-brain barrier.

- Crizotinib was shown to be probably phototoxic in an in vitro assay. High exposures in pigmented skin (>100 times those in blood) were demonstrated in rats. Therefore, phototoxic reactions on sun-exposed skin may occur during clinical use.
- Four impurities in the drug substance were specified at limits above the ICH qualification threshold. Two of these were considered qualified at the proposed limits by the submitted data. The remaining two impurities were not considered qualified at the proposed limits. This has been referred to the Module 3 evaluator.

Conclusions and recommendation

The primary pharmacology studies are supportive of the proposed use of the drug as an oral agent for the treatment of patients with EML4-ALK positive advanced NSCLC.

Notable findings of clinical relevance in the toxicity studies include:

- CNS effects: decreased respiratory rate and hypoactivity, seizure potential;
- cardiovascular and haemodynamic effects: bradycardia; QT, PR and QRS interval prolongation; myocardial necrosis/fibrosis. These findings may indicate the potential for cardiac failure;
- hepatotoxicity (increased liver enzymes, single cell necrosis, bile duct vacuolation and hyperplasia);
- gastrointestinal disturbances (vomiting and diarrhoea);
- bone marrow toxicity with secondary haematological effects (especially anaemia, but also other cytopaenias);
- visual disturbances;
- possible phototoxic reactions on sun-exposed pigmented skin

Phospholipidosis was seen in rats (not in dogs) and is of uncertain clinical relevance and the risk for growth retardation and seizure potential raise concerns for use in a paediatric population.

The potentially clinically relevant toxicological findings are a cause for concern. Should crizotinib be registered on clinical grounds, the draft Product Information should be amended as directed (details of these recommended amendments are beyond the scope of this AusPAR).

IV. Clinical findings

Introduction

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

Clinical rationale

The sponsor's application letter of 4 November 2011 states that "[c]urrently, there are no registered treatments for ALK-positive NSCLC in Australia, and Xalkori addresses a high unmet medical need and offers a personalised treatment option specific to the molecular diagnosis". The application letter also states that based on the "unmet need for this life threatening condition and the therapeutic advances offered by crizotinib, the application submitted in the USA was granted priority review by the FDA. Xalkori was approved in the

USA on 26 August 2011". The application letter further comments that "[f]ollowing the approval of Xalkori in the USA, the latest edition of the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology, Non-Small Cell Lung Cancer.....published on 1 September 2011.....recommend crizotinib for the treatment of ALK-positive advanced NSCLC, testifying that Xalkori offers a new standard of care for patients with ALK-positive advanced NSCLC".

Comment: The sponsor's clinical rationale is acceptable. In 2007, lung cancer was the fourth most commonly diagnosed cancer in Australia in both males and females, excluding basal and squamous cell carcinoma of the skin.³⁰ In that year, a total of 5,948 lung cancers were diagnosed in males and 3,755 in females. The occurrence of lung cancer was strongly related to age, with 84% of new lung cancers in males and 80% in females diagnosed in patients aged 60 years and over. In 2007, 4,715 males and 2,911 females died from lung cancer in Australia, making it the leading cause of death in both sexes (21% of all cancer deaths in males, and 17% of cancer all cancer deaths in females). In Australia, between 1982 and 2007, the age standardised mortality rate from lung cancer for males decreased by 41%, while the mortality rate for females increased by 56%. The prognosis for patients with lung cancer remains poor, and has improved little in Australia over the 26 years from 1982 to 2007. The 5 year relative survival in 2000-2007 was 11% for males and 15% for females, which compares with 8% for males and 10% for females in 1982-1987.

Clinically, primary lung cancer is divided into small-cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). It has been estimated that NSCLC accounts for about 80% of all lung cancers.³¹ There are three main subtypes of NSCLC, squamous cell carcinoma (25%), adenocarcinoma (40%) and large cell carcinoma (10%) with the remainder consisting of other subtypes with low frequencies.³² In patients with NSCLC, the possibility of cure depends mainly on their suitability for surgical resection.³³ However, at the time of diagnosis only about 30% of patients with NSCLC are candidates for surgery while the remaining 70% have inoperable disease (30% with locally advanced inoperable disease and 40% with inoperable confirmed metastatic disease. In patients with advanced NSCLC (TNM stage IIIB and stage IV) chemotherapy is the mainstay of treatment (Goldstraw P et al., 2011).³⁴ The median duration of survival and 5 year survival rates are poor in patients with NSCLC TNM stage III B (10 months, and 7%, respectively), and TNM stage IV (6 months, and 2%) (Goldstraw P et al., 2007)³⁵.

The current application is the first to seek registration of a medicine specifically for the treatment of ALK-positive advanced NSCLC. However, there are a number of medicines registered in Australia for the first line treatment of advanced NSCLC, generally in combination with platinum

³⁰ AIHW & Cancer Australia 2011. Lung cancer in Australia: an overview an overview. Cancer series no. 64. Cat. no. CAN 58. Canberra: AIHW.

³¹ Boyer MJ. Drug therapy for lung cancer. Aust Prescr 2003; 26: 103-105.

³² NCI (2012). National Cancer Institute of the National Institute of Health.

<<http://cancer.gov/cancertopics/pdq/non-smal-cell-lung-cancer>>; last accessed on-line 11 February 2012.

³³ Carney DN, Hansen HH. Non-small cell lung cancer – stalemate or progress? N Engl J Med 2000; 343: 1261-1262.

³⁴ Goldstraw P, Ball D, Jett JR et al. Non-small-cell lung cancer. Lancet 2011; 378: 1727-40.

³⁵ Goldstraw P, Crowley JJ, Chansky K et al. The IASLC Lung Cancer Staging Project: proposals for revision of the stage groupings in the forthcoming (seventh) edition of the TNM classification for lung cancer. J Thorac Oncol 2007; 2: 706-714; Erratum in: J Thorac Oncol. 2007; 2: 985.

based chemotherapy. These include: pemetrexed in combination with cisplatin for the treatment of locally advanced or metastatic NSCLC other than predominantly squamous cell histology; bevacizumab in combination with carboplatin and paclitaxel for the treatment of patients with unresectable advanced metastatic or recurrent non-squamous NSCLC; gemcitabine as a single agent in combination with cisplatin for treatment of patients with locally advanced or metastatic NSCLC; and docetaxel for the treatment of previously untreated patients with locally advanced or metastatic NSCLC.

In addition, for patients whose disease has failed previous treatment with at least one prior chemotherapy regimen, the following drugs have been registered in Australia as monotherapy for patients with unselected NSCLC: docetaxel for the treatment of patients with locally advanced or metastatic NSCLC; pemetrexed as monotherapy for the treatment of patients with locally advanced or metastatic NSCLC other than predominantly squamous cell histology after prior platinum-based chemotherapy; erlotinib therapy in patients with locally advanced or metastatic NSCLC after failure of prior chemotherapy; and gefitinib for the treatment of patients with locally advanced or metastatic NSCLC whose tumours express activating mutations of the EGFR tyrosine kinase.

Crizotinib is a selective, ATP-competitive inhibitor of the anaplastic lymphoma kinase (ALK) receptor tyrosine kinase (RTK) and its oncogenic variants, and an inhibitor of the Hepatocyte Growth Factor Receptor (HGFR, c-Met) RTK. (sponsor's Nonclinical Summary). ALK and/or c-Met have been implicated in the regulation of oncogenic processes including cell growth and survival and subsequent development and progression of a subset of human cancers. The echinoderm microtubule associated protein like 4 and anaplastic lymphoma kinase (EML4-ALK) fusion gene has been identified as an oncogenic driver in a small subset of patients with NSCLC.³⁶ Expression of the EML4-ALK fusion gene leads to the formation of a chimeric tyrosine kinase in which the N-terminal half of the EML4 protein is fused to the intracellular kinase domain of ALK.^{4, 37}

ALK was first identified as a fusion partner of nucleophosphomin (NPM) in anaplastic large cell lymphoma in 1994.^{38,39} In 2007, the EML4-ALK fusion gene was identified in 6.7% (5/75) of a group of Japanese patients with NSCLC who were a distinct sub-group from those with the EGFR gene.⁴ The mutation arises from a small inversion within chromosome 2p that creates a fusion between the 5' portion of the EML4 gene and the 3' portion of the ALK gene.⁴ Potent oncogenic activity for EML4-ALK has been described both *in vivo* in a transgenic mouse model⁴⁰ and *in vitro*.³⁷ Multiple fusion variants of EML4-ALK have been described, and each identified variant has involved the same portion of the ALK C-terminal kinase domain resulting in the expression of catalytically active

³⁶ Solomon B. ALK gene arrangements: A new therapeutic target in a molecularly defined subset of non-small cell lung cancer. *J Thorac Oncol* 2009; 4: 1450-1454.

³⁷ Rikova K, Guo A, Zeng Q, et al. Global survey of phosphotyrosine signaling identifies oncogenic kinases in lung cancer. *Cell* 2007; 131: 1190-1203.

³⁸ Morris SW, Kirstein MN, Valentine MB, et al. Fusion of a kinase gene, ALK, to a nucleolar protein gene, NPM, in non-Hodgkin's lymphoma. *Science* 1994; 263: 1281-1284.

³⁹ Shiota M, Fujimoto J, Semba T, et al. Hyperphosphorylation of a novel 80kDa protein-tyrosine kinase similar to Ltk in a human Ki-1 lymphoma cell line, AMS3. *Oncogene* 1994; 9: 1567-1574.

⁴⁰ Soda M, Takada S, Takeuchi K, et al. A mouse model for EML4-ALK-positive lung cancer. *Proc Natl Acad Sci USA* 2008; 105: 19893-97.

kinase fusion proteins (Takeuchi et al., 2009).^{4, 41, 42, 43, 44, 45, 46, 47, 48} While EML4 has been the predominant identified fusion partner for ALK, other rare fusion partners for ALK include TRK-fused gene (TFG)³⁷ (and kinesin family member 5B (KIF5B))⁴⁵. ALK-positivity is independent of the fusion partner.

The overall prevalence of ALK gene rearrangements in NSCLC in a series of studies has been reported to be 3.8% (107 ALK rearrangements in 2835 tested tumours with a range of 0.4% to 13.4%).⁵ The difference in the prevalence rate among the series appears to be the result of pre-selection on certain characteristics, which include histology, smoking history and EGFR status that were used to enrich the sample.^{5, 49} In a study of unselected Caucasian NSCLC patients, 12 out of 447 (2.68%) were identified as ALK positive.⁶⁶ This frequency is similar to that of 2.65% reported in the largest study in which ALK positivity was identified in 16 out of 603 patients.⁵⁰ Based on the available data, ALK positivity appears to be relatively rare, with a frequency of approximately 3% of NSCLC patients.

⁴¹ Choi YL, Takeuchi K, Soda M, et al. Identification of novel isoforms of the EML4-ALK transforming gene in non-small cell lung cancer. *Cancer Res* 2008; 68(13): 4971-6.

⁴² Inamura K, Takeuchi K, Togashi Y, et al. EML4-ALK fusion is linked to histological characteristics in a subset of lung cancers. *J Thorac Oncol* 2008; 3(1): 13-7.

⁴³ Koivunen JP, Mermel C, Zejnullahu K, et al. EML4-ALK fusion gene and efficacy of an ALK kinase inhibitor in lung cancer. *Clin Cancer Res* 2008; 14(13): 4275-83.

⁴⁴ Shinmura K, Kageyama S, Tao H, et al. EML4-ALK fusion transcripts, but no NPM-, TPM3-, CLTC-, ATIC-, or TFG-ALK fusion transcripts, in non-small cell lung carcinomas. *Lung Cancer* 2008; 61(2): 163-9.

⁴⁵ Takeuchi K, Choi YL, Soda M, et al. Multiplex reverse transcription-PCR screening for EML4-ALK fusion transcripts. *Clin Cancer Res* 2008; 14(20): 6618-24.

⁴⁶ Takeuchi K, Choi YL, Togashi Y, et al. KIF5B-ALK, a novel fusion oncokininase identified by an immunohistochemistry-based diagnostic system for ALK-positive lung cancer. *Clin Cancer Res* 2009; 15(9): 3143-9.

⁴⁷ Wong DW, Leung EL, Wong SK, et al. A novel KIF5B-ALK variant in nonsmall cell lung cancer. *Cancer*. Article published online Jan 10 2011 [doi: 10.1002/cncr.25843].

⁴⁸ Takeuchi K, Choi YL, Togashi Y, et al. KIF5B-ALK, a novel fusion oncokininase identified by an immunohistochemistry-based diagnostic system for ALK-positive lung cancer. *Clin Cancer Res* 2009; 15(9): 3143-9.

⁴⁹ Horn L, Pao W. EML4-ALK: honing in on a new target in non-small cell lung cancer. *J Clin Oncol* 2009; 27: 4232-4235

⁵⁰ Perner S, Wagner PL, Demichelis F, et al. EML4-ALK fusion lung cancer: A rare acquired event. *Neoplasia* 2008; 10: 298-302.

In general, the median age of ALK-positive NSCLC patients appears to be younger relative to the general unselected population.^{42,51,46} Some studies have also identified a statistically significant relationship between ALK-positivity and a history of never smoking or light-smoking^{43, 51, 52, 46} but other studies have not observed a correlation with smoking history^{53, 42, 54}. ALK fusion genes have been identified predominantly in adenocarcinoma subtypes, but the mutation has also been reported in squamous cell subtypes.^{55, 56, 46, 57, 54, 53, 48} Co-expression with EGFR or HER2 or KRAS mutations appears to be extremely rare, suggesting that ALK is a distinct oncogenic driver.^{4, 42, 43, 44, 51, 52, 46, 53}

Formulation development

The following information has been extracted from the sponsor's Quality Overall Summary and the sponsor's Summary of Biopharmaceutical Studies and Associated Analytical Methods. The commercial formulation of crizotinib is an immediate release formulated capsule (CIC) for oral administration at two dosage strengths (200 mg and 250 mg). During the clinical development program, four additional crizotinib formulations (3 oral and 1 intravenous) were used: a powder in capsule (PIC), an immediate release tablet (IRT), an extemporaneously prepared oral suspension, and an intravenous (IV) solution.

The initial clinical dosage form was a PIC formulation, consisting only of crizotinib in a hard gelatin capsule shell. The PIC formulation was an enabling drug product that provided dosing flexibility during early Phase I clinical studies. The PIC formulation was used in the Phase I clinical efficacy and safety Study A8081001. The maximum tolerated dose and recommended Phase II dose were established based on the safety and pharmacokinetics of crizotinib administered using this dosage form. The PIC manufacturing process was not scalable due to slow rates of manufacture and conventional IRT formulations without film-coating were developed using a common granulation method to deliver 50 mg and 100 mg strengths. The bioavailability of the IRT formulation relative to the PIC formulation was evaluated in biopharmaceutical Study A8081008 in order to support the use of the IRT formulation in future clinical trials. The IRT formulation was used in subsequent clinical trials including Study A8081005 and it was also used in Study A8081001.

The capsule formulation (CIC) was developed as the commercial dosage form. A capsule formulation was deemed more amenable to the high drug loading needed to deliver 250 mg as a single unit dose due to the high sticking nature of this drug substance. The crizotinib capsule formulation was developed as a conventional immediate release hard gelatin capsule. A common granulation supplies two capsule dose strengths, 200 mg and 250 mg. A third dose strength, 150 mg, was also initially developed, but was used only for

⁵¹ Shaw AT, Yeap BY, Mino-Kenudson M, et al. Clinical features and outcome of patients with non-small-cell lung cancer who harbor EML4-ALK. *J Clin Oncol* 2009; 27(26): 4247-53.

⁵² Takahashi T, Sonobe M, Kobayashi M, et al. Clinicopathologic features of non-small-cell lung cancer with EML4-ALK fusion gene. *Ann Surgical Oncology* 2010; 17(3): 899-897

⁵³ Martelli MP, Sozzi G, Hernandez L, et al. EML4-ALK rearrangement in non-small cell lung cancer and non-tumor lung tissues. *Am J Pathol* 2009; 174(2): 661-70.

⁵⁴ Boland JM, Erdogan S, Vasmatazis G, et al. Anaplastic lymphoma kinase immunoreactivity correlates with ALK gene rearrangement and transcriptional up-regulation in non-small cell lung carcinomas. *Hum Pathol* 2009; 40(8):1152-8.

⁵⁵ Rodig SJ, Mino-Kenudson M, Dacic S, et al. Unique clinicopathologic features characterize ALK-rearranged lung adenocarcinoma in the western population. *Clin Cancer Res* 2009; 15(16): 5216-23.

⁵⁶ Yoshida A, Tsuta K, Watanabe SI, et al. Frequent ALK rearrangement and TTF-1/p63 coexpression in lung adenocarcinoma with signet-ring cell component. *Lung Cancer*. Article published online Oct 29 2010 [doi:10.1016/j.lungcan.2010.09.013].

⁵⁷ Takahashi T, Sonobe M, Kobayashi M, et al. Clinicopathologic features of non-small-cell lung cancer with EML4-ALK fusion gene. *Ann Surgical Oncology* 2010; 17(3): 899-897.

development studies and registration stability studies. The bioequivalence of the CIC (250 mg strength) to the PIC (50 mg and 100 mg strengths) and the IR tablet (50 mg and 100 mg strengths) was evaluated in Study A8081011, and the effect of food on the bioavailability of the CIC (250 mg strength) formulation was also assessed in this study.

The IV formulation was used to assess the absolute bioavailability of crizotinib in the PIC formulation in Study A8081010. The IV formulation included 5.0 mg/mL drug substance, an acetate buffer system to control pH, sodium chloride to adjust formulation tonicity, and sterile Water for Injection as solvent. The crizotinib sterile solution for IV administration was packaged in a 50 mL glass vial with a chlorobutyl rubber serum stopper and an aluminum flip-off seal.

The extemporaneously prepared oral suspension formulation was used in Study A8081009 to investigate absorption, distribution, metabolism and excretion of ¹⁴C-crizotinib.

Comment: The three biopharmaceutic studies (clinical pharmacology studies) and the single radiolabelled mass balance study referred to above have been evaluated later in this Clinical Evaluation Report (CER). In summary, the three biopharmaceutic studies showed that the absolute bioavailability of the crizotinib PIC formulation was approximately 43% (Study A8081008), the PIC and IRT formulations were bioequivalent (A8081008), the CIC formulation was bioequivalent to both the PIC and IRT formulations, and food reduced both the C_{max} and AUC_{inf} of the CIC formulation (250 mg) by approximately 14% (Study A8081011).

Scope of the clinical dossier

The clinical dossier included six clinical pharmacology studies and two interim reports from one Phase I efficacy and safety study (A8081001), and one Phase II efficacy and safety study (A8081005). Clinical development of crizotinib is ongoing and includes two Phase III studies consisting of one, multinational, multicentre, open-label, randomised study comparing crizotinib with pemetrexed or docetaxel in patients with previously treated ALK-positive advanced NSCLC (A8081007), and one multinational, multicentre, open-label, randomised study comparing crizotinib with pemetrexed plus cisplatin or carboplatin in patients with previously untreated ALK-positive advanced NSCLC (A8081014).

The submission contained the following clinical information:

- Clinical:
 - 6 completed Phase I clinical pharmacology studies in healthy volunteers including: 1 absolute bioavailability study (A8081010); 1 relative bioavailability study comparing the powder-in-capsule formulation with the immediate release tablet in 14 healthy volunteers (A8081008); 1 Phase I, single dose, bioequivalence and food effect study comparing the commercial image capsules with the immediate release tablets and powder-in-capsule formulations, and the comparing the commercial image capsule in the fasted and fed states in 36 healthy volunteers (A8081011); 1 open-label single-radiolabelled dose study to investigate the absorption, metabolism and excretion of ¹⁴C-crizotinib in 6 healthy male volunteers (A8081009); 1 fixed-sequence, cross-over study to estimate the effect of multiple doses of ketoconazole on the single dose pharmacokinetics of crizotinib in 15 healthy volunteers (A8081015); and 1 fixed-sequence, cross-over study to estimate the effect of multiple dose rifampin on the single dose pharmacokinetics of crizotinib in healthy volunteers (A8081016).

- 1 population pharmacokinetic study investigating the pharmacokinetics of the recommended Phase II dose of crizotinib (PMAR-00192).
 - 1 clinical pharmacology study analysing concentration-QTc in patients receiving crizotinib in studies A8081001 and A8081005 [PMAR-00224].
 - 1 preliminary report of a Phase I safety, pharmacokinetic and pharmacodynamic study of crizotinib administered orally to patients with advanced cancer (A8081001), identified by the sponsor as “pivotal”.
 - 1 preliminary report of a Phase II, open-label, single-arm study of the efficacy and safety of crizotinib in patients with advanced NSCLC harbouring a translocation or inversion involving the ALK gene locus (A8081005), identified by the sponsor as “supportive”.
 - Preliminary serious adverse event reports from 1, Phase III, multinational, multicentre, pivotal, randomised, open-label, efficacy and safety study of crizotinib versus standard of care chemotherapy (pemetrexed or docetaxel) in patients with advanced NSCLC harbouring a translocation or inversion event involving the ALK gene locus (A8081007).
 - 60 day clinical data update report for Study A8081001 relating to efficacy, deaths and serious adverse events (SAEs) for patients in the preliminary clinical study report (CSR); 60 day clinical data update report for Study A8081005 relating to efficacy and safety (comprehensive information) for patients in the preliminary CSR and relating to deaths and SAEs for a safety population; 60 day clinical data update report relating to deaths and SAEs in a limited number of patients in the crizotinib arm of Study A8081007; Technical Report for historical control and other retrospective analyses in advanced NSCLC using data from Study A8081001 and data from control arms of three Pfizer sponsored studies (A8501001, A8501002 and A6181087); Independent Review of Pneumonitis in Crizotinib Clinical Trials; Integrated Summary of Efficacy; Integrated Summary of Safety; Abbott Molecular ALK CH16-R2-mw001 - Vysis ALK Break Apart FISH Assay, List No. 6N38, External Performance Evaluation; and literature references.
- Important new safety information was submitted by the sponsor to the TGA during the course of the clinical evaluation. This new information related to additional reports of hepatotoxicity occurring after the dossier was submitted (4 new cases of drug related hepatic impairment including 2 cases meeting Hy’s law criteria [1 fatal] and 2 cases not meeting Hy’s law criteria [1 fatal]). The new safety data have been reviewed in the relevant sections of this CER.

In the remainder of this CER, the submitted studies with the A808 prefix will be identified by the last four numbers in their identification code (that is, the prefix A808 will be dropped).

Comment: The sponsor supports the efficacy and safety of crizotinib for the proposed indication based on one Phase I, open-label, single-arm study (1001) which it nominates as pivotal, and one Phase II, open-label, single-arm study (1005) which it nominates as supportive. The submission includes no pivotal efficacy and safety data from Phase III studies comparing crizotinib for the proposed indication with other treatments currently approved for the treatment of NSCLC. However, as previously noted there are no medicines specifically approved for the treatment of ALK-positive NSCLC.

The sponsor states that the decision to submit a marketing application for crizotinib for the treatment of ALK-positive advanced NSCLC at this time (that is, presumably to the FDA) was based on the substantial antitumor efficacy observed in Study 1001. It was also stated that the basis for this

regulatory submission was discussed with Health Authorities in the United States (US), the European Union (EU), Japan, and Korea. It is noted that in May 2009 the Sponsor sought Scientific Advice from the (EU/EMA) Committee for Medicinal Products for Human Use (CHMP) and received feedback on 20 May 2010 indicating that the committee did not support conditional approval based on objective response rate alone in the context of lack of information on prevalence and survival/treatment outcomes related to ALK status. The CHMP was also concerned about potential effects of a Marketing Authorization on accrual to the ongoing randomised previously-treated NSCLC trial (1007) and the planned additional randomised first-line NSCLC trial (1014). Nevertheless, the sponsor submitted a Marketing Authorization Application Letter of Intent to the EU on 1 December 2010 based on the continued strong signs of efficacy and continued favourable safety profile observed in ALK-positive advanced NSCLC patients treated with crizotinib, plus additional data gathered from ongoing Studies 1001 and 1005 since the Scientific Advice interactions with the CHMP in May 2010.

Paediatric data

The submission did not include paediatric data. The submission included a copy of document from the European Medicines Agency (EMA) granting the sponsor a waiver for the indication proposed for approval in the EU. The proposed indication is covered by an EMA class waiver relating to products intended to treat lung cancer (small cell and non-small cell carcinoma). As a result of the EMA waiver the sponsor states that Xalkori does not need to have a Paediatric Development Plan endorsed by the EMA's Paediatric Development Committee.

Comment: The sponsor's response is acceptable. It is considered that paediatric data are not required for the sponsor's proposed indication.

Good clinical practice

The final protocol, amendments, and informed consent documentation were reviewed and approved by the Institutional Review Board(s) (IRB) and/or Independent Ethics Committee(s) (IEC) at each of the investigational centres participating in the studies. The sponsor states that studies were conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All local regulatory requirements were followed, and all participating subjects or patients provided informed consent.

Pharmacokinetics

Studies providing pharmacokinetic data

All key PK and PK/PD data from the 6 studies in healthy volunteers, the 2 single and multiple dose studies in patients with advanced cancer, and the population pharmacokinetic report based on data from the 2 studies in patients with advanced cancer are provided in the text of the evaluation report and their significance discussed (see Attachment 2). None of the studies with pharmacokinetic (PK) data had deficiencies that excluded their results from consideration in the CER. The interim CSR for the clinical efficacy and safety Study 1001 included extensive PK data on crizotinib in patients with advanced cancer following single (250 mg) and multiple dose (250 mg twice a day (bd))

administration. However, the interim CSR for the clinical efficacy and safety Study 1005 included only limited PK information relating to trough plasma concentrations in patients with Alk-positive NSCLC. Information included in the submission indicates that the PK analysis for Study 1005 will be reported in the final CSR. The clinical studies containing relevant PK data are listed below in Table 4. The PK parameters for crizotinib and the lactam metabolite (PF-06261082) at each time point are summarised in CER1.

Table 4. Submitted clinical studies with clinical pharmacology data; n = subjects entered / evaluated.

Topic	Identification	Primary Aim	n	Comment
Healthy Volunteers – crizotinib single dose studies				
Absolute Bioavailability (sd)	1010	Absolute bioavailability	14 /14	Abs BA ~ 43%; PIC:IV 250:50 mg.
Bioequivalence (250 mg)	1008	BE (fasted) – PIC vs IRT	24/24	BE shown – 250 mg doses.
Bioequivalence (250 mg)	1011	BE (fasted) - CIC vs IRT BE (fasted) - CIC vs PIC	36/35 36/35	BE shown – 250 mg doses BE shown – 250 mg doses
Food Effect (250 mg)	1011	Food Effect - CIC fast/fed	36/35-36	Food decreases BA by ~ 14%.
Mass balance (250 mg)	1009	¹⁴ C radiolabelled crizotinib	6/6	PKs and ADME investigated.
PK Drug-Drug Interaction	1015	Ketoconazole / Crizotinib	15	Systemic exposure increased.
Patients with advanced cancer – single and multiple dose studies				
<ul style="list-style-type: none"> • Single and multiple dose; • Various qd and bd doses; • Asian vs non-Asian; • Midazolam/ Crizotinib PK interaction; • Food effect 	1001	Phase I, open-label, single-arm efficacy and safety in patients with advanced cancer.	n=208 (total)	Comprehensive PK data in patients with advanced cancer; dose-escalation (n=37), and RP2D cohorts (n=171; 250 mg bd) including ALK+ NSCLC subgroup (n=119).

Topic	Identification	Primary Aim	n	Comment
Trough concentrations Only ¹	1005	Phase II, open-label, single-arm, efficacy and safety in patients with ALK+ advanced NSCLC.	n=136	Limited data only.
Population-PK Study (dataset from Studies 1001 and 1005)	PMAR-00192	Structural PK model; population variability in CL and Vd; effects of H2 antagonists and PPIs on PKs of crizotinib.	N=250; 3184 crizotinib concentrations	Covariates weight, sex, race, and ECOG status as predictors of CL/F , weight as a predictor of $V2/F$, Q/F , and $V3/F$, and proton pump inhibitors or H2 antagonists as a predictor of ka .

CIC = commercial image capsule; IRT = immediate-release tablet; PIC = powder-in-capsule; sd = single-dose.
¹Sponsor comment: "C_{max} – 2 to 6 hours post morning dose".

In addition to the data from the clinical pharmacology studies, relevant *in vitro* data from human biomaterial studies have been reviewed and relevant information from these studies included in the CER. The information in the summary of PKs was derived from conventional pharmacokinetic studies unless otherwise stated. The summary of the pharmacokinetics studies in the CER includes an integrated description of the data from healthy subjects and patients with advanced cancer.

The PK parameters for crizotinib and its lactam metabolite (PF-06260182) were calculated from plasma concentrations by noncompartmental analysis using eNCA version 2.2.2. Wherever possible, actual PK sampling times were used to derive the PK parameters, and where actual PK sampling times were not available nominal PK sampling times were used. In all single-dose studies, blood sampling times extended for more than 3 crizotinib half-lives was sufficient to adequately describe the elimination phase of the crizotinib plasma concentration-time curve. The washout period of at least 14 days (that is, greater than 5 half-lives) between administration of different crizotinib treatments in the single-dose studies was sufficient to ensure adequate elimination of crizotinib and prevent carry-over effects.

In each study, PK parameters for crizotinib and the lactam metabolite (PF-06260182) were summarised by standard descriptive statistics. In the studies conducted using a cross-over design to assess absolute bioavailability, bioequivalence, food-effect and drug-drug interactions, natural log transformed C_{max} and/or AUC_{inf} and AUC_{last} were analysed using a mixed effect model with sequence, period and treatment as a fixed effects and subject within sequence as a random effect. Estimates of the adjusted mean differences (test-reference) and corresponding 90% confidence intervals (CIs) were obtained from the model. The adjusted mean differences and 90% CIs for the differences were exponentiated to provide estimates of the ratio of adjusted geometric means (test/reference) and 90% CIs for the ratios.

The bioanalytical methods used to measure crizotinib and the lactam metabolite (PF-06260182) in human plasma and urine (if applicable) were developed and validated at Covance Bioanalytical Services, LLC (Indianapolis, IN).

Summary of pharmacokinetics

Physicochemical characteristics of the active substance

The following information is derived from the sponsor's Quality dossier (*General Properties*) and the Quality Overall Summary. The molecular formula of crizotinib is $C_{21}H_{22}Cl_2FN_5O$ and the molecular weight is 450.34 Daltons. Crizotinib has one asymmetric centre, giving two possible stereoisomers (*R* and *S*). The absolute configuration at the 1-position of the molecule is the *R* optical isomer.

Evaluator's conclusions on pharmacokinetics

Overall, the pharmacokinetics of crizotinib were reasonably well characterised. However, there were some notable deficiencies in the data and these are listed immediately below:

- No formal PK study in patients with hepatic impairment. Crizotinib is extensively metabolized and hepatic clearance appears to be the major route of elimination of the drug. Consequently, it is likely that patients with hepatic impairment will have increased systemic exposure to crizotinib following oral administration.
- No formal PK study in patients with renal impairment. While renal elimination of unchanged crizotinib was low at 2.3% of the administered dose, the mass balance study showed that the total amount of administered radioactivity recovered in the urine was 22.2% of the dose. This result indicates that there is significant renal elimination of the metabolites of crizotinib. Consequently, it is likely that patients with renal impairment will have increased systemic exposure to crizotinib metabolites.
- No drug-drug PK interaction study between crizotinib and a P-gp efflux transporter inhibitor. The in vitro data predict that crizotinib is likely to be a substrate for the P-gp efflux transporter at therapeutic plasma concentrations. Consequently, co-administration of crizotinib and P-gp efflux transporter inhibitors has the potential to increase systemic exposure to crizotinib.
- No drug-drug PK interaction study between crizotinib a P-gp efflux transporter substrate. The in vitro data predict that crizotinib is likely to be an inhibitor of the P-gp efflux transporter. Consequently, co-administration of crizotinib and P-gp efflux transporter substrates has the potential to increase systemic exposure to such substrates.
- No drug-drug interaction study between and drugs known to increase the gastric pH (such as antacids, H2 inhibitors, PPIs). The aqueous solubility of crizotinib is pH dependent, with low (acidic) pH resulting in higher solubility. Consequently, it is possible that drugs which increase intragastric pH (that is, reduce acidity) might reduce the bioavailability of crizotinib by decreasing its solubility. In the population-PK analysis, co-administration of crizotinib and the PPIs esomeprazole, omeprazole, and lansoprazole decreased the absorption rate constant (k_a) of crizotinib.
- No in vitro data exploring potential interactions relating to crizotinib mediated induction of CYP2B and CYP2C enzymes. The submitted in vitro and in vivo data demonstrated that crizotinib can induce CYP3A. The sponsor states that most drugs that induce CYP3A are believed to do so primarily via activation of the pregnane X receptor (PXR). The sponsor notes that activation of the pregnane X receptor (PXR) can result in upregulation of CYP2B and CYP2C genes, as well as other Phase II enzymes and transporters.

There were no data exploring the potential PK/PD relationships between crizotinib exposure and clinical efficacy outcomes (such as Objective response rate (ORR), and safety (for example, ALT increased)).

The major pharmacokinetic characteristics of crizotinib are summarised below:

- In healthy male subjects, the absolute bioavailability of crizotinib 250 mg (single oral dose, IRT formulation) relative to crizotinib 50 mg (single IV dose) as assessed by the AUC_{inf} was 43.44% (95% CI: 39.68, 47.56) (study 1010). Food (high-fat meal) reduced the systemic exposure to crizotinib 250 mg (single dose, CIC formulation) by ~ 14% (AUC_{inf} and C_{max}) (study 1011). The food effect is considered to be not clinically significant and crizotinib can be administered with or without food. In a single dose (250 mg) study in healthy subjects (study 1010), bioequivalence of the market formulation (CIC) and the clinical study formulation (IRT) has been satisfactorily demonstrated and bioequivalence of the clinical study formulations IRT and PIC has been satisfactorily demonstrated.
- In patients with advanced cancer, steady state was reached at day 15 and the steady state geometric mean (%CV) C_{max} and AUC_τ values following crizotinib 250 mg bd were 411 (44) ng/mL and 3880 (36) mg.mL/hr, respectively, and the median T_{max} was 4.0 h (range 0.0-9.0 h) (Study 1001). The median AUC_τ accumulation ratio at steady state was 4.84, and mean crizotinib plasma trough concentrations remained relatively stable over the 15 to 112 day treatment period with values ranging from 275 to 319 ng/mL (Study 1001). Following a single 250 mg dose of crizotinib to patients with advanced cancer the mean (%CV) t_{1/2} was 42.4 (21) hours.
- The aqueous solubility of crizotinib is pH dependent with low (acidic) pH resulting in higher solubility. Consequently, the bioavailability of crizotinib might be reduced due to decreased solubility by co-administration with drugs known to increase intra-gastric pH. In the population PK study (PMAR-00192), co-administration of crizotinib and the proton pump inhibitors (PPIs) esomeprazole, omeprazole, and lansoprazole in patients with advanced cancer reduced the absorption rate constant (k_a) of crizotinib. In vitro, crizotinib has been demonstrated to be a substrate for the P-gp efflux transporter (Study 174737), and an inhibitor of this transporter (Study 14187).
- Crizotinib demonstrated non-linear PKs at steady state for doses of 200, 250, and 300 mg bd in patients with advanced cancer, with the C_{max} and AUC_τ values being greater than dose proportional (Study 1001). The sponsor postulates that non-linearity with greater than dose proportional increases in exposure parameters might be due to autoinhibition of CYP3A mediated metabolism of crizotinib at higher doses. The observed changes are consistent with the decreased apparent clearance (CL/F) in crizotinib observed in patients with advanced cancer at steady state with crizotinib 250 mg bd compared with single crizotinib dose 250 mg (100 L/hr and 64.5 L/hr, respectively). In patients with advanced cancer, the PKs of crizotinib showed moderate inter-subject variability with the coefficient of variance (CV) following multiple oral dosing of 250 mg bd crizotinib being 36-38% for the AUC_τ and 38-44% for the C_{max}. There were no data in the submission on the intra-subject variability of the PKs of crizotinib.
- The geometric mean (%CV) volume of distribution (V_{ss}) following crizotinib IV (50 mg) to healthy subjects was 1772 (18) L. This large V_{ss} indicates that crizotinib is extensively distributed from the plasma into the tissues. There are no data on the sites of tissue distribution in humans. However, nonclinical studies in rats indicate that crizotinib derived radioactivity was well distributed to most tissues and organs, apart from the brain and spinal cord (indicating that drug-derived radioactivity did not penetrate the blood brain barrier) (sponsor's Nonclinical Overview).

- In vitro data showed that crizotinib was highly protein bound in human plasma (~ 91%), and that binding was relatively constant over the concentration range 5 to 20 μM (Study PM-014). In vitro data also showed that crizotinib in human plasma binds preferentially to HSA (~ 94%) with lower binding to AAG (~ 74%) (Study 144558). Red blood cell (RBC)/plasma ratios of crizotinib ranged from about 1.0 to 1.4, and the blood/plasma ratio was approximately 1.0, and both ratios were independent of concentration across the range 0.1 to 10 μM (Study PDM-015)
- Following oral administration of a single radiolabelled dose of ^{14}C -rizotinib (250 mg) to healthy males, unchanged crizotinib was the predominant radiolabelled component in plasma accounting for 33% of the circulating radioactivity (Study 1009). The major circulating metabolite was crizotinib lactam (PF-06260182), accounting for 10% of the circulating metabolites. No other circulating metabolite accounted for > 10% of circulating radioactivity. The minor metabolites of crizotinib included glucuronide (M1) and sulfate (M3) conjugates of O-desalkyl crizotinib (M4, PF-03255243), O-desalkyl crizotinib lactam (M2, PF-06268935), and a sulfate conjugate of M2 (M8). Oxidation of crizotinib of the predominant lactam metabolite (PF-06260182) results in the introduction of a new chiral centre and the formation of 2 diastereomers (Study 123536).
- The major metabolic pathways for crizotinib in humans were oxidation of the piperidine ring to crizotinib lactam (PF-06260182) and O-dealkylation, with subsequent Phase II conjugation of O-desalkyl metabolites. In vitro studies with human liver microsomes and rCYP enzymes have demonstrated that CYP3A4/5 are the major enzymes involved in the metabolic clearance of crizotinib and the formation of key metabolites. The lactam metabolite (PF-06260182) is formed primarily by the action of CYP3A4/5 enzymes, with minor contributions from CYP2CB, CYP2C19, and CYP2D6 when aldehyde oxidase was present (Study 1445050). CYP3A4/5 enzymes also appear to be the primary mediators of the formation of the O-desalkyl metabolites, but the O-desalkyl metabolite (PF-03255243) was formed solely by CYP3A4. The sites of crizotinib metabolism in humans have not been identified. Presumably the major site of metabolism is the liver, but other sites (such as the gastrointestinal tract) cannot be excluded.
- In vivo, co-administration of crizotinib (150 mg, single-dose) and the potent CYP3A inhibitor ketoconazole (50 mg qd, multiple dose) increased the crizotinib geometric mean AUC_{inf} and C_{max} values by 3.2 fold and 1.4 fold, respectively compared with crizotinib alone (Study 1015). In vivo, co-administration of crizotinib (250 mg, single-dose) and the potent CYP3A inducer rifampin (200 mg bd, repeat dose) decreased the crizotinib geometric mean AUC_{inf} and C_{max} values by 86% and 69%, respectively compared with crizotinib alone (Study 1016). The results for the 2 in vivo drug-drug PK interaction studies were consistent with the in vitro data and show that CYP3A is a significant mediator of the metabolism of crizotinib.
- In vitro data indicate that crizotinib is the primary molecule contributing to the pharmacological activity of the drug. The crizotinib lactam metabolite (PF-06260182) was found to be ~ 2.5 to 7.7 fold less potent than crizotinib, while the O-desalkyl metabolites were inactive. Based on the pharmacological activity index (PAI), the 2 diastereomers of the lactam metabolite (PF-06260182) appear to have minimal pharmacology activity.
- The single-dose pharmacokinetics of the primary lactam metabolite (PF-06260182) have been reasonably well described in healthy subjects (Studies 1010, 1011, 1015, 1016), but there are only limited multiple-dose PK data on this metabolite in patients with advanced cancer (Study 1001).

- In the mass balance study, faecal excretion was the predominant route of elimination. The overall mean recovery of radioactivity following the administered single radiolabelled dose (250 mg) was 63.1% in the faeces (53% unchanged crizotinib) and 22.3% in the urine (2.3% unchanged crizotinib). The apparent geometric mean clearance of crizotinib in the mass balance study was 90.1 L/hr and the corresponding figure for renal clearance was 2.1 L/hr. These figures indicate that non-renal clearance (presumably hepatic) is the major mechanism for crizotinib elimination. Overall, hepatic metabolism appears to have a significant role in the elimination of crizotinib. However, a role for gastrointestinal metabolism of crizotinib cannot be excluded, nor can non-metabolic elimination pathways such as biliary excretion. The kidney appears to play an important role in the elimination of crizotinib metabolites. The effects of hepatic and renal impairment on the elimination of crizotinib are unknown.
- In vitro data demonstrated that crizotinib inhibits CYP3A4, and that the inhibition of this enzyme is time dependent (Studies 15304 and PDM-017). In vivo data in patients with advanced cancer showed that multiple dose crizotinib (250 mg bd) co-administered with single dose midazolam (2 mg), a CYP3A substrate, increased midazolam AUC_{inf} and C_{max} values by 3.7 fold [90% CI: 2.63-5.07] and 2.0 fold [90% CI: 1.39-2.92], respectively, relative to midazolam alone. The in vivo data indicate that crizotinib is a moderate inhibitor of CYP3A (AUC ≥ 2 fold and < 5 fold increase). This is an important finding as many oncology drugs are CYP3A4 substrates. The results suggest that downward dosing modifications with CYP3A substrates might be required if co-administered with crizotinib.
- In vitro data demonstrated that crizotinib induced rCYP3A4 but did not induce CYP3A4 activity and the sponsor comments that this finding is likely due to crizotinib mediated time-dependent inhibition of CYP3A4. In addition, the in vivo study showed that co-administration of crizotinib with midazolam increased systemic exposure to midazolam (a CYP3A substrate) rather than reduced it, suggesting that if CYP3A4 induction occurred it was significantly overshadowed by CYP3A4 inhibition. Crizotinib did not induce CYP1A2 activity. There are no data on the potential for crizotinib to induce CYP2B or CYP2C enzymes.
- In vitro data indicated that interactions are unlikely between crizotinib and drugs metabolised by CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6. In vitro data indicate that crizotinib uptake into the liver is by passive diffusion and that crizotinib is a weak, dose dependent inhibitor of the hepatic uptake transporters OATP 1B1 and OATP 1B3. Crizotinib is renally secreted and there are no in vitro (or in vivo) data exploring potential interactions between crizotinib and inhibitors of renal secretory transporters (for example, OCT 2, OAT1, OAT 3). However, as only 2.3% of an administered dose of crizotinib is excreted unchanged in the urine the absence of data relating to inhibition of renal secretory transporters is not considered to be clinically relevant.
- The population PK report (PMAR-01192) showed that the covariates of sex, race, and ECOG status⁵⁸ on AUC_{ss} demonstrated probability distributions for typical AUC_{ss} that fell within the 80% to 125% reference range for all categories except Korean race

⁵⁸ ECOG Performance Status. The Eastern Cooperative Oncology Group (ECOG) has developed criteria used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. The following are used: 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.

compared with Caucasians, and ECOG performance status of 2, 3, or 4 compared with 0 or 1. However, the addition of all covariates resulted in only a small decrease in unexplained variability in CL/F (~ 6%), suggesting that the tested covariates explain only a small portion of the variability in CL/F. Exploratory analyses in patients with advanced cancer from Study 1001 showed that steady state AUC_τ and C_{max} values following 250 mg bd were marginally lower in males than in females, were higher in Asians than non-Asians and were unrelated to age.

- The drug-drug PK interaction Study 1015 showed that co-administration of single-dose crizotinib (150 mg) with multiple dose ketoconazole (200 mg bd) (a potent CYP3A inhibitor) markedly increased systemic crizotinib exposure compared with crizotinib administered alone. The crizotinib AUC_{inf} and C_{max} increased 3.16 fold and 1.44 fold, respectively, following co-administration, and the corresponding increases in the lactam metabolite (PF-06260182) AUC_{inf} and C_{max} were 5.17 fold and 1.61 fold, respectively. The results of this study indicate that co-administration of crizotinib and potent inhibitors of CYP3A should be avoided due to the possibility of increased risks resulting from increased crizotinib systemic exposure.
- The drug-drug PK interaction Study 1016 showed that co-administration of single-dose crizotinib (250 mg) with multiple dose rifampin (600 mg once a day (qd)), a potent inducer of CYP3A, markedly reduced systemic crizotinib exposure compared with crizotinib administered alone. The crizotinib AUC_{inf} and C_{max} decreased 81.8% and 68.5%, respectively, following co-administration, and the corresponding decreases in the lactam metabolite (PF-06260182) AUC_{inf} and C_{max} were 94.3% and 89.0%, respectively. The results of this study indicate that co-administration of crizotinib and potent inducers of CYP3A should be avoided due to the possibility of reduced efficacy resulting from reduced crizotinib systemic exposure.

Pharmacodynamics

Studies providing pharmacodynamic data

Population modelling analysis report (PMAR-00224)

Overview

The submission included 1 PK/PD analysis in patients with advanced cancer from ongoing Studies 1001 (Phase I) and 1005 (Phase II) aimed at characterising the effects of crizotinib exposure on the QT interval (QT_c or heart rate corrected QT), evaluating Asian patients as a covariate on the concentration-QT_c relationship, and assessing the effect of crizotinib exposure on heart rate (PMAR-00224). The report was dated 7 February 2011.

ECG assessments were pre-specified in each protocol to be time-matched with selected PK samples in order to conduct a concentration-QT_c analysis. ECG, and matched PK samples were taken through to Cycle 2, Day 1. Three consecutive 12-lead ECGs were scheduled to be performed at least 2 minutes apart prior to blood sampling for PK assessment, except for the screening visit in 1005 which only took a single ECG measurement. All ECG measurements were automated machine read. The baseline observation was designated as the measurements taken prior to the start of the multiple dosing in each study.

PK-ECG data were created for population analysis using NONMEM software (v6.2). In addition to QtcB and QTcF data⁵⁹, a study-specific QT correction factor (QTcS) was estimated using the un-averaged triplicate ECG data. Linear mixed effects modelling was used to assess the relationship between plasma concentrations and QTc or RR with inter-individual variability on both the intercept and slope. Sex was included as structural covariate on the intercept for analysis of the QTc interval. Asian group as a covariate was tested for significance on both the slope and intercept in the analysis of RR and QTc intervals. The population PK/PD analysis report was comprehensive and was consistent with the requirements for population PK studies outlined in the relevant TGA adopted guideline⁶⁰.

Results

Data sets: There were 342 patients in the analysis dataset and 326 (95%) had PK-ECG matched data. The crizotinib exposure-response models for ECG endpoints (RR-, QTc-intervals) were developed from the dataset of 326 patients contributing a total of 964 crizotinib concentration-ECG matched pairs from Studies 1001 (640 pairs, 66.4%) and 1005 (324 pairs, 3.6%). The study population consisted of 326 patients (161 males [49.4%] and 165 females [50.6%]), with mean±SD age of 51.5±12.6 years (range, 19-82 years) and mean± SD baseline weight of 70.6±17.7 kg (range, 32-152 kg). The 326 patients included 82 (25.2%) patients of Asian origin.

Baseline data: In the patients with PK-ECG matched data, the mean heart rate, RR, QT, QTcB, QTcF and QTcS at baseline was, respectively, 82.1 bpm, 765 ms, 373 ms, 429 ms, 409 ms and 419 ms.

Crizotinib concentration data: Crizotinib doses ranged from 50 mg qd to 300 mg bd, and the concentration data are summarised below in Table 5.

Table 5. PMAR-0024 – Summary of crizotinib concentration data.

Concentration Group	Statistic	All Data	PK-ECG Matched Data *
		Value	Value
All (ng/mL)	N	2066	743
	Mean (SD)	216 (180.5)	212 (183.2)
	Median (min, max)	194 (0.228, 1040)	158 (0.228, 1030)
Multiple Dose Phase (ng/mL)	N	1379	425
	Mean (SD)	295 (168.3)	310 (182.5)
	Median (min, max)	278 (0.572, 1040)	291 (0.608, 1030)

* Only non-zero concentration summarized; SD = standard deviation; Step ID: 334301

Plasma concentration – RR relationship: The slope of the linear relationship between crizotinib concentrations and the RR-interval was estimated to be 0.388 ms/ng/mL [90% confidence interval (CI): 0.338, 0.438]. The slope is positive and indicates that as crizotinib concentration increases, the length of the RR-interval increases. Based on this model, an average decrease of 4 bpm in heart rate would be expected for a 100 ng/mL increase in crizotinib concentration. The estimated decrease in heart rate at the mean steady-state C_{max} of 478 ng/mL after crizotinib 250 mg bd (Study 1001 CSR) was 15.9 bpm (90% CI:

⁵⁹ QTc: The QT interval is dependent on the [heart rate](#) (the faster the heart rate, the shorter the QT interval). To correct for changes in heart rate and thereby improve the detection of patients at increased risk of ventricular arrhythmia, a heart rate-corrected QT interval QTc is often calculated. The standard clinical correction is to use *Bazett's formula*, named after [physiologist](#) Henry Cuthbert Bazett (QTcB) (Bazett HC. (1920). "An analysis of the time-relations of electrocardiograms". *Heart* (7): 353–370) or an alternative correction formula using the cube-root of RR developed by [Fridericia](#) (Fridericia LS (1920). "The duration of systole in the electrocardiogram of normal subjects and of patients with heart disease". *Acta Medica Scandinavica* (53): 469–486) giving QTcF.

⁶⁰Guideline on Reporting the Results of Population Pharmacokinetic Analyses, CHMP/EWP/185990/

14.3, 17.5). The Asian group (Asian versus Non-Asian) as a covariate on the intercept and slope was not statistically significant ($p > 0.05$).

QTcS (study specific correction factor): The study-specific QT correction factor was estimated to be 0.3964 for Study 1001 and 0.4217 for Study 1005 and was used to calculate QTcS. The three QT correction methods (QTcB, QTcF and QTcS) were evaluated graphically for their relationship with RR-interval. QTcB and QTcF demonstrated downwards and upwards trends in relationship to RR interval, respectively. In contrast, QTcS best corrected for the effect of heart rate on QT and therefore was selected for the primary analysis.

Plasma concentration – QTcS relationship: The slope of the linear relationship between crizotinib concentrations and QTcS-interval was estimated to be 0.0071 ms/ng/mL [90% CI: 0.0019, 0.0122]. Based on this model, an average QTcS increase of 0.7 ms (90% CI: 0.2, 1.2) occurs for each 100 ng/mL increase in crizotinib concentration. At the highest observed mean C_{max} of 478 ng/mL after crizotinib 250 mg bd (Study 1001), a crizotinib induced increase in QTcS is predicted to be 3.4 ms [90% CI: 0.9, 5.8].

Plasma concentration – QTcS relationship (Asian): An Asian group was added to the concentration-QTcS linear mixed effects model as a covariate on the intercept and slope parameters. The effect of Asian group was not statistically significant for either parameter ($p > 0.05$). Higher concentrations of crizotinib were observed in Asian patients after multiple dosing, and the predicted upper limit of 90% confidence interval of QTcS increase was 6.5 ms at the highest observed mean C_{max} in Asian patients of 535 ng/mL (Study 1001).

Plasma concentration - QTc, QTcB and QTcF relationships: The concentration-QTc slope was -0.0107 ms/ng/mL (90% CI: -0.0163, -0.0051) for QTcB and for (non-Asian subjects) 0.0149 ms/ng/mL [90% CI: 0.0079-0.0219] for QTcF, respectively. These results show that the QTcB decreases as crizotinib concentration increases and QTcF increases as crizotinib concentration increases. The sponsor states that it is important to note that the modelling results for QTcF and QTcB should not be used for the clinical interpretation as they were affected by the correlation with RR.

Comment: The submission did not include a formal QT/QTc interval prolongation study. Instead, the submission included a population-PK analysis based on ECG data collected on patients with advanced cancer from Studies 1001 and 1005. In this analysis, the sponsor used QT data corrected by a study specific correction factor (QTcS data) to interpret the clinical relevance of the observed concentration – QT data, rather than the standard correction factors used in clinical practice (that is, Bazett's correction [QTcB] and Fridericia's correction [QTcF]). The QTcS was estimated for each study (1001 and 1005) using the un-averaged triplicate ECG data. The study graphically investigated the three correction methods (QTcB, QTcF, and QTcS) for their relationship with RR interval. The QTcB and the QTcF demonstrated downwards and upwards trends in relationship to RR interval, respectively, and the sponsor considers that these two intervals should not be used for clinical interpretation of the concentration – QT relationship.

The QTcS best corrected for the effect of heart rate on QT and was selected for the primary analysis as the sponsor considered it to be the most appropriate QT correction method for the ECG data in this analysis. The mean increase in the QTcS at the highest observed mean C_{max} in patients with advanced cancer is predicted to be 3.4 ms (90% CI: 0.9, 5.8). The mean increase was < 5 ms and the upper bound of the 90% CI was < 10 ms. The sponsor considers that, based on the observed mean increase in QTcS, the

predicted mean increase in QTc is small indicating no clinically relevant QT prolongation at the recommended clinical dose. However, if the data for the QTcF are considered then the mean increase in the QTcF at the highest C_{max} in patients with advanced cancer is predicted to be 7.1 ms (90% CI: 3.8, 10.5). The figures for the QTcF (non-Asian subjects) are concerning as the mean predicted increase at the highest C_{max} was 7.1 ms (greater than > 5 ms noted to be of regulatory concern to the TGA), and the upper bound 90% CI was > 10 ms.

It should be noted that the ECG data used in the population pharmacokinetic analysis were not specifically designed to assess the effect of crizotinib on the QT interval. The nonclinical studies indicated that QT/QTc interval increased in the 13 week study in dogs following administration of crizotinib at doses \geq 100 mg/m² (males) and 500 mg/m² (females) at both the Week 6 and Week 13 pre-dose time points. In addition, *in vitro* studies showed that crizotinib inhibited the hERG channel at all concentrations tested with an IC₅₀ of 1.1 μ M, supporting the *in vivo* finding in dogs that the drug has the potential to prolong the QT interval. Overall, it is considered that the effect of crizotinib on QTc interval prolongation in humans has not been adequately characterised in the submitted data. Therefore, it is recommended that the sponsor undertake a formal QT/QTc interval prolongation study complying with the relevant TGA adopted "note for guidance"⁶¹.

⁶¹ CHMP/ICH/2/04 The Clinical Evaluation Of Qt/QtC Interval Prolongation And Proarrhythmic Potential For Non-Antiarrhythmic Drugs

Efficacy

Dosage selection for the pivotal studies

The crizotinib dose used in the ALK-positive NSCLC cohort in pivotal study (1001) and the supportive study (1005) was derived from the dose escalation phase of Study 1001. In the dose escalation phase of this study, the crizotinib starting dose was 50 mg qd in the first cohort of patients enrolled. Each dose level cohort initially included a minimum of 3 evaluable patients for assessment of toxicity within the first cycle (that is, first 4 weeks of dosing). Dose escalation occurred in 100% increments until either of the following occurred: (1) drug related toxicity of Grade 2 severity occurred in 2 or more patients within a dose level; or (2) mean unbound area under the concentration-time profile from zero time to 24-hours postdose (AUC_{24}) exceeded 2.4 $\mu\text{g}\cdot\text{h}/\text{mL}$ (the highest unbound area under the concentration-time profile [AUC] tested in the 1 month toxicology studies).

Escalation increments were then to become 40%. In any cohort, if 1 patient experienced a dose-limiting toxicity (DLT), 3 additional patients were enrolled to that dose level. If 2 of 3 or 2 of 6 patients experienced a DLT, no further dose escalation occurred. DLTs definitions are summarised below in Table 6.

Table 6. Dose-limiting toxicities (DLTs).

Toxicity Category	Toxicity/Grade
Hematologic	Prolonged Grade 4 neutropenia for >7 days
	^a Febrile neutropenia, defined here as Grade 4 neutropenia with fever >38.5°C, both sustained over a 24-hour period.
	Neutropenic infection: Grade ≥ 3 neutropenia with Grade ≥ 3 infection
	Grade ≥ 3 thrombocytopenia with bleeding, or Grade 4 thrombocytopenia lasting ≥ 7 days Lymphopenia was not considered a DLT unless accompanied by infection.
Non-hematologic	Grade 3 or 4 toxicities (except for alopecia, Grade 3/4 hypophosphatemia, Grade 3 hypertension with controlled blood pressure [$<140/90$ mm Hg], and Grade 3/4 hyperuricemia without signs and symptoms of gout). Nausea, vomiting, or diarrhea must have persisted at Grade 3 or 4 despite maximal medical therapy.

Abbreviations: DLT=dose-limiting toxicity; mm Hg=millimeters of mercury

^a Febrile neutropenia qualified as a DLT only if the fever and neutropenia were documented to be coincident in time and reconfirmed

The maximum tolerated dose (MTD) was defined as the dose level at which no more than 1 of 6 patients experienced a DLT after 28 days of treatment (end of Cycle 1) with the next higher dose having at least 2 of 3 or 2 of 6 patients experiencing a DLT. By agreement between the sponsor and investigators, the cohort could be expanded beyond 6 patients to better define the safety profile.

The primary DLT observation period was defined as Cycle 1 of crizotinib treatment. Toxicities were graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events v3.0 (CTCAE). During Cycle 1, doses were not to be modified unless a DLT occurred, but temporary dosing interruptions could be used to ensure patient safety. Dosing interruptions for more than 3 days was considered a DLT. The occurrence of a DLT necessitated immediate interruption of treatment in that patient, and resumption was permitted if the event resolved to Grade ≤ 1 severity and interruption in treatment was not longer than 4 weeks. Treatment was to resume at the next lower dose level tested. Patients who discontinued treatment before completing Cycle 1 for reasons other than treatment related toxicity (such as development of rapidly progressing disease) were to be replaced. Dose escalation was to be stopped if: (1) a dose level of crizotinib produced concentrations at least 5 fold greater than the projected target

concentration; (2) exposure plateaued as the dose increased, or (3) the MTD could not be reached within a reasonable dose range (up to 2000 mg).

Comment: Doses evaluated in the dose-escalation cohort were 50 mg qd, 100 mg qd, 200 mg qd, 200 mg bd, 300 mg bd, and 250 mg bd. The frequency of dosing was changed from qd to bd in order to better manage nausea and vomiting observed at the lower qd dose levels. There were a total of 3 DLTs observed in 3 of 34 patients in the dose-escalation cohort. The first DLT was a Grade 3 ALT increased reported at the 200 mg qd dose level. This DLT triggered expansion of 200 mg qd cohort by an additional 3 patients. No other DLTs were reported at 200 mg qd, and dose escalation proceeded as per protocol. At 300 mg bd, 2 of 6 patients experienced Grade 3 fatigue. Consequently, dose escalation was halted and the next cohort of 3 patients was enrolled and treated at the 250 mg bd dose level. No DLTs were observed in the 3 patients initially treated with 250 mg bd, and the cohort was further expanded to have 6 evaluable patients (2 patients were not evaluable) with no DLTs reported. Therefore, 250 mg bd was considered to be the MTD due to the absence of DLTs in 8 patients treated at this dose level, and 2 DLTs of Grade 3 fatigue in 2 of 6 patients treated at the 300 mg bd dose level.

Evaluator's conclusions on clinical efficacy

The efficacy assessment of crizotinib for the proposed indication is based primarily on the data from two, Phase I/II clinical efficacy and safety studies (1001/1005), supported by exploratory data from non-protocol specified retrospective covariate-matched and covariate-adjusted analyses (Technical Report). The Phase I study (1001) data were more mature than the Phase II study (1005) data at the date of the submission to the FDA, and the sponsor designated the two studies as "pivotal" and "supportive", respectively. The efficacy data described in the preliminary CSRs are based on snapshots of the clinical database taken on 1 November 2010 (Study 1001) and 29 October 2010 (Study 1005). The efficacy data also included 60 day update reports based on snapshots taken on 15 March 2011 (Study 1001) and 17 March 2011 (Study 1005).

Both the Phase I and II studies are ongoing, open-label, single-arm studies in which crizotinib 250 mg bd is being investigated for the treatment of ALK-positive NSCLC. In both studies, the majority of patients had metastatic disease (95.8%, n=[114] Study 1001; 94.1% [n=128] Study 1005), and the remainder had locally advanced disease. In both studies, the tumours were adenocarcinomas in nearly all patients (97.5% [n=116] Study 1001; 94.1% [n=128] Study 1005). In both studies, the majority of patients had been treated with at least 1 prior systemic drug therapy for NSCLC (86.6% [n=103] Study 1001; 100% [n=136] Study 1005), and had undergone prior surgery for the disease (98.3% [n=117] Study 1001; 97.8% [n=133] Study 1005).

The objective response rate (ORR) was pre-specified as the primary efficacy endpoint in Study 1005, while in Study 1001 the ORR was one of six listed efficacy endpoints none of which were pre-specified as primary. In the Technical Report containing the retrospective analyses, the ORR was designated as the primary efficacy endpoint, and both the sponsor's Clinical Overview and the sponsor's Summary of Clinical Efficacy based their favourable assessments of the efficacy of crizotinib primarily on the ORR results from Studies 1001 and 1005. Consequently, it is considered that the assessment of the efficacy of crizotinib in the current submission should be based primarily on the ORR results from Studies 1001 and 1005.

The ORR results from the two Phase I/II studies based on both investigator assessment and blinded independent radiological review (IRR) are encouraging and provide evidence of antitumour activity for crizotinib. In both Phase I/II studies, the primary analysis of the

ORR was based on investigator assessment of best response according to RECIST criteria⁶². In Study 1001, the ORR was 61.2% (95%CI: 51.7, 70.1) in 116 patients in the RE population at the database snapshot of 1 November 2010. Of the 71 patients contributing to the ORR, 2 (1.7%) had a CR and 69 (59.5%) had a PR. In Study 1005, the ORR was 51.5% (95%CI: 42.3, 59.5) in 133 patients in the RE population at the database snapshot of 17 March 2011. Of the 68 patients contributing to the ORR, 1 (0.8 %) had a CR and 67 (50.4%) had a PR. Based on the blinded IRR, the ORR was 52.4% (95%CI: 42.4, 62.2) in Study 1001 (55/105), and 41.9% (95%CI: 32.3, 51.9) in Study 1005 (41/105). Overall, in Study 1001, 86 of 105 patients were assessed in the same best response category by both the investigator and the IRR for a total agreement rate of 81.9%, and the corresponding figures in Study 1005 were 75 of 102 patients for a total agreement rate of 73.5%.

The preliminary median estimate of duration of response (DR) in Study 1001 (preliminary CSR) was 48.1 weeks (95%CI: 35.9, not reached), based on the Kaplan-Meier (KM) method, but only 26 (36.6%) of the 71 patients who had an objective response had subsequently progressed or died at the time of the analysis while the remaining 45 (63.7%) patients had not progressed or died. Descriptive statistics for the 26 patients who had progressed or died showed that the median duration of response was 26.2 weeks (range: 8.1, 72.9 weeks). The 60 day update report for Study 1005 included an estimated median DR of 18.1 weeks (range: 7.1 to 14.9) for the 14 patients with an objective response who subsequently progressed or died, but did not include an estimate based on the KM method. Overall, the additional efficacy endpoints of time to tumour response, and disease control rate supported the ORR results in both Study 1001 and 1005.

The major limitation of the submitted efficacy data is the absence of Phase III, randomised, controlled studies confirming that the encouraging ORRs observed in the two Phase I/II studies translate into clinically meaningful benefits such as improved overall survival (OS) and/or progression-free survival (PFS). The relevant TGA adopted guideline relating to the clinical evaluation of anticancer medicines indicates that Phase III therapeutic confirmatory studies should demonstrate that the investigational product confers a clinical benefit. The guideline also states that acceptable primary endpoints for Phase III studies are OS and PFS/DFS, and that if PFS/DFS is the selected primary endpoint OS should be reported as a secondary endpoint and *vice versa*.

There were limited preliminary data on OS and PFS in Study 1001. In Study 1001, the 60 day update report stated that the median OS in Study 1001 had not been reached. In the 136 patients in the SA population, death had occurred in 40 (29.4%) patients, and 96 (70.6%) patients had been censored. The estimated 6 month and 12 month survival probabilities were 87.5% (95%CI: 80.4, 92.2) and 75.7% (95%CI: 66.8, 82.5), respectively. In Study 1001, the preliminary estimated median PFS was 10 months (95%CI: 8.2, 14.7) in the SA population (n=119) in the preliminary CSR. No OS or PFS data were provided for Study 1005, which reflects the relative immaturity of the data from this study compared with Study 1001.

In the absence of pivotal Phase III therapeutic confirmatory studies supporting the Phase I (1001) and Phase II (1005) studies, the sponsor submitted a Technical Report containing covariate-matched analyses and covariate-adjusted modelling analyses of the efficacy data from Study 1001 and efficacy data from the control arms of three Pfizer sponsored studies in patients with NSCLC (that is, historical controls). The control arms of the three Pfizer-sponsored studies were first-line paclitaxel/carboplatin (Study 1); first-line gemcitabine/cisplatin (Study 2); and second/third-line erlotinib (Study 3).

The covariate-matched analysis matched patients from Study 1001 with patients from each of the three Pfizer studies. The objectively observed ORR for crizotinib from Study

⁶² RECIST: The Response Evaluation Criteria in Solid Tumors (RECIST) is a voluntary, international standard using unified, easily applicable criteria for measuring tumour response using X-ray, CT and MRI.

1001 (61% [95%CI: 52, 70]) was higher than the covariate-matched ORRs for the three historical control groups (12.0% to 21.5% with paclitaxel/carboplatin; 20.7% to 24.1% with gemcitabine/cisplatin; and 10.0% to 13.8% with erlotinib). Similar results were observed for covariate-adjusted modelling where 8 covariates were added simultaneously into a logistic regression analysis model resulting in estimated predictive ORRs of 15.0% to 21.4% for the historical controls for the 116 response evaluable patient from Study 1001, compared with the observed ORR of 61.2% for the 119 response evaluable patients from Study 1001.

The results for PFS and OS from the covariate-matched and covariate-adjusted analyses were consistent with the results for the ORR obtained from these analyses and supported a clinical benefit of crizotinib compared with the historical controls. The Technical Report referred to an abstract presentation from the 2008 American Society of Clinical Oncology (ASCO) Annual Meeting⁶³ which investigated whether PFS could be considered to be a valid surrogate for OS in NSCLC by reviewing a large number of trials comparing docetaxel with vinca alkaloids for first-line treatment. The abstract concluded that treatments which reduce the PFS hazard ratio by at least 30% are expected to lead to significant benefits in terms of OS. In the Technical Report, the hazard ratios for PFS of crizotinib relative to each of the three historical controls ranged from 0.28 and 0.38 (covariate-matched analysis), and from 0.21 to 0.43 (covariate-adjusted analysis). The Technical Report concludes that the information from Buyse *et al*, 2008,⁶³ “although not a substitute for that obtained from an adequately controlled randomised trial, coupled with the observed crizotinib ORR (>50% higher than that observed in the first-line treatment setting) provides supporting evidence that crizotinib treatment may provide clinical benefit for the treatment of ALK-positive advanced NSCLC”. However, it should be noted that the Buyse *et al*, 2008 data were not from a peer reviewed study report, but were from an abstract of a meeting presentation.

Despite the absence of Phase III studies the sponsor “believes the robust and clinically meaningful ORR and DR (plus preliminary [estimated median] PFS and 1 year OS probability) from crizotinib treatment with an acceptable safety profile in an ALK-positive NSCLC patient population are likely to predict the clinical benefit of crizotinib thereby warranting submission of non-randomised data from Studies A8081001 and A8081005 for approval of crizotinib for the treatment of ALK-positive advanced NSCLC while the randomised Phase III studies (A8081007 and A8081014) are ongoing”. In contrast to the sponsor’s position, it is considered that the submitted data cannot support registration of crizotinib for the treatment of ALK-positive NSCLC due to the absence of pivotal data from a Phase III, randomised, controlled study confirming the clinical benefit of crizotinib (that is, OS and/or PFS).

The ORR data from Studies 1001 (Phase I) and 1005 (Phase II) are encouraging. However, there are no Phase III, randomised, controlled data showing that the observed ORR results translate into clinically meaningful benefits (OS and/or PFS). In Study 1001, the preliminary estimated median PFS was 10 months (95%CI: 8.2, 14.7), and the 1 year OS probability of survival was 75.7% (95%CI: 66.8, 82.5). However, in the absence of pivotal Phase III, randomised, controlled data it is difficult to interpret the significance of the submitted PFS and OS data from Study 1001. The retrospective covariate-matched and covariate-adjusted analyses provided evidence that crizotinib may provide clinical benefit for the treatment of ALK-positive NSCLC, but these analyses are considered to be exploratory as they were not pre-specified and were undertaken to “give perspective to the efficacy results from the single arm Study 1001”. It is considered that the results from

⁶³Buyse, ME, Squifflet, P, Laporte, S. et al. Prediction of survival benefits from progression free survival in patients with advanced non small cell lung cancer: Evidence from a pooled analysis of 2,838 patients randomized in 7 trials. *Journal of Clinical Oncology*, 2008; 26; May 20 Supplement; Abstract 8019.

the retrospective analyses cannot substitute for Phase III, randomised, controlled, confirmatory studies.

The results from the sponsor's ongoing Phase III controlled studies (1007 and 1014) might resolve the question relating to whether the ORRs observed with crizotinib in the Phase I/II studies (1001/1005) translate into meaningful clinical benefits. Study 1014 is comparing crizotinib with pemetrexed/cisplatin and pemetrexed/carboplatin in previously untreated patients with ALK-positive NSCLC. Study 1007 is comparing crizotinib with standard of care chemotherapy (pemetrexed of docetaxel) in patients with advanced ALK-positive NSCLC after failure of one previous chemotherapy regimen that included one platinum drug. In both ongoing Phase III studies the primary endpoint is PFS and the secondary endpoints include OS.

Safety

Overview

The primary population for evaluating safety in the clinical studies was all patients in Studies 1001 and 1005 who received at least 1 dose of crizotinib starting on Cycle 1, Day 1 (safety analysis population). All adverse events (AEs) reported after the start of treatment on Cycle 1 Day 1, as well as pre-existing conditions that worsened during the treatment period, were considered to be treatment-emergent AEs. Treatment related AEs were those judged by the investigator to be at least possibly related to crizotinib, or for which drug relatedness was recorded as unknown by the investigator.

All AEs experienced during the safety evaluation period (from first dose through to at least 28 days after the last dose of crizotinib) were to be reported to the sponsor, irrespective of whether the AE was considered by the investigator to be treatment related. All treatment related AEs occurring at any time after initiation of treatment were to be reported to the sponsor and were to be followed until they resolved, or until the investigator assessed them as chronic or stable, or until the patient was lost to follow-up.

Severity grading for AEs was consistent with the NCI CTCAE Version 3.0 for Study 1001 and Version 4.0 for Study 1005. NCI CTCAE includes Grades 1 through 5 with unique clinical descriptions of severity for each AE based on the following general guideline: Grade 1 mild AE; Grade 2 moderate AE; Grade 3 severe AE; Grade 4 life-threatening or disabling AE; and Grade 5 death related to AE.

Abnormal laboratory test results were considered AEs if they were associated with symptoms, required additional diagnostic testing, resulted in a change in trial dosing, and/or were otherwise considered to be an adverse event by the investigator. Laboratory results assigned adverse events status were graded in accordance with NCI CTCAE.

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 13.0) and were summarised by descending frequency, Clustered term or Preferred Term, and maximum severity grade, or by System Organ Class (SOC), Preferred Term, and maximum severity grade.

Descriptive statistical analyses (descriptive) of safety data were provided, and the data were summarised using tables, listings, and figures. Presentations of routine safety evaluations in Studies 1001 and 1005 included summaries of the frequency and severity of AEs (including summary by demographic subsets [age, gender, and race] and summary of time to onset, duration, and prevalence of selected AEs), the frequency of deaths and other SAEs, the proportions of subjects who prematurely discontinued study treatment or who had a dosing interruption or dose reduction associated with an AE, the frequency of laboratory test abnormalities, and the assessment of vital signs and ECG variables.

Initial data

The submission included an integrated (sponsor) Summary of Clinical Safety that included data on 450 subjects at the dates of the initial database snapshots. Of these 450 subjects:

- 255 subjects had ALK-positive NSCLC and received crizotinib 250 mg orally bd in Studies 1001 (n=119) and 1005 (n=136); the target last visit date was 15 September 2010 for both studies and database snapshot dates were undertaken on 1 November 2010 for Study 1001 and 29 October 2010 for Study 1005;
- 85 subjects had advanced cancer (other than ALK-positive NSCLC) and were enrolled in Study 1001; and
- 110 subjects were healthy volunteers enrolled in the clinical pharmacology studies.

Additional SAE data were also provided for 36 crizotinib treated patients with ALK-positive NSCLC in ongoing Study 1007 from the database snapshot of 27 October 2011.

60 day clinical update data

The submission also included 60 day clinical data updates for patients enrolled in Studies 1001, 1005, and 1007. The updated safety data included information on:

- deaths and SAEs for 136 patients with ALK-positive NSCLC in Study 1001 at the target visit date cut-off of 1 February 2011 and snapshot date of 15 March 2011;
- deaths, SAEs, AEs, laboratory abnormalities, ECGs, vital signs, and ophthalmological assessments for 136 patients in Study 1005 (the preliminary CSR safety analysis population) at the target visit date cut-off 1 February 2011 and snapshot date of 17 March 2011;
- deaths and SAEs in the safety analysis population for 261 patients in Study 1005 at the target visit date cut-off 1 February 2011 and snapshot date of 17 March 2011;
- SAEs, including fatal SAEs, for 71 patients in Study 1007 at the target visit date cut-off 1 February 2011 and snapshot date of 17 March 2011.

Other safety data

The submission included an Independent Review of Pneumonitis in Clinical Trials (Studies 1001 and 1005) dated 10 February 2011. Data from this report have been examined and relevant information has been included in the relevant sections of the CER.

On 3 January 2012, the sponsor provided the TGA with information on 4 new cases of hepatic injury reported in Study 1005 subsequent to the submission (2 Hy's law cases and 2 cases of fatal hepatic failure). This information has been examined and is included in relevant sections of the CER.

Exposure

The primary population for evaluating safety in the clinical studies is considered to be all patients in Study 1001 (preliminary CSR) and Study 1005 (preliminary CSR 60 day update) who received at least 1 dose of crizotinib starting on Cycle 1, Day 1. The median duration of exposure was 31.9 weeks (range: 0.9 to 101.9 weeks) in Study 1001 (n=119) and 22.3 weeks (range: 0.9 to 53.1 weeks) in Study 1005 (n=136). Dosing interruptions of greater than 1 day were reported in 55 (46.2%) patients in Study 1001 and 49 (36.0%) patients in Study 1005, with respective maximum interruptions of less than 1 week being reported in 24 (20.2%) and 19 (14.0%) patients. The mean (standard deviation (SD)) actual dose intensity was 491.5 (25.5) mg/day in Study 1001 and 466.9 (63.1) mg/day in Study 1005, and the respective mean (SD) relative dose intensities were 98.3 (5.1)% and

93.4 (12.6)%. Exposure parameters for crizotinib in ALK-positive NSCLC patients from Study 1001 (preliminary CSR) and Study 1005 (preliminary CSR 60 day update) were summarised.

In Study 1001 (preliminary CSR), a total of 119 patients have been treated, 49 (41.2%) for > 24 to ≤ 52 weeks, and 30 (25.2%) for > 52 to ≤ 104 weeks.

In Study 1005 (preliminary CSR 60 day update), a total of 136 patients have been treated, 50 (36.8%) for > 24 to ≤ 52 weeks, and 1 (0.7%) for > 52 to ≤ 104 weeks.

Comment: No 60 day updated exposure data were provided for patients in Study 1001 due to the small number of new patients between the cut-off dates for the preliminary CSR and the 60 day update.

Evaluator's conclusion on clinical safety

Overview

The submitted safety data for crizotinib for the proposed indication are derived from interim reports from ongoing open-label clinical efficacy and safety Studies 1001, 1005 and 1007. No safety data were provided comparing crizotinib with either placebo or active control.

The primary safety population for assessment of ALK-positive NSCLC consists of 119 patients in Study 1001 (preliminary CSR) and 136 patients in Study 1005 (preliminary CSR 60 day update) who received at least 1 dose of crizotinib starting on Cycle 1, Day 1. The safety profiles of crizotinib 250 mg bd for patients with ALK-positive NSCLC from these two studies were consistent. In addition, within both studies all causality and treatment related AE profiles were comparable. The comprehensive safety data (n=255) from Studies 1001 (preliminary CSR) and 1005 (preliminary CSR 60 day update) were supplemented by the 60 day updated safety data relating to SAEs and deaths in the preliminary CSR population from Study 1001 (n=136), the safety analysis population from Study 1005 (n=261), and the preliminary CSR population from the crizotinib arm of Study 1007 (n=71).

Discussion in the section of the CER relating to the safety of crizotinib (250 mg bd) for the proposed indication focuses primarily on the data from the 255 patients from Study 1001 (preliminary CSR) and Study 1005 (preliminary CSR 60 day update). In Study 1001, the median duration of exposure in 119 patients was 31.9 weeks (range: 0.9 to 101.9 weeks). Dose interruptions of more than 1 day occurred in 46.2% of patients and 19.3% of patients experienced dose interruptions of more than 2 weeks. In Study 1005, the median duration of exposure in 136 patients was 22.3 weeks (range: 0.9 to 53.1 weeks). Dose interruptions of more than 1 day occurred in 36% of patients and 12.5% of patients experienced dose interruptions of more than 2 weeks. The difference in total exposure duration between the two studies reflects the earlier start day for Study 1001 compared with Study 1005.

In the pooled population (n=255) from Study 1001 (preliminary CSR) and Study 1005 (preliminary CSR 60 day update), 81 (31.8%) patients have been treated for > 12 to ≤ 24 weeks, 99 (38.8%) for > 24 to ≤ 52 weeks, 31 (12.2%) for > 52 to ≤ 104 weeks, and 1 (0.4%) for > 104 weeks. Patient numbers exposed to crizotinib for at least 6 months and 1 year appear to be about 99 and 1, respectively. These patient numbers are notably lower than those specified in the TGA adopted guideline relating to the extent of population exposure to assess safety for medicines intended for long-term treatment of non-life threatening conditions (that is, 300-600 patients for 6 months, and 100 patients for 1 year). However, these guidelines are not directly relevant to the ALK-positive NSCLC as the disease is life-threatening. Nevertheless, patient exposure numbers for 6 months and 1 year are low in the submitted data.

Commonly reported treatment related adverse events

Treatment related adverse events (all grades of severity) were reported in 95.8% (n=114) and 96.3% (n=131) of patients in Studies 1001 (preliminary CSR) and 1005 (preliminary CSR 60 day update), respectively. The incidence of patients with Grade 3 or 4 adverse events were 16.0% (n=19) and 23.5% (n=32), Study 1001 and 1005, respectively. Consequently, although at least one treatment related adverse event was reported in nearly all patients in Studies 1001 and 1005, the majority of these events were Grade 1 or 2 in severity.

In Study 1001 (preliminary CSR), treatment related adverse events (all grades) reported in $\geq 10\%$ of patients were nausea (48.7%), diarrhoea (42.9%), visual impairment (47.9%), vomiting (35.3%), constipation (26.9%), oedema peripheral (24.4%), dizziness (19.3%), decreased appetite (16.8%), fatigue (14.3%), ALT increased (14.3%) and AST increased (10.9%). Treatment related adverse events of Grade 3 or 4 severity reported in $\geq 1\%$ of patients were ALT increased (4.2%), AST increased (3.4%), neutropenia (3.4%), lymphopenia (1.7%), fatigue (1.7%) and hypophosphataemia (1.7%).

In Study 1005 (preliminary CSR 60 day update), treatment related adverse events (all grades) reported in $\geq 10\%$ of patients were nausea (57.4%), vomiting (43.4%), diarrhoea (42.6%), visual impairment (42.6%), constipation (27.2%), oedema peripheral (25.7%), fatigue (25.0%), decreased appetite (21.3%), dysgeusia (14.7%), ALT increased (12.5%), and dizziness (12.5%). Treatment related adverse events (Grade 3 or 4) reported in $\geq 1\%$ of patients were ALT increased (6.6%), neutropenia (4.2%), lymphopenia (2.2%), dyspnoea (2.2%), fatigue (1.5%), ECG QT prolongation (1.5%) and hyponatraemia (1.4%).

Deaths

There were a total of 72 (18.1%) deaths in 136 patients from Study 1001 (preliminary CSR) and 261 from Study 1005 (SA population 60 day update). Of these 72 deaths, 45 (11.3%) occurred within 28 days of the last dose ("on-treatment"). Of the 45 deaths occurring "on-treatment, the majority (35 deaths) were due to the disease under study (including disease progression), and 3 were considered to be related to the study drug. The 3 treatment related deaths occurring "on-treatment" were due to disseminated intravascular coagulation (x1), pneumonitis (x1), and unknown cause (x1). Causes of death occurring "on-treatment" included 10 respiratory events (3x pneumonia, 2x hypoxia, 1x pneumonitis, 1x empyema, 1x pulmonary haemorrhage, 1x respiratory failure, and 1x worsening of dyspnoea). Other causes of death occurring "on-treatment" included sepsis (x1), septic shock (x1), and arteriosclerotic cardiovascular disease (x1). The sponsor reports that there have been 2 additional deaths in Study 1005 since the submission date, both due to hepatic failure and both considered to be related to treatment with crizotinib.

In Study 1007 (preliminary CSR 60 day update), death occurred in 6 of 71 patients. Of these 6 deaths, 5 occurred "on treatment" including 3 considered to be unrelated to treatment (1x disease progression, 1x pneumonia, 1x infection / acute respiratory distress syndrome) and 2 considered to be treatment related (1 x cardiac arrest / respiratory failure; 1x interstitial lung disease). There has been 1 additional death due to treatment related pneumonitis reported after the data cut-off date for the 60 day update.

Serious adverse events (SAEs) – all causality

All causality SAEs (all grades) were reported in 50 (36.8%) patients and 62 (23.8%) patients in Studies 1001 (preliminary CSR 60 day update) and 1005 (SA population 60 day update), respectively. In the pooled population (n=397), 112 (28.2%) patients experienced all causality SAEs (all grades). All causality SAEs (all grades) occurring in $\geq 10\%$ of patients in both studies (Study 1001 and 1005, respectively) were disease

progression (9.6% and 5.4%), pneumonia (4.4% and 3.1%), and dyspnoea (2.9% and 3.1%).

All causality SAEs (Grade 3 or 4) were reported in 24 (17.7%) patients and 32 (12.2%) patients in Studies 1001 and 1005, respectively. In the pooled population (n=397), 56 (14.1%) patients experienced all causality SAEs (Grade 3 or 4). In Study 1001, all causality SAEs (Grade 3 or 4) reported in $\geq 1.0\%$ of patients included pulmonary embolism (3.7%), syncope (2.9%), dyspnoea (2.9%), pneumonia (2.2%), convulsion (1.5%), and deep vein thrombosis (1.5%). In Study 1005, all causality SAEs (Grade 3 or 4) reported in $\geq 1\%$ of patients were disease progression (5.4%), pneumonia (3.1%), dyspnoea (3.1%), and pyrexia (1.1%).

Serious adverse events (SAEs) – treatment related

In Study 1001 (preliminary CSR 60 day update), treatment related SAEs (all grades) were reported in 8 (5.9%) patients, and the only event reported in ≥ 2 patients was pneumonitis (n=2; 1.5%). Treatment related SAEs (Grade 3 or 4) were reported in 5 (3.7%) patients, and these events were pneumonitis (1.5%), constipation (0.7%), ALT increased (0.7%), and liver function test abnormal (0.7%).

In Study 1005 (SA population 60 day update), treatment related SAEs (all grades) were reported in 12 (4.6%) patients, and the only event occurring in ≥ 2 patients was pneumonitis (n=2; 0.8%). Treatment related SAEs (Grade 3 or 4) were reported in 8 (3.1%) patients and these events were febrile neutropenia (0.4%), infection (0.4%), pneumonia (0.4%), hepatic enzyme increased (0.4%), hypokalaemia (0.4%), hyponatraemia (0.4%), haematuria (0.4%), renal cyst (0.4%), dyspnoea (0.4%) and pneumonitis (0.4%).

In Study 1007 (preliminary CSR 60 day update), all causality SAEs were reported in 19 (26.8%) patients and in 10 (14.1%) patients the events were considered to be treatment related. The SAEs considered to be treatment related were ALT and AST increased in 2 patients, pneumonia in 2 patients, and in 1 patient each decreased appetite, neutropenia, ECG QT prolonged, multiseptated renal cyst, interstitial lung disease, and cardiac arrest / respiratory failure.

Discontinuations and dose reductions

In the pooled population from Studies 1001 (preliminary CSR) and 1005 (preliminary CSR 60 day update), permanent treatment discontinuations due to all causality and treatment related AEs were reported in 23 (9.0%) and 11 (4.3%) patients, respectively. In Study 1001, treatment related AEs resulting in permanent discontinuation were reported in 3 patients (2 with pneumonitis; 1 with ALT increased). In Study 1005, the most commonly reported treatment related AEs resulting in permanent discontinuation were ALT increased (3 patients; 2.2%) and pneumonitis (2 patients; 1.5%). Other treatment related AEs resulting in permanent discontinuation in Study 1005 were AST increased (1 patient; 0.7%), death (1 patient; 0.7%), dyspnoea (1 patient; 0.7%) and nausea (1 patient; 0.7%).

In Study 1001 (preliminary CSR 60 day update) (n=136), all causality SAEs resulting in permanent treatment discontinuation were reported in 14 (10.3%) patients (6x disease progression; 3x pneumonia; and 1x each for nausea, oedema peripheral, dyspnoea, pneumonitis, pulmonary haemorrhage, respiratory failure and subcutaneous emphysema).

In the pooled population from Studies 1001 (preliminary CSR) and 1005 (preliminary CSR 60 day update), temporary treatment discontinuations due to all causality and treatment related AEs were reported in 86 (33.7%) and 31 (12.1%) patients, respectively. All causality AEs resulting in temporary treatment discontinuation and reported in $\geq 2\%$ of patients in both Studies 1001 and 1005, respectively, were ALT increased (5.9% and 5.1%), pneumonia (4.2% and 3.7%) and neutropenia (3.4% and 4.4%).

In the pooled population from Studies 1001 (preliminary CSR) and 1005 (preliminary CSR 60 day update), dose reductions due to all causality and treatment related AEs occurred in 24 (9.4%) and 22 (8.6%) patients, respectively. ALT increased was the only all causality AE resulting in dose reductions in both Study 1001 (4.2%) and Study 1005 (4.4%).

Laboratory tests

In both studies the highest frequency of shifts from Grade ≤ 2 at baseline to Grade 3 (0.5 to $0.2 \times 10^9/L$) or Grade 4 ($< 0.2 \times 10^9/L$) post-baseline in haematology parameters were observed for lymphocytes (absolute). In the pooled population ($n=247$), shifts to Grade 3 were reported in 24 (9.7%) patients and shifts to Grade 4 were reported in 4 (1.6%) patients.

In the pooled population ($n=247$), shifts in the neutrophil count from baseline Grade ≤ 2 to post-baseline Grade 3 (1.0 to $0.5 \times 10^9/L$) or Grade 4 ($< 0.5 \times 10^9/L$) in the neutrophil count were observed in 10 (4.0%) and 3 (1.2%) patients, respectively. In the pooled data ($n=247$), shifts in the white blood cell counts (WBC) from baseline Grade ≤ 2 to post-baseline Grade 3 (3.0 to $2.0 \times 10^9/L$) or Grade 4 ($< 1.0 \times 10^9/L$) were reported in 6 (2.4%) and 0 patients, respectively. In the pooled population ($n=247$), shifts in the platelet count and the haemoglobin level from baseline Grade ≤ 2 to post-baseline Grade 3 or 4 were reported in 1 patient for each parameter.

In the clinical biochemical laboratory tests, the only investigations resulting in shifts from baseline Grade ≤ 2 to post-baseline Grade 3+4 in $\geq 5\%$ of patients in the pooled population were ALT increased (6.0%; 15/248) and hyponatraemia (5.2%; 13/249). ALT increased Grade 3 and Grade 4 were defined as > 5.0 to 20.0 upper limit of normal (ULN) and > 20.0 ULN, respectively, and hyponatraemia Grade 3 and 4 were defined as < 130 to 120 mmol/L and < 120 mmol/L, respectively.

Adverse events of special interest

In this section, unless otherwise stated, reference to Study 1001 relates to the preliminary CSR population ($n=119$) and reference to Study 1005 relates to the preliminary CSR 60 day update population ($n=136$). Reference to the pooled population refers to pooled patients from these two studies ($n=255$).

Nausea, diarrhoea, vomiting: Treatment related nausea, diarrhoea, vomiting all occurred very commonly in Studies 1001 and 1005. In the pooled population ($n=255$), treatment related nausea, vomiting, and diarrhoea were reported in 53.3% ($n=136$), 42.7% ($n=109$), and 39.6% ($n=101$) of patients, respectively. In the pooled population, all three of these treatment related AE events were predominantly Grade 1 severity with a small number of cases being Grade 2. No SAEs were reported for treatment related nausea, vomiting or diarrhoea. Permanent treatment discontinuation was reported in 1 (0.4%) patient for treatment related nausea, and temporary treatment discontinuation was reported in 2 (0.8%) patients for treatment related nausea and 4 (1.6%) patients for treatment related vomiting.

The median time to first onset of both treatment related nausea and vomiting was 2 days in Studies 1001 and 1005, with the median duration of the events being 111 days for nausea and 18 days for vomiting (Study 1001). The prevalence of treatment related nausea and vomiting was highest in Cycle 1 and decreased for both events in subsequent Cycles with the decrease being more marked for vomiting than for nausea (Study 1001). For treatment related diarrhoea, the median duration of time to onset varied from 2 days (Study 1001) to 13.5 days (Study 1005) and the median duration of the event was 102 days (Study 1005). The prevalence of treatment related diarrhoea was highest in Cycle 1, and decreased in subsequent cycles (Study 1001).

Oesophageal-related disorders: In the pooled population for Studies 1001 (preliminary CSR) and 1005 (preliminary CSR 60 day update), treatment related oesophageal-related

disorder (clustered term) occurred in 7.5% (n=19) of patients, and nearly all events (n=16) were Grade 1 severity with the remainder (n=3) being Grade 2. There was 1 (0.4%) treatment related SAE (oesophageal ulcer).

Vision disorder: Treatment related vision disorder (clustered term) occurred very commonly in both Study 1001 and Study 1005, and was reported (all grades) in 60.4% (n=154) of patients in the pooled population. In both studies, the most common individual treatment related PT contributing to vision disorder (clustered term) was visual impairment which was reported in 45.1% (n=115) of patients in the pooled population. Nearly all treatment related vision disorder (clustered term) events in the pooled population were Grade 1 (n=151) with the remainder being Grade 2 (n=3). There were no permanent discontinuations for treatment related vision disorder (clustered term), and temporary treatment discontinuation was reported in 1 (0.4%) patient due to Grade 2 diplopia. The cause of the visual disorders is unknown. Limited ophthalmological assessment of patients in Study 1005 showed a small number of abnormalities but did not identify a cause.

Increased ALT: Treatment related increased ALT (clustered term) occurred very commonly ($\geq 10\%$) in both Study 1001 and Study 1005, and was reported (all grades) in 13.3% (n=34) of patients in the pooled population. Most of the treatment related event were reported as Grade 1/2 severity, with Grade 3/4 events being reported in 5.5% (n=14) of patients in the pooled population. The median time to onset of treatment related ALT increased (clustered term) varied from 22 days (Study 1001) to 31.5 days (1005), with the range in the pooled population being from 1 to 183 days. The median duration of the event was 74 days and ranged from 4 to 513 days (Study 1001). In the pooled population, permanent treatment discontinuations (treatment related), temporary treatment discontinuations (all causality), and dose reductions (all causality) were reported in 1.8% (n=4), 5.5% (n=14), and 4.3% (n=11) of patients, respectively. Treatment related SAEs for ALT increased were reported in 1 (0.4%) patient in the pooled population.

Hepatic impairment: Post-submission information provided by the sponsor indicates that there have now been 5 treatment related cases of hepatic impairment. Three (3) of these cases satisfied criteria for Hy's law for drug induced liver injury (DILI), and 1 of these cases resulted in fatal hepatic failure. In the remaining 2 cases, 1 patient died due to fatal hepatic failure and 1 patient recovered. Based on more than 1400 patients in clinical trials being exposed to crizotinib (information provided by the sponsor post-submission), the incidence of treatment related hepatic impairment is estimated to be 0.4%.

QT prolongation: In Studies 1001 and 1005, in the pooled population maximum increases in QTcF of ≥ 500 ms were reported in 0.8% (2/251) of patients, and maximum changed in QTcF of ≥ 60 ms were reported in 3.8% (9/237) of patients. There were no reports of seizure, ventricular tachycardia, or ventricular arrhythmia in Study 1001 or Study 1005 (preliminary CSR). However, there were 8 reports of pre-syncope or syncope and 4 reports of convulsion from these two studies but all reports appeared to be unrelated to primary cardiac events. The AE of treatment related ECG QT prolongation was reported in 4 (1.6%) patients in the pooled population from Studies 1001 and 1005. The central tendency analysis in Study 1005 (preliminary CSR) demonstrated that the mean increase in QTcF from baseline at steady state ranged from 7.2 to 10.3 ms, and the highest upper bound of the two-sided 90% CI was 13.3 ms. These central tendency results are of regulatory concern as the mean increases in QTcF were greater than 5 ms, and the highest upper bound 95% CI was greater than 10 ms.

Oedema: In the pooled population for Studies 1001 (preliminary CSR) and 1005 (preliminary CSR 60 day update), treatment related oedema (clustered term) occurred in 28.2% (n=72) of patients, and the majority of these events were Grade 1 (n=53) with the remainder being Grade 2 (n=19). The median time to onset varied from 47 days (Study

1005) to 74 days (Study 1001), with the range in the pooled population being from 7 to 450 days. The main "oedema" related PT was peripheral oedema, which was reported in 25.1% (n=64) of patients in the pooled population (n=255), with the majority of cases being Grade 1 (n=50) and the remainder being Grade 2 (n=9). There was 1 (0.4%) reported of SAE (Grade 2) for peripheral oedema but there were no reports of permanent or temporary treatment discontinuation with this AE.

Neuropathy: In the pooled population, treatment related neuropathy (clustered term) occurred in 13.3% (n=34) of patients and the majority of these events were Grade 1 (n=28) with the remainder being Grade 2 (n=5) and Grade 3 (n=1). The median time to onset varied from 36 days (Study 1005) to 57 days (Study 1001), with the range in the pooled population being from 1 to 253 days. The median duration of the event was 188 days with a range of 29 to 487 days (Study 1001). No SAEs or permanent treatment discontinuations were reported for treatment related neuropathy in the pooled population and temporary treatment discontinuation was reported in 1 (0.4%) patient due to treatment-emergent hypoaesthesia.

Neutropenia: In the pooled population (n=247), shift from normal pre-treatment neutrophil count to Grade 1 (< LLN to $1.5 \times 10^9/L$), Grade 2 (< 0.8 to $1.0 \times 10^9/L$), Grade 3 (< 1 to $0.5 \times 10^9/L$) or Grade 4 (< $0.5 \times 10^9/L$) on-treatment occurred in 38 (15.4%), 40 (16.1%), 10 (4.0%) and 3 (1.2%), respectively. In the pooled population (n=255), treatment related neutropenia (clustered term) was reported in 18 (7.1%) patients, with Grade 1, 2, 3 or 4 events being reported in 2 (0.8%), 4 (1.6%), 10 (3.9%) and 2 (0.8%) of patients, respectively. The median time to onset varied from 64 days (Study 1005) 197 days (Study 1001) and the range in the pooled population was 15 to 356 days. The median duration of the event was 16 days with a range of 3 to 380 days (Study 1001). The prevalence of treatment-emergent neutropenia was relatively stable across the treatment cycles (1% to 2%). There were no treatment related SAEs for neutropenia but there was 1 (0.4%) case of treatment related febrile neutropenia reported as a SAE (Grade 4). There were no permanent discontinuations due to treatment related neutropenia but temporary treatment discontinuations were reported in 6 (2.4%) patients and dose reductions in 2 (0.8%) patients. There were no deaths attributed to neutropenia.

Pneumonitis: In the pooled population, treatment related pneumonitis was reported in 4 (1.6%) patients and the median time to first onset was 12 to 13 days. In an independent review of pneumonitis cases reported in Studies 1001 and 1005, the review committee concluded that 3 cases of drug induced pneumonitis had occurred in 340 patients (incidence of 0.9%), and that 1 of these cases had been fatal (fatality rate of 33.3%). The committee also identified 2 cases of radiation pneumonitis associated with crizotinib (1 new case, 1 pre-existing case worsening) but were unable to determine whether these events were causally related to treatment.

Other conditions of interest (treatment related in the pooled population, Grade = G):

Fatigue was reported in 41 (16.1%) patients (G1=30, G2=17, G3=4). *Dizziness* was reported in 40 (15.7%) patients (G1=37, G2=3). *Dysgeusia* was reported in 30 (11.8%) patients (G1=27, G2=3). *Rash* was reported in 21 (8.2%) patients (G1 = 21, G2 = 1), and *photosensitivity reactions* were reported in 1 (0.4%) patient (G1=1). *Leucopenia* was reported in 11 (4.3%) patients (G1=6, G2=4, G1=1). *Bradycardia* was reported in 9 (3.5%) patients (G1=7, G2=2). *Lymphopenia* was reported in 6 (2.4%) patients (G2=1; G3=5).

Clinical summary and conclusions

First round benefit-risk assessment

First round assessment of benefits

The observed objective response rates ORRs for crizotinib from Study 1001 (Phase I) and Study 1005 (Phase II) provide evidence of antitumour activity.

In both studies, the primary analysis of the ORR was based on investigator assessment of best response according to RECIST criteria and the results of this analysis were consistent with a supportive assessment of the ORR based on independent radiological review. In Study 1001, the ORR (primary analysis) was 61.2% (95%CI: 51.7, 70.1) in 116 patients in the RE population, and in Study 1005, the ORR (primary analysis) was 51.5% (95%CI: 42.3, 59.5) in 133 patients in the RE population. In Study 1001, 71 patients achieved an objective response (2 CR; 69 PR) and in Study 1005, 68 patients achieved an objective response (1 CR; 67 PR). Nearly all patients in both studies with an objective response achieved a partial rather than complete response. The results for the independent review of the ORR were 52.4% (95%CI: 42.4, 62.2) in Study 1001 (55/105 patients) and 41.9% (95%CI: 32.3, 51.9) in Study 1005 (43/105 patients).

In Study 1001, the majority of patients had been treated with at least 1 prior systemic treatment for NSCLC (86.6%), while in Study 1005 such treatment was an inclusion criteria and all patients had been treated with at least 1 prior systemic treatment for NSCLC (100%). There were no submitted studies in patients with NSCLC naïve to prior systemic treatment for the condition. However, no studies other than those submitted have included patients with ALK-positive NSCLC only. The proposed indication does not limit crizotinib to second-line treatment.

Both studies included patients with locally advanced or metastatic ALK-positive NSCLC while the proposed indication includes patients with advanced disease otherwise unspecified. However, it is considered that the study populations in Studies 1001 and 1005 are consistent with the proposed treatment population.

While the observed ORRs are encouraging there are no Phase III, randomised, controlled data showing that these results translate into clinically meaningful benefits (that is, OS and/or PFS). In Study 1001, the estimated median PFS was 10 months (95% CI: 8.2, 14.7), and the estimated 1 year OS probability was 75.7% (95%CI: 66.8, 82.5). In the absence of pivotal Phase III, randomised, controlled, comparative data it is difficult to interpret the significance of the estimated PFS and the predicted OS results. The information from the retrospective covariate-matched and covariate-adjusted analyses in the Technical Report suggest superior benefits for crizotinib compared with historical controls based on the ORR, PFS and OS. However, these analyses are considered to be exploratory and require confirmation by Phase III, randomised, controlled clinical studies.

First round assessment of risks

Nearly all patients with ALK-positive NSCLC exposed to crizotinib 250 mg bd in Studies 1001 (preliminary CSR) and 1005 (preliminary CSR 60 day update) experienced at least one treatment related adverse event (all grades). In the pooled population (n=255) from these two studies, 96.1% (n=245) of patients experienced a treatment related adverse event and Grade 3 or 4 events were reported in 20.0% (n=51) of patients.

However, while nearly all patients treated with crizotinib experienced at least one treatment related adverse event, the majority of these events were Grade 1 or 2 in severity, and did not result in permanent treatment discontinuation. The data from Studies 1001 and 1005 suggest that treatment related adverse events can be managed by temporary treatment discontinuation or temporary dose reductions rather than permanent treatment discontinuation. In the pooled population (n=255) from Studies

1001 and 1005, 4.3% (n=11) of patients permanently discontinued due to treatment related adverse events, while temporary treatment discontinuation and dose reductions due to treatment related AEs were reported in 7.5% (n=19) and 8.6% (n=22) of patients, respectively.

The most commonly reported treatment related adverse events in both Studies 1001 and 1005 related to gastrointestinal disorders of nausea, vomiting, diarrhoea and constipation. In the pooled population (n=255), treatment related nausea, diarrhoea, vomiting, and constipation were reported in 53.3%, 42.7%, 39.6%, and 27.1% of patients, respectively. All of these events were Grade 1 or 2 in severity (apart from one Grade 3/4 event for constipation) and permanent and temporary treatment discontinuations due to these events were negligible. The median time to onset of nausea and vomiting was 2 days, and the prevalence of these events was highest in the first treatment cycle and decreased in subsequent cycles. Treatment related oesophageal-related disorder (clustered term) was also frequently reported in the pooled population (n=255), with 7.5% of patients reporting an event and nearly all events being Grade 1.

Treatment related vision disorder (clustered term), including diplopia, photopsia, vision blurred, visual field defect, visual impairment, and vitreous floaters was reported in 60.4% of patients in the pooled population (n=255). The median time to first onset of vision disorder (clustered term) was 7 days in Study 1005 and 13 days in Study 1001. The most commonly reported vision disorder (clustered term) was visual impairment which was reported in 45.1% of patients in the pooled population (n=255). There were no data on the nature of the visual impairments. However, nearly all reports of vision disorder (clustered term) were Grade 1 and did not result in permanent treatment discontinuation. There was 1 patient with Grade 2 diplopia in whom treatment was temporarily discontinued. Ophthalmological data in a limited number of patients did not identify the cause of the treatment related vision disorder (clustered term). The sponsor reported that in a nonclinical dark adaptation study in rats, effects on retinal function were observed indicating a delay in dark adaptation. However, the sponsor stated that the ability to achieve dark adaptation in this nonclinical study was not affected.

Treatment related oedema (clustered term), including localised oedema, oedema, and peripheral, was reported in 28.2% of patients in the pooled population (n=255). Peripheral oedema was the main individual oedema related event and was reported in 25.1% of patients in the pooled population (n=255). The majority of reports of oedema (clustered term) were Grade 1, and there were no reports of permanent or temporary treatment discontinuation due to this event.

Treatment related neuropathy (clustered term), including burning sensation, hypoaesthesia, hypoaesthesia facial, neuralgia, neuropathy peripheral, paraesthesia, peripheral motor neuropathy, peripheral sensory neuropathy, and sensory disturbance, was reported in 13.3% of patients in the pooled population (n=255). The majority of reports of neuropathy (clustered term) were Grade 1 events with only 1 Grade 3/4 event. No permanent treatment discontinuations were reported for treatment related neuropathy (clustered term) and 1 patient in the pooled population temporarily discontinued due to hypoaesthesia. Other nervous system disorders of dizziness and dysgeusia were also commonly reported in the pooled population (n=255), 15.7% and 11.8% of patients, respectively.

Treatment-emergent ALT increased (all grades) was reported in 13.3% of patients in the pooled population (n=255), with Grade 3 or 4 events being reported in 5.5% of patients. The median time to onset was 22 days in Study 1001 and 31.5 days in Study 1005. In the pooled population, permanent treatment discontinuations (treatment related), temporary treatment discontinuations (all causality) and dose reductions (all causality) were reported in 1.8% (n=4), 5.5% (n=14), and 4.3% (n=11) of patients, respectively.

Laboratory test abnormalities of shifts from baseline Grade \leq 2 to Grade 3 or 4 on-treatment were reported in 11.3%, 5.3%, 2.5%, and 0.4% of patients for lymphopenia, neutropenia leucopenia, and thrombocytopenia.

There have been uncommon reports of treatment related hepatotoxicity, pneumonitis and ECG QT prolongation. However, each of these events are potentially life threatening.

There have been 5 cases of drug related hepatotoxicity (3 of which fulfilled Hy's law criteria for drug induced liver injury) and fatal hepatic failure has been reported in 2 of these cases (1 in one of the 3 patients with Hy's law criteria). The available data suggests that the incidence of treatment related hepatotoxicity is 0.4% (based on at least 1400 patients being exposed in the clinical trial program). Treatment related increased ALT has been observed frequently (13.3%) in the pooled population (n=255) and it is possible that this condition might predispose to the development of treatment related hepatotoxicity. Regular liver function monitoring appears to be warranted with at least temporary discontinuation treatment in patients with Grade 3 or 4 elevations. However, crizotinib related hepatotoxicity is likely to be idiosyncratic and regular liver function monitoring might not reduce the incidence this event due to the unpredictable nature of the condition and its often abrupt onset.

An independent review committee has identified 3 reports of drug related pneumonitis in 340 patients from Studies 1001 and 1005 (incidence of 0.9%) and confirmed that 1 of these cases has been fatal (fatality rate of 33.3%). The committee also identified 2 cases of radiation pneumonitis associated with crizotinib but was unable to determine whether these events were causally related to treatment. Study investigators have identified 4 cases of pneumonitis from Studies 1001 and 1005 (3 of which were confirmed by the independent review committee), and the 60 day update report identified 1 fatal case of interstitial lung disease considered to be treatment related. Permanent treatment discontinuation occurred in 3 (1.2%) of the 4 patients with treatment related pneumonitis reported in Studies 1001 and 1005. Pooling the results from Studies 1001, 1005 and 1007 for investigator determined treatment related pneumonitis identifies 5 cases out of 326 patients (an incidence of 1.5%).

In the pooled population from Studies 1001 and 1005, maximum increases in QTcF of \geq 500 ms and maximum change in QTcF of \geq 60 ms were reported in 0.8% (2/251) and 3.8% (9/237) of patients, respectively. There were no reports of seizure, ventricular tachycardia or ventricular arrhythmia in the Study 1001 (preliminary CSR) or Study 1005 (preliminary CSR), and reports of 8 reports of pre-syncope or syncope and 4 reports of convulsion appeared to be unrelated to primary cardiac events. In the pooled population (n=255), ECG QT prolonged has been reported as a treatment related AE in 4 (1.6%) patients, and in 2 of these patients the event was Grade 3/4. Crizotinib should be avoided in patients with congenital long QT syndrome. In addition, concomitant administration of crizotinib and drugs known to prolong the QT intervals should be avoided.

There are no safety data in patients with hepatic or renal impairment. There are limited safety data in patients aged \geq 65 years.

Other notable risks associated with crizotinib include increased systemic exposure when co-administered with CYP3A inhibitors, reduced systemic exposure when co-administered with CYP3A inducers and inhibition by crizotinib of the metabolism of co-administered CYP3A substrates

There were no data on the development of treatment resistance to crizotinib due to mutations in the EML4-ALK gene. This appears to be an emerging issue related to crizotinib treatment for ALK-positive NSCLC.⁶⁴

First round assessment of benefit-risk balance

It is considered that the benefit-risk balance of crizotinib, given the proposed usage, is unfavourable. While the ORRs observed in Studies 1001 and 1005 are encouraging, there are no Phase III, randomised, controlled data showing that these results translate into clinically meaningful benefits (OS and/or PFS). The information from the retrospective analyses in the Technical Report (covariate-matched and covariate-adjusted analyses) suggests superior clinical benefits as assessed by ORR, PFS, and OS for crizotinib compared with historical controls. However, these retrospective analyses are considered to be exploratory as they were not pre-specified and were undertaken “to give perspective to the efficacy results from the single arm Study 1001” (Technical Report). It is considered that the data from the retrospective analyses cannot substitute for confirmatory data from Phase III, randomised, controlled clinical studies.

In the absence of evidence of clinically meaningful benefits for crizotinib for the proposed indication from Phase III, randomised, controlled studies, it is considered that the treatment related adverse event profile for the medicine (particularly the uncommon but potentially life threatening risks of hepatotoxicity and pneumonitis) results in an unfavourable benefit-risk balance. It is possible that favourable results relating to PFS and OS from the two, ongoing, randomised, active-controlled Phase III studies might reverse the currently unfavourable benefit-risk balance assessment.

First round recommendation regarding authorisation

It is recommended that the submission to register crizotinib for the proposed indication should be rejected on the following grounds:

- Lack of evidence of clinically meaningful benefits (OS and/or PFS) for crizotinib for the proposed indication from Phase III, randomised, controlled studies. The results for the ORR from the single-armed Phase I (1001) and 2 (1005) studies are encouraging, but there are no Phase III, randomised, controlled data confirming that these results translate into clinically meaningful benefits. The information from the retrospective analyses in the Technical Report suggest clinically meaningful benefits for crizotinib compared with historical controls for PFS and OS, but these data are considered to be exploratory and require confirmation by Phase III, randomised, controlled clinical studies.
- In the absence of evidence of clinically meaningful benefits associated with crizotinib for the proposed indication from Phase III, randomised, controlled studies, it is considered that the treatment related adverse event profile of crizotinib (particularly the uncommon but potentially life threatening risks of hepatotoxicity and pneumonitis) make the benefit-risk balance unfavourable.

Benefit-risk balance assessment

The benefit-risk balance of crizotinib, given the proposed usage, is considered to be unfavourable. While the ORRs observed in Studies 1001 and 1005 are encouraging, there are no Phase III, randomised, controlled data showing that these results translate into

⁶⁴ Camidge DR, Theodoros M, Maxson DA, et al. Correlations between the percentage of tumor cells showing an ALK (anaplastic lymphoma kinase) gene rearrangement, ALK signal copy, and response to crizotinib therapy in ALK fluorescence in situ hybridization-positive nonsmall cell lung cancer. Cancer 2012. Early view published on-line [doi: 10.1002/cncr.27411].

clinically meaningful benefits (OS and/or PFS). It is noted that information from the retrospective covariate-matched and covariate-adjusted analyses in the Technical Report (covariate-matched and covariate-adjusted analyses) suggests superior benefits for crizotinib compared with historical controls as regards the ORR, PFS and OS. However, the retrospective analyses are exploratory as they were not pre-specified and were undertaken “to give perspective to the efficacy results from the single arm Study 1001” (Technical Report). It is considered that the data from the retrospective analyses cannot substitute for confirmatory data from Phase III, randomised, controlled clinical studies.

In the absence of evidence of clinically meaningful benefits for crizotinib for the proposed indication from Phase III, randomised, controlled studies, it is considered that the treatment related adverse event profile for crizotinib (particularly the uncommon but potentially life threatening risks of hepatotoxicity and pneumonitis) results in an unfavourable benefit-risk balance. It is possible that favourable results relating to PFS and OS from the two, ongoing, randomised, active-controlled Phase III studies might reverse the currently unfavourable benefit-risk balance assessment (that is, Studies 1007 and 1014).

The sponsor is requested to comment on the unfavourable benefit-risk balance assessment for crizotinib for the proposed indication.

Second round clinical report: first round clinical questions and sponsor response/evaluator comments

Clinical pharmacokinetics

Question 1

The submission did not include a formal clinical PK study in patients with hepatic impairment. Crizotinib is extensively metabolized and hepatic clearance appears to be the major route of elimination of the drug. Consequently, it is likely that patients with hepatic impairment will have increased systemic exposure to crizotinib following oral administration. Does the sponsor intend to undertake a formal PK study in patients with hepatic impairment? If not please provide a justification for not providing such data.

Sponsor's response

In addition to collection and analysis of adverse event reports in patients with underlying hepatic impairment through routine pharmacovigilance practices, the sponsor plans to conduct a clinical trial to determine the effect of hepatic impairment on multiple-dose pharmacokinetics of crizotinib: Study A8081012 - A Phase I Study to Evaluate the Effect of Hepatic Impairment on the Pharmacokinetics of Crizotinib in Advanced Cancer Patients. The sponsor commits to submitting the final CSR for this study upon availability (estimated Q1 2014).

Furthermore, the sponsor proposes to conduct a 3 year post-approval multinational database study in Europe to further characterize the safety of crizotinib in patients, including those with hepatic impairment, in real-world settings.

Clinical evaluator's comment

The sponsor's response is satisfactory. The draft PI includes a statement in the *Dosage and Administration* section indicating that treatment with Xalkori should be used with caution in patients with hepatic impairment, and the *Precautions* section includes a statement that the drug should not be used in patients with severe hepatic impairment (Child-Pugh class C). However, the updated PI has deleted the statement indicating that as “*crizotinib is extensively metabolised in the liver, hepatic impairment is likely to increase plasma*

crizotinib concentrations". It is considered that this statement should be reinstated in the PI.

Question 2

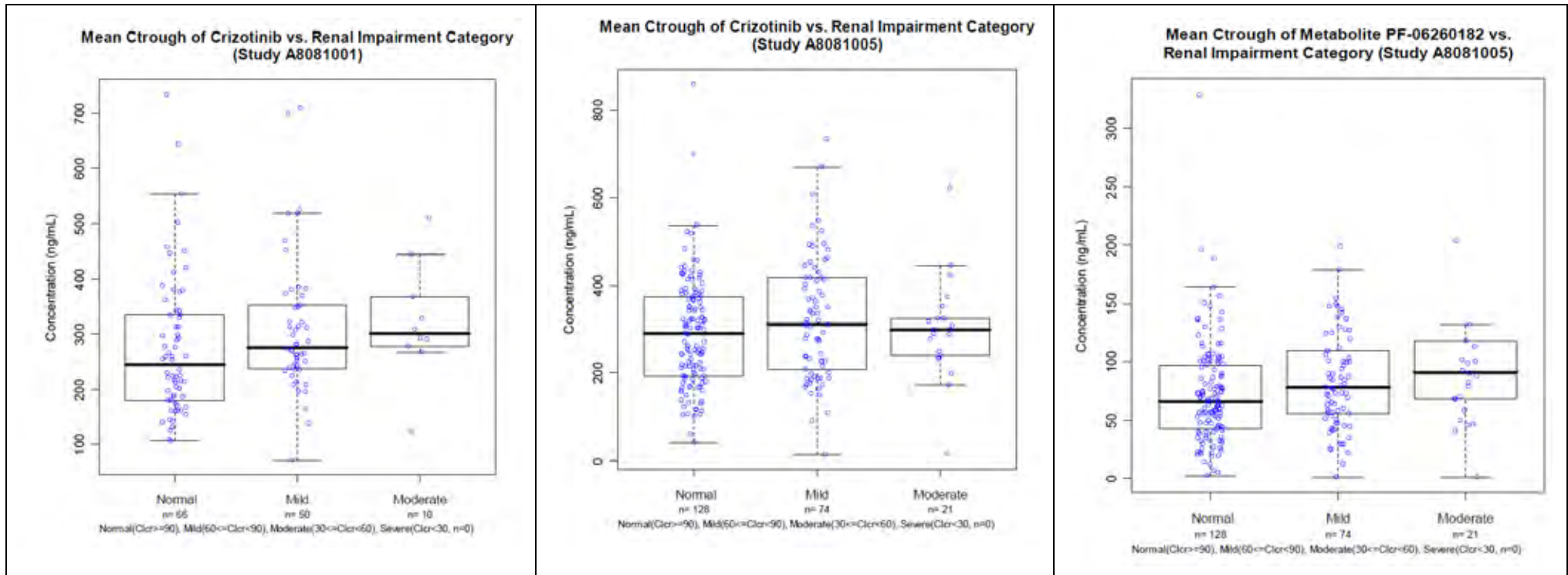
The submission did not include a formal clinical PK study in patients with renal impairment. While renal elimination of unchanged crizotinib was low (2.3% of the administered dose), the total amount of administered radioactivity recovered in the urine was 22.2% of the dose. This result indicates that there is significant renal elimination of the metabolites of crizotinib. Consequently, it is likely that patients with renal impairment will have increased systemic exposure to crizotinib metabolites. Does the sponsor intend to undertake a formal PK study in patients with renal impairment? If not please provide a justification for not providing such data.

Sponsor's response

Based on the radio-labelled mass balance study in humans (A8081009 CSR), the overall mean recovery of radioactivity in urine was 22.2% of dose, with values from individual subjects ranging from 15.1% to 28.8%. Profiling of ¹⁴C-crizotinib-related radioactivity in urine showed that the percent of dose excreted as unchanged crizotinib was 2.30%. The major excreted component in urine, accounting for an average of 4.5% of dose, was a sulfate conjugate of O-desalkyl crizotinib lactam. No other metabolites accounted for >1% of total administered dose in excreta. Considering that no major metabolites were identified in urine and conjugates in general have minimal pharmacological activities, accumulation of metabolites would postulate little risk in renal impaired patients.

The sponsor conducted an analysis to evaluate the effect of renal function on crizotinib PK using baseline creatinine clearance (CLcr) and mean steady-state trough concentration ($C_{trough,ss}$) of crizotinib and its metabolite PF-06260182 using data from Studies A8081001 RP2D (only crizotinib concentrations were measured) and A8081005. In the analysis, patients were divided into 4 groups based on their stages of renal impairment according to K/DOQI guidelines (2002): normal (CLcr greater than 90 mL/min), mild (CLcr 60 to 90 mL/min), moderate renal impairment (CLcr 30 to 60 mL/min) and severe renal impairment (CLcr <30 mL/min, no PK data available for this group). Results of the analysis indicated that $C_{trough,ss}$ of crizotinib and its metabolite PF-06260182 in mild and moderate renal impairment groups were higher (not statistically significant) than those in patients with normal renal function in both studies (see Box-Plots below).

Figure 1. Box-Plots of Trough Concentrations of Crizotinib and its Metabolite PF-06260182 versus Renal Function Groups in Studies A8081001 RP2D (only crizotinib concentrations were measured) and A8081005.



Due to the small size of the increases (7-12%), no starting dose adjustment is recommended for patients with mild and moderate renal impairment. The guidance on the need for starting dose adjustment in patients with severe renal impairment cannot be provided at this time due to the current lack of pharmacokinetic data in this population. Thus, the sponsor plans to conduct a clinical trial to determine the effect of severe renal impairment on single-dose pharmacokinetics of crizotinib (Study A8081020: "A Phase I, Single-Dose, Parallel-Group Study to Evaluate the Pharmacokinetics of Crizotinib (PF-02341066) in Subjects with Impaired Renal Function"). The sponsor commits to submitting the final clinical study report for this study.

The sponsor realises that a precise prediction of the effect of severe renal impairment on multiple dose PK from single-dose PK data presents a challenge, as crizotinib exhibits nonlinear PK due to auto-inhibition of CYP3A (sponsor's *Summary of Clinical Pharmacology studies*). However, results of a single-dose study are likely to be predictive of the multiple-dose scenario in a case where severe renal impairment exhibits little or no effect on single-dose crizotinib PK. A single-dose study is proposed as a first step in the evaluation of the effect of severe renal impairment on crizotinib PK. If severe renal impairment is shown to have an effect (at least 50% increase in crizotinib AUC compared to the crizotinib AUC for patients with normal renal function) on single-dose crizotinib PK, then further investigations, including clinical and mechanistic SimCYP simulation, may be explored.

In addition, the sponsor plans to complete an updated population PK analysis to definitively assess the CL_{Cr} effect on crizotinib PK using pooled data from clinical trials including but not limited to Studies A8081001 and A8081005. The final report will be submitted to the TGA.

Clinical evaluator's comment

The sponsor's response is satisfactory. The sponsor provided data summarising crizotinib and metabolite PF-06260182 C_{trough.ss} levels in patients with normal renal function and mild and moderate renal impairment. No PK data were provided on the effects of renal impairment on crizotinib and metabolite PF-06260182 C_{max.ss} and AUC_{.ss} levels, or on C_{trough.ss} levels in patients with severe renal impairment. However, the sponsor has undertaken to conduct a single-dose PK study in patients with renal impairment and to update the population pharmacokinetic analysis from pooled clinical trial data in order to "definitively assess the CL_{Cr} effect on crizotinib PK".

The new data summarised the analysis of co-variance (ANCOVA) results of steady state crizotinib (PF-02341066) and steady state crizotinib metabolite (PF-06260182) C_{trough.ss} concentrations in patients with renal impairment treated with a total daily dose of 500 mg. The results for the analyses of crizotinib (PF-02341066) C_{trough.ss} are summarised below in Table 7 (Study 1001) and Table 8 (Study 1005). The analyses showed that mild and moderate renal impairment had no marked effects on C_{trough.ss} crizotinib concentrations compared with patients with normal renal function. This is not unexpected as renal excretion of unchanged crizotinib is low (2.3% of the administered dose). In Study 1001, C_{trough.ss} increased by about 10% to 12% in patients with renal impairment (mild/moderate) compared with subjects with normal renal function, and in Study 1005 the corresponding increases were about 7% to 8%.

Table 7. Study 1001 – ANCOVA steady state plasma crizotinib Ctrough – renal impairment.

Parameter (Units)	Comparison (Test vs. Reference)	Adjusted Geometric Means		Ratio (%) (Test / N Reference)	90% CI (%)
		Test	N Reference		
Ctrough (ng/ml)	Renal impairment: Mild vs Normal	304.87	50 272.62	66 111.83	(98.38, 127.12)
	Renal impairment: Moderate vs Normal	300.89	10 272.62	66 110.37	(88.43, 137.76)

Based on a log transformed ANCOVA with final values back-transformed from the log scale.

The model for ANCOVA has renal impairment as a factor and ethnicity (Asian vs Non-Asian) and BSA as covariates.

Renal function categories: normal (CLcr \geq 90 mL/min), mild (60 mL/min \leq CLcr < 90 mL/min) and moderate (30 mL/min \leq CLcr < 60 mL/min).

Ctrough mean was calculated for each subject from all pre-dose concentrations after Cycle 1 Day 1, collected within the allowable time window (-1.2H to 0H for BID dosing schedule)), for subjects receiving 500mg total daily dose.

Data cutoff: 13Sep2010

PFIZER CONFIDENTIAL Source Data: B5.1a, B5.2.1.2a Date of Reporting Dataset Creation: 18JAN2012 Date of Table Generation: 28FEB2012 (20:29)

Table 8. Study 1005 – ANCOVA steady state plasma crizotinib Ctrough – renal impairment.

Parameter (Units)	Comparison (Test vs. Reference)	Adjusted Geometric Means		Ratio (%) (Test / N Reference)	90% CI (%)
		Test	N Reference		
Ctrough (ng/ml)	Renal impairment: Mild vs Normal	294.58	73 273.78	128 107.60	(96.92, 119.45)
	Renal impairment: Moderate vs Normal	292.40	20 273.78	128 106.80	(89.99, 126.75)

Based on a log transformed ANCOVA with final values back-transformed from the log scale.

The model for ANCOVA has renal impairment as a factor and ethnicity (Asian vs Non-Asian) and LBW as covariates.

Renal function categories: normal (CLcr \geq 90 mL/min), mild (60 mL/min \leq CLcr < 90 mL/min) and moderate (30 mL/min \leq CLcr < 60 mL/min).

Ctrough mean was calculated for each subject from all pre-dose concentrations after Cycle 1 Day 1, collected within the allowable time window (-1.2H to 0H for BID dosing schedule), for subjects receiving 500mg total daily dose.

Two extreme low values of Ctrough mean (15.9 ng/ml from subject 10131004 and 13.5 ng/ml from subject 10751024) were excluded in the ANCOVA.

Data cutoff: 01Jun2011

PFIZER CONFIDENTIAL Source Data: B5.1a, B5.2.1.2a Date of Reporting Dataset Creation: 18JAN2012 Date of Table Generation: 28FEB2012 (20:43)

In Study 1005, the mean metabolite (PF-062601820) to parent crizotinib (PF-02341066) ratio in 277 subjects was 0.235 (0.076) with a range from 0.050 to 0.610. In an ANCOVA of steady state plasma metabolite (PF-062601820) C_{trough} levels from Study 1005, mean levels were about 16% higher (ratio = 115.5 [90%CI: 99.07, 134.65]) in subjects with mild renal impairment (71.69 mg/mL, n=73) compared with subjects with normal renal function (62.07 ng/mL, n=128) and about 26% higher (ratio = 126.30 [95%CI: 98.23, 162.41]) in subjects with moderate renal impairment (78.40 ng/mL, n=20) compared with subjects with normal renal function.

Question 3

The submission did not include a formal clinical drug-drug PK interaction study between crizotinib and a P-gp efflux transporter inhibitor. The *in vitro* data predict that crizotinib is likely to be a substrate for the P-gp efflux transporter at therapeutic plasma concentrations. Consequently, co-administration of crizotinib and P-gp efflux transporter inhibitors has the potential to increase systemic exposure to crizotinib. Does the sponsor intend to undertake a formal PK interaction study between crizotinib and a P-gp efflux transporter inhibitor? If not please provide a justification for not providing such data.

Sponsor's response

Although crizotinib is a P-gp substrate based on the *in vitro* data, the sponsor does not anticipate drug-drug interactions (DDIs) that result from alterations of either absorption or systemic clearance following coadministration of crizotinib with a P-gp inhibitor/inducer for the following reasons:

1. *P-gp is not expected to interfere with oral absorption of crizotinib.*

Categorisation of crizotinib as a low-permeability drug is based on observations from human studies where absolute bioavailability and recovery of the administered drug unchanged in urine were both <90%. Due to inherent limitations of the influence of transporters, the low permeability observed in *in vitro* Caco-2 studies may be not reliable (sponsor's quality submission). Crizotinib (0.1 to 50 μ M [45 to 22,500 ng/mL]) was evaluated for its potential as a substrate for the efflux transporters P-gp in the MDCK transfected cell line (sponsor's *Summary of Clinical Pharmacology*, Pfizer report PF-02341066_03Aug10_174737). The BA/AB ratios in the P-gp-transfected MDCK cell lines indicated that crizotinib was a substrate for P-gp. The efflux ratio for P-gp-transfected MDCK cells decreased with increasing crizotinib concentrations and P-gp-mediated efflux was saturable at high concentrations (≥ 50 μ M [22,500 ng/mL]). The gastrointestinal concentration of crizotinib after oral administration of 250 mg (12) is calculated to be 2220 μ M (250 mg crizotinib/250 mL), ~ 40 fold higher than the *in vitro* concentrations where P-gp saturation was observed. Moreover, the absolute bioavailability of crizotinib in humans was determined to be 43% (sponsor's *Clinical Summary*, A8081010 CSR) indicating a moderate to high fraction absorbed ($F_a > 43\%$). Based on these observations, it is unlikely that absorption of crizotinib will be limited by this efflux transporter at therapeutic doses.

2. *P-gp is not expected to interfere with the overall clearance of crizotinib.*

In vitro studies clearly demonstrated that CYP3A4/5 were major enzymes involved in crizotinib clearance and in the formation of key metabolites in the pathways of crizotinib elimination from the body (sponsor's *Nonclinical Summary*). Using the *in vitro* metabolic data and the SIMCYP simulation, the change in crizotinib AUC when a single dose of crizotinib is coadministered with ketoconazole was predicted to be ~ 4.1 fold⁶⁵, consistent with that observed in the clinical study with ketoconazole (sponsor's *Clinical Summary*;

⁶⁵ Johnson TR, Zhou S, Lee CA, Clouser-Roche A, Freiwald S, Youdim, KA, Aherne K, Batugo MR, Skaptason J, Yamazaki S, Wester MR and Smith BJ. *Drug Metabolism Reviews*, 2011; 43(S2): Poster 251.

Study A8081015 CSR), indicating that CYP-mediated metabolism is the predominant elimination pathway of crizotinib. Non-metabolic elimination pathways seem to play a minimal role in the elimination of crizotinib. Renal excretion of crizotinib is negligible, as reflected by only 2.3% of the administered dose recovered in urine as unchanged crizotinib (sponsor's *Clinical Summary*; A8081009 CSR). Although biliary excretion of crizotinib in humans cannot be conclusively ruled out, unchanged crizotinib was not observed in bile collected from rats following oral administration of [¹⁴C]crizotinib (sponsor's *Nonclinical Summary*). Therefore, biliary excretion of unchanged crizotinib is not anticipated to be a significant clearance pathway in humans, as rats are typically considered to be more efficient biliary excretors relative to humans (Kwon, 2001).

3. *Clinically significant interference with P-gp in the blood-brain barrier (BBB) is low.*

P-gp-mediated transport may play a role in preventing penetration of crizotinib across the normal blood-brain barrier (BBB). In a tissue distribution study in rats orally administered ¹⁴C-crizotinib, crizotinib-derived radioactivity was below the limit of quantitation in the brain and spinal cord (sponsor's *Nonclinical Summary*). A low crizotinib concentration in CSF was reported in 1 ALK-positive NSCLC patient in Study A8081001 treated with crizotinib (250 mg bd) who developed metastatic brain disease (Costa et al., 2011).⁶⁶ In this case, the crizotinib plasma concentration was 237 ng/mL, whereas the concurrent CSF concentration was 0.616 ng/mL. The CSF-to-plasma ratio of 0.0026 was markedly lower than the unbound fraction in human plasma (0.093), suggesting poor BBB penetration of the drug in this patient.

These data suggest that it is possible that the degree of CNS penetration of crizotinib could be altered in the presence of a P-gp inhibitor. However, clinical examples of interactions involving transport proteins at the BBB which result in increased drug exposure in the brain are rare.⁶⁷ Moreover, in examples where interactions were observed, the effects were relatively modest, with less than 2 fold increase in CNS penetration (.⁶⁸ There are currently no consistent clinical examples in which inhibition of P-gp on the BBB resulted in adverse effects.⁶⁹

Based on the rationale presented above, P-gp-mediated DDIs are unlikely to result in clinically relevant increases in crizotinib plasma levels. The sponsor does not intend to undertake a formal PK interaction study between crizotinib and a P-gp efflux transporter inhibitor.

Clinical evaluator's comment

The sponsor's response is satisfactory.

Question 4

The submission did not include a formal clinical drug-drug PK interaction study between crizotinib and P-gp efflux transporter substrate. The in vitro data predict that crizotinib is likely to be an inhibitor of the P-gp efflux transporter. Consequently, co-administration of crizotinib and P-gp efflux transporter substrates has the potential to increase systemic exposure to such substrates. Does the sponsor intend to undertake a formal PK interaction study between crizotinib and a P-gp efflux transporter substrate? If not please provide a justification for not providing such data.

⁶⁶Costa DB, Kobayashi S, Pandya SS. CSF concentration of the anaplastic lymphoma kinase inhibitor crizotinib. *J Clin Oncol* 2011; 29(15):e443-e445.

⁶⁷Ayrton A, Morgan P. Role of transport proteins in drug absorption, distribution, and excretion. *Xenobiotica*. 2001;31(8/9):469-497.

⁶⁸Ayrton A, Morgan P. Role of transport proteins in drug discovery and development: a pharmaceutical perspective. *Xenobiotica*. 2008;38(7/8):676-708.

⁶⁹Eyal S, Hsiao P, Unadkat JD, Drug interactions at the blood-brain barrier: fact or fantasy. *Pharmacol. Ther.* 123, 80-104 (2009)

Sponsor's response

The potential of crizotinib to inhibit P-gp was evaluated in an *in vitro* study in Caco-2 cells using digoxin (5 μM), a probe P-gp substrate, in the absence or presence of crizotinib (0.1 to 20 μM ; 45 to 9010 ng/mL) (sponsor's *Nonclinical Summary*; Pfizer report PF-02341066_11May10_141847). The IC_{50} of crizotinib inhibition of P-gp-mediated digoxin efflux was 5.8 μM (2610 ng/mL). Based on the mean unbound crizotinib plasma C_{max} (38 ng/mL, 0.085 μM) at the 250 mg bd therapeutic dose, crizotinib is unlikely to have systemic interaction with substrates of P-gp. Crizotinib demonstrated time-dependent inhibition of CYP3A *in vitro* [sponsor's *Nonclinical Summary*] and was shown to be a moderate inhibitor of CYP3A in clinical trial [sponsor's *Clinical Summary*]. Many P-gp substrates are also metabolised by the cytochrome P450 system (including colchicine as cited in the question). In the event such a drug is coadministered with crizotinib, it is likely that the resulting systemic exposure will be influenced by the dual inhibition of CYP3A and P-gp. It is probable that crizotinib-mediated CYP3A-inhibition will play a more dominant role than P-gp in drug-drug interactions (DDIs) involving these systems. In fact, few clinically relevant DDIs attributable solely to P-gp have been reported.⁷⁰ In contrast to CYP-mediated changes, DDIs related to changes in P-gp activity are generally not clinically significant (PK ratios ≤ 2).⁷¹ As crizotinib's CYP3A inhibitory activity predominates, information from a DDI study with a probe P-gp substrate would only provide useful information for drugs that are solely substrates of P-gp.

Currently, there are only two clinically used drugs known to be sole P-gp substrates without the confounding influence of CYP-mediated metabolism, namely, digoxin and dabigatran.⁷² Digoxin is a narrow therapeutic window drug that requires therapeutic drug monitoring in its normal use and when there are possibilities of DDIs. Similarly, use of the oral anticoagulant dabigatran requires patients stabilized on this agent to be monitored for altered response if P-gp inhibitors or inducers are added or removed from their treatment regimen. It is highly unlikely that the monitoring requirements for either of these drugs would be changed based on the results of a DDI study with crizotinib.

Therefore, a clinical DDI study with a probe P-gp substrate (digoxin or dabigatran) would not add meaningful value to any recommendations regarding the coadministration of crizotinib with P-gp substrates. The sponsor does not intend to undertake a formal PK interaction study between crizotinib and a P-gp efflux transporter substrate.

⁷⁰Lin, JH. Transporter-mediated drug interactions: clinical implications and *in vitro* assessment. *Expert Opin Drug Metab Toxicol* 3, 81–92 (2007).

⁷¹Fenner, KS, et al. Drug–drug interactions mediated through P-glycoprotein: clinical relevance and *in vitro*–*in vivo* correlation using digoxin as a probe drug. *Clin Pharmacol Ther* 85 (2), 173–181 (2009).

⁷²Giacomini, KM, et al. Membrane transporters in drug development. *Nature Reviews/Drug Discovery* 9, 215–235 (2010).

Clinical evaluator's comments

The sponsor considers that a “systematic interaction” between crizotinib and P-gp substrates is unlikely based on a comparison between the mean unbound crizotinib C_{max} (38 ng/mL, 0.085 μ M) and the IC_{50} of crizotinib inhibition of P-gP mediated digoxin efflux (2610 ng/mL, 5.8 μ M). It is noted that the sponsor has referred to the unbound crizotinib C_{max} when formulating its opinion. However, the mean steady-state total (unbound+bound) crizotinib C_{max} was 411 ng/mL (0.91 μ M) in patients with cancer (Study 1001). The literature suggests that when correlating drug concentrations which inhibit enzymes *in vitro* with C_{max} concentrations derived from clinical studies the total (unbound + bound) C_{max} at steady with the highest clinical dose should be used.^{73,74 75} Furthermore, the 2012 FDA Drug Interaction Studies guidance document, recommends that an *in vivo* drug interaction study with a P-gp substrate such as digoxin be undertaken when $[I]_1/IC_{50} \geq 0.1$; $[I]_1$ represents the mean-steady state total (free and bound) C_{max} following administration of the highest clinical dose. Applying the FDA criteria to the relevant *in vitro* and *in vivo* data results in a ratio of 0.16 (i.e., $0.91/5.8 = C_{max,ss}/IC_{50}$).

Based on the approach recommended by the FDA, an *in vivo* drug interaction study with a P-gp substrate would be appropriate. However, the sponsor notes that there are only two clinically used drugs known to be sole P-gp substrates without the confounding influence of CYP-mediated metabolism, namely, digoxin and dabigatran.⁷² Furthermore, the sponsor notes that many P-gp substrates are also metabolized by the cytochrome P450 system and that it is probable that crizotinib mediated CYP3A inhibition will play a more dominant role than P-gp in drug-drug interactions involving these systems. The sponsor considers that clinical drug-drug interaction study with a probe P-gp substrate (digoxin or dabigatran) would not add meaningful value to any recommendations regarding the coadministration of crizotinib with P-gp substrates and intends not to undertake such a study. Overall, although it is considered that there is the potential for drug-drug interactions between crizotinib and P-gp substrates, the sponsor's arguments relating to confounding influences due to the inhibitory effect of crizotinib on CYP3A are acceptable.

Question 5

The submission did not include formal clinical PK drug-drug interaction studies between crizotinib and drugs known to increase the gastric pH. The aqueous solubility of crizotinib is pH dependent, with low (acidic) pH resulting in higher solubility. Consequently, it is possible that drugs which increase intragastric pH (reduce acidity) might reduce the bioavailability of crizotinib by decreasing its solubility. In the population-PK analysis, co-administration of crizotinib and PPIs esomeprazole, omeprazole, and lansoprazole decreased the absorption rate constant (k_a) of crizotinib. Does the sponsor intend to undertake formal PK interaction studies between crizotinib and antacids, PPIs and H2 inhibitors. If not please provide a justification for not providing such data.

Sponsor's response

The sponsor plans to conduct the following clinical trial to determine the effect of gastric pH elevation on crizotinib pharmacokinetics (PK): Study A8081035, “A Phase I, Single-Dose, Randomized, Cross-Over Study to Estimate the Effect of Esomeprazole on the Pharmacokinetics of Crizotinib in Healthy Volunteers”.

⁷³Zhang et al. Predicting drug-drug interactions: an FDA perspective. AAPS Journal 11, (2) (2009).

⁷⁴FDA (Draft Guidance, 2012) – Guidance for Industry Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations. Clinical Pharmacology, February 2012.

⁷⁵Bjornsson TD et al. The conduct of *in vitro* and *in vivo* drug-drug interaction studies: a pharmaceutical research and manufacturers of America (PhRMA) perspective. Drug Metabolism and Disposition 31 (7) (2003).

Clinical evaluator's comment

The sponsor's response is satisfactory.

Question 6

The submission did not include *in vitro* data exploring potential interactions relating to crizotinib mediated induction of CYP2B and CYP2C enzymes. The submitted *in vitro* and *in vivo* data demonstrated that crizotinib can induce CYP3A. The sponsor states that most drugs that induce CYP3A are believed to do so primarily via activation of the pregnane X receptor (PXR). The sponsor notes that activation of the pregnane X receptor (PXR) can result in upregulation of CYP2B and CYP2C genes, as well as other Phase II enzymes and transporters. Does the sponsor intend to undertake *in vitro* studies exploring potential interactions relating to crizotinib mediated induction of CYP2B and CYP2C enzymes? If not please provide a justification for not providing such data.

Sponsor's response

The key elements of the sponsor's response are summarised below:

- As crizotinib is both an inducer and modest time-dependent inhibitor of CYP2B6 *in vitro*, an additional *in vitro* induction study with CYP2B6 has been initiated (4Q 2011) using enzyme activity as an endpoint to allow assessment of the net interaction. If the results of this follow-on study demonstrate that crizotinib elicits a change in CYP2B6 activity that is $\leq 40\%$ of rifampicin, per the FDA and EMA draft guidance documents, the sponsor recommends that further evaluation of the potential of crizotinib to induce CYP2B6 would not be warranted.
- Appreciable pharmacokinetic drug interactions ($>20\%$ decrease in area under the concentration-time curve [AUC]) via crizotinib-mediated induction of drugs that are substrates of CYP2C8 and CYP2C9 are not anticipated. Neither crizotinib nor the positive control rifampicin elicited statistically significant induction of CYP2C19 mRNA expression, suggesting that the *in vitro* method utilised may not be sufficiently sensitive for this CYP enzyme. However, given the lack of effect predicted for the other CYP2C enzymes, it is unlikely that appreciable induction of CYP2C19 would be expected with crizotinib. Consequently, the sponsor recommends that further evaluation of the potential of crizotinib to induce CYP2C8, CYP2C9 or CYP2C19 is not warranted.

Clinical evaluator's comments

The sponsor's response indicates that an *in vitro* induction study with CYP2B6 has been initiated. The sponsor also indicated that it has no plans to further evaluate the potential of crizotinib to induce CYP2C8, CYP2C9, or CYP2C19. This decision is considered to be acceptable. However, the TGA might wish to obtain the opinion of the nonclinical evaluator on the decision not to conduct further *in vitro* studies to assess the effect of crizotinib on inducing CYP2C8, CYP2C9 or CYP2C19. The sponsor supported its decision not to further evaluate the potential of crizotinib to induce CYP2C8, CYP2C9 or CYP2C19 with data from the following new documents:

- the final study report for PF-02341066/17DEC10/120808 investigating the potential for crizotinib to induce CYP3A4, CYP2B6, CYP2C8, CYP2C9, and CYP2C19 mRNA *in vitro* using cryopreserved human hepatocytes;
- the final study report for XT115053 investigating the potential for crizotinib to inhibit cytochrome P450 (CYP) CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5 activities *in vitro*, using pooled human liver microsomes; and
- the Cover Memo entitled "In vitro studies to investigate the potential of crizotinib to induce cytochrome P450s 2B6 and 2C".

The sponsor stated that a “robust *in vitro-in vivo* understanding of non-3A CYP enzyme induction has not been established, and therefore, represents an immature area of drug disposition science. Given these limitations, the results of the *in vitro* studies were interpreted within the context of: (1) draft guidances on drug interactions issued by the FDA (2006) and EMA (2010), (2) predictive mathematical approaches originally developed for CYP3A induction interactions and (3) comparison of the mathematical approach-predicted drug interactions for the control inducer rifampin with reported clinical interactions”.

In Study PF-02341066/17Dec10/120808, the potential for crizotinib to induce CYP3A4, CYP2B6, CYP2C8, CYP2C9, and CYP2C19 was evaluated using human cryopreserved hepatocytes (2 lots) incubated with crizotinib at concentrations of 0.25 to 7 μ M, with rifampin (10 μ M) being used as used as a positive control inducer. Statistically significant induction of CYP3A4, CYP2B6 and CYP2C8 was observed in both lots of human hepatocytes treated with crizotinib or rifampin (Hu8064, Hu4165), while statistically significant induction of CYP2C9 was observed in only one of the two lots and CYP2C19 was not significantly induced in either of the two lots. The magnitude of induction from baseline was lower for non-CYP3A4 enzymes than for the CYP3A4 enzyme, which the sponsor states is consistent with the profile of a PXR activator.⁷⁶ For CYP3A4, CYP2B6, CYP2C8, and CYP2C9, the magnitude of crizotinib mediated induction was lower relative to the positive control rifampin, with average maximal induction values relative to rifampin of 37%, 31%, 37%, and 81%, respectively. The results are summarised in CER1.

Based on consideration of the criteria outlined in the draft FDA (2006) guideline, the EMEA (2010) guidance document, and published mathematical prediction approaches, the sponsor estimates that appreciable pharmacokinetic drug interactions (> 20% decrease in AUC) via crizotinib mediated induction of drugs that are substrates of CYP2C8 and CYP2C9 would not be anticipated. Consequently, the sponsor recommends that further evaluation of the potential of crizotinib to induce CYP2C8 and CYP2C9 is not warranted. Neither crizotinib nor the positive control rifampin statistically significantly induced CYP2C19 mRNA expression ($p < 0.05$). Consequently, the sponsor postulates that the *in vitro* methods utilised may not be sufficiently sensitive to assess potential induction risk of this CYP enzyme. However, given the lack of effect predicted for the other CYP2C enzymes, the sponsor considers it unlikely that appreciable induction of CYP2C19 would be expected with crizotinib. In Study XT115053, crizotinib was demonstrated to be a metabolism dependent inhibitor (time and NADPH-dependent) of CYP2B6 and CYP3A4/5 but not of CYP1A2, CYP2C8, CYP2C9, CYP2C19, or CYP2D6.

Question 7

The submission did not include data exploring the potential PK/PD relationships between crizotinib exposure and clinical efficacy (ORR) or safety outcomes (hepatotoxicity). Does the sponsor intend to undertake such studies? If not please provide a justification for not providing such data.

Sponsor's response

The sponsor has completed preliminary exposure-response analyses using data from Studies A8081001 and A8081005 which are summarised in PMAR-0242 and PMAR-0266, respectively. These studies included exposure-response analyses for objective response rate (ORR), progression-free survival (PFS) and 4 selected adverse events (AEs), namely, pneumonitis, ALT elevation, neutropenia, and fatigue. These selected AEs were a combination of most commonly observed AEs of Grade ≥ 3 in severity and had the

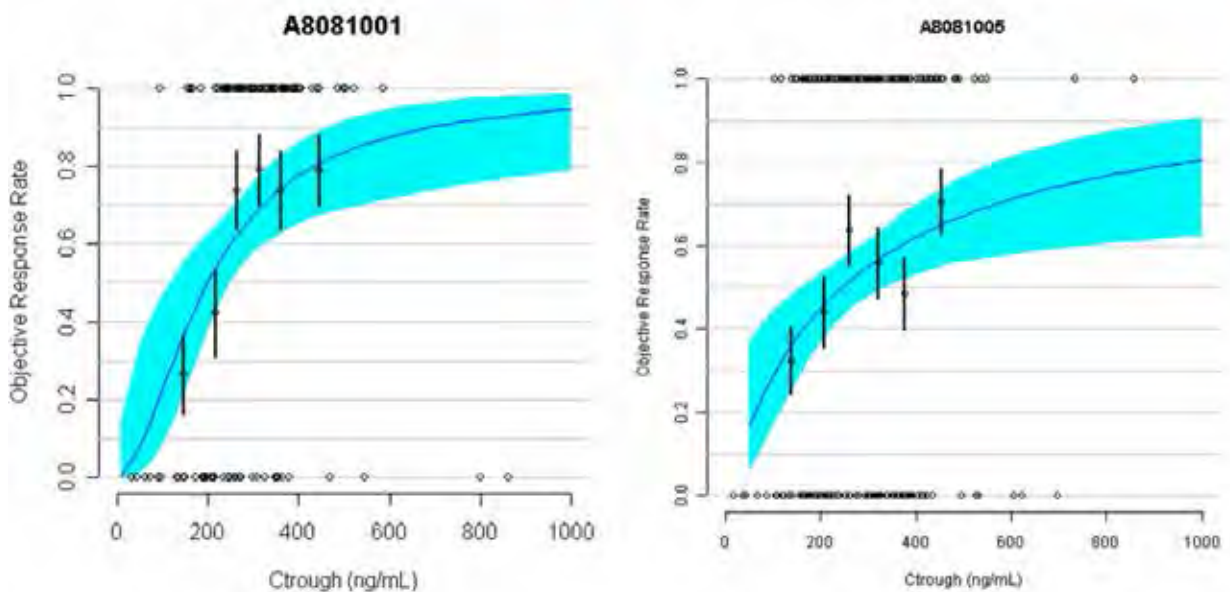
⁷⁶ Fahmi OA, Hurst S, Plowchalk D, et al. Comparison of different algorithms for predicting clinical drug-drug interactions, based on the use of CYP3A4 *in vitro* data: predictions of compounds as precipitants of interaction. *Drug Metab Dispos.* 2009;37(8):1658-1666.

potential to limit crizotinib dose based on clinical safety observations. Since OS data is currently limited from these studies, the exposure-response analysis for OS was not included. The overall integrated results are summarised below.

1. Exposure-Response Relationships for Efficacy

There were statistically significant exposure-response relationships for objective response, with higher exposure being associated with higher ORR in both studies. The exposure-response relationship in Study A8081005 was shallower than that seen in Study A8081001 (Figure 2). The exposure-response relationship for PFS in both studies showed the same trend seen with ORR, with higher exposure corresponding to longer PFS; however, this relationship was not statistically significant.

Figure 2. Logistic Regression Models for Objective Response to Crizotinib versus Ctrough in Studies A8081001 and A8081005.



Open circles represent observed data, vertical bars represent the 95% confidence interval of the observed ORR for 1/6th quantiles, solid lines represent model fitted probability (no confounders), and shaded areas represent the 95% confidence interval of the model-based probability.

2. Exposure-Response Relationships for Safety

Logistic regression modelling analyses did not show meaningful exposure-response relationships for the selected AEs (pneumonitis, ALT elevation, neutropenia, fatigue) in both Studies A8081001 and A8081005. There were trends toward less risk of fatigue and ALK elevation with higher exposure in Study A8081001, and the same trend for fatigue in Study A8081005. In Study A8081005, an association between ALT elevations and exposure was not apparently present. For neutropenia, there were trends toward higher risk with higher exposure. The estimated exposure-response relationships for neutropenia were not statistically significant at the 5% level in Study A8081001 but significant in Study A8081005. Because of the small number of pneumonitis events, no modelling was conducted for this AE.

3. Low exposure correlates

Based on logistic regression analysis, the primary driver of low exposure appeared to be the average daily dose. Patients who had an average daily dose less than 450 mg were more likely to be in the lowest 1/6th quantile of exposures, the group with the lowest ORR in both studies. In Study A8081001, Asians were generally at a lower risk of having low exposure than non-Asians. There was also some indication that patients with concomitant use of CYP3A inducers (primarily corticosteroids) were more likely to have low exposures.

Similar relationship was also observed in Study A8081005. In Study A8081001, Asian patients and non-Asian patients with an average daily dose ≥ 450 mg were not likely to have a low exposure (C_{trough}), and the ORR for these patients was $>50\%$.

4. Summary

Results from the above analyses demonstrated a direct crizotinib exposure response relationship for efficacy in Studies A8081001 and A8081005. Due to the currently limited number of patients with these safety endpoints, clinically meaningful exposure-response relationships for safety were not observed. The collection of additional safety and efficacy data from the ongoing clinical trials will allow better characterization of the exposure-response relationships, which in turn will inform potential recommendations with regards to dose schedule optimization strategies. Based on the current exposure-response analyses, compliance with the recommended 250 mg bd dosing regimen for crizotinib is an important determinant to achieve optimal efficacy. Overall, results from the preliminary exposure-response analyses from Studies A8081001 and A8081005 support the favourable benefit/risk assessment at the intended 250 mg bd dosing regimen for ALK-positive advanced NSCLC patients.

Clinical evaluator's comment

The sponsor's response is satisfactory. The exposure-response analysis showed a statistically significant relationship between C_{trough} crizotinib concentration (ng/ml) and the objective response rate (ORR), with higher exposure being associated with higher ORR. However, although the sponsor reports a trend towards higher exposure being associated with longer progression free survival (PFS) the relationship was not statistically significant. No analysis of the exposure-response relationship for overall survival (OS) was provided due to limited data. The sponsor states that logistic regression modelling analyses did not show meaningful exposure-response relationships for the selected AEs of pneumonitis, ALT elevation, neutropenia or fatigue.

Question 8

In vivo data in patients with advanced cancer showed that multiple dose crizotinib (250 mg bd) co-administered with single dose midazolam (2 mg), a CYP3A substrate, increased midazolam AUC_{inf} and C_{max} values by 3.7 fold [90% CI: 2.63-5.07] and 2.0 fold [90% CI: 1.39-2.92], respectively, relative to midazolam alone. The *in vivo* data indicate that crizotinib is a moderate inhibitor of CYP3A (AUC increase ≥ 2 fold and < 5 fold). This is an important finding as many oncology drugs are substrates for CYP3A. What is the sponsor's advice relating to co-administration of crizotinib with drugs that are CYP3A4 substrates?

Sponsor's response

The sponsor's recommendations relating to co-administration of crizotinib with drugs that are CYP3A4 substrates are included in the proposed Australian Product Information and are as follows:

Agents whose plasma concentrations may be altered by crizotinib

Crizotinib has been identified as an inhibitor of CYP3A both *in vitro* and *in vivo*. Caution should be exercised in administering crizotinib in combination with drugs that are predominantly metabolised by CYP3A, particularly those CYP3A substrates that have narrow therapeutic indices, including but not limited to alfentanil, cyclosporin, fentanyl, quinidine, sirolimus and tacrolimus.

Coadministration of crizotinib with CYP3A substrates with narrow therapeutic indices and which are associated with life-threatening arrhythmias, such as pimozide, and ergot derivatives should be avoided.

Coadministration of Crizotinib and CYP3A Substrates

Following 28 days of crizotinib dosing at 250 mg taken twice daily in cancer patients, the oral midazolam AUC was 3.7 fold (90% CI: 2.63-5.07) those seen when midazolam was administered alone, suggesting that crizotinib is a moderate inhibitor of CYP3A.

Clinical evaluator's comment

The sponsor's response is satisfactory.

Question 9

The PK drug-drug interaction data provided in the submission suggests that crizotinib is likely to be a difficult drug to use in clinical practice because of the number of potentially significant interactions with co-administered drugs: that is, avoid co-administration with potent CYP3A4 inhibitors; avoid co-administration with CYP3A4 inducers; safety concerns associated with increased exposure to CYP3A4 substrates when co-administered with crizotinib; efficacy concerns associated with crizotinib due to decreased bioavailability when co-administered with drugs which increase gastric pH; safety concerns associated with crizotinib due to increased bioavailability when co-administered with P-gp efflux transporter inhibitors; and safety concerns associated with increased exposure to P-gp efflux transporter substrates when co-administered with crizotinib. The sponsor is requested to comment on the potential difficulties associated with the use of crizotinib in clinical practice due to the potential for significant drug-drug interactions.

Sponsor's response

Crizotinib is a substrate of CYP3A4/5 and also a moderate inhibitor of CYP3A based on *in vitro* and clinical data. Due to the potential CYP3A-mediated drug-drug interactions, the sponsor recommends that patients should avoid the use of strong CYP3A inhibitors/inducers and substrates that have narrow therapeutic indices and are associated with life-threatening arrhythmias during crizotinib treatment. However, as discussed in the responses to TGA questions d) and e), the potential for P-gp-mediated drug-drug interactions are low. Moreover, based on population PK modelling, coadministration of antacids is unlikely to result in changes in steady-state crizotinib exposure. Therefore, the use of antacids was permitted during crizotinib treatment in clinical trials.

As of the data cut-off date (1 June 2011), 148 and 439 ALK-positive NSCLC patients had been enrolled in Studies A8081001 and A8081005, respectively. Strong CYP3A inhibitors/inducers (such as itraconazole, clarithromycin, carbamazepine, phenobarbitone, etc.) and CYP3A substrates with narrow therapeutic indices (such as dihydroergotamine, ergotamine, and pimozide) were not allowed in these trials. More than 95% patients had any concomitant drug treatment. The most commonly reported concomitant medications (i.e., $\geq 25\%$ of patients) included analgesics, psycholeptics, drugs for acid-related disorders, laxatives, mineral supplements, anti-emetics and antinauseants, ophthalmologicals, antidiarrhoeals, intestinal anti-inflammatory/anti-infectious agents, antithrombotic agents, nasal preparations, corticosteroids for systemic use, vitamins, drugs for functional gastrointestinal disorders, and cough and cold preparations. These concomitant medications include mild and moderate CYP3A inducers/inhibitors, CYP3A substrates and gastric pH-elevating agents including antacids, histamine-receptor antagonists (HRAs) and proton-pump inhibitors (PPIs). PK/PD analysis dataset indicated that about 22-31% patients used CYP3A inducers and inhibitors, and 36-53% used HRAs and PPIs (PMAR-0242 and PMAR-0266). Since the adverse event and laboratory abnormality profile demonstrated that crizotinib treatment was generally safe and well-tolerated and since concomitant medications, including CYP3A substrates, were commonly used in these studies, the risk of potential difficulties associated with the use of crizotinib due to the potential for significant drug-drug interactions is anticipated to be low.

Therefore, the sponsor considers that the potential drug-drug interactions with crizotinib can be reasonably managed in clinical practice.

Clinical evaluator's comment

The sponsor's response is acceptable.

Clinical – pharmacodynamics

Question 10

The submission did not include a formal QT/QTc interval prolongation study complying with the relevant TGA adopted "note for guidance" (CHMP/ICH/2/04)⁶¹. While the submission included a population pharmacokinetic analysis [PMAR-00224] exploring the relationship between crizotinib concentration and QT interval prolongation in selected patients from Studies 1001 and 1005, the ECG data used in the analysis were not specifically designed to assess the effect of crizotinib on the QT interval. Furthermore, nonclinical and clinical studies indicate that the crizotinib can increase the QT interval. Does the sponsor intend to undertake a study assessing the effect of crizotinib on QT/QTc interval prolongation that complies with the relevant TGA adopted "note for guidance" (CHMP/ICH/2/04)? If not please provide a justification for not providing such data.

Sponsor's response

A "thorough QT study" in healthy volunteers will not be conducted due to the lack of clinical safety data to support the administration of the recommended 250 mg bd dose to healthy volunteers. Although single 250-mg crizotinib doses have been safely administered to healthy volunteers in a number of trials, a single-dose study is not suitable for QT evaluation with crizotinib since the plasma concentrations are about 1/5 those seen at steady state with multiple dosing.

In lieu of a "thorough QT study", a formal QTc assessment for crizotinib includes an ongoing dedicated ECG substudy in 40 evaluable patients in the crizotinib arm of Study A8081007 (recently added to Study A8081005 to assist in completing ECG substudy enrollment). This assessment involves triplicate ECGs at 0 (pre-dose), 4, and 8 hours following morning crizotinib dosing on Day 1 of Cycle 1 and 0 (pre-dose), 2, 4, 6 and 8 hours following morning crizotinib dosing on Day 1 of Cycle 2 (1 cycle = 21 days). All ECG tracings from this subgroup assessment are being sent electronically to a core ECG laboratory for blinded manual interval measurement. A random-effect model suitable for the repeated measures will be used to estimate the mean change in QTc (QTcB [QT interval calculated using Bazett's correction factor], QTcF, and/or QTcS [QT interval corrected by study-specific method]) from baseline at each nominal time point. The 90% CI for the true mean change will be estimated at each nominal time point. The results of this substudy will be used as the inferential assessment of QTc changes. The overall QTc prolongation risk for crizotinib will be assessed based on the results from the described ECG substudy and other ECG assessments from patients that have received crizotinib. The final report for this ECG substudy will be submitted to the TGA (estimated second half of 2014).

Clinical evaluator's comment

The sponsor's response is acceptable.

Clinical safety**Questions 11 (ALT)**

Please provide a summary of the ALT results from Study 1001 (preliminary CSR) and Study 1005 (preliminary CSR 60 day update) grouped by 3x, 5x, 10x and 20x ULN elevations.

Sponsor's response

The requested ALT data were provided.

Clinical evaluator's comment

The updated ALT data from the Day 120 CDA (01 June 2011 cut-off) is provided in CER1. Maximum increases in ALT ≥ 3 ULN occurred commonly in patients treated with crizotinib and were consistent in both Study 1001 and Study 1005. In the total population, 15.8% (n=63) of patients had ALT levels ≥ 3 xULN and all but 1 of these patients had baseline levels < 3 xULN, and 7.5% (n=30) had ALT levels ≥ 5 xULN with all patients having baseline levels ≤ 5 xULN.

Question 12 (total bilirubin)

Please provide a summary of total bilirubin result from Study 1001 (preliminary CSR) and Study 1005 (preliminary CSR 60 day update) for > 1.5 x ULN and > 2 x ULN elevations.

Sponsor's response

The requested total bilirubin data were provided.

Clinical evaluator's comment

The updated bilirubin data from the Day 120 CDA (01 June 2011 cut-off) is provided in CER1. Maximum increases in total bilirubin ≥ 2 xULN in the total population (Studies 1001 plus 1005) occurred in 1.0% (n=4) of patients, all with baseline total bilirubin levels ≤ 2 xULN.

Question 13 (alkaline phosphatase)

Please provide a summary of ALP results from Study 1001 (preliminary CSR) and Study 1005 (preliminary CSR 60 day update) for > 1.5 x ULN.

Sponsor's response

The requested alkaline phosphatase (ALP) data were provided.

Clinical evaluator's comment

The alkaline phosphatase (ALP) data from the Day 120 CDA (01 June 2011 cut-off) is provided in CER1. Maximum increases in ALP ≥ 1.5 xULN occurred in 32.9% (n=131) of patients in the total population (Studies 1001 plus 1005), and 52 of these patients had baseline ALP levels ≥ 1.5 xULN.

Questions 14 and 15 (genetic mutations)

Please comment on the potential for resistance to crizotinib to develop due to genetic mutations in the EML-ALK gene (Question 14). Please comment on the potential for resistance to crizotinib to develop due to genetic mutations in the EML-ALK gene (Question 15).

Sponsor's response

To date, approximately 36 evaluable lung cancer patients from Studies A8081001 or A8081005 have been subjected to biopsies taken at disease progression to assess potential mechanisms of resistance to crizotinib. The mechanisms of crizotinib resistance have been assessed by several independent investigators. Collectively, the clinical

collaborations involving crizotinib resistance have indicated *ALK* secondary mutations have been identified after demonstrating evidence of radiologic progression in a total of 11 of 36 cases (31%) of non-small cell lung cancer. The mutations identified included L1196M, G1269A, C1156Y, L1152R, and F1174L. Each of these mutations has been mechanistically characterized *in vitro* cell based assays and was demonstrated to confer resistance to crizotinib. Additional studies involving *ALK* positive tumours suggest involvement of alternative pathways as potential mechanisms of *ALK*-mutation independent resistance.^{77, 78, 79, 80} Studies of crizotinib resistance in patients are still ongoing to get a better understanding of the frequency of secondary mutations in *ALK* as well as the potential involvement of other genes/pathways in resistance.

Clinical evaluator's comment

The sponsor provided a detailed clinical summary from the published literature and personal communications of the current findings relating to crizotinib resistance due to genetic mutations in the *EML-ALK* gene. Only the summary from the sponsor's detailed response has been provided above. The available data suggests that resistance to crizotinib due to genetic mutations is likely to be a significant underlying mechanism accounting for disease progression despite treatment. Ongoing studies might provide further information on the incidence of crizotinib resistance due to genetic mutations and the relationship between the duration of treatment and emergence of resistance.

Benefit-risk balance assessment

Question 16

The benefit-risk balance of crizotinib, given the proposed usage, is considered to be unfavourable. While the ORRs observed in Studies 1001 and 1005 are encouraging, there are no Phase III, randomised, controlled data showing that these results translate into clinically meaningful benefits (OS and/or PFS) it is noted that information from the retrospective covariate-matched and covariate-adjusted analyses in the Technical Report (covariate-matched and covariate-adjusted analyses) suggests superior benefits for crizotinib compared with historical controls as regards the ORR, PFS and OS. However, the retrospective analyses are exploratory as they were not pre-specified and were undertaken "to give perspective to the efficacy results from the single arm Study 1001" (Technical Report). It is considered that the data from the retrospective analyses cannot substitute for confirmatory data from Phase III, randomised, controlled clinical studies.

The absence of evidence of clinically meaningful benefits for crizotinib (particularly the uncommon but potentially life threatening risks of hepatotoxicity and pneumonitis) results in an unfavourable benefit-risk balance. It is possible that favourable results relating to PFS and OS from the two, ongoing, randomised, active-controlled Phase III studies might reverse the currently unfavourable benefit-risk balance assessment (Studies 1007 and 1014).

Please comment on the unfavourable benefit-risk balance assessment for crizotinib for the proposed indication.

⁷⁷Doebele RC, Pilling AB, Aisner D, et al. Mechanisms of resistance to crizotinib in patients with *ALK* gene rearranged non-small cell lung cancer. *Clin Cancer Res* 2012, in press.

⁷⁸Katayama R, Shaw AT, Khan TM, et al. Mechanisms of Acquired Crizotinib Resistance in *ALK*-Rearranged Lung Cancers. *Science Transl. Med. Rapid Publication* January 25, 2012.

⁷⁹Sasaki T, Koivunen J, Ogino A., et al. A novel *ALK* secondary mutation and *EGFR* signaling cause resistance to *ALK* kinase inhibitors. *Cancer Res* 2011; 71:6051-60.

⁸⁰Sasaki T, Okuda K, Zheng W, et al. The neuroblastoma associated F1174L *ALK* mutation causes resistance to an *ALK* kinase inhibitor in *ALK* translocated cancers. *Cancer Res* 2010; 70:10038-43.

Sponsor's response

The sponsor provided a comprehensive response to the above question that included a substantial amount of new and updated clinical efficacy and safety data. The data provided by the sponsor are listed below and the clinical comments presented below include review and evaluation of these data.

1. Day 120 Clinical Data Addendum (CDA)

This addendum presents updated safety, efficacy and patient-reported outcome data as of 01 June 2011 from the ongoing crizotinib clinical program

2. Efficacy Data for Study A8081005 as of 02 January 2012

2.1 Objective Response

2.2 Progression-Free Survival

3. Objective Response Data in Previously Untreated Patients (Study A8081001)

4. Retrospective Analyses

4.1 Covariate-matched and Covariate-adjusted Analyses – Study A8081001

4.2 Covariate-matched and Covariate-adjusted Analyses – Study A8081005

4.3 Time to Tumour Progression Analyses – Study A8081005

4.4 Natural History of ALK-positive NSCLC from the Literature

5. Safety Assessment

5.1 Updated Safety Profile

5.2 Hepatotoxicity

5.3 Pneumonitis

6. Patient Reported Outcomes

7. Benefit/Risk Assessment

Clinical evaluator's comment

(1) Updated efficacy and safety data - Study A8081001 (1001)

(1.1) Background – Study 1001

Study 1001 has been designated by the sponsor as being the “pivotal” efficacy and safety study, and the evaluator’s concerns associated with this designation have been discussed in the original CER. The study is a Phase I, multicentre, multinational, open-label, dose-escalation, safety, PK, PD, and antitumor activity study of crizotinib (250 mg bd) in patients with advanced malignancies. The study includes “pivotal” efficacy and safety data in patients with ALK-positive NSCLC and is ongoing in this patient population.

The sponsor’s s31 response to the TGA included updated clinical efficacy and safety data from patients in the ALK-positive NSCLC cohort as of 01 June 2011 (that is, Day 120 CDA). The safety analysis (SA) population included 149 patients consisting of 125 (83.9%) patients who had received prior systemic treatment for locally advanced or metastatic disease and 24 (16.1%) patients who had not received such treatment. The response evaluable (RE population) included 143 patients of the 149 included in the safety analysis. Of the 143 patients in the RE evaluable population, 121 had received prior systemic treatment for locally advanced or metastatic disease, and 22 (14.4%) had not received such treatment. The RE population was defined as all patients in the SA population who had an adequate baseline disease assessment and met 1 of the following 2 criteria: 1) had at least 1 post baseline disease assessment (at least 6 weeks from first dose), 2) withdrew from the study or experienced progression/death at any time on study.

The disposition of the ALK-NSCLC safety analysis populations as of the 01 June 2011 data cut-off are summarised below in Table 9. In the safety analysis populations, the median duration of treatment was 43.1 weeks (range: 0.1, 138.6 weeks) in all patients (n=149), and 42.3 weeks (range: 0.1, 138.4 weeks) in previously treated patients (n=125). In both populations, the majority of patients were still ongoing at the data cut-off date, and the main reasons for discontinuation were disease progression or death.

Table 9. Study 1001 – Disposition ALK-positive NSCLC cohort; safety analysis population as of 01 June 2011 data cut-off.

Disposition N, %	Previously Treated Patients	All Patients
Safety Analysis Population	125	149
Ongoing as of data cutoff	64 (51.2)	82 (55.0)
Completed	0	0
Discontinued	61 (48.8)	67 (45.0)
Objective disease progression	37 (29.6)	41 (27.5)
Death	15 (12.0)	15 (10.1)
General health deterioration	0	0
Adverse Event	4 (3.2)	6 (4.0)
Patient withdrew consent	0	0
Other ^a	5 (4.0)	5 (3.4)

^a Other included patients who had clinical progression not consistent with RECIST.

The demographic characteristics of the patients in the previously treated (n=125) and all patient (n=149) groups in the safety analysis populations were similar. Most patients were relatively young with the median age in the two groups being 50.9 years and 51.5 years (previously treated and all, respectively) and there were approximately equal numbers of men and women in both groups. Most patients had never smoked (approximately 70%). Most patients were White (about 64%) with the majority of the remainder being Asian (about 28%).

The disease characteristics of the patients in the previously treated (n=125) and all patient (n=149) groups in the safety analysis populations were similar, with all patients having locally advanced or metastatic ALK-positive NSCLC, with the majority (about 94%) having metastatic disease, and nearly all having adenocarcinomas. The majority of patients had a baseline ECOG PS 1 or 2.

Prior tumour treatments in the previously treated (n=125) and all patient (n=149) groups in the safety analysis populations: All patients had undergone prior surgery and about 58% had received prior radiotherapy. Previous systemic therapy for advanced or metastatic disease was not an entry requirement for Study 1001 but most patients had received prior systemic treatment and over half (52.3%) had received 2 or more prior treatment regimens for locally advanced or metastatic disease.

(1.2) Efficacy results – Study 1001

The objective response rate (ORR) updated for all RE (n=149) ALK-positive NSCLC patients was 61.5% (95% CI: 53.0, 69.5); N=88/143) (see Table 10, below). The updated result for the ORR in all RE patients is consistent with the ORR in previously treated patients, and with the preliminary CSR results in the RE population presented in the original submission. In both the preliminary and updated analyses, the best overall response was based on investigator assessed tumour data using RECIST.

Table 10. Study 1001 – ORR from the preliminary CSR (original submission) and Day 120 CDA. (RE all and previously treated patients).

Efficacy Parameter	Preliminary CSR RE Population N = 116	Day 120 Clinical Data Addendum Previously Treated Patients RE Population (N=121)	Day 120 Clinical Data Addendum All Patients RE Population (N=143)
Best Response, n (%)			
Confirmed CR	2 (1.7)	3 (2.5)	3 (2.1)
Confirmed PR	69 (59.5)	70 (57.9)	85 (59.4)
SD for at least 6 weeks	31 (26.7)	37 (30.6)	42 (29.4)
PD	6 (5.2)	5 (4.1)	6 (4.2)
Early death ^a	3 (2.6)	4 (3.3)	4 (2.8)
Indeterminate ^b	5 (4.3)	2 (1.7)	3 (2.1)
ORR (CR + PR), % (n)	71 (61.2)	73 (60.3)	88 (61.5)
[95% CI]	[51.7, 70.1]	[51.0, 69.1]	[53.0, 69.5]
PD or Death after Response n/N of responders (%)	26/71 (36.6)	40/73 (54.8)	45/88 (51.1)
TTR Median, weeks (Range)	7.7 (4.3 - 39.6)	7.9 (2.1 - 39.6)	7.9 (2.1 - 57.3)
DR, Median weeks (Kaplan- Meier estimate)	48.1	48.1	49.1
[95% CI]	[35.9, NR]	[35.7, 64.1]	[39.3, 89.3]

a Early death was death within 42 days (6 weeks) from first dose of crizotinib; b Indeterminate = patients having available on-study scans that could not be evaluated or patients who discontinued prior to obtaining adequate scans to evaluate response.

In the Day 120 CDA, the median time to first response (TTR) (that is, CR or PR) in the all patients RE population was 7.9 weeks (range: 2.1, 57.3 weeks), with 51.5% (n=45) of patients achieving a first response within the first 8 weeks of treatment, 30.7% (n=27) from Week 8 to < 16, 11.4% (n=10) from 16 to < 24 weeks, and 6.8% (n=6) ≥ 24 weeks.

The updated ORRs in the all patients RE population with prior systemic treatment for locally advanced or metastatic disease with 1, 2, and ≥ 3 regimen were: 59.1% (95% CI: 43.2, 73.7; N=26/44); 64.5% (95% CI: 45.4, 80.8; N=20/31); and 58.7% (95% CI: 43.2, 73.0; N=27/46), respectively. In the 22 (14.4%) patients without prior systemic treatment for locally advanced or metastatic disease in the total RE population, the ORR was 68.2% (95% CI: 45.1, 86.1; N=15/22). Overall, the results show that the ORR is relatively independent of prior systemic treatment for locally advanced or metastatic ALK-positive NSCLC, suggesting that crizotinib is equally effective in first and later-line settings.

In the Day 120 CDA, of the 42 patients in the all patients RE population with best response stable disease (SD) (≥ 6 weeks from Cycle 1, Day 1), 23.8% (n=10) had SD duration of 0 to < 3 months, 42.9% (n=18) had SD duration of 3 to < 6 months, 19.0% (n=8) had SD duration of 6 to < 9 months, 7.1% (n=3) had SD duration of 9 to < 12 months, and 7.1% (n=3) had SD duration of ≥ 12 months.

In the Day 120 CDA, in the all patients RE population the disease control rate (DCR) was 82.5% ([95% CI: 75.3, 118], N=118/143) at Week 8 and 70.6% ([95% CI: 62.4, 77.9], N=101/143) at Week 16. The results for the DCR at Week 8 and 16 in previously treated patients in the RE population was similar to all patients in this population. In both the all patients and previously treated RE populations, over 90% of patients had experienced some degree of tumour shrinkage by the data cut-off date.

The Day 120 CDA included updated ORR results for subgroups based on baseline characteristics of age, gender, race (Asian, non-Asian), ECOG performance status, and number of prior systemic treatment regimens for advanced NSCLC. The ORR was higher in patients aged ≥ 65 years (72.2%) than in those < 65 years old (58.3%). However, there were only 18 patients in the older age group which precludes meaningful conclusions being drawn regarding the difference between the two age groups. The ORR was notably higher in Asians (77.1%) compared with non-Asians (53.5%). There were no marked

differences in the ORR between the sexes, or in patients based on the number of prior metastatic treatment regimens.

As of the data cut-off date for the Day 120 CDA, 127 patients in the all patients RE population were considered evaluable by an independent third-party core imaging laboratory. In this group, 70 patients achieved a confirmed PR and 1 patient had a CR, resulting in an independently-assessed ORR of 55.9% (95% CI: 46.8%, 64.7%). The independently-assessed ORR is consistent with the investigator-assessed ORR in the all patient RE population (55.9% and 61.5%, respectively). There was agreement between the two assessment methods on response and non-response for 61 and 33 patients, respectively, for a total event agreement rate of 74.0%.

In the Day 120 CDA, the updated median time to progression-free survival (PFS) in all patients (n=149) in the safety analysis population was 9.9 months (95% CI: 7.7, 13.4), and 55.7% (n=83) of patients experienced an event (45.0% [n=67] objective progression, 10.7% [n=16] death). The updated median time to PFS in previously treated patients (n=125) in the safety analysis population was 9.2 months (95% CI: 7.3, 12.7), which is consistent with the results for all patients. The PFS data from the original preliminary CSR, and the updated Day 120 CDA for previously treated and all patients are summarised in CER1.

In Day 120 CDA, the updated median time to overall survival (OS) in all patients in the safety analysis populations for the Day 120 CDA data had not yet been reached. The 6 month and 1 year survival probabilities in the Day 120 CDA data for all patients (n=149) in the safety analysis were 87.9% (95%CI: 81.3, 92.3) and 74.8% (95% CI: 66.4, 81.5), respectively. These probabilities were similar to those for the updated previously treated patient population, but lower than those reported in the preliminary CSR. In the Day 120 CDA, the median follow-up for OS was 16.6 months for both the all patients and the previously treated populations. The OS data from the original preliminary CSR, and the updated Day 120 CDA for previously treated and all patient populations were summarised in CER2.

(1.3) Safety assessment – Study 1001

The safety profiles (death, SAE, Grade 3/4 AEs, and selected treatment related adverse events) in the ALK-positive NSCLC groups for the preliminary CSR analysis (original submission) and the Day 120 CDA analyses (previously treated and all patients) are summarised below in Table 11.

Table 11. Study 1001 – Deaths, SAEs, Grade 3 or 4 AEs, and selected treatment related AEs in the ALK-positive cohorts; SA populations.

	ALK+ NSCLC RP2D Safety Analysis Population for CSR (N=119)	Previously Treated ALK+ NSCLC RP2D Safety Analysis Population for Day 120 Clinical Data Addendum (N=125)	All Patients ALK+ NSCLC RP2D Safety Analysis Population for Day 120 Clinical Data Addendum (N=149)
Duration of Treatment			
Median (Range) in weeks	31.9 (0.7-101.7)	42.3 (0.1-138.4)	43.1 (0.1-138.6)
Deaths, n (%)			
Total	23 (19.3)	43 (34.4)	46 (30.9)
Within 28 days of last dose of study drug	13 (10.9)	21 (16.8)	22 (14.8)
>28 days after last dose of study drug	10 (8.4)	22 (17.6)	24 (16.1)
Due to disease progression	17 (14.3)	35 (28.0)	37 (24.8)
Related to study drug	0	0*	0*
Serious Adverse Events, n (%)			
All-causality	33 (27.7)	52 (41.6)	58 (38.9)
Treatment-related	7 (5.9)	7 (5.6)	9 (6.0)
Associated with permanent discontinuation	5 (4.2)	15 (12.0)	17 (11.4)
Grade 3 or 4 Adverse Events, n (%)			
All-causality	43 (36.1)	70 (56.0)	77 (51.7)
Treatment-related	19 (16.0)	30 (24.0)	36 (24.2)
Treatment-Related, Adverse Events, n (%) Associated With:			
Permanent discontinuation	3 (2.5)	3 (2.4)	3 (2.0)
Temporary treatment discontinuation	14 (11.8)	19 (15.2)	22 (14.8)
Dose reduction	6 (5.0)	8 (6.4)	10 (6.7)

Death: In the all patient group (n=149), 22 (47.8%) of 46 deaths occurred on study (i.e., within 28 days after the last dose of study drug). Of the 22 deaths occurring on study, 18 were considered to be due to disease progression and 4 were considered to be due to other illnesses or events, none of which were considered related to the study drug. Of the total 46 deaths, none appear to be related to the study drug (although there appears to be some uncertainty about the relationship with disseminated intravascular coagulation in 1 patient). The updated 30 day and 60 day all-cause mortality rates (death within 30 and 60 days of the first dose of study drug, respectively) in the 149 patients in the all patient group were 2.7% (n=4) and 3.4% (n=5), respectively.

SAEs (all causality and treatment related, all cycles): In the all patient group (n=149), all causality and treatment related SAEs occurred in 38.9% (n=58) and 6.0% (n=9) of patients, respectively. The incidences of SAEs (all causality) for Grade 0, 1, 2, 3, 4, and 5 events were 0% (n=0), 4.0% (n=6), 12.8% (n=19), 7.4% (n=11), and 14.8% (n=22). The SAEs (all causality, all grades) were disease progression (n=15, 10.1%), pneumonia (n=8, 5.4%), pulmonary embolism (n=5, 3.4%), dyspnoea (n=4, 2.7%), syncope (n=4, 2.7%), convulsion (n=3, 2.0%), vomiting (n=3, 2.0%), anaemia (n=2, 1.3%), atrial fibrillation (n=2, 1.3%), constipation (n=2, 1.3%), deep vein thrombosis ((n=2, 1.3%), haemoptysis (n=2, 1.3%), headache (n=2, 1.3%), nausea (n=2, 1.3%), nephrolithiasis (n=2, 1.3%), pleural effusion (n=2, 1.3%), pneumonitis (n=2, 1.3%), and pyrexia (n=2, 1.3%). The 9 treatment related SAEs (all grades) included pneumonitis x 2, and 1 each for spontaneous abortion, ALT increased, cerebral cyst, constipation, disseminated intravascular coagulation, liver function tests abnormal, oesophageal ulcer and renal abscess.

AEs (all causality, all cycles): In the all patient group (n=149), 98.7% (n=147) of patients experienced at least 1 treatment-emergent, all causality AE, with the incidences of Grade 1, 2, 3, 4, and 5 events being 23.5% (n=35), 20.8% (n=31), 30.2% (n=45), 8.7% (n=13), and 15.4% (n=23), respectively. AEs (all causality, all grades) occurring in ≥ 20 % of patients were nausea 58.4% (n=87), diarrhoea 53.7% (n=80), visual impairment 53.0% (n=79), vomiting 47.0% (n=70), constipation 40.9% (n=61), oedema peripheral 36.9% (n=55), dizziness 33.6% (n=50), fatigue 28.9% (n=43), decreased appetite 25.5% (n=38) and rash 21.5% (n=32).

AEs (treatment related, all cycles): In the all patient group (n=149), 96.6% (n=144) of patients experienced at least 1 treatment-emergent, treatment related AE, with the incidence for Grade 3 or 4 events being 24.2% (n=36). Treatment related AEs occurring in $\geq 20\%$ of patients were nausea 56.4% (n=84), visual impairment 51.7% (n=77), diarrhoea 49.7% (n=74), vomiting 38.9% (n=58), oedema peripheral 29.5% (n=44), constipation 27.5% (n=41), and dizziness 20.8% (n=31). These events were predominantly Grade 2 or 3 events. Grade 3 or 4 treatment-emergent, treatment related AEs occurring in 2 or more patients were neutropenia (n=9, 6.0%), hypophosphataemia (n=6, 4.0%), ALT increased (n=6, 4.0%), AST increased (n=5, 3.4%) and fatigue (n=2, 1.3%). The most frequently reported treatment related AEs for all patients were the same as those for patients who had been previously treated, with the exception of bradycardia and leukopenia both of which did not reach 5% in previously treated patients. Treatment-emergent, treatment related AEs occurring with an incidence of $\geq 5\%$ in the all patients and previously treated groups are summarised below in Table 12.

Table 12. Study 1001 - Treatment related adverse events with frequency $\geq 5\%$ in either group of ALK-positive NSCLC patients; safety analysis population as of 01 June 2011 cut-off.

MedDRA Preferred Term	Previously Treated Patients (N=125)		All Patients (N=149)	
	All Grades	Grade 3/4	All Grades	Grade 3/4
<i>Any Adverse Events</i>	121 (96.8)	30 (24.0)	144 (96.6)	36 (24.2)
Nausea	69 (55.2)	1 (0.8)	84 (56.4)	1 (0.7)
Visual impairment	64 (51.2)	0	77 (51.7)	0
Diarrhoea	62 (49.6)	0	74 (49.7)	0
Vomiting	46 (36.8)	1 (0.8)	58 (38.9)	1 (0.7)
Oedema peripheral	35 (28.0)	0	44 (29.5)	0
Constipation	35 (28.0)	0	41 (27.5)	1 (0.7)
Dizziness	25 (20.0)	0	31 (20.8)	0
Decreased appetite	19 (15.2)	0	24 (16.1)	0
Fatigue	17 (13.6)	2 (1.6)	24 (16.1)	2 (1.3)
Alanine aminotransferase increased	14 (11.2)	4 (3.2)	18 (12.1)	6 (4.0)
Rash	15 (12.0)	0	17 (11.4)	0
Dysgeusia	10 (8.0)	0	16 (10.7)	0
Aspartate aminotransferase increased	10 (8.0)	2 (1.6)	15 (10.1)	5 (3.4)
Joint swelling	12 (9.6)	0	13 (8.7)	0
Hypophosphataemia	7 (5.6)	4 (3.2)	12 (8.1)	6 (4.0)
Muscle spasms	11 (8.8)	0	12 (8.1)	0
Dyspepsia	11 (8.8)	0	11 (7.4)	0
Neutropenia	11 (8.8)	9 (7.2)	11 (7.4)	9 (6.0)
Photopsia	8 (6.4)	0	11 (7.4)	0
Paraesthesia	7 (5.6)	0	10 (6.7)	0
Bradycardia	6 (4.8)	0	9 (6.0)	0
Gastrooesophageal reflux disease	7 (5.6)	0	9 (6.0)	0
Periorbital oedema	7 (5.6)	0	9 (6.0)	0
Leukopenia	4 (3.2)	0	8 (5.4)	0

Clustered AE terms: AEs of interest were reported as clustered AE terms, and the frequencies of the most commonly reported clustered terms were comparable in the all patients and previously treated patient groups. In the all patients group (n=149), the most commonly reported all causality clustered terms (any grade) reported with an incidence of $\geq 10\%$ were vision disorder (n=98, 65.8%), oedema (n=62, 41.6%), fatigue (n=49, 32.9%), neuropathy (n=29, 19.5%), oesophageal related disorder (n=27, 18.1%), ALT increased (n=26, 17.4%) and anaemia (n=17, 11.4%).

AEs resulting in permanent treatment discontinuation: In the all patients group (n=149), 19 (12.8%) patients permanently discontinued due to treatment-emergent AEs. The AEs resulting in permanent treatment discontinuation were primarily disease progression 5.4% (n=8) with the remainder being due to pneumonia 2.0% (n=3), pneumonitis 1.3% (n=2), and 1.0% (n=1) each for ALT increased, dyspnoea, hypoxia, pulmonary haemorrhage, respiratory failure and subcutaneous emphysema.

AEs resulting in temporary treatment discontinuation: In the all patients group (n=149), treatment-emergent, all causality AEs resulting in temporary treatment discontinuation were reported in 41.6% (n=62) of patients. AEs occurring in $\geq 2\%$ of patients resulting in temporary treatment discontinuation were neutropenia 6.0% (n=9), vomiting 4.7% (n=7), pyrexia 4.7% (n=7), pneumonia 4.0% (n=6), ALT increased 4.0% (n=6), anaemia 2.7% (n=4), nausea 2.7% (n=3), atrial fibrillation 2.0% (n=3), AST increased 2.0% (n=3), convulsion 2.0% (n=3) and syncope 2.0% (n=3).

AEs resulting in dose reduction: In the all patients group (n=149), dose reductions were reported in 7.4% (n=11) of patients. The only AEs (all causality) resulting in dose reduction in 2 or more patients were ALT increased 4.0% (n=6), AST increased 2.7% (n=4), and neutropenia 1.3% (n=2).

Laboratory results: In the all patients group, shifts in laboratory values from CTCAE severity Grade ≤ 2 at baseline to Grade ≥ 3 post-baseline were observed in $\geq 5\%$ of patients for decreased lymphocytes (16.0%, N=23/144), decreased phosphate (11.8%, N=17/144), decreased neutrophils (8.3%, N=12/144), decreased sodium (7.6%, N=11/144), increased ALT (6.9%, N=10/144) and increased glucose (5.6%, N=8/144). Shifts from Grade ≤ 2 at baseline to Grade 4 post-baseline included increased ALT and decreased lymphocytes in 2 patients each (1.4%), and decreased neutrophils in 1 patient (0.7%).

Vital signs: In the all patients group, maximum increases from baseline in systolic blood pressure (BP) of ≥ 40 mmHg and diastolic BP of ≥ 20 mmHg were reported in 2.8% (N=4/144) and 10.4% (N=15/144) of patients, respectively; maximum decreases from baseline in systolic BP ≥ 40 mmHg and diastolic BP ≥ 20 mmHg were reported in 4.2% (N=6/144) and 30.6% (N=44/144) of patients, respectively; maximum increases and decreases from baseline in pulse rate ≥ 30 beats per minute (bpm) were reported in 5.6% (N=8/144) and 39.6% (N=57/144) of patients, respectively; maximum (> 120 bpm) and minimum (< 50 bpm) pulse rates on study were reported in 6.3% (N=9/144) and 18.1% (N=26/144) of patients, respectively. Maximum increases and decreases from baseline in body weight of $\geq 10\%$ were reported in 26.0% (N=33/127) and 8.7% (N=11/127) of patients, respectively.

ECG changes QTcF interval: In the all patient group, the maximum QTcF intervals of < 450 , 450 to < 480 , 480 to < 500 , and ≥ 500 ms were reported in 87.1% (N=128/147), 11.6% (N=17/147), 0.7% (N=1/147), and 0.7% (N=1/147) of patients, respectively. Maximum increases in QTcF from baseline of < 30 , ≥ 30 to < 60 , and ≥ 60 ms were reported in 87.4% (N=118/135), 9.6% (N=13/135) and 3.0% (N=4/135) of patients, respectively.

Ophthalmological evaluations: Ophthalmological assessments were added by a protocol amendment during the study, and less than 10% of patients have been assessed. The data on ophthalmological assessment from Study 1001 are considered to be too limited to make meaningful conclusions.

(2) Updated efficacy and safety data – Study A8081005 (1005)

(2.1) Background – Study 1005

Study 1005 has been designated as “supportive” by the sponsor. It is a Phase II, ongoing, multicentre, multinational, open-label, single-arm study of crizotinib (250 mg bd) in patients with locally advanced or metastatic ALK-positive NSCLC who have been treated with prior systemic therapy.

The Day 120 CDA provided in the sponsor’s s31 response to the TGA included updated efficacy and safety data on the patients in Study 1005 at the cut-off date of 01 June 2011. The Day 120 CDA included mature safety data on 261 patients who had been included in the Day 60 CDA safety analysis population in the initial submission, and data on a larger, less mature dataset of 439 patients in an all patients’ safety analysis population. The

updated response evaluable (RE) population included patients in the mature efficacy population consisting of 255 patients with data as of 01 June 2011, 259 patients with data as of 02 January 2012 (additional snapshot) and an all RE population consisting of 340 patients. The efficacy data from the additional snapshot of Study 1005 as of 02 January 2012 included ORR and DR results from 259 patients.

The disposition of patients in the safety analysis populations as of 01 June 2011 is summarised below in Table 13. The median duration of treatment was 24.6 weeks (range: 0.9, 68.4 weeks) in the “mature safety” analysis population (n=261) and 15.7 weeks (range: 0.1, 68.4 weeks) in the “all patients” safety analysis population. The majority of patients were still ongoing in the study at the date of data cut-off (all safety population [74.9%]; mature safety population [63.6%]), and the most common reason for discontinuation in both populations was disease progression or death.

Table 13. Study 1005 – Disposition; safety analysis populations as of 01 June 2011 data cut-off.

Characteristic	Mature Safety Population	All Patients
Safety Analysis Population	261	439
Ongoing as of data cutoff	166 (63.6)	329 (74.9)
Completed ^a	2 (0.8)	2 (0.5)
Discontinued	93 (35.6)	108 (24.6)
Objective disease progression	49 (18.8)	55 (12.5)
Death	19 (7.3)	25 (5.7)
General health deterioration	5 (1.9)	5 (1.1)
Adverse Event	13 (5.0)	16 (3.6)
Patient withdrew consent	5 (1.9)	5 (1.1)
Lost to Follow-up	1 (0.4)	1 (0.2)
Other ^b	1 (0.4)	1 (0.2)

^aTwo patients from Study 1005 were incorrectly reported as “Completed” at the time of analysis for this Day120 Clinical Data Addendum. The reason for discontinuation from study has since been updated to “No longer willing to participate” for Patient 11681001, and to “Global deterioration of health status” for Patient 11831001. ^bOther included patients who had clinical progression not consistent with RECIST.

The baseline demographics for the safety analysis populations (mature safety [n=261], and all patients [n=439]) were similar for patients in both safety analysis populations. Most patients were relatively young, with a median age of 53.0 years in the “all patients” population and 52.0 years in the “mature safety” population. There were marginally more women (53.1% [all patients] and 54.4% [mature safety]) than men (about 45.6% [mature safety] and 46.9% [all patients]). The majority of patients were White (about 60% in both groups) and the remainder were predominantly Asian (36.8% [mature safety] and 34.9% [all patients]). Most patients had never smoked (65.1% [all patients] and to 67.4% [mature safety]) and few patients were current smokers (4.6% in both populations).

The baseline disease characteristics for the safety analysis populations (mature safety [n=261], and all patients [n=439]) were similar for patients in both safety analysis populations. All patients had locally advanced or metastatic NSCLC, and 91.1% (all patients) and 92.0% (mature safety) had metastatic disease. Nearly all patients in both groups had adenocarcinomas (91.6% [mature safety] and 92.7% [all patients]). The majority of patients in both groups had baseline ECOG PS scores of 0 or 1.

Prior tumour treatment for the safety analysis populations (mature safety [n=261] and all patients [n=439]) were similar for the two populations. Most patients had undergone prior surgery [96.2% [mature safety] and 92.7% [all patients]], and more than half had been treated with prior radiation therapy (59.2% [all patients] and 58.6% [mature safety]). The entry criteria for the study included prior systemic therapy for locally advanced or metastatic disease and all patients in the two populations appear to have met this criterion with the majority of patients having undergone 2 or more regimens.

(2.2) Efficacy assessment – Study 1005

The objective response related endpoint data (investigator-assessed) in the “mature efficacy” RE population with data cut-offs as of 01 June 2011 and 02 January 2012 are summarised below in Table 14. The mature efficacy population in the Day 120 CDA included those patients in the safety analysis population (n=261) with relevant efficacy data as of 01 June 2011 (n=255) and 02 January 2012 (n=259). In the Day 120 CDA (“mature efficacy” population), the ORR as of 02 January 2012 (59.1%) was higher than as of 01 June 2011 (53.3%).

Table 14. Study 1005 – Objective response related endpoint (investigator-assessed); RE populations.

Efficacy Parameter	Day 120 Clinical Data Addendum Mature Efficacy Population (as of 01 JUN 2011) N=255	Day 120 Clinical Data Addendum Mature Efficacy Population (as of 02 JAN 2012) N=259*
Best Response, n (%)		
Confirmed CR	4 (1.6)	4 (1.5)
Confirmed PR	132 (51.8)	149 (57.5)
SD for at least 6 weeks	80 (31.4)	69 (26.6)
PD	18 (7.1)	20 (7.7)
Early death ^a	12 (4.7)	11 (4.2)
Indeterminate ^b	9 (3.5)	6 (2.3)
ORR (CR + PR), n (%)	136 (53.3)	153 (59.1)
[95% CI]	[47.0, 59.6]	[52.8, 65.1]
DR Median weeks, Kaplan-Meier Estimate, [95% CI]	42.9 [36.1, 49.7]	45.4 [34.1, 54.1]

a Early death was death within 42 days (6 weeks) from first dose of crizotinib; b Indeterminate = patients having available on-study scans that could not be evaluated or patients who discontinued prior to obtaining adequate scans to evaluate response; * Response evaluable population now includes 259 patients of the 261 mature safety population.

Efficacy data (ORR, TTR, DR, DCR) from the first CDA CSR-SA RE population (n=133) from the original submission, the Day 120 CDA “mature efficacy” population as of 1 June 2011 (n=255) and the Day 120 CDA “all RE” population (n=340) were summarised. With additional crizotinib treatment and patient follow-up through 2 January 2012, the ORR (59.1%) was greater than the ORR (51.1%) in the first CDA in the CSR-SA RE population presented in the original submission.

The time to first response (CR or PR) in the Day 120 “mature efficacy” population (n=255) was 6.1 weeks (range: 4.9, 30.4 weeks), with 77.2% (n=105) having a first response in the first 8 weeks, 14.0% (n=19) from 8 to < 16 weeks, 7.4% (n=10) from 16 to < 24 weeks, and 1.5% (n=2) ≥ 24 weeks.

As of the Day 120 CDA data cut-off date of 01 June 2011, 250 patients were considered evaluable by an independent third-party core imaging laboratory. In this independently-assessed group of patients (n=250), 125 achieved a confirmed PR and 2 had a CR, resulting in an independently-assessed ORR of 50.8% (95% CI: 44.4, 57.2). The independently-assessed ORR of 50.8% (95% CI: 44.4, 57.32) is consistent with the investigator-assessed ORR of 53.3% (95% CI: 47.0, 59.6) in the 255 patients in the RE population as of 01 June 2011. Out of the 250 patients evaluable by independent-assessment, 5 were not included in the RE population. Therefore, a total of 245 patients were evaluable by independent and investigator assessments, with agreement on response and non-response for 98 and 86 patients, respectively, for a total event agreement rate of 75.1%.

Progression-free survival (PFS) data in the mature safety population (n=261) for the 120 Day CDA as of 01 June 2011 and 02 January 2012: The median PFS (02 January 2012 data cut-off) was 8.1 months (95% CI: 6.8, 9.7), and 66.5% (N=171/261) of patients had PFS

events (i.e., 142 [54.4%] patients with disease progression and 29 [11.1%] deaths). The median duration of treatment for the mature safety population (n=261) was 47.7 weeks as of 02 January 2012. There was no analysis of PFS for in the first (Day 60) CDA for this study because the data were not mature enough for meaningful evaluation. The sponsor believes the new PFS data from Study 1005 are important and further support the positive benefit/risk assessment based on the primary endpoint of ORR, along with the secondary endpoint of duration of response (DR). Of the 153 patients with objective responses in the mature RE population (02 January 2012 data cut-off), 84 (54.9%) have had subsequent disease progression or death and the Kaplan-Meier estimate of median duration of response (DR) was 45.4 weeks (95% CI: 34.1, 54.1).

Median overall survival (OS) had still not been reached at the time of the Day 120 CDA analysis. Death has been reported in 67 (15.3%) of all 439 patients in the safety analysis population, with the remaining 372 patients (84.7%) being censored for OS. The probabilities of survival at 6 and 12 months are now estimated to be 84.6% (95% CI: 79.9%, 88.2%) and 61.6% (95% CI: 49.7%, 71.5%), respectively.

(2.3) Safety assessment – Study 1005

A total of 439 patients were included in the “all patient safety analysis (SA)” population as of 01 June 2011, and these were defined as patients who had received at least 1 dose of crizotinib. The “all SA” population (n=439), included 261 patients who were defined as the “the mature safety analysis (SA)” population. As of the data cut-off date for the Day 120 CDA, 370 (84.3%) of all 439 patients remained in the study, and 329 (74.9%) remained on study treatment.

The safety results for the CSR “SA” population from the first CDA (n=136), and the updated data for patients in the “SA” populations (all [n=439] and mature [n=261] populations) are summarised below in Table 15. The median duration of treatment is longer in the updated “mature SA” population” (n=261) than in both the updated “all SA” population” (n=459) and the “original CSR” (n=136) safety population.

Table 15. Study 1005 – Deaths, SAEs, Grade 3 or 4 AEs, and selected treatment related AEs in the ALK-positive cohorts; SA populations.

	CSR Safety Analysis Population at Data Cutoff for First Clinical Data Addendum (N=136)	Mature Safety Analysis Population at Data Cutoff for Day 120 Clinical Data Addendum (N=261)	All Patients Safety Analysis Population at Data Cutoff for Day 120 Clinical Data Addendum (N=439)
Duration of Treatment			
Median (Range) in weeks	22.3 (0.9-53.1)	24.6 (0.9-68.4)	15.7 (0.1-68.4)
Deaths, n (%)			
Total	21 (15.4)	58 (22.2)	67 (15.3)
Within 28 days of last dose	16 (11.8)	40 (15.3)	49 (11.2)
>28 days after last dose	5 (3.7)	18 (6.9)	18 (4.1)
Due to disease progression	18 (13.2)	52 (19.9)	57 (13.0)
Related to study drug	2 (1.5)	2 (0.8)	3 (0.7)
Serious Adverse Events, n (%)			
All-causality	43 (31.6)	89 (34.1)	126 (28.7)
Treatment-related	10 (7.4)	15 (5.7)	29 (6.6)
Grade 3 or 4 Adverse Events, n (%)			
All-causality	61 (44.9)	115 (44.1)	152 (34.6)
Treatment-related	33 (24.3)	64 (24.5)	82 (18.7)
Treatment-Related, Adverse Events, n (%), Associated With:			
Permanent discontinuation	8 (5.9)	10 (3.8)	14 (3.2)
Temporary treatment discontinuation	25 (18.4)	51 (19.5)	66 (15.0)
Dose reduction	16 (11.8)	38 (14.6)	39 (8.9)

Death (on study): In the “mature SA” population (n=261), 40 (15.3%) of the total 58 (22.2%) deaths occurred on study (i.e., within 28 days after the last dose of study drug). Of these 40 deaths, 33 were considered to be due to disease progression and 7 were

considered to be due to other illnesses or events. In the “all SA” population (n=439), there were 49 deaths (11.2%) reported on study, 38 of these deaths were associated with disease progression, 3 were considered to be treatment related (1x pulmonary embolism, 1x pneumonitis, 1x unknown cause), and the remaining 8 were considered to be due to other illnesses or AEs. The updated estimated 30 and 60 day all-cause mortality rates for the 439 patients in the “all patient SA” population were 3.9% (n=17) and 5.7% (n=25), respectively.

SAEs: In the “mature SA” population (n=261), the incidences of all causality and treatment related SAEs were 34.1% (n=89) and 5.7% (n=15), respectively. In the “all SA” population (n=439), the incidences of all causality and treatment related SAEs were 28.7% (n=126) and 6.6% (n=29), respectively. In the “all SA” population (n=439), all causality SAEs occurring in ≥ 4 (0.9%) patients were disease progression (n=28, 6.4%), pneumonia (n=19, 4.3%), dyspnoea (n=16, 3.6%), pneumonitis (n=4, 0.9%), pulmonary embolism (n=4, 0.9%), pyrexia (n=4, 0.9%), and sepsis (n=4, 0.9%), while treatment related SAEs occurring in ≥ 4 (0.9%) of patients were dyspnoea (n=4, 0.9%) and pneumonitis (n=4, 0.9%).

Adverse events (all causality): In the “mature SA” population (n=231⁸¹), at least one treatment-emergent, all causality AE was reported in 98.9% (n=258) of patients. Similarly, in the “all SA” population (n=439), at least one treatment-emergent, all causality AE was reported in 95.4% (n=419) of patients. In the “mature SA” population (n=231), treatment-emergent, all causality AEs reported with an incidence of $\geq 10\%$ were nausea 57.9% (n=151), vomiting 48.3% (n=126), diarrhoea 43.3% (n=113), visual impairment 41.8% (n=109), constipation 39.8% (n=104), fatigue 32.2% (n=28), oedema peripheral 31.0% (n=81), dizziness 21.1% (n=55), cough 20.7% (n=54), dyspnoea 20.7% (n=54), dysgeusia 16.9% (n=44), ALT increased 16.1% (n=42), AST increased 11.9% (n=31), headache 11.9% (n=31), rash 11.1% (n=29), neutropenia 11.1% (n=29) and disease progression 10.7% (n=28).

Adverse events (treatment related): In the “mature SA” population (n=231)⁸², at least one treatment-emergent, treatment related AE was reported in 93.1% (n=243) of patients. Similarly, in the “all SA” population (n=439), at least one treatment-emergent, treatment related AE was reported in 89.5% (n=393) of patients. The most commonly reported treatment related AEs reported in $\geq 5\%$ of patients in either the “mature SA” population or the “all SA” population are summarised below in Table 16.

⁸¹ Sponsor correction: “261”.

⁸² Sponsor correction: “261”.

Table 16. Study 1005 – Treatment-emergent, treatment related AEs in ≥ 5% patients in either group; SA populations, 01 June 2011 data cut-off.

MedDRA Preferred Term	Mature Safety Population (N=261)		All Patients (N=439)	
	All Grades	Grade 3/4	All Grades	Grade 3/4
<i>Any Adverse Events</i>	243 (93.1)	63 (24.1)	393 (89.5)	81 (18.5)
Nausea	139 (53.3)	1 (0.4)	202 (46.0)	1 (0.2)
Vomiting	111 (42.5)	2 (0.8)	172 (39.2)	2 (0.5)
Visual impairment	105 (40.2)	1 (0.4)	154 (35.1)	1 (0.2)
Diarrhoea	98 (37.5)	2 (0.8)	153 (34.9)	3 (0.7)
Constipation	76 (29.1)	0	105 (23.9)	0
Oedema peripheral	58 (22.2)	0	77 (17.5)	0
Fatigue	59 (22.6)	4 (1.5)	74 (16.9)	4 (0.9)
Decreased appetite	54 (20.7)	0	71 (16.2)	0
Dysgeusia	41 (15.7)	0	55 (12.5)	0
Alanine aminotransferase increased	39 (14.9)	16 (6.1)	53 (12.1)	18 (4.1)
Dizziness	34 (13.0)	0	45 (10.3)	0
Photopsia	27 (10.3)	0	39 (8.9)	0
Aspartate aminotransferase increased	28 (10.7)	5 (1.9)	36 (8.2)	5 (1.1)
Neutropenia	28 (10.7)	17 (6.5)	30 (6.8)	18 (4.1)
Rash	20 (7.7)	0	28 (6.4)	0
Leukopenia	13 (5.0)	2 (0.8)	15 (3.4)	2 (0.5)
Vision blurred	13 (5.0)	0	21 (4.8)	0

Treatment related Grade 3 or Grade 4 AEs were observed at considerably lower frequencies than Grade 1 or 2 events. Treatment related Grade 3 or 4 AEs in the “mature SA” population (n=261) occurring in ≥ 2% of patients were neutropenia (n=17, 6.5%) and ALT increased (n=16, 6.1%). Similarly, treatment related Grade 3 or Grade 4 AEs in the “all SA” population (n=439) occurring in ≥ 2% of patients were also and neutropenia (n=18, 4.1%) and ALT increased (n=18, 4.1%).

Clustered AE terms: Treatment-emergent, all causality clustered AE terms in the “mature SA” population (n=261) are summarised below in Table 17.

Table 17. Study 1005 – All causality, all cycles, treatment-emergent AEs by MedDRA clustered preferred term and maximum CTC; “mature SA” population, 01 June 2011 data cut-off.

Preferred Term	Grade 1		Grade 2		Grade 3		Grade 4		Grade 5		Missing or Unknown		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Any AEs	110	(42.1)	65	(24.9)	41	(15.7)	11	(4.2)	0		0		227	(87.0)
Vision disorder	146	(55.9)	8	(3.1)	1	(0.4)	0		0		0		155	(59.4)
Fatigue	61	(23.4)	32	(12.3)	7	(2.7)	2	(0.8)	0		0		102	(39.1)
Oedema	63	(24.1)	30	(11.5)	2	(0.8)	0		0		1	(0.4)	96	(36.8)
Neuropathy	40	(15.3)	12	(4.6)	1	(0.4)	0		0		0		53	(20.3)
Alanine aminotransferase increased	17	(6.5)	9	(3.4)	15	(5.7)	2	(0.8)	0		0		43	(16.5)
Neutropenia	4	(1.5)	10	(3.8)	14	(5.4)	6	(2.3)	0		0		34	(13.0)
Oesophageal related disorder	15	(5.7)	4	(1.5)	3	(1.1)	0		0		0		22	(8.4)
Anaemia	7	(2.7)	5	(1.9)	2	(0.8)	0		0		0		14	(5.4)
Thrombocytopenia	8	(3.1)	1	(0.4)	1	(0.4)	1	(0.4)	0		0		11	(4.2)
Bradycardia	8	(3.1)	0		0		0		0		0		8	(3.1)
Seizure	0		1	(0.4)	0		0		0		0		1	(0.4)

AEs resulting in permanent treatment discontinuation: In the “mature SA” population (n=261), 16.5% (n=43) of patients had treatment-emergent, all causality AEs associated with permanent treatment discontinuation. AEs (all causality) resulting in permanent treatment discontinuation in this population occurring in ≥ 2 patients were disease progression 6.9% (n=18), dyspnoea 1.4% (n=4), ALT increased 1.1% (n=3), and pneumonitis 0.8% (n=2), with all other AEs occurring in 1 patient only (eye disorder, abdominal pain, nausea, death, general health deterioration, cholecystitis, cytolytic hepatitis, pneumonia, pyothorax, sepsis, AST increased, hypokalaemia, completed suicide, renal failure, acute respiratory failure, atelectasis, respiratory failure and arteriosclerosis). In the “mature SA” population (n=261), 3.8% (n=10) of patients discontinued permanently due to treatment-emergent, treatment related AEs: 2 patients each for pneumonitis and ALT increased; 1 patient each for both ALT and AST increased, death, nausea, dyspnoea, hypokalemia, and cytolytic hepatitis.

AEs resulting in temporary treatment discontinuation: In the “mature SA” population (n=261), 33.0% (n=86) of patients had treatment-emergent, all causality AEs associated with temporary treatment discontinuation. In this population, all causality AEs resulting in temporary treatment discontinuation in ≥ 2 patients were neutropenia 6.1% (n=16), ALT increased 4.6% (n=12), pneumonia 3.8% (n=10), vomiting 3.1% (n=8), AST increased 2.3% (n=6), neutrophil count decreased 1.5% (n=4), fatigue 1.5% (n=4), oedema peripheral 1.5% (n=4), nausea 1.1% (n=3), hypokalaemia 1.1% (n=3), dizziness 1.1% (n=3), leukopenia 0.8% (n=2), visual impairment 0.8% (n=2), dysphagia 0.8% (n=2), blood creatinine increased 0.8% (n=2), and pathological fracture 0.8% (n=2). All other events associated with temporary treatment discontinuation occurred in 1 patient only. In the “mature SA” population (n=261), 19.5% (n=51) of patients had treatment-emergent, treatment related AEs that were associated with temporary treatment discontinuation. In the “all SA” population (n=439), 25.1% (n=110) of patients had treatment-emergent AEs that were associated with temporary treatment discontinuation and the pattern of events was similar to that seen in the “mature SA” population.

AEs resulting in dose reduction: In the “mature SA” population (n=261), 16.1% (n=42) of patients had treatment-emergent, all causality AEs resulting in dose reductions, while 14.6% (n=38) of patients had treatment-emergent, treatment related AEs associated with dose reduction.

Laboratory results: Shifts in laboratory values were marginally more frequent in the “mature SA” population (n=261) than in the “all SA” population (n=439). In this review, only the shift results for the “mature SA” population (n=261) will be presented. In this population, shifts in laboratory values from CTCAE severity Grade ≤ 2 at baseline to Grade ≥ 3 post-baseline were observed in $\geq 5\%$ of patients for decreased lymphocytes (13.9%, N=35/242), decreased neutrophils (8.7%, N=22/252), increased ALT (7.9%, N=20/254), and hypophosphatemia (7.5%, N=19/252). Shifts from severity Grade ≤ 2 at baseline to Grade 4 post-baseline included decreased neutrophils for 6 patients (2.4%), decreased lymphocytes for 4 patients (1.6%), increased ALT for 3 patients (1.2%), and for 1 (0.4%) patient each, decreased calcium, decreased platelets, increased glucose, decreased potassium and decreased sodium.

Vital signs: The proportion of patients experiencing changes in vital signs (minimum and maximum categories) was marginally higher in patients in the “mature SA” population than in the “all SA” population. In this review, only the results from the “mature SA” population will be presented. In this population, maximum increases from baseline in systolic BP of ≥ 40 mmHg and diastolic BP of ≥ 20 mmHg were reported in 5.2% (N=13/250) and 8.4% (N=21/250) of patients, respectively; maximum decreases from baseline in SBP ≥ 40 mmHg and diastolic BP ≥ 20 mmHg were reported in 2.4% (N=6/250) and 34.4% (N=86/250) of patients, respectively; maximum increases and decreases from baseline in pulse rate ≥ 30 bpm were reported in 3.6% (N=9/250) and

41.2% (N=103/250) of patients, respectively; maximum (> 120 bpm) and minimum (< 50 bpm) pulse rates on study were reported in 1.6% (N=4/251) and 11.6% (N=29/251) of patients, respectively. Maximum increases and decreases from baseline in body weight of $\geq 10\%$ were reported in 17.6% (N=42/239) and 9.6% (N=23/239) of patients, respectively.

ECG changes QTcF interval: The proportion of patients experiencing changes in QTcF parameters were similar in the “mature SA” and “all SA” populations. In this review, only the results from the “mature SA” population will be presented. In this population, the maximum QTcF intervals of < 450, 450 to < 480, 480 to < 500, and ≥ 500 ms were reported in 90.3% (N=234/259), 6.9% (N=18/259), 1.2% (N=3/259) and 1.5% (N=4/259) of patients, respectively. Maximum increase in QTcF from baseline of < 30, ≥ 30 to < 60, and ≥ 60 ms were reported in 84.4% (N=211/250), 10.8% (n=27/250) and 4.8% (N=12/250) of patients, respectively.

Visual impairment: In Study 1005, ophthalmological examinations were protocol-specified. In the “all SA” population (n=439), approximately 20% of patients (depending on the specific assessment) were evaluable for changes from baseline for ophthalmological assessments. The most frequent finding was lens change (11.4% [N=10/88] right eye, 12.5% [N=77/88] left eye), and all other changes occurred in less than 5% of the evaluable patients (i.e., anterior chamber change, cornea change, iris change, fundus change, optic disc notching, optic nerve head, retina macula, retina non-macula [peripheral], vitreous body). Among the 14% of patients who were evaluable for visual acuity (right eye, 61; left eye, 62), the number of patients with decreased visual acuity measured as a loss of ≥ 2 lines (5 [8.2%] for right eye, 5 [8.1%] for left eye) was comparable with the number of patients with increased visual acuity measured as a gain of ≥ 2 lines (5 [8.2%] for right eye, 6 [9.7%] for left eye).

(3) Safety updates for studies A8081007 and A8081014

The Day 120 CDA included updated safety assessments relating to SAEs for crizotinib treated patients in Study 1007 (n=116) and study 1014 (n=19). In Study 1007 (n=116), 30 (25.9%) patients had all causality SAEs and 13 (11.2%) had treatment related SAEs. Treatment related SAEs occurring in 2 (1.7%) patients each were pneumonia, ALT increased and AST increased. Treatment related SAEs occurring in 1 (0.9%) patient each were, neutropenia, cardiac arrest, abdominal pain upper, vomiting, malaise, pyrexia, ECG QT prolonged, decreased appetite, renal cyst, acute respiratory failure, interstitial lung disease, pneumonitis, and drug eruption. Overall, SAEs reported in Study 1007 were consistent with those reported in Studies 1001 and 1005. In study 1014 (n=19), 3 patients had SAEs one of which was considered treatment related (oesophagitis).

(4) Patient reported outcomes (PROs) – Study 1005

In Study 1005, PROs of lung cancer-specific functioning, global quality of life (QOL), and disease related/treatment related symptoms, were assessed by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 Questionnaire (EORTC QLQ-C30) and its lung cancer module QLQ-LC13. In addition, generic health status was assessed using the EuroQol-5D (EQ-5D) visual analog scale (VAS). The visual symptom assessment questionnaire (VSAQ-ALK) was also included as part of a protocol amendment to assess visual effects and their impact on activities of daily living (ADL) reported by patients treated with crizotinib. Time points of administration for the patient reported questionnaires were baseline and Day 1 of each 3-week cycle and end of treatment. The primary analysis set for the PRO endpoints was the safety analysis population. However, the change from baseline analyses for the EORTC and EQ-5D VAS scores were conducted in the PRO-evaluable population, which is a subset of the safety analysis population.

The EORTC QLQ-C30 and QLQ-LC13 were scored according to the third edition of the EORTC Scoring Manual. Each scale of the EORTC QLQ-C30 and the QLQ-LC13 were transformed as indicated in the EORTC scoring manual, so that scale scores ranged from 0 to 100. Higher scores on the global QOL and functioning scales indicate better QOL or functioning, whereas higher scores on the symptom scales reflect more (worse) symptoms. Completion of at least 1 question from the EORTC QLQ-C30 and QLQ-LC13 ranged from 92% to 100% for the first 20 cycles. The sponsor reports that a clinically meaningful (≥ 10 -point) improvement from baseline was observed early in treatment and maintained throughout treatment in patient reported symptoms of cough (Cycle 2 onwards), pain (Cycles 2 to 11, 13 to 15, and 17 to 19), dyspnoea from QLQ-C30 (Cycles 2 to 11 and 13 to 19), pain in chest (Cycles 3 to 19 except for Cycle 12 and 18), pain in arm and shoulder (Cycles 3 to 5, 7, and 11 to 19), insomnia (Cycles 3 to 11) and fatigue (Cycles 4 to 16 and 18 to 20). The sponsor reports that a clinically meaningful (≥ 10 -point) improvement from baseline was observed for global quality of life (Cycles 4 to 8, 13 and 17). Increases (worsening) were reported in constipation and diarrhoea symptom scales and these were clinically meaningful (≥ 10 -point) in some cycles. EQ-5D VAS scores showed an improvement in health status from Cycle 2 through to Cycle 17.

The VSAQ-ALK showed that the most commonly experienced visual events were appearance of flashing lights. Most patients (61% to 89%) reported each event lasting ≤ 1 minute and 50% to 78% of patients reported event frequency in each cycle of < 7 days/week. Visual events were reported as occurring mostly in the morning in 52% to 62% of patients and in the morning and/or evening in 62% to 73% of patients. Among patients reporting an experience with a visual disturbance in each cycle, most or all patients (71% to 100%) reported that visual effects were not at all or a little bothersome, and most or all patients (83% to 100%) indicated that the visual symptoms had little or no impact on ADL.

(5) New retrospective analyses - Study A8081005 and historical controls

The sponsor's s31 response to the TGA included new retrospective analyses based on updated data from Study 1005 in patients with ALK-positive NSCLC and from the control arms of three Pfizer-sponsored studies in patients with NSCLC (A8501001, A8501002 and A6181087). The new retrospective analyses were provided in a Technical Report (Version Final 1.0) dated 15 March 2012. The methodology used to retrospectively analyse data from Study 1005 and the historical controls in the new technical report was similar to the methodology used to analyse data from Study 1001 and historical controls in the technical report provided in the original submission. Both the original and new technical reports were prepared by employees of the sponsor.

In the new report, the ORR analysis was based on data from Study 1005 (Day 120 CDA) from the 255 patients in the "mature RE" population as of 01 June 2011, and the PFS and OS analyses were based on the patients in the "all SA" population (n=439) as of 01 June 2011.

The objective of the new report was to give perspective to the efficacy results from the single arm Study 1005 by performing two retrospective analyses outlined below:

- A covariate-matched analysis was conducted in which the efficacy outcomes of ALK-positive, advanced NSCLC patients in Study 1005 were compared with those from matched patients drawn from the control arms of 3 other Pfizer-sponsored advanced NSCLC studies in order to simulate outcomes of randomised controlled trials of crizotinib versus standard NSCLC treatments; and
- A covariate-adjusted modelling analysis was performed to retrospectively predict the ORR of 255 response-evaluable ALK-positive advanced NSCLC patients and the expected PFS/OS of 439 safety-evaluable ALK-positive, advanced NSCLC patients from

Study 1005 as if they had been treated with one of the agents from the control arms of the 3 Pfizer-sponsored studies.

The study populations for the control arms came from three Pfizer-sponsored studies identified immediately below as Studies 1, 2, and 3. These historical control studies were identical to those used in the technical report in the original submission.

Study 1 (A8501001): an international, randomised, open-label, Phase III trial of paclitaxel/carboplatin plus PF-3512676 (that is, Toll-Like Receptor 9 Agonist) versus paclitaxel/carboplatin alone as first-line treatment of patients with advanced NSCLC; the paclitaxel/carboplatin regimen was paclitaxel 225 mg/m² over 3 hours and carboplatin AUC 6 mg/min/mL, each administered on Day 1 and repeated every 3 weeks.

Study 2 (A8501002): an international, randomised, open-label Phase III trial of gemcitabine/cisplatin plus PF-3512676 (Toll-Like Receptor 9 Agonist) versus gemcitabine/cisplatin alone as first-line treatment of patients with advanced NSCLC; the gemcitabine/cisplatin regimen was gemcitabine 1250 mg/m² (Day 1, Day 8) and cisplatin 75 mg/m² (Day 1, then every 21 days).

Study 3 (A6181087): a multicentre, randomised, double-blind, controlled Phase III efficacy and safety study of sunitinib in patients with advanced/metastatic NSCLC treated with erlotinib 150 mg once daily.

The baseline characteristics and efficacy outcomes of the studies included in the new analyses relative to the historical control were summarised in two tables. Baseline characteristics of patients in the “mature RE” population from Study 1005 and the “safety analysis” population from Study 1005, and in the historical control arms from the three Pfizer studies by matching scheme were summarised in a series of tables.

Results for the covariate matched analysis (ORR): In patients with advanced ALK-positive NSCL (Study 1005), crizotinib treatment was associated with a higher ORR (53.3% [95% CI: 46.8, 59.9]) in the “mature RE” population (n=255) than in the covariate matched controls from Pfizer studies 1-3 in patients with advanced NSCLC. Covariate matched ORRs ranged from 14.9% to 21.2% with paclitaxel/carboplatin in the first-line setting (Study 1), 20.2% to 24.0% with gemcitabine/cisplatin in the first-line setting (Study 2), and 10.0% to 14.5% with erlotinib in the second/third line setting (Study 3). Overall, the point estimates for ORRs for the three historical control regimens were more than 50% lower than the observed ORR in crizotinib treated patients in Study 1005, and the lower limit of the 95% CI (47%) for the ORR in crizotinib treated patients was higher than the upper 95% CI for the ORR in any of the three historical control regimens.

Results for covariate matched analysis (PFS): The observed median PFS for patients treated with crizotinib in the “safety analysis” population was 8.5 months (95% CI: 6.2, 9.9) which was longer than the observed covariate-matched median PFS values for the three historical control regimens. The PFS ranged from 4.7 to 5.9 months with first line paclitaxel/carboplatin treatment, 5.0 to 5.3 months with first line gemcitabine/cisplatin treatment, and 2.1 to 3.4 months with second/third line erlotinib treatment. The hazard ratios for PFS of crizotinib versus any of the three control regimens all favoured crizotinib and ranged from 0.37 to 0.55.

Results for the covariate matched analysis (OS): OS data in Study 1005 are still immature and the median OS has not been reached due to a relatively short median follow-up of 4.7 months (95% CI: 4.2, 5.2 months). The covariate-matched observed median OS ranged from 10.6 to 14.2 months with first line paclitaxel/carboplatin, from 11.0 to 15.0 months with first line gemcitabine/cisplatin and from 9.9 to 12.6 months with second/third line treatment as erlotinib. The hazard ratios for OS of crizotinib versus all three control regimens ranged from 0.43 to 0.77, suggesting treatment with crizotinib could potentially result in longer OS than treatment with the covariate-matched historical controls.

Results for the covariate-adjusted analyses for the ORRs: After simultaneously adjusting for eight baseline characteristics (histology, gender, race, smoking classification, disease stage, ECOG performance status, age and weight), estimated ORRs for the “mature RE” patients (n=255) in Study 1005 for the three historical control regimens were all lower than that reported with crizotinib in Study 1005 (53.4% [95%CI 46.8, 59.9]). The sponsor notes that the 95% CIs of the estimated ORRs for the control regimens do not overlap with the 95% exact CI of the observed ORR for crizotinib. In particular, the sponsor comments that the lower 95% CI for crizotinib (46.8%) exceeds the upper 95% CIs for all three historical control regimens (all <30%). The logistic regression estimators for the ORRs for the three historical control regimens in the “mature RE” population from Study 1005 are summarised below:

- estimated predictive response rate to paclitaxel/carboplatin (Study 1) for the 255 “mature RE” patients in Study 1005: 21.1% (95% CI: 13.8, 28.4);
- estimated predictive response rate to gemcitabine/cisplatin (Study 2) for the 255 “mature RE” patients in Study 1005: 20.9% (95% CI: 14.7, 27.2);
- estimated predictive response rate to erlotinib (Study 3) for the 255 “mature RE” patients in Study 1005: 14.2% (95% CI: 7.3, 21.1).

(6) New retrospective analysis (PFS and TTP) – data from Study A8081005

The submission included new retrospective analyses comparing median progression-free-survival (PFS) or median time to disease progression (TTP) from the start of crizotinib therapy in Study 1005 with the median TTP from the start of prior pemetrexed or docetaxel. The analyses were presented in a new report (Version Final 1.0) dated 15 March 2012, and written by an employee of Pfizer. Data included in the analysis were derived from subsets of the 439 patients included in the safety analysis (SA) population, as of 01 June 2011 (Day 120 CDA).

The data were analysed in three ways in three patient groups; Analysis 1/Group 1 and Analysis 2/Group 2 were within-patient analyses and Analysis 3/Group 3 was a between-patient analysis (see Table 18 below). In analyses/groups 1 and 2, in order to account for intra-subject correlation in the analysis of multiple events per subject, the data were analysed using the Anderson-Gill extension method to the standard Cox proportional hazards model approach (with/without prognostic factors). All Group 1 patients included in Analysis 1 (within-patient analysis) consisted of the same cohort of patients which controls for potential selection bias and confounding when comparing TTP with historical controls, and the same applied for all Group 2 patients included in Analysis 2 (within-patient analysis). In Analysis 3 (between-patient analysis), the Group 3 patients were compared using the standard Cox proportional hazards model, with/without adjustment for potential prognostic factors.

Table 18. Number of subjects in groups 1-3 for retrospective analyses 1-3 in Study 1005 (n=439).

	Analysis 1/Group 1		Analysis 2/Group 2		Analysis 3/Group3	
Sample size* (%**)						
Pemetrexed/ Docetaxel	287 (65.4%)		117 (26.7%)		117 (26.7%)	
Crizotinib					62 (14.1%)	
Line & Usage (%***)						
Pemetrexed/ Docetaxel	1 st line combination	112(39%)				
	2 nd line single agent	117(41%)	2 nd line single agent	117	2 nd line single agent	117
	2 nd line combination	58 (20%)				
Crizotinib	2 nd line single agent	37 (13%)	3 rd line single agent	76(65%)	2 nd line single agent	62
	≥3 rd line single agent	250(87%)[3,9]†	≥4 th line single agent	41(35% [4,9]†		

*Sample sizes in:

Analysis 1: Data of prior pemetrexed or docetaxel treated patients and crizotinib treated patients are from the same 287 patients. If a patient was treated with pemetrexed or docetaxel both in 1st and 2nd line, only the 1st line observation was included.

Analysis 2: Data of prior pemetrexed or docetaxel treated patients and crizotinib treated patients are from the same 117 patients.

Analysis 3: Data of prior pemetrexed or docetaxel treated patients and crizotinib treated patients are from mutually exclusive patients, who received different treatment in 2nd line single agent setting.

** Based on 439 patients in the SA population. *** Based on the sample size in Group 1, Group 2 respectively.

† Range of lines of crizotinib treatment in ≥ 3rd line, 4th line category respectively.

The results for the three analyses are summarised below in Table 19. Median TTP and PFS times for crizotinib and pemetrexed or docetaxel in Groups 1-3 are presented using the Kaplan-Meier method with two-sided 95% confidence intervals (CI; by the Brookmeyer-Crowley method). Median TTP and median PFS times for the prior therapies (pemetrexed/docetaxel) are identical within groups, as patients enrolled in Study 1005 could not have experienced death as a PFS event prior to enrollment. Median TTP values observed for crizotinib were longer than median PFS values, which is generally the case for these two outcomes as TTP events include only disease progression while PFS events include both disease progression and death.

Table 19. Summary of median for TPP and PFS and Hazard Ratios (HR) of crizotinib versus pemetrexed or docetaxel in Study 1005.

	Analysis 1†		Analysis 2‡		Analysis 3#	
TTP						
Treatment	Criz	Pem/Doc	Criz	Pem/Doc	Criz	Pem/Doc
Median (months)	9.7 [6.2, 11.3]	5.0 [4.2, 5.7]	11.1 [5.5, 13.0]	3.5 [2.8, 5.3]	NA [9.7, NA]	3.5 [2.8, 5.3]
HR Criz vs. Pem/Doc [95% CI]	0.451 [0.341, 0.595]		0.464 [0.317, 0.678]		0.242 [0.113, 0.522]	
HR* Criz vs. Pem/Doc [95% CI]	0.431 [0.310, 0.550]		0.428 [0.290, 0.631]		0.285 [0.131, 0.620]	
PFS						
Treatment	Criz	Pem/Doc	Criz	Pem/Doc	Criz	Pem/Doc
Median (months) §	8.2 [5.6, 10.8]	5.0 [4.2, 5.7]	5.7 [5.3, 12.0]	3.5 [2.8, 5.3]	NA [9.7, NA]	3.5 [2.8, 5.3]
HR Criz vs. Pem/Doc [95% CI]	0.595 [0.461, 0.767]		0.631 [0.443, 0.899]		0.311 [0.157, 0.615]	
HR* Criz vs. Pem/Doc [95% CI]	0.543 [0.417, 0.708]		0.587 [0.406, 0.847]		0.369 [0.185, 0.738]	

†Based on Anderson-Gill model ‡ based on Anderson-Gill model; # based on standard Cox model.

§Patients who were enrolled in Study 1005 could not have death as PFS event prior to enrollment in the study thus leading to identical TTP and PFS for prior pemetrexed or docetaxel; A total of 20, 10 and 1 patients experienced death as PFS events on crizotinib in Groups 1, 2 and 3, respectively.

* Adjusted HR. Factors used in variable selection included: smoking status (Ex. or Current vs. Never), age (yr), gender (Male vs. Female), ECOG performance status (≥1 vs 0), and race (Asian vs. Non-Asian). Final variables for model were selected using a backward selection process and a 2-sided alpha level of 0.10. Variables adjusted for in the final model are - TTP/PFS Analysis 1: ECOG performance status, age; TTP/PFS Analysis 2: age; TTP/PFS Analysis 3: ECOG performance status.

Results for Analysis 1 (within-patient analysis):

In Group 1, the median TTP of any prior first or second-line pemetrexed/docetaxel therapy was 5.0 months. No information is available in the literature to put these observed values in historical perspective. For this same group of patients when treated with ≥ second-line crizotinib, the median TTP and median PFS were 9.7 months and 8.2 months, respectively. The analysis of crizotinib PFS (median 8.2 months) vs prior pemetrexed/docetaxel TTP (median 5.0 months), after adjustment for ECOG performance status and age, resulted in a HR of 0.543 (95% CI: 0.417, 0.708). These results indicate that improvement in PFS with crizotinib treatment (irrespective of whether it occurred beyond line 2 and up to line 9) was greater than that for TPP following pemetrexed/docetaxel therapy in first-line combination, or second-line single-agent or combination settings.

Results for Analysis 2 (within-patient analysis):

In Group 2, the median TTP of prior, single-agent, 2 second line, pemetrexed/docetaxel, was 3.5 months (95% CI: 2.8, 5.3 months). This is consistent with historical data for

median TTP (3.4 months) and median PFS (3.5 months) following second-line, single-agent treatment with pemetrexed.⁸³ TTP,⁸⁴ PFS For this same group of patients treated with \geq third-line crizotinib, the median TTP and PFS were 11.1 months and 5.7 months, respectively. Analysis of crizotinib PFS (5.7 months) vs prior pemetrexed/docetaxel TTP (3.5 months), after adjustment for age, resulted in a HR of 0.587 (95% CI: 0.406, 0.847). This result indicates that improvement in PFS with crizotinib treatment (irrespective of whether it occurred beyond third-line 3 and up to line 9) was greater than that for TTP following prior pemetrexed or docetaxel in the second-line, single-agent setting.

Results for Analysis 3 (between-patient analysis):

In Group 3 (between-patient analysis), the median TTP of prior, single-agent, second-line pemetrexed or docetaxel was 3.5 months (95% CI: 2.8, 5.3 months), which were the same values as reported above for Group 2. The median PFS for patients treated with second-line crizotinib had not yet been reached due to small sample and data maturity limitations. However, the HR of crizotinib PFS vs prior pemetrexed/docetaxel TTP, after adjustment for ECOG performance status, was 0.369 (95% CI: 0.185, 0.738).

(7) New retrospective analysis – Salgia et al; 2012.

The original submission (sponsor's Clinical Overview, Section 2.5.4.5) provided summaries of investigator assessed ORR and TTP in ALK-positive advanced NSCLC patients from Studies 1001 and 1005 treated with prior pemetrexed or docetaxel, in any line, first-line combination and second-line, single-agent or combination settings. The sponsor's s31 response to the TGA included a report (Salgia et al., 2012)⁸⁵ updating the data relating to prior pemetrexed treatment based on the Day 120 CDA (as of 01 June 2011) for Study 1005. The report from Salgia et al (2012) was published in the form of a poster (#B31) presented at the AACR-IASLC Joint Conference on Molecular Origins of Lung Cancer, Biology, Therapy, and Personalized Medicine, January 8-11, 2012. The objective of the report was to retrospectively assess TTP and ORR with prior pemetrexed treatment in patients with ALK-positive NSCLC who subsequently received crizotinib in Study 1005. The report indicated that, as of June 2011, 439 ALK-positive NSCLC patients had been enrolled into Study 1005, and that the majority of these patients (369 patients; 84.1%) had received pemetrexed as a single-agent or in combination and for any line of treatment prior to enrollment. The overall ORR for pemetrexed for these patients was 18.7% (95% CI not provided). In patients who had received second-line, single-agent pemetrexed (n=80), ORR was 12.5% and median TTP was 5.3 months (95% CI: 3.0, 6.6). In patients who received pemetrexed as third-line or later therapy (n=138), ORR was 16.7% (95% CI not provided). The observed results for crizotinib for ORR (53.3% [95%CI: 47.0, 49.6]) and PFS (8.5 months [95% CI: 6.5, 9.9]) from the "mature efficacy" population (n=255) in Study 1005 were both notably superior to the corresponding ORR and TTP results for prior pemetrexed therapy.

(8) Hepatotoxicity

The sponsor's s31 response included an updated summary of hepatotoxicity (fatal or potentially meeting Hy's law criteria). In summary, there are now 4 cases of hepatotoxicity considered to meet Hy's law criteria (1 fatal and 3 recoveries), and 1 case of hepatotoxicity resulting in fatal hepatic failure considered by the sponsor not to have met Hy's law

⁸³Hanna N, Shepherd FA, Fossella FV, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. *J Clin Oncol* 2004;22:1589-1597.

⁸⁴Scagliotti G, Hanna N, Fossella F, et al.: The differential efficacy of pemetrexed according to NSCLC histology: a review of two Phase III studies. *Oncologist* 14 (3): 253-63, 2009.

⁸⁵Salgia R, Ou S, Kim DW, Shaw AT, Wilner K, Tang Y, Selaru P, Polli A, Scagliotti GV. Single-agent pemetrexed in patients with ALK-positive NSCLC: a retrospective analysis of Investigator-reported Outcomes. Poster #B31 presented at the AACR-IASLC Joint Conference on Molecular Origins of Lung Cancer, Biology, Therapy, and Personalized Medicine, January 8-11, 2012.

criteria. The sponsor estimates that, as of 13 December 2011, there have been a total of 5 cases of crizotinib related hepatotoxicity reported in approximately 1399 patients across Pfizer-sponsored clinical studies. Therefore, the incidence of crizotinib related, severe, life-threatening hepatotoxicity is approximately 0.4% (N=5/~1399), as of 13 December 2011. Overall, assessment of severe, life-threatening hepatotoxicity remains unchanged from that discussed in the original CER.

(9) Pneumonitis

The sponsor's s31 response included an updated summary of cases of pneumonitis. In the updated safety assessment for Studies 1001 (n=149, SA) and 1005 (n=439, "mature SA") at 01 June 2011 data cut-off (n=588, pooled population), there were 16 (2.7%) patients with treatment-emergent, all-causality pneumonitis-type events, which included 10 (1.7%) patients with pneumonitis, 3 patients (0.5%) with radiation pneumonitis, 2 (0.3%) patients with acute respiratory distress syndrome (ARDS), and 1 (0.2%) patient with bronchiolitis. Of these 16 events, 9 (pneumonitis) were considered by the sponsor to be related to crizotinib treatment, and 7 were considered not to be treatment related. The updated data from Study 1007, includes 1 patient with crizotinib related interstitial lung disease (that is, 0.9% [N=1/116]) that appears as yet not to have been confirmed. The incidence of treatment related pneumonitis identified by the Independent Review Committee based on the data in the original submission was 0.9% (N=3/340).

Second round benefit-risk assessment

Second round assessment of benefits

General comments

Overall, it is considered that the submitted data (original, updated and new) establish that crizotinib treatment provides meaningful clinical benefits for patients with ALK-positive NSCLC. The prospective clinical studies (1001, 1005) show that crizotinib markedly inhibits tumour progression based on RECIST in patients with ALK-positive NSCLC, while the retrospective analyses suggest that crizotinib provides meaningful clinical benefits for patients treated with the drug compared with relevant historical controls.

The major limitation of the submission is the absence of prospective, Phase III, randomised, controlled studies demonstrating that treatment with crizotinib provides meaningful clinical benefits, such as improvement in overall survival or progression free survival, for patients with ALK-positive NSCLC compared with relevant active controls. However, the sponsor believes that, while the retrospective analyses may not substitute for confirmatory Phase III controlled data, the results from these analyses are robust and in the absence of randomised data, provide valuable information in describing the benefit profile of crizotinib for treatment of ALK-positive NSCLC. The sponsor's position is considered to be reasonable, based on evaluation of the submitted retrospective analyses (original, updated and new). The retrospective analyses are considered to aid interpretation of the crizotinib single-arm efficacy data from Studies 1001 and 1005 by providing robust statistically significant comparisons between these data and clinically relevant efficacy outcomes from historical controls.

A further significant limitation of the submitted data is the absence of studies investigating the effects of crizotinib as first-line treatment for ALK-positive NSCLC. In Study 1001 (Day 120 CDA), the majority of patients in the total response evaluable (RE) population had been treated with at least 1 prior systemic treatment for NSCLC, while in Study 1005 such treatment was an inclusion criteria and all patients had been treated with at least 1 prior systemic treatment. However, there are prospective data (albeit limited) in the submission from Study 1005 suggesting that there are unlikely to be notable differences in patient

benefits following crizotinib treatment in the first-line setting compared with second-line and beyond settings. In Study 1001 (Day 120 CDA), the efficacy outcomes were similar in the all patient and previously treated patient groups. However, this comparative efficacy data should be interpreted cautiously as the majority of patients in the all patient RE population had been previously treated (N=121/143, 84.6%), suggesting that the results in the all patient group are being driven primarily by previously treated patients. There are data from the subgroup analyses in Study 1001 showing that the ORR in the relatively small number of patients who had not been previously treated (n=22, 15.4%) did not notably differ from the ORR in patients who had been previously treated with 1, 2, or 3 or more advanced/metastatic therapies for NSCLC. Furthermore, the retrospective analyses consistently showed that crizotinib was more efficacious than standard first-line systemic treatment regimens for NSCLC.

Updated efficacy data from key Studies 1001 and 1005

The updated efficacy data from Studies 1001 and 1005 continue to provide convincing evidence of crizotinib's antitumour activity. In both studies, the primary efficacy endpoint was the objective response rate (ORR), and the primary analysis of this endpoint was based on investigator assessment of best response according to RECIST. In Study 1001 (Day 120 CDA), the ORR (primary analysis) was 61.5% (95% CI: 53.0, 69.5) in all patients in the RE population (N=88/143), and this result was consistent with that observed in the preliminary CSR RE population. In Study 1005 (Day 120 CDA), as of 02 January 2012, the ORR (primary analysis) was 59.1% (95% CI: 52.8, 65.1) in the mature efficacy population (N=153/259), which was higher than the ORR in the Day 60 CDA (original submission) of 51.1% (95% CI: 42.3, 59.9) observed in the RE population (N=68/133). In the primary analyses in both studies, nearly all patients contributing to the ORR (CR + PR) were reported as having confirmed partial responses rather than confirmed complete responses.

In both Studies 1001 and 1005, the primary analysis of the ORR based on investigator assessed RECIST was supported by independent radiological review of the imaging data. The use of independent assessment of imaging data is more methodologically sound than investigator assessment as it mitigates the potential for observer bias. In Study 1001 (Day 120 CDA), the independently assessed ORR was 55.9% (95% CI: 46.8, 64.7), N=71/127, which was similar to the ORR based on investigator assessment (61.5%). There was agreement between independent and investigator assessments on response and non-response for 61 and 33 patients, respectively, for a total event agreement rate of 74.0%. In Study 1005 (Day 120 CDA), the independently assessed ORR was 50.8% (95% CI: 44.4, 57.2), N=127/250, which was lower than the ORR based on investigator assessment as of 02 January 2012 (59.1%), but comparable with the investigator assessment as of 01 June 2011 (53.5%). In 245 patients with evaluable imaging data independently and investigator assessed as of 01 June 2011, agreement on response and non-response occurred for 98 and 86 patients, respectively, for a total event agreement rate of 75.1%.

In both studies, the median time to response (TTR) was relatively rapid at about 6 to 8 weeks, and the median duration of response (DR) was about 45 to 49 weeks. In Study 1001 (Day 120 CDA), in all patients in the RE population the median TTR was 7.9 weeks (range: 2.1, 57.3) and in Study 1005 (120 Day CDA) as of 01 June 2011, the median TTR was 6.1 weeks (range: 4.9, 30.4). The median duration of response was 49.1 weeks (95% CI: 39.3, 89.3) in Study 1001 (Day 120 CDA) all patients in the RE population, and 45.4 weeks (95% CI: 34.1, 54.1) in Study 1005 (Day 120 CD) as of 02 January 2012.

In Study 1001 (Day 120 CDA), the subgroup analyses of the ORRs based on prior treatment with advanced/metastatic therapies for ALK-positive NSCLC with 0, 1, 2, and ≥ 3 regimens in the total RE population (n=143) were: 68.2% (95% CI: 45.1, 86.1), N=15/22; 59.1% (95% CI: 43.2, 73.7), N=26/44; 64.5% (95% CI: 45.4, 80.8), N=20/31; and 58.7% (95% CI: 43.2, 73.0), N=27/46, respectively. These results show that the ORR was highest

in the patient group who had not been previously treated with prior systemic advanced/metastatic therapies, and was independent of the number of prior treatments with systemic advanced/metastatic therapies.

Progression-free survival (PFS) was defined as a secondary efficacy endpoint in Studies 1001 and 1005. In Study 1001 (Day 120 CDA), the median PFS in the safety analysis (SA) population (n=149) was 9.9 months (95% CI: 7.7, 13.4) and in Study 1005 (Day 120 CDA) as of 02 January 2012 the median PFS was 8.1 months (95% CI: 6.8, 9.7) in the "mature SA" population (n=261). The percentage of patients with PSF events in Studies 1001 and 1005 was 55.7% (N=83/149) and 65.5% (N=171/261), respectively, with the majority of events in both studies being objective disease progression rather than death.

Overall survival (OS) was defined as a secondary efficacy endpoint in Studies 1001 and 1005. However, median OS could still not be determined in either study as the Day 120 CDA survival data were too immature to determine this endpoint. In Study 1001 (Day 120 CDA), death was reported for 46 (30.9%) of all 149 patients in the SA population, with nearly all of the remaining patients (67.8%) being censored due to still being in follow-up for survival. The median follow-up for OS was 16.6 months for all treated patients. The probabilities of survival at 6 and 12 months in the SA population (Study 1001) are now estimated to be 87.9% (95% CI: 81.3, 92.3) and 74.8% (95% CI: 66.4, 81.5), respectively. In Study 1005 (Day 120 CDA), death was reported for 67 (15.3%) of all 439 patients in the "all SA" population, with nearly all of the remaining patients (84.7%) being censored due to still being in follow-up for the OS analysis. The probabilities of survival at 6 and 12 months in the "all SA" population (Study 1005) are now estimated to be 84.6% (95% CI: 79.9, 88.2) and 61.6% (95% CI: 49.7, 71.5), respectively.

In Study 1005 (Day 120 CDA), clinically meaningful (≥ 10 -point) improvement from baseline in patient reported outcomes (PROs) were observed in various cycles for global quality of life, physical functioning, role functioning, social functioning and emotional functioning, and for patient reported symptoms of cough, pain, dyspnea, pain in chest, pain in arm and shoulder, insomnia and fatigue. The only clinically meaningful worsening was reported in symptom scales of constipation and diarrhoea in some cycles. Improvement in health status as measured by the EQ-5D VAS scores was observed as early as Cycle 2 and the improvement maintained through Cycle 17. The PRO data are promising, but difficult to interpret in the absence of a control group.

Data from the new retrospective analyses

The sponsor's s31 response to the TGA included new retrospective analyses comparing the efficacy data from Study 1005 (Day 120 CDA) in patients with advanced ALK-positive NSCLC with historical control data from three Pfizer sponsored studies in patients with advanced NSCLC. In these retrospective analyses, the efficacy outcomes associated with crizotinib in Study 1005 were assessed relative to control regimen regimens by: (1) generating comparable patient populations using the control arms of three Pfizer-sponsored studies (covariate-matched analysis); and (2) retrospectively estimating the ORRs and expected PFS/OS curves in Study 1005 patients as if they had been treated with the control regimens from the 3 Pfizer sponsored studies (covariate-adjusted analysis). The results of the new retrospective analyses of the efficacy data from Study 1005 are consistent with those of the retrospective analyses of the efficacy data from Study 1001 in the original submission. The original submission did not include retrospective analyses of the efficacy data from Study 1005 as the data from that study at that time were considered to be too immature for these types of analyses.

In the new retrospective analyses based on efficacy data from Study 1005, treatment with crizotinib was associated with a higher ORR (53.3% [95% CI: 46.8, 59.9]) than that of covariate-matched historical controls (that is, 14.9% to 21.2% for paclitaxel/carboplatin in the first-line setting; 20.2% to 24.0% for gemcitabine/cisplatin in the first-line setting;

10.0% to 14.5% for erlotinib in the second/third line setting). Similar results were observed using the covariate-adjusted modelling approach with estimated ORRs for the historical controls being 21.1% (95% CI: 13.8, 28.4) for paclitaxel/carboplatin, 20.9% (95% CI: 14.7, 27.2) for gemcitabine/cisplatin, and 14.2% (95% CI: 7.3, 21.1) for erlotinib. In the covariate-matched analysis, assessment of the secondary endpoints of PFS and OS produced similar results to assessment of the primary efficacy endpoint of ORR. The doses of paclitaxel/carboplatin and gemcitabine/cisplatin control arms from the sponsor's historical Studies 1 and 2 might be used in Australian clinical practice but the sponsor acknowledges that a more conservative approach to dosage with these agents "is taken for less fit patients by many oncologists". The dose of erlotinib in the control arm of the sponsor's historical Study 3 is that approved in Australia.

The sponsor's s31 response to the TGA included a new retrospective analysis assessing efficacy outcomes of PFS and TTP associated with crizotinib in Study 1005 (Day 120 CDA) relative to TTP from prior pemetrexed or docetaxel treatment regimens. Results from the analyses suggest that crizotinib was more efficacious than any of the comparator first or second-line, single-agent or combination pemetrexed or docetaxel treatment regimens. In this analysis, the doses of pemetrexed and docetaxel were not captured in the clinical database, and actual doses could differ for each patient.

The sponsor's s31 response to the TGA included an updated retrospective analysis of the efficacy outcomes (ORR and TTP) associated with prior pemetrexed treatment in patients subsequently enrolled in Study 1005 (Salgia et al., 2012).⁸⁵ The analysis was based on the updated data as of 01 June 2011 from the Day 120 CDA. The results showed that the observed results for crizotinib for both ORR and PFS in the "mature efficacy" population as of 01 June 2011 in Study 1005 were notably superior to the corresponding ORR and TTP results in the population treated with pemetrexed as a single-agent or in combination prior to enrollment in the study. In this analysis, the doses of pemetrexed were not captured in the clinical database, and actual doses could differ for each patient.

Second round assessment of risks

Overall, the risks of crizotinib following assessment of the updated safety data are considered to be consistent with those discussed in the original CER. The most significant risks associated with crizotinib relate to life-threatening hepatotoxicity and pneumonitis. There are a number of other risks that occurred commonly in both studies but were generally manageable by temporary treatment discontinuation or dose reduction rather than by permanent treatment discontinuation. The updated adverse reactions (treatment-emergent, treatment related adverse events) from Studies 1001 (n=149, SA) and 1005 (n=261, "mature SA") were summarised in a table. The sponsor has included the data from this table in the amended Adverse Effects section of the revised PI provided with its s31 response to the TGA.

Hepatotoxicity

The updated data included 5 cases of serious hepatotoxicity (4 cases meeting Hy's law criteria, and 1 case not meeting the criteria but resulting in fatal hepatic failure). The overall incidence of severe life-threatening hepatotoxicity (n=5) in the total clinical safety database was 0.4% in the total number of patients treated with crizotinib (n ~ 1399) across Pfizer-sponsored clinical studies as of 13 December 2011.

In order to mitigate the risk of life-threatening toxicity the sponsor recommends that liver function tests, including ALT and total bilirubin, should be monitored once a month and as clinically indicated, with more frequent repeat testing for Grades 2, 3, or 4 elevation. However, clinical experience suggests that regular liver function monitoring cannot completely mitigate idiosyncratic drug related life-threatening hepatic toxicity. The sponsor also recommends dose modifications for patients who develop ALT or AST

elevations, with and without elevations in total bilirubin. In the pooled updated laboratory data from Studies 1001 (SA) and 1005 (“mature SA”), maximum increases in ALT \geq 5xULN were reported in 7.5% (N=30/398) of patients and maximum increases in total bilirubin \geq 2xULN were reported in 1.0% (N=4/398).

Pneumonitis

The updated data included 10 (1.7% of 588) patients with pneumonitis reported in pooled data from the safety populations of Studies 1001 (n=149, SA) and 1005 (n=439, “all SA”), and pneumonitis in 9 (1.5%) of these patients was considered by the sponsor to be treatment related. Of the 10 cases of pneumonitis, there were: 1x Grade 1; 2x Grade 2; 4x Grade 3; 2x Grade 4; and 1x Grade 5 (death) events.

In the updated data, based on a smaller pooled population of 410 patients from Studies 1001 (n=149, SA) and 1005 (n=261, “mature SA”), there have been 5 (1.2%) cases of pneumonitis (n=3 and n=2, respectively). The 5 events include 3x Grade 3, 1x Grade 4, and 1x Grade 5 (death).

Commonly reported treatment related risks

Nearly all patients treated with crizotinib in Study 1001 (n=149, SA) and Study 1005 (n=261, “mature SA”) experienced at least one, treatment-emergent, treatment related AE (n=144, 96.8% and n=243, 93.1%, respectively). Commonly reported treatment related AEs associated with crizotinib in Studies 1001 (n=149, all SA) and 1005 (n=261, “mature SA”) and reported in \geq 10 % of patients in at least one of the two studies included, respectively, vision disorders clustered term (64.4% and 57.1%), nausea (56.4% and 53.3%), diarrhoea (49.7% and 37.5%), vomiting (38.9% and 42.5%), oedema clustered term (32.9% and 24.9%), constipation (27.5% and 29.1%), dizziness (20.8% and 13.0%), decreased appetite (16.1% and 20.7%), fatigue clustered term (16.1% and 26.4%), ALT increased (12.1% and 14.9%), AST increased (10.1% and 10.7%), dysgeusia (10.7% and 15.7%), rash (11.4% and 7.7%), neuropathy clustered term (9.4% and 12.6%), oesophageal related disorders clustered term (12.8% and 3.8%) and neutropenia (7.4% and 10.7%).

Vision disorders

Vision disorders (clustered term) were the most commonly reported treatment-emergent, treatment related AEs reported in both Study 1001 (n=149, SA) and Study 1005 (n=261, “mature SA”): 64.4% (n=96) and 57.1% (n=149) of patients, respectively. Nearly all reports of vision disorders (clustered term) were Grade 1 or 2 events, with only 1 Grade 4 event being reported in the pooled population (n=410). In Study 1005, protocol specified ophthalmological assessments were undertaken in about 20% of the “all SA” population and the most frequent finding was lens change, which was reported in about 12% of evaluable patients (n=88). All other changes observed with protocol ophthalmological assessment occurred in less than 5% of evaluable patients. Visual acuity was assessed in about 14% of the population (61, Right eye; 62, Left eye), and no marked deterioration in visual acuity was detected.

In Study 1001 (n=149, SA), treatment-emergent, all causality AEs were reported in 103 (69.1%) patients and consisted primarily of visual impairment (n=79, 53.0%). Other eye disorders reported in \geq 1% of patients were photopsia (n=12, 8.1%), peri-orbital oedema (n=9, 6.0%), vision blurred (n=5, 3.4%), vitreous floaters (n=3, 2.0%), conjunctivitis (n=2, 1.3%), cataract (n=2, 1.3%) and diplopia (n=2, 1.3%), with all other eye disorders occurring in 1 patient only. Visual field defect (Nervous system disorder SOC) was reported in 3 (2.0%) patients. Nearly all visual disorders were Grade 1 or 2 events.

In Study 1005 (n=261, “mature SA”), treatment-emergent, all causality AEs were reported in 172 (65.9%) patients and consisted primarily of visual impairment (n=109, 41.8%). Other eye disorders reported in \geq 1% of patients were photopsia (n=28, 10.7%), blurred

vision (n=16, 6.1%), vitreous floaters (n=7, 2.7%), photophobia (n=7, 2.7%), diplopia (n=6, 3.3%), dry eye (n=6, 2.3%), vitreous detachment (n=4, 1.7%), blurred vision (n=4, 1.5%), cataract (n=4, 1.5%), lacrimation increased (n=3, 1.1%), eye disorder (n=3, 1.1%), conjunctival hyperaemia (n=3, 1.1%) and asthenopia (n=3, 1.1%), with all other disorders occurring in ≤ 2 patients. Visual field defect (nervous system disorder SOC) was reported in 3 (1.1%) patients. Nearly all visual disorders were Grade 1 or 2 events.

The VSAQ-ALK questionnaire showed that the most commonly experienced visual events reported by patients were transient flashing lights. Among patients reporting an experience with a visual disturbance at each cycle, most or all reported that visual effects were not at all or a little bothersome and most or all indicated that the visual symptoms had little or no impact on activities of daily living.

Most commonly reported Grade 3 or 4 CTC adverse events

The commonly reported treatment related AEs in the pooled population (n=410) from Studies 1001 (n=149, SA) and 1005 (n=261, "mature SA") were primarily Grade 1 or 2 events. The most commonly reported Grade 3 or 4 events ($\geq 2\%$ patients) in the pooled population (n=410) were neutropenia (6.3%, n=26), ALT increased (5.4%, n=22), lymphopenia (2.7%, n=11), and AST increased (2.4%, n=10).

Mortality risks

The updated 30 day and 60 day all-cause mortality rates were 3.6% and 5.1%, respectively, in the 588 patients pooled from Study 1001 (n=149, SA) and Study 1005 (n=439, "all SA"). In the pooled population from these two studies (n=588), 71 (12.1%) patients died while on-study (within 28 days of the last dose of the study drug), and the majority of these deaths have been attributed to disease progression. In Study 1001 (n=149, SA), 22 (14.8%) deaths occurred on study and 18 of these were considered to be due to disease progression, while 1 of the remaining 4 deaths were attributed to crizotinib treatment (disseminated intravascular coagulation). In Study 1005 (n=439, "all SA"), 49 (11.2%) deaths occurred on study and 38 of these were considered to be due to disease progression, while 3 of the remaining 11 deaths were attributed to treatment with crizotinib (pneumonia, pulmonary embolus, and death due to unknown cause). In Study 1007 (n=116), crizotinib related deaths were reported in 3 (2.6%) patients in the updated SAE data (cardiac arrest and respiratory failure, interstitial lung disease, and pneumonitis).

In the updated data based on a smaller pooled population of 410 patients, there have been 62 (15.1%) on-study deaths: Study 1001 (SA), N=22/149; Study 1005 ("mature SA"), N=40/261. The causes of the 62 on study deaths were disease progression (n=50); respiratory events (n=6), including pneumonia (n=2), hypoxia (n=1), adult respiratory syndrome (n=1), pneumonitis (n=1), pulmonary haemorrhage (n=1); and other causes (n=6), including 1 each for suicide, disseminated intravascular coagulation, cardiovascular event, renal failure, infection and death due for unknown cause.

Serious adverse events

In both Studies 1001 and 1005, the majority of SAEs were considered to be unrelated to treatment. In Study 1001 (n=149, SA), all causality and treatment related SAEs occurred in 38.9% (n=58) and 6.0% (n=9) of patients, respectively. In this population, all causality SAEs were disease progression (n=15, 10.1%), pneumonia (n=8, 5.4%), pulmonary embolism (n=5, 3.4%), dyspnoea (n=4, 2.7%), syncope (n=4, 2.7%), convulsion (n=3, 2.0%), vomiting (n=3, 2.0%), anaemia (n=2, 1.3%), atrial fibrillation (n=2, 1.3%), constipation (n=2, 1.3%), deep vein thrombosis (n=2, 1.3%), haemoptysis (n=2, 1.3%), headache (n=2, 1.3%), nausea (n=2, 1.3%), nephrolithiasis (n=2, 1.3%), pleural effusion (n=2, 1.3%), pneumonitis (n=2, 1.3%) and pyrexia (n=2, 1.3%).

In Study 1005 (n=439, "all SA"), all causality and treatment related SAEs occurred in 28.7% (n=126) and 6.6% (n=29) of patients, respectively. In this population, all causality SAEs occurring in ≥ 4 (0.9%) patients were disease progression (n=28, 6.4%), pneumonia (n=19, 4.3%), dyspnoea (n=16, 3.6%), pneumonitis (n=4, 0.9%), pulmonary embolism (n=4, 0.9%), pyrexia (n=4, 0.9%) and sepsis (n=4, 0.9%), while treatment related SAEs occurring in ≥ 4 (0.9%) of patients were dyspnoea (n=4, 0.9%) and pneumonitis (n=4, 0.9%). In Study 1005 (n=261, "mature SA"), the incidences of all causality and treatment related SAEs were 34.1% (n=89) and 5.7% (n=15), respectively.

AEs resulting in permanent discontinuation

In Study 1001 (n=149, SA), 12.8% (n=19) of patients permanently discontinued treatment due to treatment-emergent AEs. These discontinuations (all causality) were primarily due to disease progression 5.4% (n=8) with the remainder being due to pneumonia 2.0% (n=3), pneumonitis 1.3% (n=2), and 1.0% (n=1) each for ALT increased, dyspnoea, hypoxia, pulmonary haemorrhage, respiratory failure and subcutaneous emphysema.

In Study 1005 (n=231, "mature SA"), 16.5% (n=43) of patients permanently discontinued treatment due to treatment-emergent AEs. These discontinuations (all causality) were primarily due to disease progression 6.9% (n=18), with other events occurring in ≥ 2 patients being disease progression 6.9% (n=18), dyspnoea 1.4% (n=4), ALT increased 1.1% (n=3), and pneumonitis 0.8% (n=2), with all other AEs occurring in 1 patient only (that is, eye disorder, abdominal pain, nausea, death, general health deterioration, cholecystitis, cytolytic hepatitis, pneumonia, pyothorax, sepsis, AST increased, hypokalaemia, completed suicide, renal failure, acute respiratory failure, atelectasis, respiratory failure and arteriosclerosis).

AEs resulting in temporary treatment discontinuation or dose reduction

In both Study 1001 (n=149, SA) and Study 1005 (n=261, "mature SA"), the risk of temporary treatment discontinuation due to treatment-emergent AEs was greater than the risk of permanent treatment discontinuation due such events. In Study 1001 (n=149, SA), treatment-emergent, all causality AEs resulting in temporary treatment discontinuation were reported in 41.6% (n=62) of patients. AEs occurring in $\geq 2\%$ of patients and resulting in temporary treatment discontinuation were neutropenia 6.0% (n=9), vomiting 4.7% (n=7), pyrexia 4.7% (n=7), pneumonia 4.0% (n=6), ALT increased 4.0% (n=6), anaemia 2.7% (n=4), nausea 2.7% (n=3), atrial fibrillation 2.0% (n=3), AST increased 2.0% (n=3), convulsion 2.0% (n=3) and syncope 2.0% (n=3). In this population, dose reductions due to treatment-emergent, all causality AEs were reported in 7.4% (n=11) of patients, and AEs resulting in dose reduction in 2 or more patients were ALT increased 4.0% (n=6), AST increased 2.7% (n=4) and neutropenia 1.3% (n=2).

In Study 1005 (n=261, "mature SA"), 33.0% (n=86) of patients had treatment-emergent, all causality AEs that were associated with temporary treatment discontinuation. In this population, AEs (all causality) resulting in temporary treatment discontinuation in ≥ 2 patients were neutropenia 6.1% (n=16), ALT increased 4.6% (n=12), pneumonia 3.8% (n=10), vomiting 3.1% (n=8), AST increased 2.3% (n=6), neutrophil count decreased 1.5% (n=4), fatigue 1.5% (n=4), oedema peripheral 1.5% (n=4), nausea 1.1% (n=3), hypokalaemia 1.1% (n=3), dizziness 1.1% (n=3), leukopenia 0.8% (n=2), visual impairment 0.8% (n=2), dysphagia 0.8% (n=2), blood creatinine increased 0.8% (n=2) and pathological fracture 0.8% (n=2). All other events associated with temporary treatment discontinuation occurred in 1 patient only. In this population, 16.1% (n=42) of patient had treatment-emergent, all causality AEs resulting in dose reductions.

Laboratory results

In both Study 1001 (SA) and Study 1005 ("mature SA"), shifts in laboratory values from CTC/AE severity Grade ≤ 2 at baseline to Grade ≥ 3 post-baseline were observed in $\geq 5\%$ of

patients (respectively) for decreased lymphocytes (16.0%, N=23/144 and 13.9%, N=35/252), hypophosphataemia (11.8%, N=17/144 and 7.5%, N=19/252), decreased neutrophils (8.3%, N=11/144 and 8.7%, N=22/252) and increased ALT (6.9%, N=10/144 and 7.9%, N=20/254). In Study 1001 (SA) shifts from Grade ≤ 2 at baseline to Grade 4 post-baseline included increased ALT and decreased lymphocytes in 2 patients each (1.4%), and decreased neutrophils in 1 patient (0.7%). In Study 1005 ("mature SA") shifts from severity Grade ≤ 2 at baseline to Grade 4 post-baseline included decreased neutrophils for 6 patients (2.4%), decreased lymphocytes for 4 patients (1.6%), increased ALT for 3 patients (1.2%) and decreased calcium, decreased platelets, increased glucose, decreased potassium and decreased sodium in 1 patient each (0.4%)

Vital signs and ECG changes

Formally assessed reductions in pulse rate and reductions in diastolic blood pressure occurred commonly in patients in both Study 1001 (n=149, SA) and Study 1005 (n=261, "mature SA"). Consequently, there are potential risks of bradycardia and hypotension in patients treated with crizotinib.

In the pooled data from Studies 1001 (SA) and Study 1005 ("mature SA"), maximum post-dose QTcF intervals of < 450, 450 to < 480, 480 to < 500, and ≥ 500 ms occurred in 89.2% (N=362/406), 8.6% (N=35/406), 1.0% (N=4/406), and 1.2% (N=5/406) of patients, respectively. In this pooled population, maximum increases in QTcF from baseline of < 30, ≥ 30 to < 60, and ≥ 60 ms were reported in 85.5% (N=329/385), 10.4% (N=40/385), and 4.2% (N=16/385) of patients, respectively. There were no reports of Torsades de Pointes in Studies 1001 or 1005. There are potential risks of QTc prolongation when crizotinib is combined with drugs known to increase the QTc interval and in patients with congenital QTc prolongation.

Patient reported outcomes

In Study 1005, there were early and maintained clinically meaningful improvements in patient reported symptoms of cough, pain, dyspnoea, pain in chest, pain in arm and shoulder, insomnia, fatigue and global quality of life. However, in the absence of a control arm these subjectively reported outcomes are difficult to interpret. Patient reported clinically meaningful worsening of symptoms of constipation and diarrhoea were also noted for some treatment cycles.

Other risks

Other notable risks associated with crizotinib include increased systemic exposure when co-administered with CYP3A inhibitors, reduced systemic exposure when co-administered with CYP3A inducers, and crizotinib mediated inhibition of the metabolism of co-administered CYP3A substrates. The development of treatment resistance to crizotinib due to mutations in the EML4-ALK gene is a potential risk but the extent of this risk will only become apparent over time.

Limitations of the safety data

There are no safety data in patients with hepatic or renal impairment. There are limited safety data in patients aged ≥ 65 years.

Second round assessment of benefit-risk balance

Overall, it is considered that the benefits of crizotinib for the treatment of ALK-positive NSCLC outweigh the risks. The submitted data are considered to have satisfactorily established clinically meaningful benefits associated with crizotinib for the treatment of locally advanced and metastatic ALK-positive NSCLC, a condition for which no other treatments have been approved. While crizotinib is associated with small, life-threatening risks of hepatotoxicity and pneumonitis, these risks are considered to be outweighed by

the benefits of treatment. Similarly, while crizotinib is associated with a number of commonly occurring risks, these are predominantly Grade 1 or 2 AEs, and appear to be manageable by temporary treatment discontinuation or dose reduction rather than permanent treatment discontinuation.

The updated data from the Day 120 CDA showed that the ORR, based on the primary analysis of investigator-assessed RECIST, was 61.5% (95% CI: 53.0, 69.5) in all patients (n=149) in the RE evaluable population in Study 1001, and 59.1% (95% CI: 52.8, 65.1) in the mature efficacy population (n=259) in Study 1005 as of the 02 January 2011 data cut-off. In the small number of previously untreated patients from Study 1005, the ORR was 68.2% ([95% CI: 45.1, 86.1]; n=15/22), which was marginally higher than for the subgroups who had received prior systemic treatment for the disease.

In both studies (1001 and 1005), the median time to response was about 6 to 8 weeks and the median duration of response was 45.5 to 49 weeks. In the updated data in the safety populations, the median PFS in Study 1001 (n=149, SA) was 9.9 months (95% CI: 95% CI: 7.7, 13.4), while in Study 1005 (n=261, "mature SA") the median PFS was 8.1 months (95% CI: 6.8, 9.7). PSF events in the two studies were reported in 55.7% (n=83) of patients in Study 1005 and 65.5% (n=171) of patients in Study 1005, with the majority of events in both studies being objective disease progression rather than death. In both studies, the median OS had still not been reached in the updated data.

There were no controlled data in Study 1001 or 1005 which make it difficult to interpret the clinical significance of the single-arm crizotinib efficacy outcomes from these studies. However, the submission includes supportive retrospective analyses comparing the efficacy outcomes from Studies 1005 and 1001 with the efficacy outcomes from historical controls. While the data from these retrospective analyses cannot substitute for data from prospective, Phase III, confirmatory, therapeutic studies, it is considered that they provide strong evidence supporting the clinical benefits of treatment with crizotinib compared with paclitaxel/carboplatin in the first-line setting, gemcitabine/cisplatin in the first line setting, erlotinib in the second/third line setting, pemetrexed and docetaxel as single-agents or in combination in first and second line settings, and pemetrexed as a single agent or in combination for any line of treatment.

The most significant risks associated with crizotinib treatment are life threatening hepatotoxicity (about 0.4%) and pneumonitis (about 1.7%). Crizotinib is also associated with a number of commonly occurring risks (predominantly Grade 1 or 2 AEs) which appear to be primarily manageable by temporary treatment discontinuation or dose reduction. These commonly occurring risks are vision disorders, nausea, diarrhoea, vomiting, oedema, constipation, dizziness, decreased appetite, fatigue, ALT increased, AST increased, dysgeusia, rash, neuropathy, oesophageal related disorders, and neutropenia.

The sponsor considers that crizotinib "continues to have a positive benefit/risk profile for the treatment of ALK-positive advanced NSCLC as a single agent" according to the updated efficacy data from Studies 1001 and 1005 and the updated safety data from Studies 1001, 1005, 1007 and 1014. In the s31 response of 27 April 2012 to the TGA, the sponsor provided statements supporting its position from the principal investigators participating in Studies 1001, 1005, 007, and 1014. One of the principal investigators stated that, in their opinion, "there are few anticancer drugs with as favourable a risk benefit ratio as crizotinib in ALK positive NSCLC". Another principal investigator stated that while waiting for the results of the Phase III studies "it would be very much in the interests of patients with ALK translocated non-small cell lung cancer to be able to have access to crizotinib following failure of standard chemotherapy. There is currently no other treatment available for these patients that is likely to make a meaningful difference to their disease, and for these patients the risk benefit ratio, in my opinion, is firmly in favour of them receiving treatment with crizotinib. Even the risk of rare and serious complications such as hepatotoxicity would not lead me to withhold treatment from these patients who

typically face a rapid and steady downhill course culminating in death from progressive cancer. By contrast, crizotinib can reduce or eliminate their symptoms and significantly prolong their life". The third principal investigator stated that his "limited experience [with patients treated with crizotinib] coupled with detailed knowledge of the published clinical study lends me to believe crizotinib has an extremely favourable therapeutic window".

In addition, the sponsor stated that its "position is further supported by an excerpt from the signed foreword to the recent European Journal of Cancer article entitled, 'ALK translocation and crizotinib in non-small cell lung cancer: An evolving paradigm in oncology drug development' (Scagliotti et al., 2012)". The excerpt follows:

Efficacy and safety data published to date for crizotinib provide evidence that this agent has a positive benefit/risk ratio in advanced ALK-positive NSCLC with rapid and prolonged responses observed. Indeed, our own clinical experience has been that it is a highly effective therapy and is well tolerated, with patients experiencing rapid improvements in symptoms specific to their condition and in their general well being. Although results to date were reported from single-arm studies, benefits were consistent from the earliest through to later analyses of the Phase I study, and in the Phase II trial. Further randomised Phase III studies of crizotinib compared with standard chemotherapy should provide further evidence of the robust efficacy outcomes reported to date.

Second round recommendation regarding authorisation

It is recommended that crizotinib be approved for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC). It should be noted that approval is being recommended for the indication proposed by the sponsor and it is recommended that the indication should not be limited to second-line treatment.

It is recommended that the following be conditions of registration:

That the final reports from

- ongoing Studies 1001 and 1005;
- ongoing Phase III studies A8081007 and A8081014;
- Phase I study A081012 designed to evaluate the effect of hepatic impairment on the PKs and safety of crizotinib after multiple dosing in patients with advanced cancer;
- the proposed, European, 3-year, multinational, post-approval database surveillance study to further characterize the safety of crizotinib in patients with pre-existing hepatic impairment in real world settings;
- Phase I Study A8081020 designed to evaluate the safety and single-dose PKs of crizotinib in subjects with severely impaired renal function;
- the planned updated population PK analysis to definitively assess the CL_{cr} effect on crizotinib PKs using pooled data from clinical trials, including but not limited to studies A8081001 and A8081005;
- the a proposed, multi-national post-approval database surveillance study in 2Q 2013 planned to collect safety data on elderly patients and long-term safety data;
- Study A8081001 Amendment #18 designed to evaluate the effect of ketoconazole (a strong inhibitor of CYP3A) and rifampin (a strong inducer of CYP3A) on the multiple-dose PKs of crizotinib;

Study A8081035 designed to study the actions of proton pump inhibitors or H₂ antagonists on the PKs of crizotinib should be submitted to the TGA for evaluation.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

The sponsor provided a summary of Ongoing Safety Concerns which are shown at Table 20.

Subject to the evaluation of the non-clinical aspects of the Safety Specification (SS) by the Toxicology area of the OSE and the clinical aspects of the SS by the OMA, the summary of the Ongoing Safety Concerns as specified by the sponsor is as follows:

Table 20. Ongoing Safety Concerns

Important identified risk:	<ul style="list-style-type: none"> • Hepatotoxicity • Pneumonitis • QTc Prolongation • Bradycardia • Vision Disorder
Important potential risks:	<ul style="list-style-type: none"> • Renal Cyst • Oedema • Leukopenia • Neuropathy • Reproductive Toxicity
Important missing information:	<ul style="list-style-type: none"> • patients with hepatic impairment • patients with renal impairment • elderly patients • pediatric patients • pregnant and lactating women • patients taking CYP3A inhibitors, inducers, P-glycoprotein substrates, proton pump inhibitors, or H2 antagonists • patients undergoing long-term treatment

OPR reviewer comment

Pursuant to the evaluation of the nonclinical and clinical aspects of the SS, the above summary of the Ongoing Safety Concerns is considered acceptable.

Pharmacovigilance plan

Proposed pharmacovigilance activities

The sponsor states that routine pharmacovigilance activities, consistent with the activities outlined in the TGA adopted guideline *Note for Guidance on Planning Pharmacovigilance Activities*⁸⁶, are proposed to monitor all the specified Ongoing Safety Concerns.

For the Important identified risk: 'Hepatotoxicity', targeted follow-up using a questionnaire to capture critical hepatic events is also proposed. However, a copy of this questionnaire was not provided.

⁸⁶3.1.2 Routine pharmacovigilance practices Note for Guidance on Planning Pharmacovigilance Activities (CPMP/ICH/5716/03). EMEA 2006

To further monitor the Important identified risk: 'QTc Prolongation' a QTc sub-study is ongoing as part of Study A8081007: [Phase III, randomised, open-label study of the efficacy and safety of PF-02341066 versus standard of care chemotherapy (pemetrexed or docetaxel) in patients with advanced non-small cell lung cancer (NSCLC) harbouring a translocation or inversion event involving the anaplastic lymphoma kinase (ALK) gene locus], with patients from Study A8081005: [Phase II, Open-Label, Single-Arm Study of the same persuasion] also eligible to participate. A final protocol was provided in Annex 5 of the RMP and the sponsor states a clinical study report (CSR) is anticipated in June 2014.

The Important identified risk: 'Vision Disorder' will continue to be evaluated and monitored in the ongoing Study A8081001, Amendment #17: Phase I safety, pharmacokinetic and pharmacodynamic study of PF-02341066, a c-Met/HGFR selective tyrosine kinase inhibitor, administered orally to patients with advanced cancer. A final protocol was provided in Annex 5 of the RMP and the sponsor states a CSR is anticipated in June 2014.

For the Important missing information: 'Patients with hepatic impairment', 'Elderly patients' & 'Patients undergoing long-term treatment', the sponsor is planning to start a 3 year multi-national post-approval database surveillance study in Europe to further characterise the safety of crizotinib in patients with pre-existing hepatic impairment and elderly patients, as well as collecting long-term safety data in real-world settings. The sponsor anticipates this study will commence in second quarter of 2013 (after crizotinib is commercially available and reimbursed in these countries) and complete data collection in second quarter of 2016. Accordingly the final study report will be submitted in 2Q 2018. The sponsor's correspondence, dated 23 May 2012, advises that a draft protocol for this study (the Prospective Multinational Active Safety Surveillance Study of Xalkori) is currently being written and is available on request by 15 June 2012.

In addition the ongoing Phase I Study A8081012 is designed to evaluate the effect of hepatic impairment on PK and safety of crizotinib in advanced cancer patients to further advise the important missing information: 'Patients with hepatic impairment'. A final protocol was provided in Annex 5 of the RMP and the sponsor states a CSR is anticipated in January 2014.

The ongoing Phase I, single dose, parallel-group Study A8081020 is designed to evaluate the single-dose PK of crizotinib in subjects with severely impaired renal function to further advise the important missing information: 'Patients with renal impairment'. A final protocol was provided in Annex 5 of the RMP and the sponsor states a CSR is anticipated in October 2012. In addition the sponsor plans to complete an updated population PK analysis to definitively assess the CL_{cr} effect on crizotinib PK using pooled data from clinical trials including but not limited to the ongoing Studies A8081001 and A8081005.

The planned open label, multi-centre Phase I dose escalation, safety, pharmacokinetic and exploratory Study A8081001 Amendment #18 (Ketoconazole and Rifampin substudies): is designed to evaluate the effect of ketoconazole (a strong inhibitor of CYP3A) and rifampin (a strong inducer of CYP3A) on the multiple-dose PK of crizotinib in advanced cancer patients to further advise the important missing information: 'Drug interaction with CYP3A inhibitors, inducers, P-glycoprotein substrates, proton pump inhibitors, or H2 antagonists'. The sponsor's correspondence, dated 23 May 2012, advises that the rifampin sub-study is likely to begin screening and enrolment in September 2012, and the ketoconazole sub-study is planned to start following the completion of the rifampin interaction sub-study. A final protocol was provided in Annex 5 of the RMP and the sponsor states a CSR is anticipated in July 2015. In addition the ongoing Phase I, single dose, randomised, cross-over Study A8081035 is designed to study the actions of proton pump inhibitors or H2 antagonists on the PK of crizotinib in healthy volunteers. A final protocol was provided in Annex 5 of the RMP and the sponsor states a CSR is anticipated in September 2013.

OPR reviewer's summary in regard to the pharmacovigilance plan (PP) and appropriateness of milestones

A copy of the targeted questionnaire used to capture critical hepatic events should be provided and included in the RMP when this document is next updated.

The draft protocol for the Prospective Multinational Active Safety Surveillance Study of Xalkori should be provided to the TGA for review if this application is approved and included in Annex 5 of the RMP when this document is next updated. The sponsor should also justify why it is anticipated to take 2 years to submit the final study report once data collection for this study has been completed.

The ongoing studies and studies with final protocols are not considered to be part of the planned clinical studies in the pharmacovigilance plan. Therefore the related study protocols will not be reviewed. Nevertheless an update on the progress/results/analysis of these studies and any retrospective analysis, as outlined in the updated RMP, will be expected in future PSURs.

For the Important missing information: 'Patients with hepatic impairment', Table 28 [in the RMP and not in the AusPAR]: 'Overall Summary of the Risk Management Plan' should be amended to indicate that the planned multi-national post-approval database surveillance study is an additional pharmacovigilance activity, not an additional risk minimisation when the RMP is next updated. This is consistent with Table 25 [in the RMP and not in the AusPAR]: 'Summary of Safety Concerns and Planned Pharmacovigilance Actions' and Table 26 [in the RMP and not in the AusPAR]: 'Detailed Action Plan for Specific Safety Concerns'.

For the Important missing information: 'Patients undergoing long-term treatment', Table 28 [in the RMP and not in the AusPAR]: 'Overall Summary of the Risk Management Plan' should be amended to include the planned multi-national post-approval database surveillance study as an additional pharmacovigilance activity when the RMP is next updated. This is consistent with Table 25 [in the RMP and not in the AusPAR]: 'Summary of Safety Concerns and Planned Pharmacovigilance Actions' and Table 26 [in the RMP and not in the AusPAR]: 'Detailed Action Plan for Specific Safety Concerns'.

Risk minimisation activities***Planned actions***

Routine risk minimisation activities will comprise labelling, including special warning and precaution statements, instructions for use, drug interactions and/or notification of undesirable effects for all the specified Ongoing Safety Concerns.

OPR reviewer comment

The sponsor's proposed application of routine risk minimisation activities would appear to be reasonable and therefore acceptable. However, for the Important missing information: 'Pregnant and lactating women', the information relating to the use of crizotinib in breastfeeding women found in Table 27 [in the RMP and not in the AusPAR]: 'Summary of Planned Actions' of the RMP should be included in Table 28 [in the RMP and not in the AusPAR]: 'Overall Summary of the Risk Management Plan' when the document is next revised.

In regard to the proposed routine risk minimisation activities, revisions to the draft product information document were recommended to the Delegate but the details of these are beyond the scope of this AusPAR.

In addition both the Nonclinical and Clinical evaluators have recommended various amendments to the draft product information.

In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the draft consumer medicine information document be revised to adequately reflect any changes made to the Australian PI as a result of the above recommendations.

Summary of recommendations

The OPR provides these recommendations in the context that the submitted RMP is supportive to the application; the implementation of a RMP satisfactory to the TGA is imposed as a condition of registration; and the submitted EU RMP is applicable without modification in Australia unless so qualified:

- The nonclinical aspects of the safety specifications in the RMP should be amended according to the recommendations of the Nonclinical Evaluator when this document is next updated.
- The extensively rewritten and updated EU RMP appears to have addressed the concerns raised by the clinical evaluator. Nevertheless final advice on the acceptability of the changes made to clinical aspects of the safety specification of the updated RMP has been sought from the OMA.
- A copy of the targeted questionnaire used to capture critical hepatic events should be provided and included in the RMP when this document is next updated.
- The draft protocol for the Prospective Multinational Active Safety Surveillance Study of Xalkori should be provided to the TGA for review if this application is approved and included in Annex 5 of the RMP when this document is next updated. The sponsor should also justify why it is anticipated to take 2 years to submit the final study report once data collection for this study has been completed.
- The ongoing studies and studies with final protocols are not considered to be part of the planned clinical studies in the pharmacovigilance plan. Therefore the related study protocols will not be reviewed. Nevertheless an update on the progress/results/analysis of these studies and any retrospective analysis, as outlined in the updated RMP, will be expected in future PSURs.
- For the Important missing information: 'Patients with hepatic impairment', Table 28: 'Overall Summary of the Risk Management Plan' should be amended to indicate that the planned multi-national post-approval database surveillance study is an additional pharmacovigilance activity, not an additional risk minimisation when the RMP is next updated. This is consistent with Table 25: 'Summary of Safety Concerns and Planned Pharmacovigilance Actions' and Table 26: 'Detailed Action Plan for Specific Safety Concerns'.
- For the Important missing information: 'Patients undergoing long-term treatment', Table 28: 'Overall Summary of the Risk Management Plan' should be amended to include the planned multi-national post-approval database surveillance study as an additional pharmacovigilance activity when the RMP is next updated. This is consistent with Table 25: 'Summary of Safety Concerns and Planned Pharmacovigilance Actions' and Table 26: 'Detailed Action Plan for Specific Safety Concerns'.
- Given the proposed indications, the target population and the likely prescribers of this medication, the sponsor's justification and conclusion that routine risk minimisation activities are sufficient for all the specified Ongoing Safety Concerns would appear to be reasonable and therefore acceptable. However, for the Important identified risk: 'Hepatotoxicity', Table 28: 'Overall Summary of the Risk Management Plan' refers to "Dosing recommendations specify for Grade 3-4 ALT or AST elevation (with total

bilirubin Grade < 2): Withhold until recovery to Grade < 1 or baseline, then resume at 200 mg twice daily;” while the draft Australian PI & EU SPC and the approved US monograph refer to a concomitant Grade < 1 total bilirubin. This summary table should be amended accordingly when the document is next revised.

- For the Important missing information: ‘Pregnant and lactating women’, the information relating to the use of crizotinib in breastfeeding women found in Table 27: ‘Summary of Planned Actions’ of the RMP should be included in Table 28: ‘Overall Summary of the Risk Management Plan’ when the document is next revised.
- In regard to the proposed routine risk minimisation activities, revisions to the PI were recommended to the Delegate.
- In addition both the nonclinical and clinical evaluators have recommended various amendments to the draft product information.
- In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the draft consumer medicine information document be revised to adequately reflect any changes made to the Australian PI as a result of the above recommendations.

VI. Overall conclusion and risk/benefit assessment

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

Quality

Registration was recommended with respect to chemistry, quality and biopharmaceutic aspects.

Nonclinical

There were no objections to registration on nonclinical grounds.

The nonclinical evaluator noted signals from *in vitro* and animal studies suggesting adverse effects in humans. Multiple organs were implicated, including: the CNS; heart; liver; gastrointestinal tract; bone marrow; eyes; and skin. Concern was raised regarding use in any paediatric population, due to the risks of growth retardation and seizures.

Clinical

The evaluator recommends approval of the proposed indication (CER2).

Table 21 shows clinical studies and some reports included in the submission. Study names are abbreviated in this document (for example, Study A8081001 is referred to as Study 1001). Key studies are ongoing and final Clinical Study Reports (CSRs) have not been submitted to the TGA. The sponsor has submitted interim reports analysing datasets that use various cut-off dates. Table 22 attempts to summarise these datasets. Thanks to this ‘incremental’ reporting, different results below are from datasets with different cut-off dates. An attempt has been made to use the most recent available reliable information.

Table 21. Key clinical studies and reports

Study name/s	Type	Brief description
A8081001 ("1001")	PK, safety, efficacy	Various interim reports. Phase I study of safety, PK, PD and antitumour activity in patients with advanced cancer. Called "Study A" in PI.
A8081005	safety, efficacy	Various interim reports. Phase II single-arm study of efficacy and safety in advanced NSCLC harbouring translocation or inversion involving the ALK gene locus. Called "Study B" in Product Information.
A8081007	safety, efficacy	<i>Ongoing randomised Phase III study. Compares crizotinib with pemetrexed or docetaxel in patients with previously treated ALK-positive advanced NSCLC. Limited SAE data submitted.</i>
A8081008	PK	Healthy volunteers; single crizotinib dose. Relative bioavailability (PIC vs IRT)
A8081009	PK	Healthy volunteers; single crizotinib dose. Single radiolabelled dose study
A8081010	PK	Healthy volunteers; single crizotinib dose. Absolute bioavailability
A8081011	PK	Healthy volunteers; single crizotinib dose. Relative bioavailability (CIC vs IRT and PIC) AND Food effect (CIC; fasting and fed states). <i>NB: CIC = commercial formulation.</i>
A8081014	safety, efficacy	<i>Ongoing randomised Phase III study. Compares crizotinib with pemetrexed plus cisplatin or carboplatin in patients with previously untreated ALK-positive advanced NSCLC.</i>
A8081015	PK	Healthy volunteers; single crizotinib dose. Interaction with steady-state ketoconazole.
A8081016	PK	Healthy volunteers; single crizotinib dose. Interaction with steady-state rifampin
PMAR-00192	PK/PD	Population PK (dataset from Studies A8081001 and A8081005)
PMAR-00224	PK/PD	Concentration-QTc in patients from A8081001 and A8081005
Technical Report	efficacy	Historical control and other retrospective analyses in advanced NSCLC using data from A8081001, data from control arms of A8501001, A8501002 and A6181087 (all three are Pfizer-sponsored studies), etc.

Table 22. Datasets for Studies 1001, 1005, 1007, 1014

	Study 1001 ALK-positive NSCLC subset of study only			Study 1005			Study 1007		Study 1014
	Preliminary CSR	60 day update	120 day update	Preliminary CSR	60 day update	120 day update	60 day update	120 day update	
<i>CER</i>	1	1	2	1	1	2	1	2	2
Number in safety population	119 ^a	136 ^b	149	136 ^a	261 ^b	439 (mature safety population 261)	71	116	19
Key efficacy populations	RE n=116		RE n=143	RE n=76	RE n=133	RE n=259 See note 'd'			
First visit	19.4.2006			7.1.2010					
Cut-off	15.9.2010	1.2.2011	1.6.2011	15.9.2010	1.2.2011	1.6.2011	1.2.2011		
Comment	Comprehensive safety data	Information on SAEs and deaths	Updated safety and efficacy data	Comprehensive safety data	Information on SAEs and deaths	Updated safety ^c and efficacy ^d data	Information on SAEs and deaths only	Information on SAEs	Information on SAEs

Study 1001 ALK-positive NSCLC subset of study only		Study 1005		Study 1007		Study 1014	
		only			only		
Further snapshots	1.11.2010	15.3.2011	29.10.2010	17.3.2011	2.1.2012	17.3.2011	See note 'e'
<p>a – a pooled population of 255 is derived from these two figures; b – used as denominator in reporting of SAEs in CER1 c – mature safety data for those 261 patients in the 60 day update (i.e. “mature safety population”); d – “mature efficacy” data in n=255 as of 1.6.2011 and n=259 as of database snapshot 2.1.2012; total (as opposed to mature) RE population of 340; e – a letter from the sponsor dated 19.6.2012 gives rudimentary efficacy information about n=347 patients in Study 1007; RE = response evaluable</p>							

Overview of clinical study data.

Study 1001 is an ongoing Phase I, single-arm, open-label trial in patients with various advanced solid tumours. Emphasis in analysis was given to subjects with ALK-positive NSCLC given 250 mg bd (n=149 in the most recent dataset provided). Most of these patients had received prior systemic treatment for advanced disease. Publications from this study are listed in CER1. The study was described by the sponsor as pivotal (before updated information from Study 1005 was presented).

Study 1005 is an ongoing, Phase II, single-arm, open-label trial in patients with ALK-positive NSCLC. All patients had received prior systemic treatment for advanced disease. The study was described by the sponsor as supportive.

There were six completed clinical pharmacology studies.

The commercial dosage form is a conventional immediate release hard gelatine capsule. Bioequivalence of the 250 mg capsule to formulations used in key trials was shown. The capsule fills for the 200 mg and 250 mg strengths are direct scales.

Pharmacokinetics (PK)

Pharmacokinetics are summarised in CER1 and briefly below.

Absolute bioavailability of crizotinib is ~43% (Study 1010). High fat food reduced C_{max} and AUC_{inf} of the commercial formulation by ~14% in healthy volunteers (Study 1011). A similarly minor effect was seen in a small food interaction sub-study within Study 1001.

Dose proportionality was assessed within Study 1001 by comparing PK results across cohorts given doses in the range 50-600 mg daily. Relative to the 400 mg daily dose, the increase in C_{max} and AUC observed with 500 mg and 600 mg daily doses was greater than expected, indicated non-linearity. The sponsor speculated this was due to auto-inhibition of CYP3A4 by crizotinib with increasing dose. Steady state was attained by Day 15 in Study 1001.

Geometric mean volume of distribution in Study 1010 was 1772 L (coefficient of variation: 18%) (CER1) and suggests extensive tissue distribution. Crizotinib is >91% bound to plasma proteins (see below). Tissue distribution was not well defined; nonclinical data suggested poor CNS penetration but otherwise high tissue distribution (for example, 20-40 times higher than blood levels in rats) and very high exposure in the eye.

Metabolism is principally via CYP3A4/5 enzymes. The most prominent circulating metabolite was crizotinib lactam (CER1); it and other metabolites are unlikely to contribute substantially to anti-tumour activity. The liver is presumably the major site of metabolism but the gastrointestinal tract and other sites have not been excluded.

Renal clearance of crizotinib is not prominent. In mass balance Study 1009, 53% of orally administered crizotinib was recovered unchanged in faeces and 2.3% was recovered unchanged in urine. Renal mechanisms are more important in excretion of crizotinib metabolites.

Drug interactions. Study 1015 (interaction with steady-state ketoconazole) indicated a 3 fold increase in single dose crizotinib AUC in the presence of CYP3A4/5 inhibition, and a 5 fold increase in crizotinib lactam exposure (suggesting greater dependence on CYP3A4/5 for metabolism of crizotinib lactam). Induction of CYP3A4 decreased crizotinib exposure (Study 1016). The proposed PI does not contraindicate concomitant use of strong CYP3A4 inhibitors/inducers, but the '*Interactions with other medicines*' section states that concomitant use should be avoided.

A sub-study of Study 1001 (involving administration of single dose midazolam before crizotinib therapy and during steady state crizotinib exposure) suggested crizotinib is a moderate CYP3A4 inhibitor.

There was some indication crizotinib can induce CYP enzymes via activation of the pregnane X receptor, but perhaps also inhibit activity of these enzymes. The clinical relevance of this finding from *in vitro* studies is uncertain.

Issues below reflect the immaturity of the clinical pharmacology dataset for crizotinib.

1. The submission did not include a PK study in patients with hepatic impairment, despite hepatic clearance being the dominant means of clearance. The sponsor proposes a Phase I study and PI statements (CER2).
2. The submission did not include a PK study in patients with renal impairment (CER2). The concern is that renal impairment may lead to a build-up of crizotinib metabolites. The sponsor's analysis of patients in Studies 1001 and 1005 (CER2) suggested relatively small increases in trough concentrations of crizotinib and its main metabolite in mild and moderate renal impairment. There were no patients with severe renal impairment in this analysis. The sponsor proposes a Phase I study, arguing that a single-dose study may still be useful in ruling out significant effects of severe renal impairment on multiple dose PK.
3. The sponsor did not include a PK interaction study between crizotinib and a P-gp inhibitor, despite *in vitro* data predicting that crizotinib may be a substrate for P-gp at therapeutic plasma concentrations (CER2).
4. The sponsor argues that gastrointestinal tract concentrations of crizotinib are much higher than the concentration at which crizotinib efflux via P-gp becomes saturated. The Non-Clinical evaluator notes that *in vitro-in vivo* correlations for predicting drug interactions involving P-glycoprotein have not been adequately validated.
5. The sponsor notes that P-gp-mediated transport "may play a role in preventing penetration of crizotinib across the normal blood-brain barrier" (CER2), based on a tissue distribution study in rats and CSF/plasma crizotinib concentrations in one ALK-positive NSCLC patient. Presumably because plasma concentrations are much lower than gastrointestinal tract concentrations of crizotinib, the sponsor notes that P-gp inhibitors may therefore alter the degree of CNS penetration of crizotinib.
6. The sponsor did not include a PK interaction study between crizotinib and a P-gp substrate, despite *in vitro* data predicting that crizotinib is likely to inhibit P-gp (CER2). Significant inhibition of a probe P-gp substrate (digoxin) was at levels higher than the mean steady-state total crizotinib C_{max} (CER2). An *in vivo* study might decide whether exposure to sole P-gp substrates (digoxin, dabigatran) is affected by concomitant crizotinib. The sponsor's argument that monitoring requirements for digoxin will not change is reasonable. The sponsor argues that patients stabilised on dabigatran should be monitored for altered response if P-gp inhibitors or inducers are added or removed. Unfortunately, "monitoring for response" is more difficult to achieve with dabigatran and the first sign of altered response may be dangerous bleeding if crizotinib does increase dabigatran exposure. Given the lack of *in vivo* data, it is safer to recommend avoiding co-administration with dabigatran.
7. The sponsor did not include formal PK interaction studies between crizotinib and gastric pH-lowering medicines (CER2). The evaluator drew attention to crizotinib's decreasing solubility with increasing pH, and noted that the population PK study PMAR-00192 found a decreased absorption rate constant in concomitant users of proton-pump inhibitors (CER1). The concern is that drugs that reduce gastric acidity (or achlorhydria) may reduce bioavailability of crizotinib. The sponsor intends to conduct a Phase I study. The sponsor notes that in Studies 1001 and 1005, 36-53% of

subjects used histamine-receptor antagonists and proton-pump inhibitors (CER2)– although efficacy analysis in these subgroups was not reported.

8. The sponsor did not comprehensively study potential induction by crizotinib of CYP2B and CYP2C enzymes (CER2). An *in vitro* CYP2B6 activity induction study has started. Although the sponsor argues that appreciable drug interactions due to induction of CYP2C9 are not anticipated, the level of induction of CYP2C9 mRNA by crizotinib is similar to induction by rifampin (CER2). Lack of effect for CYP2C19 is extrapolated by the sponsor from the supposed lack of effect for CYP2C8 and CYP2C9.
9. The nonclinical evaluator states that based on *in vitro* studies, crizotinib induces CYP2C8 and CYP2C9 at clinically relevant concentrations and concludes that “crizotinib induction of CYP2C8 and 2C9 needs to be considered as clinically relevant until adequate *in vivo* data are presented to suggest otherwise”.
10. Clinically relevant induction of CYP2B and CYP2C enzymes has not been ruled out.
11. There is contention about whether plasma protein binding to crizotinib results in a fixed unbound fraction at the *in vitro* tested concentrations 0.5, 5 and 20 μM . The 0.5 μM concentration equals 230 ng/mL (and mean steady-state C_{max} is 478 ng/mL). The clinical evaluator contests that the unbound fraction is lower (at 5.8%) at 0.5 μM than at 5 and 20 μM (f_u 10.8-11.3%) (CER1). The sponsor responds that experimental error explains this variation. Key *in vitro* results (PDM-014) follow:

Table 23. Unbound fraction (f_u) of PF-02341066 in plasma from preclinical species and humans determined using Equilibrium analysis.

Concentration (μM)	Mouse ^a	Rat ^b	Dog ^b	Monkey ^b	Human ^b
0.5	0.028 \pm 0.007	0.029 \pm 0.003	0.045 \pm 0.021	0.049 \pm 0.022	0.058 \pm 0.043
5	0.047 \pm 0.008	0.044 \pm 0.010	0.042 \pm 0.003	0.030 \pm 0.007	0.113 \pm 0.004
20	0.033 \pm 0.009	0.097 \pm 0.023	0.043 \pm 0.016	0.137 \pm 0.085	0.108 \pm 0.010
Mean (f_u)	0.036 \pm 0.010	0.057 \pm 0.036	0.043 \pm 0.001	0.072 \pm 0.057	0.093 \pm 0.031
Mean Recovery (%)	63	107	67	124	151

Note: Data presented are mean \pm SD (Mean of triplicate determinations at each concentration).

^aUsing 4 hours equilibrium time.

^bUsing 7 hours equilibrium time.

The lowest concentration tested in humans resulted in a value with high standard deviation. In PDM-014 states that “mean unbound fraction of PF-02341066 in rat, monkey, and human plasma tended to increase when concentrations increased from 0.5 to 20 μM ; however, the increase may not be significant due to the large variability observed in some cases.”

The Delegate concluded that concentration-independence has only been demonstrated satisfactorily in the 5-20 μM range (2300-9000 ng/mL, above the mean steady-state C_{max} in humans). There is a suggestion that at clinically relevant concentrations, f_u may vary with (total) crizotinib concentration, so that subjects with lower concentrations would have lower f_u .

Speculatively, this is consistent with the finding that crizotinib exposure correlates positively with ORR (see below). It is possible that in subjects with, for whatever reason, lower plasma total crizotinib concentrations, there is distinctly less free crizotinib to interact with targets in tumours. The effects of varying albumin or AAG levels are unclear.

Pharmacodynamics (PD)

Relevant exposure-response studies are referred to below.

Efficacy

Evidence of efficacy is from Studies 1001 and 1005. Table 22 helps navigate different datasets referred to in the submission and evaluation reports; the table also refers to Studies 1007 and 1014 (which contributed limited safety data and no efficacy data).

Study 1001

This ongoing Phase I study is open-label and uncontrolled, and has been subject to design modification as results have emerged (CER1).

Subjects were adults with various tumour types (not leukaemias) with a common requirement of advanced malignancy either refractory to “standard of care” therapy or without available “standard of care” therapy. Specific tumour genotype / gene expression characteristics were often required, but tumour eligibility requirements were complex (CER1).

Emphasis in analysis was given to those subjects in the study with ALK-positive NSCLC given 250 mg BD (n=149 in the most recent dataset provided; see Table 22). These patients required measurable disease according to RECIST criteria; ECOG performance status of 0, 1 or 2, and adequate organ function (CER1).

Baseline characteristics of the 149 patients with ALK-positive NSCLC in the 120 day update are summarised in CER2. Most patients had metastatic adenocarcinomas. Prior to study enrolment, all patients had undergone surgery for NSCLC, and 57.7% had received radiation therapy. Notably, 125/149 patients (83.9%) had received systemic therapy for locally advanced or metastatic disease (CER2).

Study objectives are described in CER1; one was to determine the Recommended Phase 2 dose (RP2D) and another was to assess anti-tumour activity. Efficacy assessment (CER1) was generally by the investigator using RECIST but an independent radiology review resulted in an additional efficacy analysis.

For efficacy, the response-evaluable (RE) set was analysed. This was all patients in the safety analysis (SA) set (that is, all enrolled patients who received at least one dose of crizotinib on Day 1) who had adequate baseline disease assessment (CER1).

Objective Response Rate (ORR; complete response + partial response). Results are shown in Tables 24-26 and Figure 3. At the 120 day update, the ORR was 61.5% (95% CI 53.0-69.5%) (88/143). Independent radiology review resulted in a lower ORR of 55.9%.

ORRs were similar in subgroups with 1, 2 or ≥ 3 prior lines of treatment for locally advanced or metastatic disease; also, 15/22 (68.2% of) evaluable patients without prior treatment achieved an objective response. The ORR was higher in Asians (77.1%) than non-Asians (53.5%) (CER2). Other updated efficacy endpoints are detailed in CER2.

Progression-free survival (PFS); At the 120 day update, median PFS in the SA set (n=149) was 9.9 months (see Tables 24-26 and Figure 3 below).

Overall survival (OS). At the 120 day update, median OS had not been reached after a median follow-up of 16.6 months. Probabilities of survival at 6 and 12 months were 87.9% and 74.8% respectively (see Table 10 above and Tables 24-25 and Figure 3).

Quality of life measures were not assessed.

Table 24. Progression-Free Survival, Study 1001

	Preliminary CSR (N=119)	Day 120 Clinical Data Addendum Previously Treated Patients (N=125)	Day 120 Clinical Data Addendum All Patients (N=149)
Number with event, n (%)	50 (42.0)	74 (59.2)	83 (55.7)
Type of event, n (%)			
Objective progression	40 (33.6)	60 (48.0)	67 (45.0)
Death without objective progression	10 (8.4)	14 (11.2)	16 (10.7)
Number censored, n (%)	69 (58.0)	51 (40.8)	66 (44.3)
Reason for censorship			
No adequate baseline assessment	2 (1.7)	1 (0.8)	2 (1.3)
No on-study disease assessments	4 (3.4)	3 (2.4)	4 (2.7)
Given new anticancer treatment prior to tumor progression	2 (1.7)	2 (1.6)	2 (1.3)
Unacceptable gap (>16 weeks) between PD or death to the most recent prior adequate assessment	1 (0.8)	3 (2.4)	4 (2.7)
Lost to follow-up ^a	1 (0.8)	0	0
In follow-up for progression ^b	59 (49.6)	42 (33.6)	54 (36.2)
Probability of being event free at Month 6 ^c (95% CI) ^d	71.9 (61.8, 79.7)	68.6 (59.1, 76.2)	70.0 (61.5, 77.1)
Kaplan-Meier estimates of time to event (months)			
Quartiles (95% CI) ^e			
25%	5.5 (4.4, 7.2)	5.4 (4.0, 6.5)	5.5 (4.4, 6.7)
50%	10.0 (8.2, 14.7)	9.2 (7.3, 12.7)	9.9 (7.7, 13.4)
75%	- (14.2, -)	19.4 (14.7, -)	23.9 (18.4, -)

^a Progression-free survival status of Patient 10021084 was unknown at the time of the preliminary Study 1001 CSR; this patient was reported as death (cause unknown) at the time of analysis for this Day 120 Clinical Data Addendum.

^b Includes Patient 10051009 who withdrew from treatment without PD.

^c Estimated from the Kaplan-Meier curve.

^d Derived from the CI for the log-transformed cumulative hazard function.

^e Based on the Brookmeyer and Crowley method.

Abbreviations: ALK=Anaplastic lymphoma kinase; CI=Confidence interval; CSR=Clinical study report; N/n=Number of patients; NSCLC=Non-small cell lung cancer; PD=Progressive disease; RP2D=Recommended Phase 2 dose

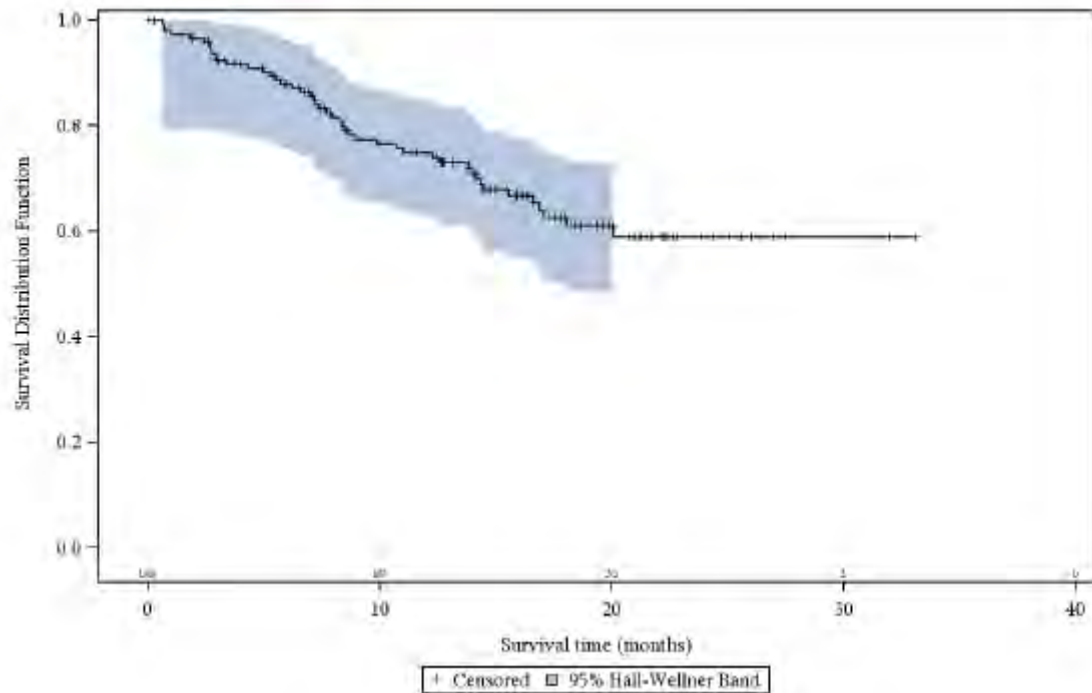
Table 25. Overall Survival, Study 1001

	Preliminary CSR (N=119)	Day 120 Clinical Data Addendum Previously Treated Patients (N=125)	Day 120 Clinical Data Addendum All Patients (N=149)
Number of deaths, n (%)	23 (19.3)	43 (34.4)	46 (30.9)
Number censored, n (%)	96 (80.7)	82 (65.6)	103 (69.1)
Patient remains on follow-up	94 (79.0)	80 (64.0)	101 (67.8)
Patient no longer being followed	2 (1.7) ^a	2 (1.6)	2 (1.3)
Median OS, months (95% CI)	NR	NR	NR
6-month Survival Probability, % (95% CI)	90.0 (82.7, 94.4)	87.5 (80.1, 92.3)	87.9 (81.3, 92.3)
1-year Survival Probability, % (95% CI)	80.5 (70.9, 87.2)	72.3 (62.9, 79.7)	74.8 (66.4, 81.5)

^a Includes Patient 10021084, who was lost to follow-up at the time of the preliminary Study 1001 CSR; this patient's death was subsequently reported and included in this update.

Abbreviations: ALK = Anaplastic lymphoma kinase; CI = Confidence interval, CSR = Clinical study report; N/n = Number of patients; NR = Not reached; NSCLC = Non-small cell lung cancer; OS = Overall survival; RP2D = Recommended Phase 2 dose

Figure 3. Kaplan Meier Plot of Overall Survival for all ALK positive NSCLC patients in the RP2D cohort of Study 1001. Safety Analysis Population.



Curve refers to 120 day clinical update population (n=149)

Study 1005

This ongoing, open-label, single-arm, Phase II study enrolled subjects with advanced (locally advanced or metastatic) NSCLC with translocation or inversion involving the ALK gene locus. All patients had failed at least 1 line of chemotherapy for NSCLC.

There were 439 subjects in the most recent dataset provided (see Table 22). Subjects were given crizotinib 250 mg BD on a continuous dosing schedule, without regard to meals.

In the “all patients” (n=439) dataset, mean age was 53.0 years (range 19-83). Baseline subject and tumour characteristics are described in CER2. Notably, 402/439 (91.6%) of subjects had adenocarcinoma (consistent with most ALK fusion events being observed in adenocarcinoma subtypes of NSCLC); and 91.1% had metastatic disease. 92.7% of patients had undergone surgery, 59.2% had received radiotherapy and 85.9% had received 2 or more prior systemic treatments (commonly platinum-based therapy or EGFR tyrosine kinase inhibitors) (CER2).

The primary efficacy endpoint was ORR, based on investigator assessment of tumour data. In the 120 day update (snapshot 2.1.2012), the response-evaluable population was 340 (out of 439 subjects who had received at least 1 dose of crizotinib), however emphasis was given to n=259 with ‘mature’ efficacy data.

Objective response rate. Results are shown in Tables 26-27 and Figure 4. In the 120 day update, based on the “mature efficacy” population (n=259; CER2), the ORR was 59.1% (95% CI 52.8-65.1%). There were 4 complete responses (1.5%), although it seems only 2/4 were confirmed by independent radiology review, and 149 partial responses (57.5%). Using other datasets, the ORR was different and as low as 45.9% in the “all response evaluable” population (n=340; CER2).

Progression-free survival. In the 120 day update, PFS data were presented for the “mature safety” population (n=261; CER2). At the 2.1.2012 snapshot, median PFS was 8.1 months (95% CI 6.8-9.7 months) (Tables 26-27 and Figure 4). This is lower than in Study 1001.

Overall survival. Median OS has not been reached (Tables 26-27 and Figure 4). Probabilities of survival are estimated to be 84.6% at 6 months and 61.6% at 12 months (CER2).

Patient-reported outcomes in Study 1005 are discussed in CER2; global quality of life was improved for a period after 12 weeks on treatment (that is, from 'Cycle 4'), but this improvement was not consistently maintained.

Efficacy results, Study 1005 (ALK-positive NSCLC)

Table 26. Objective Response Rate, Study 1005

Efficacy Parameter	First Clinical Data Addendum CSR-SA RE Population N=133	Day 120 Clinical Data Addendum Mature Efficacy Population N=255	Day 120 Clinical Data Addendum All RE Patient Population N=340
Best Response, n (%)			
Confirmed CR	1 (<1.0)	4 (1.6)	4 (1.2)
Confirmed PR	67 (50.4)	132 (51.8)	152 (44.7)
SD for at least 6 weeks	45 (33.8)	80 (31.4)	129 (37.9)
PD	10 (7.5)	18 (7.1)	26 (7.6)
Early death ^a	5 (3.8)	12 (4.7)	16 (4.7)
Indeterminate ^b	5(3.8)	9 (3.5)	13 (3.8)
ORR (CR + PR), n (%)	68 (51.1)	136 (53.3)	156 (45.9)
[95% CI]	[42.3, 59.9]	[47.0, 59.6]	[40.5, 51.3]
TTR Median, weeks (Range)	6.1 (5.1 - 24.3)	6.1 (4.9 - 30.4)	6.1 (4.9 - 30.4)
N (%) with PD or Death after Response	14/68 (20.6)	35/136 (25.7)	35/156 (22.4)
n/N of responders (%)			
DR Median weeks (Range), Kaplan-Meier Estimate, [95% CI]^c	12.8 [7.1, 41.9]	42.9 [36.1, 49.7]	42.9 [36.1, 49.7]
DCR (CR+PR+SD) at 6 weeks, % (n) [95% CI]	85.0 (113) [77.7, 90.6]	84.7 (216) [79.7, 88.9]	83.8 (285) [79.5, 87.6]
DCR (CR+PR+SD) at 12 weeks, % (n) [95% CI]	73.7 (98) [65.3, 80.9]	74.5 (190) [68.7, 79.7]	60.0 (204) [54.6, 65.2]

^a Early death was death within 42 days (6 weeks) from first dose of crizotinib

^b Indeterminate = patients having available on-study scans that could not be evaluated or patients who discontinued prior to obtaining adequate scans to evaluate response

^c DR from the first Clinical Data Addendum is the median duration and range of observed values (a descriptive statistic); DR for this Day 120 Clinical Data Addendum is the Kaplan-Meier estimate.

Abbreviations: CI = Confidence interval; CR = Complete response; CSR = Clinical study report; DR = Duration of response (a descriptive statistic); DCR = Disease control rate; N/n = Number of patients; ORR = Objective response rate;

PD = Progressive disease; PR = Partial response; RE = Response evaluable; SA = Safety Analysis; SD = Stable disease;

TTR = Time to tumor response

Table 27. Progression-Free Survival, Study 1005

	Day 120 Clinical Data Addendum Mature Safety Population (as of 01 JUN 2011) (N=261)	Day 120 Clinical Data Addendum Mature Safety Population (as of 02 JAN 2012) (N=261)
Number with event, n (%)	109 (41.8)	171 (65.5)
Type of event, n (%)		
Objective progression	83 (31.8)	142 (54.4)
Death without objective progression	26 (10.0)	29 (11.1)
Number censored, n (%)	152 (58.2)	90 (34.5)
Reason for censorship		
No adequate baseline assessment	6 (2.3)	2 (<1.0)
No on-study disease assessments	2 (0.8)	1 (<1.0)
Given new anticancer treatment prior to tumor progression	3 (1.1)	3 (1.1)
Unacceptable gap (>16 weeks) between PD or death to the most recent prior adequate assessment	0	3 (1.1)
Lost to follow-up		
Withdrew consent for follow-up	1 (0.4)	1 (<1.0)
In follow-up for progression	1 (0.4)	4 (1.5)
	139 (53.3)	76 (29.1)
Probability of being event free at Month 6 ^a (95% CI) ^b	59.7 (52.4, 66.2)	59.8 (53.4, 65.5)
Kaplan-Meier estimates of time to event (months)		
Quartiles (95% CI) ^c		
25%	4.2 (3.9, 5.3)	4.1 (3.8, 5.3)
50%	8.5 (6.5, 9.9)	8.1 (6.8, 9.7)
75%	12.5 (11.1, -)	16.0 (13.7, -)

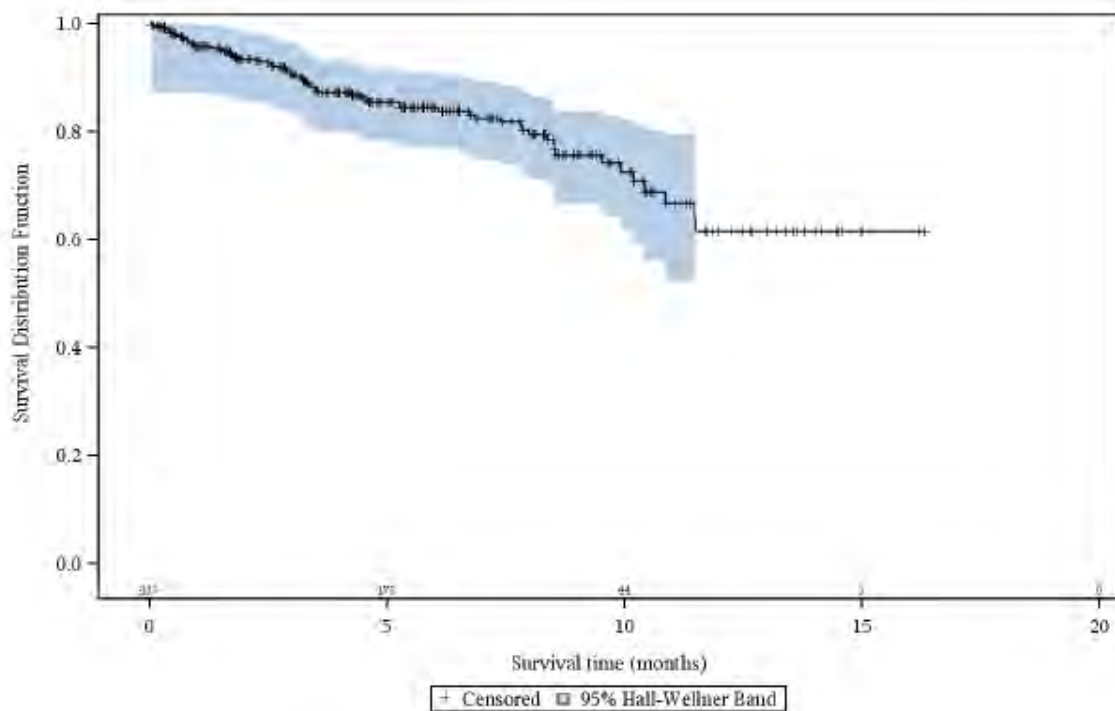
^a Estimated from the Kaplan-Meier curve.

^b Derived from the CI for the log-transformed cumulative hazard function.

^c Based on the Brookmeyer and Crowley method.

Abbreviations: CI = Confidence interval; N/n = Number of patients; PD = Progressive disease

Figure 4. Overall Survival, Study 1005. Kaplan-Meier plot of Overall Survival for patients in Study 1005. All patients-Safety Analysis Population.



(1.6.2011, 120 day clinical update)

Study 1007

This ongoing Phase III open-label study randomises patients with ALK-positive advanced NSCLC to crizotinib or standard of care (pemetrexed or docetaxel); patients had been previously treated for advanced disease. On 19 June 2012 the sponsor communicated to TGA two paragraphs of relevant information regarding efficacy in this study:

- The Phase III Study A8081007 demonstrated a statistically significant improvement in the primary efficacy endpoint of progression-free survival (PFS) for crizotinib over chemotherapy (approximately 60% of patients received pemetrexed) as determined by independent radiology review in 347 patients with previously treated advanced NSCLC whose tumours harbour ALK gene rearrangements.
- The numbers of survival events are currently too limited to draw firm conclusions on the secondary efficacy endpoint of overall survival (OS).

The study has not been evaluated, and the information above is not helpful beyond providing vague reassurance regarding the promise of crizotinib.

Historical control analyses

In lieu of controlled trials, the sponsor provided various analyses of historical controls.

Covariate- matching and modelling using Study 1001 (CER1). Control arms of three Pfizer-sponsored Phase III studies of advanced NSCLC were used (CER2). The control arms received paclitaxel / carboplatin (Study 1), gemcitabine / cisplatin (Study 2) and erlotinib (Study 3). While Study 1001 was a study of patients who had generally received prior systemic therapy for advanced disease, historical Studies 1-2 were of first-line treatment of advanced NSCLC (only Study 3 was of second- or third line treatment).

There were major imbalances for known prognostic factors in NSCLC across Study 1001, the control arms of the three Pfizer-sponsored studies, and studies reported in the literature (CER1), such as age, smoking status (suggesting imbalances in smoking-related

co-morbidities) and presence of metastatic disease. Imbalances favoured better outcomes in Study 1001 (for example, Study 1001 patients were younger and had smoked less).

Two approaches were used by the sponsor to control for these imbalances: covariate matching and covariate-adjusted modelling (CER1).

Covariate matching attempted to 'match' patients in Study 1001 with patients from Pfizer Studies 1-3 (CER1), based on various characteristics, then compare outcomes across matched patients.

The ORR for crizotinib (61.2%; Study 1001) was notably higher than ORRs in matched patients in Pfizer Studies 1-3 (CER1). Median PFS was also better with crizotinib. OS could not be compared directly, but median OS in historical Pfizer studies ranged from 9.3 to 15.9 months while median OS has not been reached with crizotinib in Study 1001 despite median follow-up of 11 months (16.6 months by the 120 day update). There was no indication from literature presented by the sponsor that historical outcomes have been any better elsewhere (although the strategy used by the sponsor to examine the literature in this regard was not clear).

Covariate-adjusted modelling attempted to predict efficacy outcomes of the 116 response-evaluable subjects in Study 1001 (Preliminary CSR) assuming patients had been treated as per control arms of Pfizer Studies 1-3 (CER1). Results (CER1) were similar to results of the covariate matching exercise, i.e. crizotinib's outcomes were notably better than the outcomes after paclitaxel/carboplatin, gemcitabine/cisplatin or erlotinib.

Covariate matching and modelling for Study 1005. The sponsor provided analogous retrospective analyses using Study 1005 (CER2). Outcomes were in keeping with those described above.

Historical comparison with pemetrexed/docetaxel. The sponsor compared median PFS and median time to progression (TTP) from the start of crizotinib therapy in Study 1005 (n=439) with PFS and TTP from start of prior pemetrexed or docetaxel therapy (as received earlier in each patient's history of treatment for advanced NSCLC; CER2).

Analysis 1 included 287 subjects in Study 1005 who had earlier received pemetrexed and/or docetaxel as first line and / or second line agents. Analysis 2 included only a subset of Analysis 1 subjects, namely, the 117 subjects who had earlier received either pemetrexed or docetaxel as a second line single agent. Analyses 1 and 2 examined PFS (or TTP) at different points in an individual patient's treatment history (comparison was 'across lines' within a given subject). Analysis 3 included the subjects from Analysis 2 and separate Study 1005 subjects who received crizotinib as a second line single agent (comparison was 'across subjects' for second line treatment). Doses for pemetrexed/docetaxel were not captured by the sponsor.

Results are shown in CER2. They are uniformly supportive of crizotinib. A published paper by Salgia et al (2012)⁸⁵ covered similar ground (CER2).

Relationship between exposure and efficacy

A preliminary exposure-response analysis based on Studies 1001 and 1005 was provided (CER2). This suggests high exposure is associated with higher ORR. There was a trend towards higher exposure being associated with longer PFS, but the relationship was not statistically significant. The correlation with OS was not studied due to "limited data".

Potential for resistance

Thirty-six lung cancer patients from Studies 1001 and 1005 had biopsies at disease progression, allowing assessment of potential mechanisms of resistance to crizotinib (CER2). ALK secondary point mutations have been identified in 11/36 cases, with each specific mutation shown to confer crizotinib resistance by *in vitro* assays. Other resistance

pathways may be involved (such as increased ALK copy number or mutation in EGFR or KRAS).

Safety

Exposure

The number of patients exposed to crizotinib is indicated per study in Table 22. Exposure of “at least 1400 patients” to crizotinib has been mentioned (CER1), but this is in relation to an update received by the TGA on 3rd January 2012 concerning further cases of hepatotoxicity. There is no general safety information for these 1400 subjects.

At the 120 day update for Study 1001 (n=149), median duration of treatment was 43.1 weeks. At the 120 day update for Study 1005, median duration of treatment was 24.6 weeks in the “mature safety” population (n=261) and 15.7 weeks in the “all patients” population (n=439) (frequencies of AEs in this latter population may be underestimates for those AEs with delayed onset).

Some other safety data are from non- ‘ALK-positive NSCLC’ patients (n=85) or from healthy volunteers (n=110) (CER1). In addition, SAE data from some ALK-positive NSCLC patients in Studies 1007 and 1014 were provided from a database snapshot.

Hepatotoxicity

Crizotinib produces elevated transaminases in a large fraction of subjects; a small fraction has serious (even fatal) hepatic injury. Hepatotoxicity is discussed in CER1 and in CER2.

Elevated transaminases. In Study 1001, ALT increase (all cause, all grade) was reported in 17.4% of subjects (26/147), and AST increase in 14.1%. Grade 3-4 AEs were reported in 7.3% and 4.7% respectively. In Study 1005 (with shorter duration of exposure), ALT increase was reported in 13.2% (58/439); 4.3% of all subjects had Grade 3-4 increases. Grade 3-4 AST increases were reported in 1.6%. Summarised LFT abnormalities for Studies 1001 and 1005 are in CER2.

Median time to onset for ALT increases in Study 1001 was 22 days and in Study 1005 was 31.5 days (values not based on most recent datasets; CER1). Onset of LFT abnormalities can be after limited exposure: in the single dose Study 1011, a healthy volunteer was permanently discontinued due to ALT >5 x ULN and AST >2.5 x ULN. Elevated ALT was more common in women and in non-Asians (CER1).

Serious hepatic injury. Five cases of significant hepatic injury with crizotinib were singled out by the clinical evaluator (CER1). In two of these cases, death resulted from hepatic failure. Of the five cases, four (including the two fatal cases) were observed within 2 months of starting crizotinib treatment. Presenting symptoms included anorexia and fatigue.

A frequency of 0.4% (5/1399) is quoted for crizotinib-related hepatotoxicity (that is, either meeting Hy’s Law⁸⁷ or fatal but not meeting Hy’s Law). This frequency does not take into account duration of exposure; it is likely that many of the 1399 subjects making up the denominator will not have taken crizotinib for long. On the other hand, as noted, 4/5 significant cases were observed within 2 months of treatment onset.

Crizotinib inhibits c-Met, a growth factor that plays a role in liver regeneration (CER). Hepatotoxicity may be magnified after other liver injuries (from for example other drugs and infections).

⁸⁷<<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf>>

GI disturbance

Nausea and vomiting. In Studies 1001 and 1005, nausea (all cause, all grade) was reported in 56.4% (84/149) and 49.4% (217/439) of subjects, respectively. Vomiting was reported in an only slightly lower fraction. Most of these reports were considered treatment related.

In Study 1005, there was pre-specified guidance on how to manage nausea and vomiting (CER1). Therefore, incidence of vomiting may be despite best supportive care in this regard. The clinical evaluator notes that in Study 1001 prevalence of nausea decreased after the first 'cycle' of treatment (that is, 4 weeks) but remained around 27-32% thereafter (CER1). Likewise, prevalence of vomiting fell substantially after Cycle 1.

Diarrhoea and constipation. In Studies 1001 and 1005, all-cause / all-grade diarrhoea was commonly reported (49.7% and 39.4%), as was constipation (~30%). These events were commonly considered treatment related. Diarrhoea was more common in Asian subject (CER1). Diarrhoea and constipation were both identified as problems in patient-reported outcome analyses (CER2).

Decreased appetite. In Studies 1001 and 1005, decreased appetite (all cause, all grade) was reported in 16.1% and 20.7% of subjects. This was commonly considered treatment related.

Oesophageal disorders. Oesophageal ulceration was reported once as a treatment related serious AE in Study 1001. Clustered terms describing treatment related oesophageal disorders were reported in 27/149 (18.1%) of Study 1001 subjects (CER2). In Study 1005, dysphagia was reported as a grade 3-4 AE in 0.9% (4/439). There has been an SAE of oesophagitis reported in Study 1014 (CER2).

Nausea and vomiting tended to start early (median 2 days in Studies 1001 and 1005 based on earlier datasets; CER1). Diarrhoea had a median time to onset of 2 days in Study 1001 and 14.5 days in Study 1005. Oesophageal disorders had a median onset in Study 1001 of 42 days (n=13) and in Study 1005 of 10.5 days (n=6). Vomiting tended to be relatively protracted (median duration 17.5 days in Study 1001).

Cardiac disturbance

QT prolongation. A PK/PD analysis (PMAR-00224) assessed the effects of crizotinib exposure on corrected QT interval (QTcS, a study-specific correction that was considered to outperform QTcB and QTcF). It revealed an expected increase in QTcS of 0.7 ms per 100 ng/mL increase in crizotinib concentration. At the mean steady-state C_{max} of 478 ng/mL, predicted increase in QTcS was 3.4 ms (90% CI 0.9-5.8 ms). This was higher using QTcF and in the Asian sub-group (CER1).

In Study 1001, QTcF \geq 500 ms was observed in 1/147 subjects, and change from baseline of \geq 60 ms in 3.0% (CER2). In Study 1005, treatment related Grade 3-4 QT prolongation was reported in 2/259 (mature efficacy set). QTcF \geq 500 ms was observed in 4/259 subjects, and change from baseline of \geq 60 ms in 12/250 (4.8%).

Vomiting is a concern with crizotinib, and in Study 1005, Grade 3-4 hypokalaemia was reported in 1.6% (7/439). Bradycardia (see below) and hypokalaemia are risk factors for ventricular arrhythmias in the context of drug induced QT prolongation.

Ongoing Study 1007 includes a dedicated ECG sub-study in 40 patients (CER2).

Bradycardia. The PK/PD analysis PMAR-00224 assessed the effect of crizotinib exposure on heart rate. It revealed an expected decreased in heart rate of 4 bpm per 100 ng/mL increase in crizotinib concentration. Estimated decrease in heart rate at mean steady-state C_{max} of 478 ng/mL after crizotinib 250 mg BD (Study 1001) was 15.9 bpm (CER1).

About 40% of subjects in Studies 1001 and 1005 had a maximum decrease from baseline of $>$ 30 bpm (versus $<$ 6% with a maximum increase of $>$ 30 bpm). There were some reports

of treatment related hypotension. Dizziness (for whatever reason) was commonly reported.

Pneumonitis

In a pooled Study 1001 and 1005 population as of 1.6.2011 of n=588, 16 subjects (2.7%) had pneumonitis-like events of any causality, including 10 (1.7%) with pneumonitis.

In an earlier dataset (pooled population n=397), the four cases of pneumonitis reported as an SAE had times to onset of 6, 12, 18 and 53 days. One of these cases resulted in death.

In Study 1007 (60 day SAE update in 71 patients), a subject died of drug induced interstitial lung disease and another, after the update cut-off, due to drug induced pneumonitis.

An 'independent review committee' drew parallels to gefitinib- and erlotinib-induced pneumonitis, also noting a possible interaction between crizotinib and radiation pneumonitis.

Vision disorders

In animal studies, crizotinib exposure in the eye and uveal tract was >1000 times that in blood, and elimination from these tissues was very slow ($t_{1/2}$ >500 hours).

Clustered terms describing vision disorder were reported in 98/149 (65.8% of) subjects in Study 1001 and 155/261 (59.4% of) subjects in Study 1005; most were treatment related.

Median time to onset of vision disorders was 13 days in Study 1001 and 7 days in Study 1005 (earlier dataset; CER1). Most events were Grade 1. Specific ophthalmological assessment in 20% of patients in Study 1005 found little pathology (CER2). In Study 1005, the VSAQ-ALK questionnaire suggested that the most commonly experienced visual event was the appearance of flashing lights, generally lasting less than a minute, and generally not impacting on activities of daily living (CER2). Visual acuity was not markedly affected in the fraction of subjects where this was assessed (CER2).

In the 120 day update of Study 1005, there was a report of permanent discontinuation of crizotinib due to "eye disorder"; 2/261 patients in the "mature safety" dataset temporarily suspended treatment due to visual impairment.

Neutropenia and lymphopenia

Neutropenia. Logistic regression modelling suggested a higher risk of neutropenia with higher crizotinib exposure (CER2). It is unclear how dose modification due to significant neutropenia affected this modelling.

In earlier datasets for Studies 1001 and 1005, Grade 3-4 neutropenia was reported in 3.4% and 4.2% (all cases were treatment related; one case in Study 1005 was febrile neutropenia). Median time to onset was 197 days in Study 1001 and 64 days in Study 1005.

In the 120 day update for Study 1001, incidence of Grade 3-4 treatment related neutropenia had risen to 6% (9/149). None of the nine subjects had started crizotinib lately. This is consistent with long median time to onset and suggests a cumulative toxicity issue. However, neutrophil half-life is <1 week. In all 9 subjects, only temporary treatment discontinuation was required but it is not clear whether sufficient time had elapsed in each case before the 120 day update cut-off date to capture any positive rechallenges. Similarly, in Study 1005, at the 120 day update, incidence of Grade 3-4 treatment related neutropenia had risen to 6.5%.

A possibility is that crizotinib affects neutrophil precursors; c-Met has a role in proliferation of myeloid progenitor cells in the bone marrow.

Regarding consequences of neutropenia, significant pneumonias were commonly reported but in a cohort with advanced lung cancer, this is difficult to interpret in the absence of a comparator arm. Many other types of infection were reported (CER1).

Lymphopenia was a prominent laboratory abnormality (CER1 and CER2). Interestingly given the findings with neutropenia above, in the initial dataset with a shorter median duration of exposure, the incidence of worsening lymphopenia was 11.6% but in the 120 day update the incidence was 16.0%. There was a similar progression in Study 1005.

Other significant AEs

Fatigue (all-cause, all-grade) was reported in ~30% of patients in Studies 1001 and 1005, and in the majority of cases was considered treatment related. There were trends towards *less* fatigue with increasing exposure to crizotinib, in a logistic regression modelling analysis (CER2). Also, improvements in patient-reported fatigue were noted quite consistently from cycle 4 onwards in Study 1005 (CER2).

Peripheral oedema was common in Studies 1001 and 1005 (36.9% and 31% of patients, respectively, reported all-cause, all-grade peripheral oedema). Three-quarters of reports were considered treatment related. Grade 3-4 hypoalbuminaemia was reported in 1.6% of subjects (7/439) in Study 1005. Median time to onset of oedema was 74 days in Study 1001 and 47 days in Study 1005; in keeping with this, prevalence increased after cycle 1 in Study 1001. Peripheral oedema was more common in women (CER1). In Study 1001's 120 day update it was noted that maximum increases in body weight of >10% were more common than maximum decreases in body weight of >10% (26.0% versus 8.7%)—oedema could be one of several explanations for this finding.

Dizziness/syncope. Dizziness was common in Studies 1001 and 1005 (33.6% and 21.1% of patients reported all-cause, all-grade dizziness); two-thirds of reports were considered treatment related. Dizziness was more common in women (CER1). In Study 1001, there were 4 SAEs of syncope (2.7%; all Grade 3-4), maybe relevant for a QT-prolonging/bradycardia-inducing medicine however, the clinical evaluator found no suggestion of a primary cardiac cause for these cases of syncope (CER1).

Seizures. In Study 1001, convulsion was an SAE in 2.0%. There may be a seizure risk in patients with a compromised blood-brain barrier or in the event of co-administration with a P-gp inhibitor (via inhibition of the neuronal Nav1.1 sodium channel).

Neuropathy. In Study 1001, clustered terms describing treatment related neuropathy were reported in 29/149 (19.5% of) subjects. In Study 1005, the frequency was similar. Median time to onset of neuropathy was 57 days in Study 1001 and 36 days in Study 1005 (using earlier datasets); its median duration in Study 1001 was 188 days.

Hypophosphataemia. By the 120 day update for Study 1001, grade 3-4 treatment related hypophosphataemia had been reported in 6/149 (4%); phosphate wasting may be seen with drug induced proximal tubular dysfunction.

Drug interactions

Interactions with CYP3A4 inhibitors/inducers/substrates are likely (see *Pharmacokinetics*). In logistic regression modelling, patients also using CYP3A inducers (mainly corticosteroids) were more likely to have low crizotinib exposures (CER2).

Strong CYP3A inhibitors / inducers and CYP3A substrates with narrow therapeutic indices were not allowed in Studies 1001 and 1005 (CER2). About 22-31% of patients in these studies used (other) CYP3A inducers and inhibitors.

Some other potential drug interactions have not been ruled in or out (see PK above).

Study 1007

On 19 June 2012 the sponsor communicated to TGA two paragraphs of potentially relevant but very limited information regarding safety in this study:

- The adverse event observed on crizotinib and chemotherapy in Study A8081007 were generally consistent with their respective known adverse event profiles, although there were treatment related adverse events in the crizotinib arm that were observed with higher frequency and severity than previously reported.
- All-causality and treatment related Grade 5 adverse events, including disease progression at any time on study, were numerically higher in the crizotinib arm than in the chemotherapy arm, although the incidence of treatment related Grade 5 adverse events was low and comparable to what has been previously observed for crizotinib.

Risk management plan

The proposed RMP was found generally acceptable by the TGA's Office of Product Review.

Risk-benefit analysis**Delegate's considerations****Issues***Pharmacology*

Clinical pharmacology studies are absent in some important areas, for example use in hepatic impairment and some drug interactions (see PK above). A precautionary approach is required with regard to potential drug interactions, until promised studies eventuate.

Efficacy

The clinical evaluator considers that efficacy data *do* support registration despite the absence of a Phase III, randomised, controlled study with OS or PFS outcomes (CER2).

Study design. The efficacy evidence in this submission was from an ongoing Phase I study and an ongoing Phase II study, both open-label and single-arm. Bias from the open-label design was limited to an extent by use of independent radiological review, which produced outcomes usually slightly worse than investigator-assessed outcomes. The absence of control arms was addressed 'up to a point' by inclusion of extensive historical comparisons. These were hampered, despite statistical adjustment, by major imbalances in prognostic factors.

Endpoints. The TGA-adopted EU Guideline on the Evaluation of Anticancer Medicinal Products in Man discusses choice of endpoints to support claims of efficacy; OS and PFS are preferred over ORR. In Studies 1001 and 1005, ORR outcomes were 'impressive' given the patient population. There were a handful of complete responses, but the large majority of responses were partial. Given crizotinib's undoubted toxicity, there is a risk that ORR benefits will not translate to PFS or OS benefits. The limited PFS and OS data provided some reassurance that this will not be the case.

Ongoing studies. Two Phase III studies are ongoing; see Table 21.

Safety

A key concern is life-threatening hepatotoxicity; there have been fatalities. Regular Liver function test (LFT) monitoring is warranted although it may not prevent all cases of drug induced liver injury (CER1). The proposed PI addresses this issue.

Another key concern is pneumonitis; there have been fatalities. The proposed PI addresses this issue.

Crizotinib prolongs the QT interval and can cause electrolyte disturbances and bradycardia. Other risk factors for arrhythmias will be common in patients. Although QT prolongation is not a strong surrogate for risk of ventricular arrhythmias, crizotinib should be used with caution in patients with a high overall risk, given the relative immaturity of the clinical data package. The proposed PI addresses this. For bradycardia, see Attachment 4 (not in this AusPAR).

Another concern is that significant neutropenia/lymphopenia may become more prominent with increasing duration of exposure.

Many other adverse effects are common, difficult to manage or both (such as vomiting).

There are no safety data in patients with severe hepatic or severe renal impairment.

Risk-benefit and indications

PFS data (and OS data, although immature) suggest that the safety concerns outlined above do not outweigh the promising efficacy of crizotinib in the studied population. This population was predominantly a 'second- or subsequent- line' indication.

The Delegate considered that crizotinib's risk-benefit balance is positive for the indication proposed by the sponsor, namely "treatment of patients with anaplastic lymphoma kinase (ALK) positive advanced non-small cell lung cancer (NSCLC)". This view is supported by the clinical evaluator (CER2).

This position appears to place considerable weight on a very small number of patients in Study 1001 for whom crizotinib was first-line therapy. Amongst these 22 patients, an objective response was achieved in 15 (with no complete responses). PFS and OS outcomes appeared to be comparable between the 24 first-line subjects in the safety dataset and the 125 second- or subsequent- line patients (Tables 24-26 and Figure 3).

Numbers are too small to be sure that outcomes are comparable across first and subsequent line patients but given (a) the generally poor prognosis of patients with advanced NSCLC, (b) the suggestion of comparable PFS / OS outcomes in the small 'first-line' subset and the 'subsequent-line' majority, (c) the strong suggestion from historical comparisons that crizotinib may offer some improvement in clinically relevant treatment outcomes in 'subsequent-line' treatment, and (d) access in the PI to relevant information about the toxicity of crizotinib, it seems reasonable to make crizotinib available for first-line treatment.

An alternative approach would be to restrict approval to second-line treatment of ALK-positive advanced NSCLC, in the knowledge that the sponsor is generating data regarding efficacy in first-line treatment (Study 1014).

Most subjects in Studies 1001 and 1005 had adenocarcinomas and for some other NSCLC treatments, efficacy against NSCLC of squamous cell histology could not be shown. Given the apparent mechanism of action, it seems reasonable to include all ALK-positive NSCLC in the crizotinib indication.

It is clear that the overall clinical dataset is limited in scope (see *Specific conditions of registration* below) but it may still be appropriate to register crizotinib for the identified patient population.

Product information (PI)

A description of the recommended changes to the PI are beyond the scope of this AusPAR.

Specific conditions of registration

Selected conditions of registration the Delegate intend to impose are:

- Final reports from ongoing Studies A8081001 and A8081005 should be submitted as soon as possible to the TGA for evaluation.
- The final reports from ongoing Phase III studies A8081007 and A8081014 should be submitted as soon as possible to the TGA for evaluation.
- The final report from Phase I Study A8081012 designed to evaluate the effect of hepatic impairment on the PK and safety of crizotinib after multiple dosing in patients with advanced cancer should be submitted as soon as possible to the TGA for evaluation.
- The final report from the proposed, European, 3-year, multinational, post-approval database surveillance study to further characterize the safety of crizotinib in patients with pre-existing hepatic impairment in a real-world settings should be submitted as soon as possible to the TGA for evaluation.
- The final report from Phase I Study A8081020 designed to evaluate the safety and single-dose PK of crizotinib in subjects with severely impaired renal function should be submitted as soon as possible to the TGA for evaluation.
- The final report of the planned updated population PK analysis to definitively assess the CL_{cr} effect on crizotinib PK using pooled data from clinical trials, including but not limited to Studies A8081001 and A8081005, should be submitted as soon as possible to the TGA for evaluation.
- The final report of the a proposed, multi-national post-approval database surveillance study planned to collect safety data on elderly patients and long-term safety data should be submitted as soon as possible to the TGA for evaluation.
- The final report of Study A8081001 Amendment #17 (vision disorder substudy) should be submitted as soon as possible to the TGA for evaluation.
- The final report of Study A8081001 Amendment #18 designed to evaluate the effect of ketoconazole (a strong inhibitor of CYP3A) and rifampin (a strong inducer of CYP3A) on the multiple-dose PK of crizotinib should be submitted as soon as possible to the TGA for evaluation.
- The final report of Study A8081035 designed to study the actions of proton pump inhibitors or H₂ antagonists on the PKs of crizotinib should be submitted as soon as possible to the TGA for evaluation.
- The final report of the QTc prolongation sub-study within Study A8081007 (including patients from Study A8081005) should be submitted as soon as possible to the TGA for evaluation.

The Delegate also intended to include the following condition of registration related to the RMP:

- The Risk Management Plan Version: 2.0, dated 13 March 2012, to be revised as specified in the sponsor's correspondence dated 19 June 2012, or as subsequently approved by the Office of Product Review, must be implemented.

The Delegate proposed to approve the submission. The general advice of the Committee is requested. A specific question is whether a black-box warning is necessary.

Excerpt from sponsor's response to the delegate's overview

Currently there is no standard effective therapy for patients in Australia with ALK-positive advanced NSCLC, and Xalkori fulfils an unmet medical need for the treatment of this patient population.

Crizotinib has demonstrated robust and clinically meaningful efficacy as a single agent in patients with previously untreated and heavily pre-treated ALK-positive advanced NSCLC. The observed results with crizotinib far exceeded those reported from retrospective analyses, and the clinical evaluator (CER2) stated the following:

"... the retrospective analyses consistently showed that crizotinib was more efficacious than standard first-line systemic treatment regimens for NSCLC."

The clinical benefit of crizotinib in Studies A8081001 and A8081005 was confirmed by the recent announcement of the statistically significant improvement in PFS demonstrated by crizotinib compared to standard chemotherapy in the randomised Phase III Study A8081007.

Crizotinib has an adverse event and laboratory test abnormality profile that is generally safe and well-tolerated, with the most common treatment related adverse events being gastrointestinal, visual, constitutional and neurological in nature and primarily Grade 1 or Grade 2 in severity. Also, the adverse events observed for patients in the crizotinib arm of the randomised Phase III Study A8081007 were generally consistent with those reported in Studies A8081001 and A8081005. As discussed in the pre-ACPM response, safety concerns are satisfactorily addressed in the proposed PI, and a boxed warning is not warranted in the Australian PI for Xalkori.

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM) (which has succeeded ADEC), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following (Recommendation 9678):

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, considered these products to have an overall negative benefit-risk profile.

In making this recommendation the ACPM advised that the data are inadequate to fully assess the efficacy and safety and therefore overall benefit-risk of these products, particularly in relation to the assignment of first or second line place in therapy.

The ACPM advised that while the preliminary data indicate promise it would welcome further data providing evidence from Phase III randomised trials that measure progression-free and overall survival and quality of life, especially compared to the current standard of care, for example, chemotherapy.

The ACPM also requested more data regarding use in renal and hepatic impairment and potential drug interactions, as well as more complete toxicity data, including the significant safety signal for hepatic toxicity.

In submitting further data the ACPM recommended the sponsor address the issue of availability of, and access to, assay testing to support the proposed indication.

Initial outcome

Based on a review of quality, safety and efficacy, TGA rejected the registration of Xalkori (Crizotinib). The following is an excerpt from the Delegate's decision letter:

Material findings of fact

A. Efficacy

1. Two main studies were provided that allowed assessment of crizotinib's efficacy (and safety). These were Study A8081001 ("Study 1001") and Study A8081005 ("Study 1005").
2. Study 1001 is an ongoing Phase I, open-labelled and uncontrolled study of crizotinib in various tumour types. The objective response rate (ORR) in patients with ALK-positive NSCLC given 250 mg bd was 61.5% at the 120 day update. Median progression-free-survival at the 120 day update was 9.9 months and median overall survival had not been reached after 16.6 months of follow-up. Quality of life measures were not assessed.
3. Study 1005 is an ongoing, Phase II, open-labelled and uncontrolled study of patients with advanced ALK-positive NSCLC. The ORR was 59.1% at the 120 day update. Median progression-free survival was 8.1 months; median overall survival has not been reached. Quality of life measures suggested some improvement for a period after 12 weeks on treatment, but this improvement was not consistently maintained.
4. Historical control analyses that the sponsor provided constitute indirect comparisons between efficacy of crizotinib and efficacy of various standard chemotherapy approaches. These historical control comparisons implied substantial improvement in objective response rates, progression-free survival and overall survival in patients treated with crizotinib, relative to patients treated with various standard chemotherapies.
5. Reflecting the absence of a randomisation process, there were major imbalances for known prognostic factors in NSCLC between crizotinib-treated patients and patients in the historical control studies. Your statistical analyses attempted to address these imbalances. Generally it is difficult to adjust for all potentially relevant imbalances in such analyses, because of the potential for unmeasured confounding factors to be present.

B. Safety

6. In Study 1001, 149 subjects were included in the most up-to-date safety population. In Study 1005, 439 subjects were included (although only 261 subjects were considered to be in the 'mature' safety population, that is, had been treated for sufficiently long to provide meaningful safety information). Studies 1007 and 1014 provided limited information in 116 and 19 patients respectively, concerning serious adverse events. Some other Phase I studies also contributed to safety assessment.
7. Crizotinib use is associated with liver enzyme elevation in approximately 1 in 6-7 recipients. The sponsor gave a frequency of 0.4% for serious crizotinib-related hepatotoxicity.
8. Crizotinib is associated with pneumonitis, a condition which can be serious or fatal, in 1.7% of patients. Causality assessment is difficult in patients with lung cancer.
9. Crizotinib use is commonly or very commonly associated with nausea, vomiting, diarrhoea or constipation, decreased appetite and / or oesophageal disorders.
10. Crizotinib has an exposure-dependent association with both QT prolongation and bradycardia.

11. Crizotinib use is very commonly associated with mild vision disorders.
12. Crizotinib use is frequently associated with neutropenia and/or lymphopenia.

C. Findings of fact material to establishment of both efficacy and safety

13. The crizotinib clinical package lacked some key benefits derived from randomised, controlled clinical studies. Use of a controlled study design would allow comparison of efficacy (and safety) between crizotinib and a relevant control arm. Use of randomisation in assigning each patient to crizotinib or a control arm would make it likely that factors – other than use of crizotinib or the control agent – influencing study endpoints are evenly distributed across study arms, thus minimising potential biases.
14. The ACPM has recommended that data are inadequate to fully assess the efficacy and safety and therefore the overall benefit–risk of crizotinib, in treatment regimens as either first or second line therapy.
15. The ACPM emphasised a lack of data from randomised studies that would, for example, allow direct comparison of efficacy and safety with standard chemotherapy for the condition.
16. The TGA-adopted European Union Guideline on the Evaluation of Anticancer Medicinal Products in Man⁸⁸ states:

“III.2.6 Studies in small study populations, very rare tumours

For some truly rare tumours or very narrow indications, whether due to tumour phenotype or restrictions related to target expression, it is simply not possible to recruit a sufficiently large number of patients to conduct reasonably powered, randomised studies in order to detect clearly relevant differences in anti-tumour activity.”

17. There is an ongoing, randomised, Phase III study (“Study 1007”) comparing crizotinib with either pemetrexed or docetaxel in patients with ALK-positive advanced NSCLC, however detailed data from this study were not provided for evaluation. This shows that it is possible to recruit enough patients to conduct a reasonably powered, randomised study capable of detecting relevant differences in anti-tumour activity in the setting of ALK-positive advanced NSCLC. The ongoing conduct of a further such Phase III study (“Study 1014” – again not provided for evaluation) supports this view.
18. The TGA-adopted European Union Guideline on the Evaluation of Anticancer Medicinal Products in Man states:

“III.2.7 Use of external control

The use of external control (including historical control) is discussed in ICH Topic E10 (CHMP/ICH/364/96) and it is concluded that “the inability to control bias restricts use of the external control design to situations where the treatment effect is dramatic and the usual course of the disease highly predictable”. Dramatic effects are uncommonly documented in the treatment of malignancies, but it is acknowledged that such effects, obvious to any qualified observer, are seen occasionally. In these cases, prospective confirmation in randomised, reference-controlled studies is not only unacceptable to investigators, patients and ethics committees, but also unnecessary.”

19. Examination of the TGA adopted EU guideline Note for Guidance on Choice of Control Groups in Clinical Trials⁸⁹ confirms the summary guidance on use of external controls quoted above.

⁸⁸ CPMP/EWP/205/95/Rev.3/Corr. Guideline on the evaluation of anticancer medicinal products in man

⁸⁹ CHMP/ICH/364/96 Note for guidance on choice of control group in clinical trials

20. The pharmacological characterisation of a medicine can affect the understanding of both efficacy and safety. The Delegate found the following facts most notable regarding the pharmacological characterisation of crizotinib:
21. Crizotinib is metabolised principally via CYP3A4/5 enzymes. The liver is presumably the major site of metabolism, but the gastrointestinal tract and other sites have not been excluded. The clinical pharmacology dataset for crizotinib lacked a dedicated pharmacokinetic study in patients with hepatic impairment. The sponsor proposed to conduct a Phase I study of this issue and to include relevant statements in the Product Information.
22. Renal mechanisms have a more important role in excretion of crizotinib metabolites than in clearance of crizotinib. The clinical pharmacology dataset for crizotinib lacked a dedicated pharmacokinetic study in patients with renal impairment. The sponsor's analysis of patients in Studies 1001 and 1005 suggested relatively small increases in trough concentrations of crizotinib and its main metabolite in mild and moderate renal impairment. There were no patients with severe renal impairment in this analysis. The sponsor proposed a Phase I study to examine this issue, arguing that a single-dose study may still be useful in ruling out significant effects of severe renal impairment on multiple dose PK. The sponsor also proposed to include relevant statements in the Product Information.
23. The clinical pharmacology dataset for crizotinib lacked formal pharmacokinetic studies of several potentially relevant drug-drug interactions, including: a study of the interaction between crizotinib and a P-glycoprotein inhibitor; a study of the interaction between crizotinib and a P-glycoprotein substrate; a study of crizotinib and representative gastric pH-lowering medicines; and a study of crizotinib and CYP2C enzymes.

Reasons for decision

24. The Delegate considers that the indication of a medicine is a reasonable description of the purpose for which a medicine is to be used. Therefore, in relation to s25 of the Act, the Delegate considers that the purpose for which crizotinib is to be used is treatment of patients with ALK-positive advanced non-small cell lung cancer.
25. The quality of crizotinib (Xalkori) was satisfactorily established based on the quality evaluation and the PSC advice.
26. Efficacy has not been satisfactorily established for the purpose for which crizotinib is to be used, for the following reasons:
 - a. The Delegate considers that adequate results from at least one direct comparison of crizotinib with standard chemotherapy (for example, in a well-conducted, randomised, controlled clinical trial) are required to establish efficacy satisfactorily.
 - b. This is in keeping with (a) the Guideline on the Evaluation of Anticancer Medicinal Products in Man (page 22/23, "A favourable benefit risk relationship should have been established in studies designed in conceptual compliance with the guidance outlined in section III of this document ("Phase III confirmatory studies")") and (b) ACPM advice.
 - c. The Delegate considers historical control analyses inadequate as substitutes for a randomised, controlled clinical trial, in this case. The following dot-points explain the Delegate's reasoning on this issue.
 - d. In relation to Section III.2.7 of the TGA-adopted EU Guideline on the Evaluation of Anticancer Medicinal Products in Man, the Delegate considers that the usual course of advanced ALK-positive NSCLC is highly predictable.

- e. Also in relation to Section III.2.7 of the TGA-adopted EU Guideline on the Evaluation of Anticancer Medicinal Products in Man, it is the Delegate's view that the treatment effect of crizotinib on the target population cannot be characterised as 'dramatic'.
 - f. The Delegate considers this an important issue because in the case of a dramatic treatment effect in a condition with a highly predictable course, the use of historical control analyses is a reasonable substitute for conduct of randomised, controlled studies.
 - g. To explain further why the Delegate considers crizotinib's treatment effect (in the ALK-positive advanced NSCLC population) not to be 'dramatic': (a) the differences in efficacy endpoints seen between crizotinib-treated subjects and subjects in historical control studies were substantial, but (b) such indirect comparisons are subject to bias that may magnify differences between crizotinib and historical comparators due to differences in distribution of prognostic factors across arms (despite attempts to adjust for such difference).
 - h. This position, that the treatment effect of crizotinib is not 'dramatic', is supported by the fact that the sponsor have embarked on several Phase III, randomised studies of crizotinib versus standard chemotherapies in the setting of ALK-positive advanced NSCLC (Studies 1007, 1014). As noted in the Guideline on the Evaluation of Anticancer Medicinal Products in Man, if a medicine did have a 'dramatic' benefit then "prospective confirmation in randomised, reference-controlled studies is not only unacceptable to investigators, patients and ethics committees, but also unnecessary".
 - i. In summary, the Delegate considers that use of historical control analyses is not a satisfactory substitute for the required direct, randomised comparison with standard chemotherapy in this case.
 - j. Therefore the Delegate does not consider the efficacy of crizotinib to be satisfactorily established for the purpose for which it is intended for use.
27. Safety has not been satisfactorily established for the purpose for which crizotinib is to be used, for the following reasons:
- a. The Delegate considers that adequate results from at least one direct comparison of crizotinib with standard chemotherapy (for example, in a well-conducted, randomised, controlled clinical trial) are required to establish safety satisfactorily.
 - b. The sponsor's historical control analyses did not extend to safety comparisons, except by reference to overall survival.
 - c. Even when considering overall survival the Delegate considers that the use of historical control analyses is not a satisfactory substitute for a direct, randomised comparison with standard chemotherapy, in this case, for reasons noted above.
 - d. Therefore the Delegate does not consider the safety of crizotinib to be satisfactorily established for the purpose for which it is intended for use.

Conclusions

28. The Delegate has made a decision under section 25 of the *Therapeutic Goods Act 1989* ("the Act") **not to register** crizotinib (Xalkori). The reason for the Delegate's decision is that efficacy and safety have not been satisfactorily established for the purpose for which crizotinib (Xalkori) is to be used. Consequently, the sponsor's application made on 4 November 2011 to register crizotinib (Xalkori) has been rejected.

Important additional information

29. The Delegate would like to draw to the sponsor's attention that the ACPM noted the following:
- a. The ACPM advised that while the preliminary data indicate promise it would welcome further data providing evidence from Phase III randomised trials that measure progression-free and overall survival and quality of life, especially compared to the current standard of care, for example, chemotherapy.
 - b. The ACPM also requested more data regarding use in renal and hepatic impairment and potential drug interactions, as well as more complete toxicity data, including the significant safety signal for hepatic toxicity.
 - c. In submitting further data the ACPM recommended the sponsor address the issue of availability of, and access to, assay testing to support the proposed indication.

Final outcome

Following the initial decision described above, the sponsor sought a review under the provisions of Section 60 of the Therapeutics Goods Act. The Delegate of the Minister for the review noted that paragraph 25(1)(d) of the Therapeutic Goods Act, which requires the goods to be evaluated with regard to whether the quality, safety and efficacy of the goods for the purposes for which they are to be used have been satisfactorily established, is of particular relevance.

The Delegate of the Minister reviewed the First and Second Round assessments of efficacy and safety by the clinical evaluator in the reports of Study 1001 (ALK -positive NSCLC, 250mg BID Cohort) and Study 1005 (Phase 2 on-going multi centre multinational open-label single-arm study of crizotinib (250mg BID) in patients with locally advanced or metastatic ALK-positive NSCLC who have been treated with prior systemic therapy) including the information submitted in response to the questions of the clinical evaluator.

Concerning efficacy, the Delegate of the Minister accept, subject to comments below, the evaluation of the results for Study 1001 as summarised in Tables 24-26 and Figure 3 above, Agenda of the 285th meeting of the Advisory Committee on Prescription Medicines, August 2 and 3, 2012.

The Delegate of the Minister noted that the clinical trial subjects as reported at Day 120 were not homogeneous with respect to prior treatment, including prior chemotherapies. The Delegate of the Minister also accept the evaluation of the results for Study 1005 as set out in Tables 26-27 and Figure 4 above.

Relevant to those results, the Delegate of the Minister noted that in the absence of control groups in Studies 1001 and 1005, the sponsor has developed and provided statistical analyses which seek to provide information against which the results of Studies 1001 and 1005 can be compared.

For Study 1001, two analyses were performed. In an attempt to simulate outcomes of randomised trials of crizotinib versus standard treatment of advanced Non-Small Cell Lung cancer (NSCLC), a covariate matched analysis was conducted in which the efficacy outcomes of ALK-positive advanced NSCLC patients in study 1001 were compared with those from matched patients drawn from the control arms of three other Pfizer-sponsored advanced NSCLC studies. In addition, a covariate-adjusted modelling analysis was performed to retrospectively predict the Objective Response Rate (ORR) of 16 response-evaluable ALK positive advanced NSCLC patients and the expected Progression Free Survival (PFS) Overall Survival (OS) of 119 safety-evaluable ALK~positive advanced NSCLC patients in Study 1001 as if they were treated with one of the agents from the control arms of the three Pfizer-sponsored studies.

The Delegate of the Minister noted that the three trials from which matched patients were drawn were not identical in their designs. Study A8501001 was an open label randomised international study of first-line treatment with 191 investigation sites, Study A8501002 was an open label randomised international study of first-line treatment with 121 investigation sites and Study A6181087 was a double blind randomised study in patients treated with erlotinib who had a history of prior treatment with no more than two chemotherapy regimens, including a platinum-based regimen. While described as multi centre, it is also an international study.

The Delegate of the Minister noted that for the covariate-matched analysis subjects in Study 1001 were matched with patients from the control arms of the three other Pfizer-sponsored studies by *one or more* (the Delegate of the Minister's *emphasis*) of four baseline characteristics. The Delegate of the Minister noted also that the authors of this analysis have acknowledged that "Due to limited data in the cross classification of these matching variables, simultaneous exact matching on all variables was not achievable."

The Delegate of the Minister noted that the covariate-matched ORRs ranged from 12.0% to 21.5% with paclitaxel/carboplatin, 20.7% to 24.1 % with gemcitabine/cisplatin and 10% to 13.8% with erlotinib and that in comparison the observed ORR with crizotinib was 61.2% for ALK positive advanced NSCLC patients.

The Delegate of the Minister noted that the results of the covariate-adjusted modelling are similar to those from the co-variate-matching analysis and that the results were similar to those in published literature. The results of these analyses favour crizotinib. The Delegate noted however that the figure of 61.2% masks differences between sub-populations. The ORR was 82.4% in Asian subjects compared with 52.4% in non-Asians and decreased with increasing number of prior treatments - 80.0% (no prior treatment) to 56.7% with more than 3 prior treatments. There was a better ORR in subjects with higher ECOG performance status scores (78.6% with ECOG=2; 53.8% with ECOG=0).

The Delegate of the Minister also noted that the ORR was reduced from 61.2% to 52.4% following Independent Radiological Review. The Delegate of the Minister was concerned that the methods used in these statistical analyses are novel and have not been independently validated. The possibility that the statistical methods have introduced biases favouring crizotinib remains. That would be resolved with the availability of the results of a randomised controlled study.

For Study 1005, essentially similar covariate-matched and covariate-adjusted analyses were undertaken using the safety analysis population as of 1 June 2011 (Day 120 population). The estimate of ORR was based on 255 subjects described as "Mature Response Evaluable" ("Mature RE"). They were subjects with Day 120 data that had been included in the Day 60 Clinical Data report. The PFS and OS were estimated using data for all 439 subjects in the safety analysis population. The results are shown graphically for ORRs in Figure 1 (in sponsor's Technical Report using data from Study A8081 005, 15 March 2012) and for PFS and OS in Figure 2 (page 31; not included in this AusPAR). As for Study 1001, the results of these analyses favour crizotinib. It may be noted in Figure 2 (not included in this AusPAR) that the lower bands of the 95% Hall Wellner confidence bands are mostly above the expected curves of the controls, but that this is not universal.

As for the statistical analyses of Study 1001, the Delegate of the Minister was concerned that the methods used in these statistical analyses are novel and have not been independently validated. The possibility that the statistical methods have introduced biases favouring crizotinib remains. The Delegate of the Minister was also concerned that the results seen in the analysis of OS (Mature RE population) may not be sustained when data about greater numbers of subjects becomes available. That would be resolved with the availability of the results of a randomised controlled study. Study 1007 is an ongoing Phase III open-label randomised study in patients with ALK-positive advanced NSCLC

comparing crizotinib to standard of care (pemetrexed or docetaxel). At the time of the consideration of the application by the Advisory Committee on Prescription Medicines, only very limited information about the results of this study had been provided to the TGA (Company letter of 19 June 2012).

The appeal documentation includes a "Top-Line Summary" of Study 1007 which presents "selected efficacy and safety data" based on data from visits including those on 30 March 2012. The Delegate of the Minister noted that although the document covers visits to and including 30 March 2012, the document itself is undated. On 27 November 2012, the sponsor provided in response to the Delegate of the Minister's request copies of the abstract and the slides of a presentation by Shaw AT et al. 37th meeting, European Society for Medical Oncology, Vienna, Austria, 28 September to 2 October 2012.

The data in the "Top-Line summary" and the abstract and presentation relate to similar periods. For some parameters there was more information in the presentation than the "Topline Summary". Both the abstract and slides present summaries of the same data. Between 5 February 2010 and 23 February 2012, 173 patients were randomised to the crizotinib arm and 174 to a chemotherapy arm (99 to pemetrexed; 72 to docetaxel). Crizotinib prolonged PFS compared to chemotherapy, as assessed by Independent Radiological Review (IRR). Median PFS 7.7 months compared with 3.0 months with chemotherapy. There were differences in the performance of the two possible chemotherapy arms. The median PFS in subjects treated with pemetrexed was 4.2 months while that with docetaxel was 2.6 months. The difference between crizotinib and pemetrexed was statistically significant ($p=0.0004$). In this study the point estimate for efficacy favoured Non-Asian subjects ($n=190$) over Asian subjects ($n=157$). The point estimate for efficacy favoured ECOG PS 2 subjects over ECOG PS 0/1 subjects but the number of subjects with ECOG PS 2 was small ($n=34$). Neither difference (Race; ECOG PS) was statistically significant. The Objective Response Rate as assessed by IRR was 65% for crizotinib, 29.3% for pemetrexed and 6.9% for docetaxel. The 95% Confidence Intervals for crizotinib and pemetrexed do not overlap.

At the time of the above analysis of PFS, there had been 96 deaths representing about 40% of the total number of deaths required for the pre-planned OS analysis. An interim analysis did not demonstrate that crizotinib significantly prolonged OS compared to chemotherapy. The median OS with crizotinib was 20.3 months and 22.8 months with chemotherapy. That is, the OS achieved with crizotinib is less than that for the comparator chemotherapies. The Delegate of the Minister acknowledged that the difference is not statistically significant.

Importantly, the separate OS results for the two chemotherapy comparators were not provided in either document. Given the superior effect on PFS and ORR of pemetrexed compared with docetaxel, the possibility must be considered that the difference in OS between crizotinib and pemetrexed may be greater than 2.5 months, favouring pemetrexed. The Delegate of the Minister noted that the "Top-line Summary" states that the analysis of OS data was not adjusted for the potentially confounding effect of crossover of 108 patients from the chemotherapy arm to receive crizotinib treatment under a different protocol (Study 1005). The Delegate of the Minister noted that Shaw et al's presentation includes the statement "Hazard Ratio for crossover using rank-preserving structural failure time method: 0.83 (0.36 to 1.35)" which may be compared with the Hazard Ratio reported for the Interim Analysis of 1.021 (0.677, 1.540). From the information provided in the "Top-line Summary" and the Shaw et al. presentation, the Delegate of the Minister was not able to ascertain the durations of participation in Study 1007 of those subjects who crossed over or to examine the robustness of their individual reasons for crossing-over. Further, the Delegate of the Minister was not able to determine whether the proportions of subjects who crossed over from the two comparator arms were similar or not.

The Delegate of the Minister also noted that the European Guideline states (111.1.3) that "In situations in which there is a large effect on PFS, a long expected survival after progression or a clearly favourable safety profile, precise estimates of OS may not be needed for approval." In the Delegate of the Minister's view, that does not obviate concern when the available estimates of OS suggest that it may be less with crizotinib than with pemetrexed or not statistically-significantly superior.

The Delegate of the Minister reviewed the available information about safety of crizotinib. While the Delegate of the Minister acknowledge that medicines like crizotinib are almost exclusively used under the supervision of oncologists who understand the adverse event profile of the medicine and are ready to manage such adverse events when they occur. The Delegate had noted that there was an excess of adverse hepatic events resulting in permanent discontinuations from crizotinib in Study 1007 (3 subjects) compared with none from the chemotherapy treatment arms. The nature of the "Top-line Summary" did not permit the Delegate to assess the clinical details of the events leading to the discontinuations.

Coupled with the earlier observations about serious hepatic injury (see the initial decision letter), a concern about this aspect of safety of crizotinib is not unreasonable and requires careful detailed evaluation with access to more information than has been provided to the TGA to date.

In summary, the submitted efficacy results of Studies 1001 and 1005 favour crizotinib but involve comparisons with data from other studies using novel methods which have not been validated.

To have confidence in those methods requires the results of a randomised controlled study. The Delegate of the Minister noted that the randomised Study 1007 is being conducted and that it has been indicated that a study report will be available in the first quarter of 2013. To this date the company had only provided a brief summary ("Top-line Summary") and a related abstract and presentation of results from Study 1007. Because of the limited information to date, the Delegate of the Minister was not able to adequately evaluate the efficacy and safety of crizotinib.

Reasons for the delegate of the minister's decision

The Act requires (s25) that the Secretary must evaluate the goods for registration having regard to (amongst other things):

- whether the quality, safety and efficacy of the goods for the purposes for which they are to be used have been satisfactorily established.

The purposes for which the goods are to be used means the specific therapeutic uses of the goods, that is, the indications sought for the goods: see s3 of the Act.

As the Delegate of the Minister noted above, the sponsor has applied for the registration of crizotinib (Xalkori) for the following indication:

"Xalkori is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC)."

As set out above under "The Delegate of the Minister's consideration of your company's submission", the Delegate of the Minister was of the view that the clinical information currently available does not permit the Delegate to adequately evaluate crizotinib with regard to whether the safety and efficacy of the goods for the purposes for which they are to be used have, been satisfactorily established. The Delegate of the Minister would need at least to have more detailed information as might be expected in the study report for Study 1007 in order to adequately evaluate crizotinib for the proposed indication.

For that reason, the Delegate of the Minister decided to confirm the initial decision to refuse approval of the application.

The Delegate of the Minister noted that crizotinib has been approved for supply in some other countries including the European Union, Canada and the United States of America. Those jurisdictions have provisions for types of conditional registration. Such a provision does not exist in Australia. Under the Australian legislation, conditions may be applied only after a medicine has been included on the Australian Register of Therapeutic Goods.

Result of the delegate of the minister's reconsideration of the initial decision

Pursuant to section 60 of the Therapeutic Goods Act 1989 (the Act), the Delegate of the Minister decided to confirm the initial decision to refuse registration.

Appeal to the Administrative Appeals Tribunal (AAT)

The sponsor appealed to the Administrative Appeals Tribunal (AAT) for review of the TGA's decision not to register Xalkori.

Before the AAT held a hearing on this matter, the sponsor provided to the TGA an interim clinical study report of Study 1007. This report was evaluated by the TGA (see Attachment 3). Registration of Xalkori was recommended by the evaluator and this recommendation was accepted by the TGA. The decision however rested with the AAT and not with the TGA. The TGA was provided by the sponsor with updated information about extended duration of treatment and some proposed amendments to the evaluation report. Both were taken into account by the TGA. The sponsor and the TGA reached an agreement on the conditions of registration and these were submitted to the AAT.

On 20 September 2013 the Administrative Appeals Tribunal made a decision under subsection 42C(1) of the *Administrative Appeals Tribunal Act 1975*, which was based on an agreement reached between the parties. The decision was that Xalkori would be registered subject to a number of conditions imposed under subsection 28(2B) of the *Therapeutic Goods Act 1989*, for the following indication:

'Xalkori is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK) – positive advanced non-small cell lung cancer (NSCLC).'

The following ***Specific Conditions of Registration*** apply to these therapeutic goods:

The Crizotinib Risk Management Plan (RMP), version 4.0, dated 25 February 2013 and submitted to TGA on 22 March 2013 and its Australian Specific Annex June 2013 and the Attachment to the Australian Specific Annex dated July 2013, and any subsequent revisions as agreed with the TGA, will be implemented in Australia.

An obligatory component of Risk Management Plans is Routine Pharmacovigilance. Routine Pharmacovigilance includes the submission of Periodic Safety Update Reports (PSURs). Reports are to be provided annually until the period covered by such reports is not less than three years from the date of this approval letter. No fewer than three annual reports are required. The reports are to at least meet the requirements for Periodic Safety Update Reports (PSURs) as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-Periodic Safety Update Report, Part VII. B. "Structures and processes". Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter.

The annual submission may be made up of two Periodic Safety Update Reports each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.

Attachment 1. Product Information

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Attachment 2. Extract from the Clinical Evaluation Report

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