



Australian Government  
Department of Health  
Therapeutic Goods Administration

## AusPAR Attachment 2

# Extract from the Clinical Evaluation Report for Crizotinib

Proprietary Product Name: Xalkori

Sponsor: Pfizer Australia Pty Ltd

**Date of first round CER: 27 February 2012**

**Date of second round CER: 30 May 2012**

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## About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
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## List of abbreviations

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 <sub>inf</sub>	Area under the plasma concentration-time profile from time zero to infinity
AUC <sub>τ</sub>	Area under plasma concentration-time profile from time zero to time $\tau$ , the dosing interval
BID	Twice daily
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CR	Complete response
C <sub>max</sub>	Maximum plasma concentration
C <sub>trough</sub>	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

Abbreviation	Meaning
DLT	Dose-limiting toxicity
DR	Duration of response
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
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
msec	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
SD	Stable disease

Abbreviation	Meaning
SOC	System organ class
TKI	Tyrosine kinase inhibitor
Tmax	Time of maximum plasma concentration
ULN	Upper limit of normal (range)
US	United States
VSAQ	Visual Symptom Assessment Questionnaire
WHO	World Health Organization

## 1. 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 (AIHW & Cancer Australia 2011). 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-standardized 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 (Boyer MJ, 2003). 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 (NCI, 2012). In patients with NSCLC, the possibility of cure

depends mainly on their suitability for surgical resection (Carney D and Hansen H, 2000). 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) (Carney D and Hansen H, 2000). In patients with advanced NSCLC (TNM stage IIIB and stage IV) chemotherapy is the mainstay of treatment (Goldstraw P et al., 2010). 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).

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 based chemotherapy. These include: premetrexed 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. 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 (Solomon B, et al., 2009). 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 (Soda M et al., 2007; Rikova et al., 2007).

ALK was first identified as a fusion partner of nucleophosphomycin (NPM) in anaplastic large cell lymphoma in 1994 (Morris SW et al., 1994; Shiota M et al., 1994). 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 (Soda M et al., 2007). 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 (Soda M et al., 2007). Potent



oncogenic activity for EMLA-ALK has been described both *in vivo* in a transgenic mouse model (Soda M et al., 2008), and *in vitro* (Rikova et al., 2007). 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 kinase fusion proteins (Soda M et al., 2007; Choi et al., 2008; Inamura et al., 2008; Koivunen et al., 2008; Shinumura et al., 2008; Takeuchi et al., 2008; Takeuchi et al., 2009; Wong et al., 2009). While EML4 has been the predominant identified fusion partner for ALK, other rare fusion partners for ALK include TRK-fused gene (TFG) (Rikova K et al., 2007), and kinesin family member 5B (KIF5B) (Takeuchi K et al., 2008). 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%) (Solomon et al., 2009). 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 to used to enrich the sample (Solomon et al., 2009; Horn and Pao, 2009). In a study of unselected Caucasian NSCLC patients, 12 out of 447 (2.68%) were identified as ALK positive (Varella-Garcia et al., 2010). 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 (Perner et al., 2008). Based on the available data, ALK positivity appears to be relatively rare, with a frequency of approximately 3% of NSCLC patients.

In general, the median age of ALK-positive NSLC patients appears to be younger relative to the general unselected population (Inamura et al., 2008; Shaw et al., 2009; Wong et al., 2009). Some studies have also identified a statistically significant relationship between ALK-positivity and a history of never smoking or light-smoking (Koivunen et al 2008; Shaw et al 2009; Takahashi et al. 2010; Wong et al. 2009), but other studies have not observed a correlation with smoking history (Martelli et al, 2009; Inamura et al, 2008; Boland et al, 2009). ALK fusion genes have been identified predominantly in adenocarcinoma subtypes, but the mutation has also been reported in squamous cell subtypes (Rodig et al 2009; Wong et al 2009; Yoshida et al 2010; Takeuchi et al, 2009; Takahashi et al, 2010; Boland et al, 2009; Martelli et al, 2009). Co-expression with EGFR or HER2 or KRAS mutations appears to be extremely rare, suggesting that ALK is a distinct oncogenic driver (Soda et al., 2007; Inamura et al., 2008; Koivunen et al., 2008; Shinmura et al., 2008; Shaw et al., 2009; Takahashi et al., 2010; Wong et al., 2009; Martelli et al., 2009).

### 1.1. Orphan drug designation

On 5 September 2011, crizotinib was designated as an orphan drug for the treatment of anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC). The orphan drug designation was based on an estimate of the prevalence of 830 patients with the disease in Australia in 2011. The estimated prevalence was based on 19,547 patients with lung cancer, 85% of whom would have NSCLC and with 5% of these patientd having ALK positive NSCLC disease.

**Comment:** The indication for orphan drug designation was for the treatment of ALK-positive NSCLC, while the indication proposed for registration is for the treatment of patients with ALK-positive **advanced** NSCLC. Consequently, the proposed indication is for a subset of patients (i.e., patients with advanced disease) for which orphan drug designation was granted. Consequently, the

number of patients in Australia with ALK positive advanced NSCLC is likely to be smaller than 830.

## 1.2. Guidance

There was Pre-submission between the TGA and Pfizer held on 29 June 2011. The outcomes arising from the meeting requiring sponsor action were: application for orphan drug designation for crizotinib (submitted and approved); bring pre-submission planning form forward to the end of August 2011 (submitted on 30 August 2011); nominate a 30 calendar day response time to consolidated questions (nominated in the PPF); and provide information on the chemistry of crizotinib and “quality by design” (provided on 24 August 2011).

## 2. Contents of the clinical dossier

### 2.1. 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:

- Module 5
  - 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 [<sup>14</sup>C]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 interim 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 interim 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”.

- Interim 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 NSCL 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 SAEs for patients in the preliminary 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 (i.e., 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 (i.e., presumably to the FDA) was based on the substantial antitumour 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/EMEA) 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.

## 2.2. 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.

## 2.3. 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.

# 3. Pharmacokinetics

## 3.1. 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 this evaluation report and their significance discussed. None of the studies with 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 BID) 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 1.

**Table 1: Submitted clinical studies with clinical pharmacology data; n = subjects entered/evaluated.**

Topic	Identification	Primary Aim	n	Comment
<b>Healthy Volunteers – crizotinib single dose studies</b>				
Absolute Bioavailability (sd)	1010	Absolute bioavailability	14 /14	Abs BA ~ 43%; PIC:IV 250:50 mg.
Bioequivalence (250 mg)	1008	BE (fasted) – PIC versus IRT	24/24	BE shown – 250 mg doses.

Topic	Identification	Primary Aim	n	Comment
<b>Healthy Volunteers – crizotinib single dose studies</b>				
Bioequivalence (250 mg)	1011	BE (fasted) - CIC versus IRT BE (fasted) - CIC versus 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	<sup>14</sup> C radiolabelled crizotinib	6/6	PKs and ADME investigated.
PK Drug-Drug Interaction	1015	Ketoconazole / Crizotinib	15	Systemic exposure increased.

**Table 1 continued: Submitted clinical studies with clinical pharmacology data; n = subjects entered/evaluated.**

Topic	Identification	Primary Aim	n	Comment
<b>Patients with advanced cancer – single and multiple dose studies</b>				
<ul style="list-style-type: none"> <li>• Single and multiple dose;</li> <li>• Various QD and BID doses;</li> <li>• Asian versus non-Asian;</li> <li>• Midazolam/Crizotinib PK interaction;</li> <li>• Food effect</li> </ul>	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 BID) including ALK+ NSCLC subgroup (n=119).
<ul style="list-style-type: none"> <li>• Trough concentrations only</li> </ul>	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	PMAR-00192	Structural PK model; population variability in CL and Vd; effects of H2 antagonists and PPIs	N=250; 3184 crizotinib concentrations	Covariates weight, sex, race, and ECOG status as predictors of CL/F, weight as a predictor of V <sub>2</sub> /F, Q/F, and

Topic	Identification	Primary Aim	n	Comment
<b>Patients with advanced cancer – single and multiple dose studies</b>				
1005)		on PKs of crizotinib.		V <sub>3</sub> /F, and proton pump inhibitors or H <sub>2</sub> antagonists as a predictor of <i>ka</i> .

CIC = commercial image capsule; IRT = immediate-release tablet; PIC = powder-in-capsule; sd = single-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 this 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, sufficient to adequately describe the elimination phase of the crizotinib plasma concentration-time curve. The washout period of at least 14 days (i.e., 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).

### 3.2. Summary of pharmacokinetics

**Comment:** Crizotinib has been classified by the sponsor as a biopharmaceutical class system (BCS) Class 4 compound (i.e. low solubility and low permeability). BCS class 4 compounds can have low systemic exposure due to poor absorption. The sponsor classified crizotinib as a BCS 4 compound because the maximum dose of 250 mg does not fully dissolve in 250 mL of buffers over the range of pH 1 to pH 6.8 (i.e., low solubility), and observations from human studies demonstrating that the absolute bioavailability and recovery of the administered drug unchanged in urine were both < 90% (i.e., low permeability). In addition, the sponsor stated that the low permeability categorization of crizotinib is supported by available *in vitro* Caco-2 permeability studies.

### 3.2.1. Pharmacokinetics

#### 3.2.1.1. Absorption

In patients with advanced cancer treated with crizotinib 250 mg BID (n=24), the mean  $T_{max}$  at steady state was 4 hours (range 0 to 9 hours), and the geometric mean (%CV) values for the  $C_{max}$  and  $AUC_{\tau}$  were 411 (44) ng/mL and 3880 (36) ng.hr/mL, respectively (Study 1001). In these patients, steady state was reached after 15 days, and the median accumulation ratio (Rac) was 4.8 (based on the multiple and single dose  $AUC_{\tau}$  values). In healthy subjects, the mean  $T_{max}$  of crizotinib was 5.0 to 6.0 hours (range 1.0 to 8.0 hours) following a single oral dose of crizotinib 250 mg. In healthy subjects, systemic exposure ( $AUC_{inf}$  and  $C_{max}$ ) to crizotinib was reduced by ~14% when administered with a high fat meal (Study 1009).

**Comment:** The aqueous solubility of crizotinib is pH dependent, with low (acidic) pH resulting in higher solubility. Consequently, it is possible that drugs that increase intragastric pH (i.e., reduce acidity) might reduce the bioavailability of crizotinib by decreasing its solubility. However, the sponsor comments that the use of agents which reduce gastric acidity were permitted in the clinical efficacy and safety studies. Nevertheless, in the population pharmacokinetic analysis in patients with advanced cancer, co-administration of crizotinib and PPIs (esomeprazole, omeprazole, and lansoprazole) decreased the absorption rate constant ( $k_a$ ) of crizotinib (PMAR-00192). No formal PK interaction studies with crizotinib and drugs that can reduce intragastric acidity (i.e., antacids, H<sub>2</sub> receptor antagonists, or PPIs) have been submitted. It is considered that this is deficiency in the submitted data package.

In study 174737 (*in vitro*), the BA/AB (apical to basal)/basolateral to apical ratios in the Madin-Darby canine kidney [MDCK] cell line indicated that crizotinib is a substrate for the P-glycoprotein [P-gp] efflux transporter (efflux ratio  $\geq 2.5$  for concentrations up to 20  $\mu$ M), but not a substrate for the breast cancer resistance protein (BCRP) efflux transporter (efflux ratios across the concentration range being approximately equal to 1). The efflux ratio for MDR1-MDCK cells decreased with increasing crizotinib concentrations over the range 0.1  $\mu$ M (BA/AB = 22.5) to 50  $\mu$ M (BA/AB = 1.30), indicating saturation of P-gp activity with increasing concentration. BA/AB ratios of  $> 2.5$  are considered conclusive for active efflux. The sponsor commented that, based on moderate crizotinib bioavailability observed in humans (i.e., absolute bioavailability ~43%), "the fraction of crizotinib absorbed was estimated to be moderate to high, indicating that it is unlikely that absorption of crizotinib will be limited by this efflux transporter at therapeutic doses. At sub-therapeutic doses, however, non-linear pharmacokinetics/limited absorption may occur due to P-gp mediated efflux of crizotinib". However, it is noted that in MDR1-MDCK cells the BA/AB ratios for crizotinib concentrations of 0.5  $\mu$ M and 2  $\mu$ M were 33.6 and 19.2, respectively. Therefore, at the estimated steady state  $C_{max}$  in patients with advanced disease of 0.91  $\mu$ M (i.e., 411 ng/ml) it appears that crizotinib will be a substrate for the P-gp efflux transporter. Consequently, it is possible that in clinical practice inhibition of the P-gp efflux transporter by co-administration of crizotinib and P-gp inhibitors might increase systemic exposure to crizotinib.

#### 3.2.1.2. Bioavailability

##### 3.2.1.2.1. Absolute bioavailability

**Study 1010** was a, Phase I, single-centre (Belgium), single-dose, open-label, randomised, 2-period, 2-sequence, cross-over, absolute bioavailability study in 14 healthy male subjects comparing oral administration of the IR tablet with the IV formulation of crizotinib. Each subject received 2 treatments (A and B) with a washout period of  $\geq 14$  days between each treatment.



Treatment A (Reference) consisted of a 50 mg single IV dose of crizotinib administered as 200 mL of an 0.25 mg/mL IV solution over approximately 2 hours at a constant rate. Treatment B (Test) consisted of a 250 mg single oral dose of crizotinib administered in a fasted state as 1 × 50 mg IR tablet and 2 × 100 mg IR tablets. The results of statistical analysis of the absolute bioavailability of crizotinib are summarised below in Table 2.

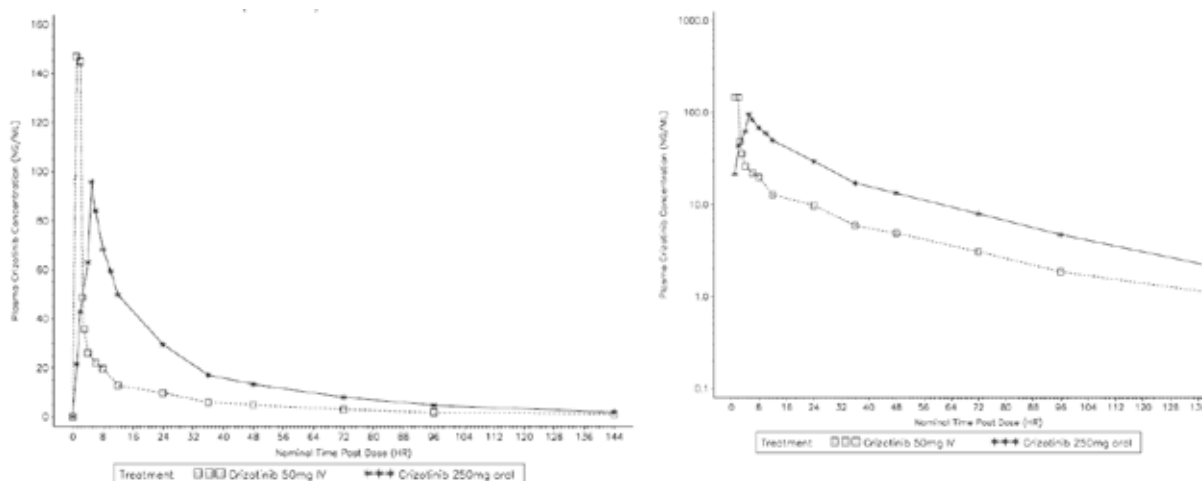
**Table 2: Study 1010 - Absolute bioavailability - adjusted geometric means (dose normalized [dn]).**

Parameter	Crizotinib 250 mg Oral (Test)	Crizotinib 50 mg IV (Reference)	Ratio (Test/Reference)	90% CI for Ratio (%)
AUC <sub>inf</sub> (dn) (ng.hr/mL/mg) *	9.281	21.36	43.44 %	(39.68, 47.56)
AUC <sub>last</sub> (dn) (ng.hr/mL/mg) *	8.998	20.14	44.67 %	(40.90, 48.78)

\* AUC values are dose normalized (AUC/dose) adjusted geometric means. The ratios (and 90% CI) are expressed as percentages. AUC = area under the curve; inf = infinity; dn = dose normalized; CI = confidence interval.

Median plasma crizotinib concentration-time profiles following IV and oral dosing are presented below in Figure 1.

**Figure 1: Study 1010 – Median plasma crizotinib concentration – time profiles following 50 mg IV and 250 mg oral doses (linear scale, left panel; semi-log scale, right panel).**



The pharmacokinetics of the oral and IV formulations were summarised in the study report, and a brief synopsis of the study was provided. The PK parameters for the lactam metabolite of crizotinib (PF-06260182) were summarised in the study report. The metabolite (PF-06260182) to parent molar ratios for the pharmacokinetic parameters (AUC<sub>last</sub> and C<sub>max</sub>) following IV and oral administration were also summarised in the study report.

**Comment:** This was a good quality absolute bioavailability study. The absolute bioavailability of crizotinib was approximately 43% in healthy male volunteers, based on adjusted geometric mean values for AUC<sub>inf</sub> (dose normalized). There were no absolute bioavailability data provided for the dose normalized C<sub>max</sub>. Intersubject variability (%CV) of AUC<sub>last</sub> and C<sub>max</sub> were higher after oral administration (35% and 28%, respectively) than after IV administration (18%



and 19%, respectively). The metabolite (PF-06260182) to parent (crizotinib) ratios for the  $AUC_{last}$  and the  $C_{max}$  after IV administration (0.03430 and 0.01880, respectively) were lower than after oral administration (0.1477 and 0.2577), suggesting that presystemic metabolism of crizotinib has a role in the formation of the metabolite.

### 3.2.1.2.2. Bioequivalence of clinical trial and market formulations

**Study 1011** was a Phase I, single centre (Belgium), open-label, randomised, 4-period, 4-treatment, 4-sequence, cross-over, single-dose study in healthy volunteers planned to: (a) demonstrate the bioequivalence of the commercial image capsule (CIC) (Test treatment) relative to immediate release tablet (IRT) (Reference treatment 1), and the powder-in-capsule (PIC) formulation (Reference treatment 2); and (b) demonstrate the lack of effect of a high fat meal on the PKs of crizotinib when administered as the CIC formulation. Each subject was randomly assigned to a treatment sequence and received 4 treatments (A, B, C, and D) with a washout period of  $\geq 14$  days between each treatment. The study assessed the pharmacokinetics of crizotinib and the lactam metabolite (PF-06260182).

There were 36 healthy volunteers assigned to treatment, and treated/completed/discontinued subjects were 35/34/1 in the fasted IRT group, 36/35/1 in the fasted PIC group, 35/35/0 in the fasted CIC group and 36/35/1 in the fed CIC group. The 36 subjects were all healthy males with a mean age of 38.9 years (range: 22-55), and 32 were white. The study plan is summarised in the below in Table 3.

**Table 3: Study 1011 – Study plan.**

Sequence	Period 1	Wash-out	Period 2	Wash-out	Period 3	Wash-out	Period 4
1	Treatment A		Treatment B		Treatment C		Treatment D
2	Treatment B		Treatment D		Treatment A		Treatment C
3	Treatment C		Treatment A		Treatment D		Treatment B
4	Treatment D		Treatment C		Treatment B		Treatment A

Treatment A (Reference 1): 1 x 50 mg IRT tablet and 2 x 10 mg IRT, fasted state.

Treatment B (Reference 2): 1 x 50 mg PIC and 2 x 100 mg PIC, fasted state.

Treatment C (Test for BE): 1 x 250 mg CIC, fasted state.

Treatment D (Test for food effect): 1 x 250 mg CIC, with a standard high-fat meal.

The pharmacokinetics of crizotinib and the lactam metabolite (PF-06260182) following oral administration of the three formulations and a brief synopsis of the study were provided in the study report. The bioequivalence results (fasted state) for crizotinib for the CIC versus IRT and CIC versus PIC comparisons are summarised below in Table 4.

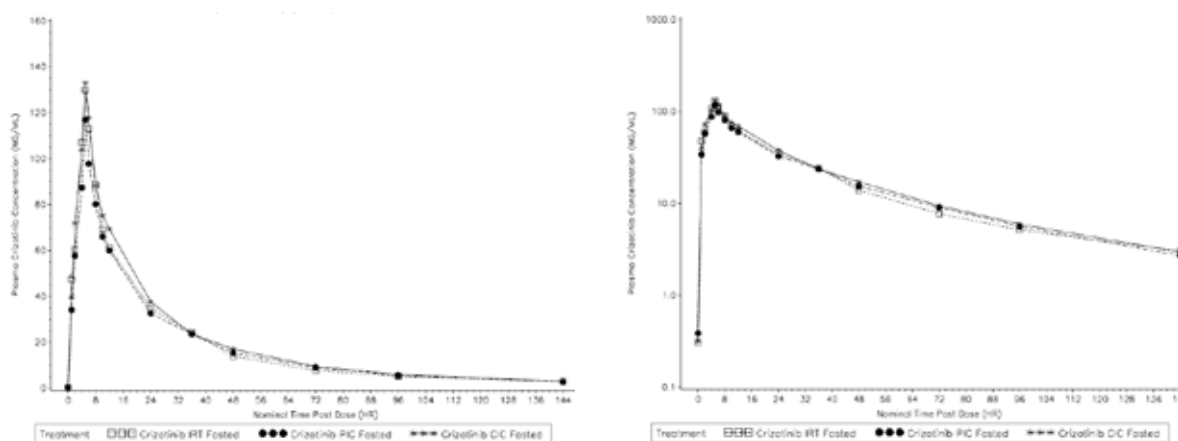
**Table 4: Study 1011 – Bioequivalence parameters (adjusted geometric means).**

Parameter	Test	Reference	Ratio (Test/Reference) <sup>a</sup>	90% CI for Ratio
	<b>CIC Fasted</b>	<b>IRT Fasted</b>		

Parameter	Test	Reference	Ratio (Test/Reference) <sup>a</sup>	90% CI for Ratio
AUC <sub>inf</sub> (ng.hr/mL)	2886	2899	99.56 %	(91.49, 108.33)
AUC <sub>last</sub> (ng.hr/mL)	2758	2769	99.60 %	(91.30, 108.66)
C <sub>max</sub> (ng/mL)	134.6	125.9	106.97 %	(96.55, 118.51)
	<b>CIC Fasted</b>	<b>PIC Fasted</b>		
AUC <sub>inf</sub> (ng.hr/mL)	2886	2699	106.93 %	(98.26, 116.35)
AUC <sub>last</sub> (ng.hr/mL)	2758	2564	107.56 %	(98.58, 117.35)
C <sub>max</sub> (ng/mL)	134.6	120.9	111.32 %	(100.47, 123.33)

The median plasma crizotinib concentration-time profiles following single oral doses (250 mg) under fasting conditions for the three formulations are provided below in Figure 2.

**Figure 2: Study 1011 – Median plasma crizotinib concentration – time profiles following single 250 mg doses in the fasted state of the three oral formulations (linear scale, left panel; semi-log scale, right panel).**



**Comment:** This was a good quality bioequivalence study. It showed that the CIC formulation (250 mg) was bioequivalent to both the PIC (250 mg) and the IRT (250 mg) formulations when the formulations were administered as single doses in the fasted state. The 90% CI for the AUC<sub>inf</sub> and C<sub>max</sub> ratios (Test/Reference) for the relevant comparisons fell entirely within the protocol specified bioequivalence range of 0.80 to 1.25. In addition, the crizotinib plasma concentration-time profiles for the three formulations were virtually superimposable. The PK parameters of the metabolite PF-06260182 were similar after administration of the three formulations in the fasted state, and inspection of the median plasma PF-06260182 concentration – time profiles for the three formulations showed them to be virtually superimposable (profiles not provided in the CER).

### 3.2.1.2.3. Bioequivalence of different dosage forms and strengths

**Study 1008** was a Phase I, single-centre (USA), open-label, randomised, 2-period, 2-treatment, 2-sequence, cross-over, single-dose study evaluating the bioavailability, safety and tolerability, of the immediate release (IR) tablet formulation (Test treatment) relative to the powder in capsule (PIC) formulation (Reference treatment). The study involved the administration of single 250 mg crizotinib doses of the PIC and IR tablet formulations in the fasted state to 24 healthy adult male volunteers of mean±SD age 32.1±9.3 years (range 19-53) who were predominantly black (n=14). Each subject received 2 treatments (A and B), with a washout period between treatments of ≥ 14 days. Treatment A (Reference) consisted of 1 x 50 mg PIC and 2 x 100 mg PICs, and Treatment B (Test) consisted of 1 x 50 mg IR tablet and 2 x 100 mg IR tablets.

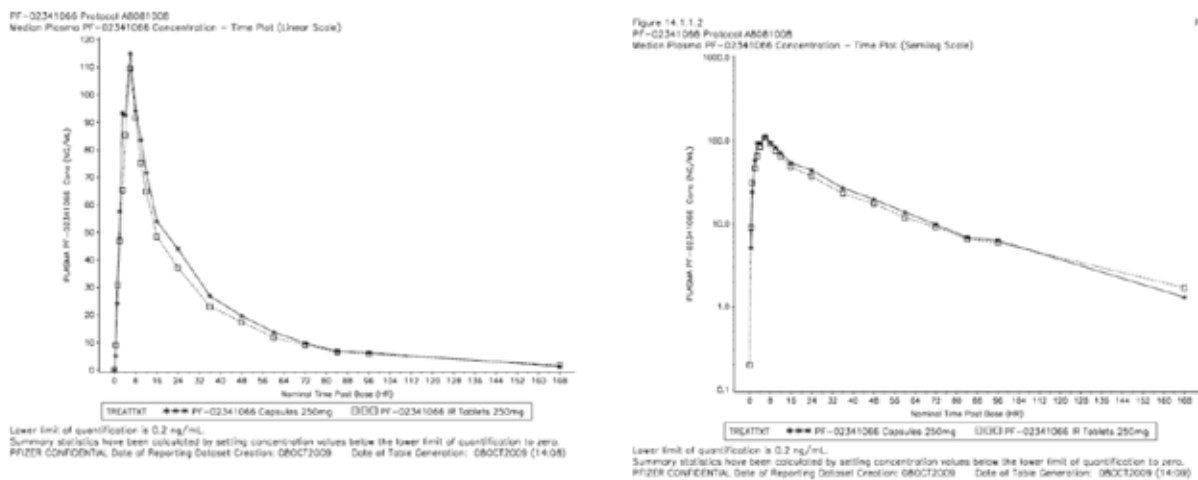
The results for the bioequivalence analysis are summarised below in Table 5, and the median plasma crizotinib concentration-time profiles following single oral doses (250 mg) under fasting conditions for the IRT and PIC formulations are provided below in Figure 3.

**Table 5: Study 1008 – BE analysis IRT (Test) and PIC (Reference), fasting single-dose 250 mg.**

Parameter	IRT 250 mg (Test)	PIC 250 mg (Reference)	Ratio (Test/Reference) <sup>a</sup>	90% CI for Ratio
AUC <sub>inf</sub> (ng.hr/mL)	2722.51	2945.49	92.43 %	84.86, 100.68
AUC <sub>last</sub> (ng.hr/mL)	597.26	2804.51	92.61 %	84.84, 101.09
C <sub>max</sub> (ng/mL)	112.11	113.35	98.91 %	90.18, 108.48

a = Ratio of adjusted geometric means; ratios (and 90% CIs) are expressed as percentages.  
PIC = powder-in-capsule; IRT = immediate-release tablet.

**Figure 3: Study 1008 – Median plasma crizotinib concentration – time profiles following single 250 mg doses of the PIC and IRT formulations (linear scale, left panel; semi-log scale, right panel).**



**Comment:** This was a good quality bioequivalence study. It showed that IRT and PIC formulations were bioequivalent when administered as single 250 mg doses in

the fasted state. The 90% CI for the AUC<sub>inf</sub> and C<sub>max</sub> ratios (Test/Reference) were entirely within the protocol specified bioequivalence range of 0.80 to 1.25.

#### 3.2.1.2.4. Influence of food

In Study 1011 (described above) the effect of food (high fat meal) on the PKs of crizotinib was investigated. The bioequivalence assessment involved the administration of a single dose of crizotinib 250 mg (1 x CIC) in the fasted and fed (high-fat meal) states to healthy subjects in a cross-over design with a washout-out period between treatments of at least 14 days. There were 36 subjects treated in the fed state and 35 subjects treated in the fasted state.

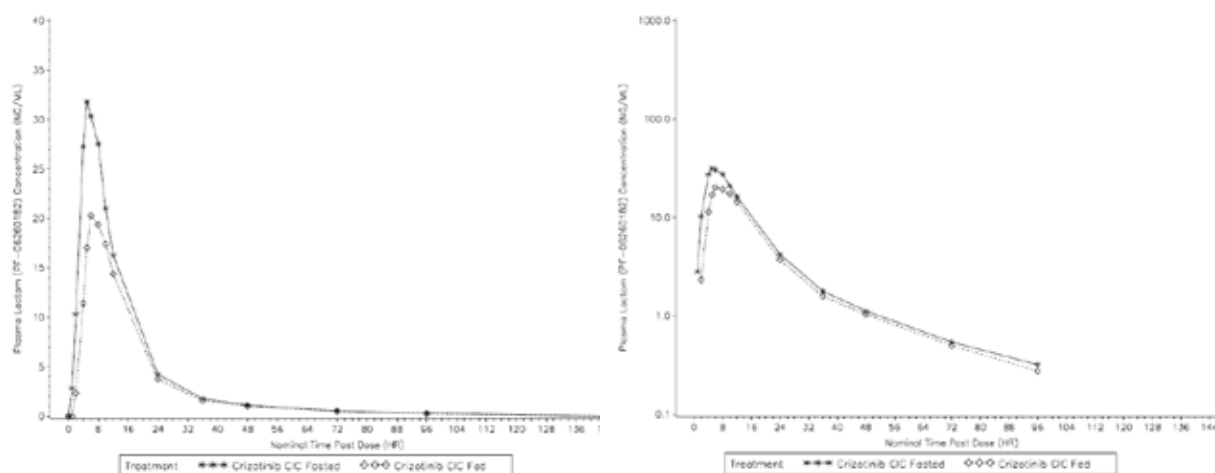
The bioequivalence results are provided below in Table 6, and the median plasma crizotinib concentration-time profiles following single oral doses of CIC (250 mg) in the fasted and fed states are provided below in Figure 4.

**Table 6: Study 1011 – PK parameters in the fasted and fed state; CIC 250 mg (single oral dose).**

Parameter	CIC Fed (Test)	CIC Fasted (Reference)	Ratio (Test/Reference) <sup>a</sup>	90% CI for Ratio
AUC <sub>inf</sub> (ng·hr/mL)	2475	2886	85.76 %	(78.88, 93.25)
AUC <sub>last</sub> (ng·hr/mL)	2359	2758	85.52 %	(78.45, 93.22)
C <sub>max</sub> (ng/mL)	116.1	134.6	86.22 %	(77.89, 95.43)

a = Ratio of adjusted geometric means; ratios (and 90% CIs) are expressed as percentages.

**Figure 4: Study 1011 – Median plasma crizotinib concentration – time profiles following CIC single 250 mg doses in the fed and fasted states (linear scale, left panel; semi-log scale, right panel).**



**Comment:** This was a good quality study investigating the effect of food (high fat meal) on the bioavailability of crizotinib when administered as the CIC formulation (single 250 mg dose). The results showed that both the crizotinib C<sub>max</sub> and AUC<sub>inf</sub> values were approximately 14% lower in the fed state relative to the fasted state. The 90% CIs for the C<sub>max</sub> and AUC<sub>inf</sub> ratios (Fed/Fasted) were not entirely within bioequivalence range of 0.80 to 1.25. However, it is considered that the

reduced bioavailability of crizotinib in the fed state is unlikely to be clinically significant. There is considerable intersubject variability in the  $C_{max}$  and  $AUC_{inf}$  values in both the fasted and fed states as assessed by the co-efficients of variation (CV). The CVs in the fasted versus fed states for the  $C_{max}$  were 36% versus 39%, and for the  $AUC_{inf}$  were 36% versus 40%. The median  $T_{max}$  was 5 hours in both the fasted and fed states, while the mean  $t_{1/2}$  was about 35 hours after both fasted and fed administration. The plasma concentration - time profiles showed that crizotinib plasma concentrations were marginally lower over the first 16 hours following administration of the CIC formulation in the fed state relative to the fasted state. Inspection of the median plasma concentration - time profiles for the PF-06260182 metabolite of crizotinib following administration of the CIC formulation (single 250 mg dose) showed them to be consistent in shape with those for crizotinib (profiles not provided in the CER).

The results of Study 1011 were consistent with the results from a small food effect study in 12 patients following a single 250 mg dose of crizotinib (Study 1001). In patients, the fed (standard high fat meal) to fasted ratios of the adjusted geometric means were 84.64% (90% CI: 65.11% to 110.05%) for the  $AUC_{24}$  and 87.65% (90% CI: 69.23% to 110.98%) for the  $C_{max}$ .

### 3.2.1.3. *Dose proportionality*

There were no formal dose proportionality studies in either healthy volunteers or patients. However, dose proportionality was assessed descriptively in the dose escalation phase of Study 1001 in patients with advanced cancer following single doses (50 mg to 300 mg) and multiple doses (50 mg to 200 mg QD, and 200 mg to 300 mg BID). There were 37 patients in the dose-escalation cohort with at least 1 measurable plasma concentration, and 36 of these patients provided crizotinib concentration-time data evaluable for PK analysis. The PK data were summarised in the study report.

**Comment:** There was no formal evaluation of dose proportionality provided in the submission. However, dose proportionality was evaluated descriptively in patients with advanced cancer based on  $AUC_{\tau}$  or  $AUC_{inf}$  and  $C_{max}$  values. The data showed that increases in steady state  $C_{max}$  and  $AUC_{\tau}$  at C1D15 following multiple oral BID doses of crizotinib 200 mg, 250 mg, and 300 mg were greater than dose proportional (i.e., increases in  $C_{max}$  and  $AUC_{\tau}$  following 250 mg BID and 300 mg BID relative to 200 mg BID were ~ 1.7-fold and ~ 2.2-fold, respectively, compared with expected increases of 1.25-fold and 1.5-fold, respectively). These results suggest that the PKs of crizotinib are non-linear, and the sponsor speculates that this might be due to autoinhibition of CYP3A by crizotinib with increasing doses.

### 3.2.1.4. *Single and multiple-dosing pharmacokinetics of crizotinib*

#### 3.2.1.4.1. *a. Single-dose pharmacokinetics (healthy subjects and patients)*

The single-dose PKs of crizotinib have been evaluated in a total of 7 studies: 6 studies in healthy subjects (1008, 1009, 1010, 1011, 1015, and 1016) and 1 study in patients with advanced cancer (1001). Of these studies, the PKs of the lactam metabolite (PF-06260182) have been evaluated in 4 studies in healthy subjects (1010, 1011, 1015, and 1016) and 1 study in patients with advanced cancer (1001). The PKs of crizotinib following a single oral dose of 250 mg from 5 studies in healthy subjects are summarised below in Table 7.

**Table 7: Single-dose PKs - summary of crizotinib PK parameters by study following a single 250 mg oral dose of crizotinib; healthy subjects.**

Study	Formulation	N	AUC <sub>inf</sub> (ng.hr/mL)	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (hr)	t <sub>1/2</sub> (hr)	CL/F (L/hr)	Vz/F (L)
1009	Suspension†	6	2777 (38)	109 (46)	3.0 (2.0-6.0)	94.0 (15)	90.1 (26)	12110 (35)
1016	IR tablet	15	2192 (27)	102 (33)	5.0 (4.0-6.0)	33.1 (21)	119 (31) §	5940 (55) §
1008	PIC	24	2946 (31)	113 (29)	6.0 (2.0-8.0)	29.5 (16)	84.9 (35)	3567 (47)
	IR tablet	24	2723 (33)	112 (30)	6.0 (2.0-8.0)	29.1 (16)	91.8 (37)	3809 (43)
1011	PIC	35	2665 (41)	119 (39)	5.0 (2.0-6.0)	35.3 (18)	93.8 (48)	4703 (53)
	IR Tablet	35	2890 (34)	126 (28)	5.0 (1.0-8.0)	34.6 (12)	86.5 (33)	4290 (37)
	FC	35	2887 (36)	135 (33)	5.0 (2.0-6.0)	34.9 (14)	86.6 (56)	4313 (77)
1010	IR tablet	14	2321 (34)	100 (28)	5.0 (4.0-6.0)	29.0 (10)	108 (32)	4478 (35)

PIC = powder in capsule, IR = immediate release, FC = formulated capsule, ND = not determined. Geometric mean (%CV) for AUC<sub>inf</sub>, AUC<sub>last</sub>, C<sub>max</sub>, CL/F, and Vz/F; arithmetic mean (%CV) for t<sub>1/2</sub>; median (range) for T<sub>max</sub>.

† Extemporaneously prepared oral suspension containing [<sup>14</sup>C]crizotinib.

§ Arithmetic mean.

The single oral dose PKs of crizotinib 250 mg in the dose escalation and the Recommended Phase II Dose (RP2D) cohorts from Study 1001 in patients with advanced cancer are summarised below in Table 8.

**Table 8: Study 1001 - summary of crizotinib PK parameters by study following a single 250 mg oral dose of crizotinib in patients; dose escalation (dose escal) and RP2D cohorts.**

Study	Formulation	N	AUC <sub>inf</sub> (ng.hr/mL)	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (hr)	t <sub>1/2</sub> (hr)	CL/F (L/hr)	Vz/F (L)
1001 *								
Dose escal	PIC	9	1817 (33) <sup>a</sup>	87.0 (34)	4.0 (1.0-9.0)	47.1 (16)	138 (32) <sup>a</sup>	9230 (30) <sup>a</sup>
RP2D all	PIC or IRT ‡	46	2489 (51) <sup>b</sup>	108 (38)	4.0 (2.0-9.3)	42.4 (21) <sup>c</sup>	100 (50) <sup>b</sup>	5946 (63) <sup>b</sup>
ALK+NSCLC		39	2510 (50) <sup>f</sup>	109 (37)	4.0 (2.0-9.3)	43.7 (20) <sup>d</sup>	99.6 (46) <sup>f</sup>	6101 (64) <sup>f</sup>
ALK-NSCLC		4	ND	96.8 (40)	5.1 (2.2-8.8)	ND	ND	ND
Other		7	2366 (61) <sup>e</sup>	104 (48)	6.0 (4.0-6.1)	33.5 (14) <sup>e</sup>	106 (70) <sup>e</sup>	5060 (65) <sup>e</sup>

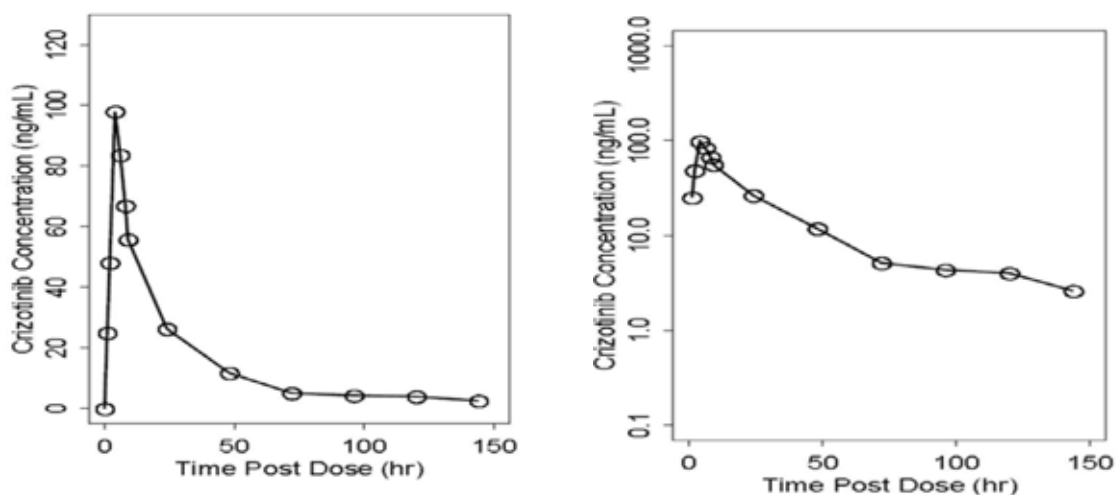
PIC = powder in capsule, IRT = immediate release tablet. ND = not determined.

Geometric mean (%CV) for AUC<sub>inf</sub>, AUC<sub>last</sub>, C<sub>max</sub>, CL/F, and Vz/F; arithmetic mean (%CV) for t<sub>1/2</sub>; median (range) for T<sub>max</sub>

\* Day -7 values presented for 1001 except Cycle 1 Day 1 data presented for ALK negative NSCLC.

<sup>a</sup> N=8; <sup>b</sup> N=29; <sup>c</sup> N=31; <sup>d</sup> N=27; <sup>e</sup> N=4; <sup>f</sup> N=25.

The median plasma crizotinib concentration – time profiles in patients with advanced cancer following single 250 mg oral dose of crizotinib are provided below in Figure 5.

**Figure 5: Study 1001 – Median plasma crizotinib concentration – time profiles following single 250 mg doses patients (linear scale, left panel; semi-log scale, right panel).**

**Comment:** In healthy subjects, values for the crizotinib AUC<sub>inf</sub>, C<sub>max</sub>, T<sub>max</sub> and CL/F were similar across the 5 studies, regardless of formulation administered. After a single oral 250 mg dose of crizotinib in the fasted state, the median T<sub>max</sub> values ranged from 3.0 to 6.0 hours, and the mean C<sub>max</sub> and AUC<sub>inf</sub> ranged from 100 to 135 ng/mL and from 2192 to 2946 ng.hr/mL, respectively. Mean estimates of terminal half-life in these studies ranged from 29 to 35 hours, with exception of



Study 1009. The longer terminal half-life (94 hours) in 1009 resulted from its prolonged blood sampling scheme.

In patients with advanced cancer, the values for the assessed PK parameters were within the range of values for the corresponding parameters in healthy volunteers. In both healthy subjects and patients, the median plasma crizotinib concentration–time profile declined in a multi-exponential manner after the  $C_{max}$  had been reached. Overall, there were no marked differences in the PKs of crizotinib following a single oral dose of 250 mg in healthy subjects and patients with advanced cancer.

#### 3.2.1.4.2. b. Multiple dose pharmacokinetics (patients)

There were no multiple dose pharmacokinetic studies in healthy volunteers. However, the multiple dose PKs of crizotinib were evaluated in the 2 clinical efficacy and safety studies in patients with advanced cancer (1001; 1005). The PKs of crizotinib were extensively investigated in Study 1001, but only limited interim PK data relating to trough plasma concentrations were provided in Study 1005. The most informative data relating to the single and multiple dose PKs of crizotinib in patients is considered to come from the RP2D (all) cohort in Study 1001. There are PK data in this cohort relating to single dose crizotinib (250 mg) and multiple dose crizotinib (250 mg BID). As of 15 September 2010, 167 patients from Study 1001 in the RP2D cohort had at least 1 measurable plasma concentration for crizotinib or the lactam metabolite (PF-06260182). The demographic characteristics of these 167 patients are summarised below in Table 9.

**Table 9: Study 1001 - Summary of demographic characteristics for the RPD2 cohorts.**

	Summary of Demographics <sup>a</sup>			
	Overall	ALK-Positive	ALK-Negative	RP2D Other
N	167	118	4	45 <sup>b</sup>
Age, years	51.0 (21-79)	51.1 (21-79)	49.5 (46-54)	50.8 (23-79)
Male, n (%)	84 (50.3%)	59 (50.0%)	2 (50.0%)	23 (51.1%)
Weight, kg	70.7 (35.5-117) <sup>b</sup>	71.3 (35.5-117) <sup>c</sup>	70.6 (56.3-84.2)	69.2 (41.0-105)
Height, cm	169 (147-193) <sup>d</sup>	169 (148-193) <sup>e</sup>	174 (168-180)	170 (147-191)
BSA, m <sup>2</sup>	1.8 (1.2-2.4) <sup>d</sup>	1.8 (1.2-2.4) <sup>e</sup>	1.8 (1.6-2.0)	1.8 (1.4-2.3)

Note: Of the 167 RP2D patients, 111 patients were white, 4 were black, 42 were Asian, and 10 were from other ethnicities which included Biracial-Black/White, Hispanic, and Indian. Abbreviations: N/n=number of patients; kg=kilogram; cm=centimeter; BSA=body surface area; ALK=anaplastic lymphoma kinase; RP2D=recommended Phase II dose.

<sup>a</sup> mean (range) for all except the number of patients (% of male) for Male

<sup>b</sup> Includes 1 patient who received midazolam only.

<sup>c</sup> n=116; <sup>d</sup> n=165; <sup>e</sup> n=116.

Of the 167 patients in the RP2D cohort, 145 provided crizotinib concentration-time data evaluable for PK analysis, and 5 Asian patients provided plasma lactam metabolite (PF-06260182) concentration data evaluable for PK analysis. Crizotinib PK parameters following single (250 mg) and multiple (250 mg BID) doses in the RPD2 cohort (all) are summarised below in Table 10. Crizotinib single (250 mg) and multiple (250 mg BID) dose PK parameters in the ALK-positive NSCLC cohort in Study 1001 were summarised in the study report. The multiple dose PKs of crizotinib (250 mg BID) in all cohorts in Study 1001 were also summarised in the study report. Limited PK data for the lactam metabolite (PF-06260182) in RP2D cohorts following single (250 mg) and multiple (250 mg BID) doses of crizotinib in small number of Asian patients (n=4) were summarised the study report.



**Table 10: Study 1001 - Descriptive summary of plasma crizotinib PK parameters following 250 mg BID dosing of crizotinib in the RP2D cohorts. <sup>a</sup>**

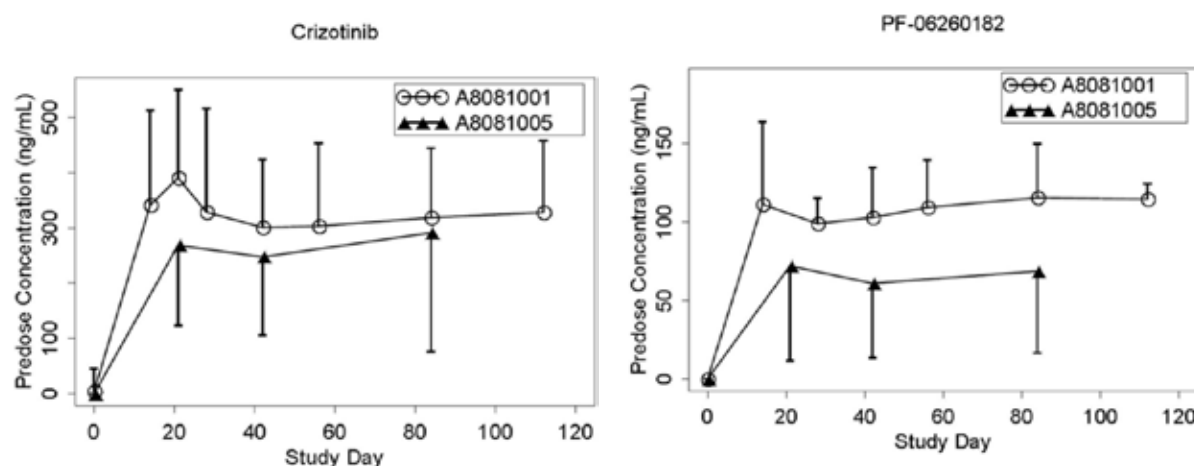
Parameters	Single Dose		Multiple Dose	
	Day -7	Cycle 1 Day 1 (C1D1)	Cycle 1 Day 15 (C1D15)	Cycle 2 Day 1 (C2D1)
N	46	98	24	18
T <sub>max</sub> , hr	4.00 (2.00-9.33)	4.05 (1.00-9.08)	4.00 (0.00-9.03)	4.00 (0.00-9.02)
C <sub>max</sub> , ng/mL	108 (38)	98.9 (45)	411 (44)	478 (38)
C <sub>trough</sub> , ng/mL	0.00 (0.00-32.6) <sup>b</sup>	0.00 (0.00-517) <sup>c</sup>	319 (1.57-1030) <sup>d</sup>	301 (3.17-849) <sup>e</sup>
AUC <sub>τ</sub> , ng.hr/mL	742 (40)	663 (45) <sup>f</sup>	3880 (36) <sup>g</sup>	4164 (38) <sup>h</sup>
AUC <sub>inf</sub> , ng.hr/mL	2489 (51) <sup>i</sup>	NA	NA	NA
CL/F, L/hr	100 (50) <sup>i</sup>	NA	64.5 (56) <sup>g</sup>	60.1 (44) <sup>h</sup>
V <sub>z</sub> /F, L	5946 (63) <sup>i</sup>	NA	NA	NA
t <sub>1/2</sub> , hr	42.4 (21) <sup>i</sup>	NA	NA	NA
Rac	NA	NA	4.84 (3.06-13.1) <sup>h</sup>	4.78 (2.75-15.4) <sup>k</sup>

<sup>a</sup> Geometric mean (%CV) for all except: median (range) for T<sub>max</sub>, C<sub>trough</sub> and Rac; arithmetic mean (%CV) for t<sub>1/2</sub>.

<sup>b</sup> n=43; <sup>c</sup> n=160; <sup>d</sup> n=109; <sup>e</sup> n=91; <sup>f</sup> n=88; <sup>g</sup> n=19; <sup>h</sup> n=16; <sup>i</sup> n=29, <sup>j</sup> n=31, <sup>k</sup> n=13.

The mean±SD trough crizotinib and lactam metabolite PF-06260182 concentrations following multiple crizotinib doses (250 mg) from Study 1001 RP2D (all) and Study 1005 are summarised below in Figure 6.

**Figure 6: Mean±SD trough crizotinib and lactam metabolite PF-06260182 concentrations following multiple crizotinib doses (250 mg) from Study 1001 RP2D all cohorts, and Study 1005 (crizotinib, left panel; PF-06260182, right panel).**



**Comment:** In patients with advanced cancer in the RP2D cohort, after reaching  $C_{max}$  following single dose crizotinib (Day-7) plasma crizotinib concentrations declined in a multi-exponential manner with a mean apparent terminal half-life of 42.4 hours. Crizotinib plasma concentrations appeared to reach steady state within 15 days following multiple dosing (250 mg BID). In Study 1001, median trough concentrations were 319 and 301 ng/mL at C1D15 and C2D1, respectively, and median trough concentrations ranged from 275 to 319 ng/mL from Day 15 (C1D15) to Day 112 (C2D1), respectively. Crizotinib  $AUC_{\tau}$  increased with multiple oral administrations and demonstrated median accumulation ratios ( $Rac$ ) of 4.84 and 4.78 at C1D15 and C2D1, respectively. The geometric mean values for  $CL/F$  at C1D15 (64.5 L/hr) and C2D1 (60.1 L/hr) were lower than that seen after a single dose on Day -7 (100 L/hr), providing further evidence that the PKs of crizotinib are non-linear. The %CV values for the  $C_{max}$  and  $AUC$  values indicate moderate inter-subject variability in exposure following both single and multiple crizotinib dosing.

### 3.2.2. Distribution

#### 3.2.2.1. Volume of distribution

The geometric mean (%CV) volume of distribution ( $V_{ss}$ ) following a single 250 mg IV dose to 14 healthy male volunteers was 1772 (18) L (Study 1010).

#### 3.2.2.2. Plasma protein binding

The extent of binding of crizotinib to human plasma proteins was determined *in vitro* using equilibrium dialysis at 7 hours at concentrations of 0.5, 5, and 20  $\mu$ M (0.23, 2.3, and 9  $\mu$ g/mL) (study PDM-014). The mean±SD unbound fraction of crizotinib in human plasma was  $0.093 \pm 0.031$ . The mean±SD unbound fractions at different crizotinib concentrations were  $0.058 \pm 0.043$  at 0.5  $\mu$ M,  $0.113 \pm 0.004$  at 5  $\mu$ M, and  $0.108 \pm 0.010$  at 20  $\mu$ M.

*In vitro* data also indicated that the mean±SD % fraction of crizotinib (concentration = 1  $\mu$ M; 450 ng/mL) binding to human serum albumin (HSA) was  $93.8 \pm 0.1\%$ , and to  $\alpha$ 1-acid glycoprotein (AAG) was  $73.7 \pm 0.1\%$  (study 144558). In this study, the total unbound fraction of crizotinib was 5.14%, based on HSA and AAG binding.

**Comment:** Binding of crizotinib to human plasma proteins was ~91%, and was independent of concentration over the range 5 to 20  $\mu$ M. Binding occurs preferentially to HSA (94%) relative to AAF (74%).

### 3.2.2.3. *Erythrocyte distribution*

*In vitro* data indicate that the mean $\pm$ SD red blood cells/plasma ratios at crizotinib concentrations 0.1  $\mu$ M, 1  $\mu$ M, and 10  $\mu$ M are  $1.41 \pm 0.20$ ,  $1.03 \pm 0.07$  and  $1.36 \pm 0.03$ , respectively, and the corresponding blood/plasma ratios are  $1.14 \pm 0.09$ ,  $1.01 \pm 0.03$ , and  $1.16 \pm 0.01$  (study PDM-015).

### 3.2.2.4. *Tissue distribution*

There were no data in humans evaluating the sites of distribution of crizotinib into the tissues (apart from distribution into red blood cells).

## 3.2.3. **Metabolism**

### 3.2.3.1. *Sites of metabolism and mechanisms / enzyme systems involved*

Following oral administration of [ $^{14}$ C]crizotinib to 6 healthy male subjects, plasma AUC<sub>inf</sub> and AUC<sub>last</sub> values of total radioactivity exceeded those of unchanged crizotinib indicating the presence of circulating metabolites (Study 1009). Metabolic profiling over 0-96 hours post-dose indicated that unchanged crizotinib was the predominant radiolabelled component in plasma, accounting for 33% of the circulating radioactivity. The major circulating metabolite was crizotinib lactam (M10, PF-06260182), accounting for 10% of the circulating radioactivity. No other single circulating component accounted for >10% of radioactivity in plasma over the time interval profiled. Minor metabolites included glucuronide (M1) and sulfate (M3) conjugates of *O*-desalkyl crizotinib (M4, PF-03255243), *O*-desalkyl crizotinib lactam (M2, PF-06268935), and the sulfate conjugate of M2 (M8).

Studies in human liver microsomes with selective chemical inhibitors demonstrated that CYP3A enzymes were the major enzymes contributing to the metabolism of crizotinib (84% inhibition by troleandomycin) (study PDM-019). Possible, but minor, involvement of CYP2D6 enzymes in the metabolism of crizotinib was also observed in human liver microsomes with selective inhibitors (17% inhibition by quinidine). However, in a subsequent study the contribution of CYP2D6 to crizotinib metabolism was not confirmed using recombinant CYP2D6 (study 163819). Recombinant CYP (rCYP) data indicated that crizotinib is mediated primarily by CYP3A4 (99.4%), with minor contributions from CYP2C19 (0.5%) and CYP2D6 (0.1%) (Study 163819), and a subsequent study indicated that both CYP3A4 and CYP3A5 mediated the metabolism of crizotinib (study 1764623).

*In vitro* studies with both human liver microsomes and rCYP also demonstrated that crizotinib was predominantly metabolized by CYP3A4/5 enzymes, with minor contributions from CYP2C8, CYP2C19, and CYP2D6 when aldehyde oxidase was present (study 145505). This study showed that CYP3A4/5 enzymes also mediated the formation of the crizotinib lactam metabolite (M10 PF-06260182), and *O*-desalkyl metabolites. However, the formation of the *O*-desalkyl metabolite (M4, PF-03255243) appears to be mediated solely by CYP3A4 (study 1445050).

Oxidation of crizotinib to the lactam metabolite (M10, PF-06260182) results in the introduction of a new chiral centre and formation of 2 possible diastereomers of the lactam metabolite (study 123536). Plasma samples from human subjects (n=4) administered a single 250 mg dose of crizotinib were analysed for each lactam diastereomer (Study 1001). The study found that the AUC of the PF-06270079 diastereomer was greater than that of the PF-06270080 diastereomer, with a mean ratio of 1.66. There are *in vitro* data showing that the mean unbound fraction in humans of the lactam metabolite PF-06260182 and its two diastereomers PF-06270079 and PF-06270080 were 0.062, 0.055, and 0.059, respectively, (study 145554).

**Comment:** The major metabolic pathways 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 have demonstrated that CYP3A4/5 are the major enzymes involved in the metabolic clearance of crizotinib and in the formation of key metabolites. The predominant

radiolabelled component in plasma was crizotinib, which accounted for 33% of the circulating radioactivity. The major circulating metabolite was crizotinib lactam (M10, PF-06260182), accounting for 10% of circulating radioactivity. None of the other identified metabolites accounted for  $\geq 10\%$  of the circulating radioactivity. Minor identified metabolites 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). The major circulating lactam metabolite was a mixture of two diastereomers, and neither accounted for  $\geq 10\%$  of radioactivity recovered from plasma. The sites of crizotinib metabolism in humans have not been identified. Presumably the major site of metabolism is the liver, but other sites (e.g., gastrointestinal tract) cannot be excluded.

### 3.2.3.2. *Non-renal clearance*

Data from Study 1009 (mass balance study), showed that the geometric mean (%CV) total plasma clearance (CL/F) of crizotinib following a single oral 250 mg dose of radiolabelled crizotinib to 6 health male volunteers was 90.1 (26) L/hr, while the geometric mean (%CV) renal clearance was 2.1 (14) L/hr. These results indicate that the crizotinib is predominantly cleared by non-renal mechanisms (presumably extensive hepatic metabolism).

### 3.2.3.3. *Metabolites identified in humans*

#### 3.2.3.3.1. *Activity of the metabolites*

Crizotinib lactam (M10, PF-06260182) and its constituent diastereomers (PF-06270079 and PF-06270080), *O*-desalkyl crizotinib (M4, PF-03255243), and *O*-desalkyl crizotinib lactam (M2, PF-06268935) were evaluated for pharmacological activity *in vitro* in ALK and c-Met/HGFR cellular pharmacodynamic assays. Crizotinib lactam was approximately 2.5 to 7.7 fold less potent than crizotinib, while the *O*-desalkyl metabolites were considered inactive. The sponsor estimates that, based on their pharmacology activity index (PAI), neither of the diastereomers of the crizotinib lactam metabolite is anticipated to contribute significantly to the primary pharmacology of crizotinib. The sponsor refers to a PAI of  $> 25\%$ , as proposed by Leclercq *et al.* (2009), as a criterion that can be used to assess the significance of contribution of a metabolite to the pharmacology of the parent drug. The PAI is defined as the ratio of the metabolite to parent AUC (corrected for  $f_u$ ) multiplied by the ratio of parent to metabolite pharmacological activity. The PAI values for both the diastereomers of the crizotinib lactam metabolite are estimated to be 2% (based on unbound AUC) or 3% (based on total AUC).

**Comment:** The data indicate that crizotinib (parent) is the primary active molecule contributing to the primary pharmacology of the drug, and that the contribution of crizotinib metabolites to the primary pharmacology of the drug appears to be insignificant.

#### 3.2.3.3.2. *Pharmacokinetics of metabolites*

The pharmacokinetics of the lactam metabolite (M10, PF-06260182) following single doses of crizotinib (150 and 250 mg) have been characterised in healthy subjects in 2 biopharmaceutic studies (1010; 1011), and 2 drug-drug interaction studies (1015; 1016). The results from these 4 studies are summarised below in Table 11. The submission included only limited preliminary information on the pharmacokinetics of the lactam metabolite (PF-06260182) in patients with advanced cancer. Information on plasma PF-06260182 concentrations was available on only 5 Asian patients with ALK+ NSCLC in the RPD2 cohort in Study 1001, and data on single and multiple dose PK parameters were available from 4 and 2 of these patients respectively.

**Table 11: Single-dose pharmacokinetics of lactam metabolite PF-06260182 in healthy volunteers.**

Study	CRZ Dose (mg) formulation	N, n	AUC <sub>inf</sub> (ng.hr/mL)	AUC <sub>last</sub> (ng.hr/mL)	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (hr)	MRA UC <sub>inf</sub>	MR AU C <sub>last</sub>	MRC <sub>max</sub>
1010	50 IV	14	NC	35.61 (45)	3.006 (45)	2.5 (2-4)	NC	0.03430 (31)	0.01880 (36)
	250 po	14, 13	360.4 (31)	342.7 (32)	26.46 (24)	5.0 (5-6.)	0.1440 (13)	0.1477 (14)	0.2577 (17)
1011	250 CIC po/fs	35	447.1 (49)	436.9 (50)	33.04 (34)	5.0 (4-10)			
	250 CIC po/fd	35	341.8 (51)	325.0 (53)	23.64 (42)	6.0 (2-10)			
1015	150 IRT po	15, 15	178.1 (31)	172.7 (31)	16.69 (28)	5.0 (4-6)	0.1371 (14)	0.1399 (14)	0.2469 (25)
	150 IRT + KET	15, 15	920.6 (35)	897.4 (35)	26.94 (20)	8 (6-10)	0.2239 (18)	0.2217 (18)	0.2766 (18)
1016	250 IRT po	15, 15	378.6 (30)	369.5 (31)	29.88 (32)	5.0 (4-8)	0.1676 (16)	0.1703 (15)	0.2839 (24)
	250 IRT + RIF	14, 14	21.78 (39)	20.28 (38)	3.291 (35)	5.0 (2-6)	0.05319 (21)	0.05332 (21)	0.09958 (37)

Note: N = number of subjects in the treatments group; n = Number of subjects contributing to the mean.

Geometric mean (%CV) for all PK parameters; except median (range) for T<sub>max</sub>.

MRC<sub>max</sub> = Metabolite to Parent Ratio C<sub>max</sub> (C<sub>max</sub>/464.33) † / ( C<sub>max</sub>/450.34) ‡

MRAUC<sub>last</sub> = Metabolite to Parent Ratio AU<sub>last</sub> (AU<sub>last</sub> /464.33) † / ( AU<sub>last</sub> /450.34) ‡

MRAUC<sub>inf</sub> = Metabolite to Parent Ratio AUC<sub>inf</sub> (AUC<sub>inf</sub> /464.33) † / ( AUC<sub>inf</sub> /450.34) ‡

† = Metabolite (PF-06260182) data corrected for molecular weights (convert ng to nmol).

‡ = Crizotinib data corrected for molecular weights (convert ng to nmol).

**Comment:** Following single oral fasted doses of crizotinib 250 mg, the PF-06260182 geometric mean C<sub>max</sub> ranged from 26.46 to 33.04 ng/mL and the geometric mean AUC<sub>inf</sub> ranged from 360.4 to 447.1 ng.hr/mL, while the median T<sub>max</sub> was 5.0 hours and ranged from 4 to 10 hours. The MRAUC<sub>inf</sub> values ranged from 0.1477 to 0.1703, and the MRC<sub>max</sub> values ranged from 0.2577 to 0.2839 following single oral fasted doses of crizotinib 250 mg. In the drug-drug interaction study (1016), the mean t<sub>1/2</sub> (%CV) of PF-06260182 following single dose crizotinib 250 mg was 22.2 (14) hours. In Study 1016, co-administration of crizotinib with rifampin increased the PF-06260182 AUC<sub>inf</sub> and C<sub>max</sub> by 5.6-fold [95% C: 4.9, 6.8] and

11.0-fold [95%CI: 9.0, 13.5], respectively, relative to crizotinib alone. In Study 1015, co-administration of crizotinib with ketoconazole increased the PF-06260182 AUC<sub>inf</sub> and C<sub>max</sub> by 5.2-fold [95%CI: 4.6, 5.8] and 1.6-fold [95% CI: 1.4, 1.6], respectively, relative to crizotinib alone.

### 3.2.4. Excretion

#### 3.2.4.1. Routes and mechanisms of excretion

In **Study 1009 (mass balance study)**, following a single radiolabelled [<sup>14</sup>C]crizotinib 250 mg oral dose, the overall mean recovery of [<sup>14</sup>C]crizotinib-related radioactivity in excreta samples was 85.2% over the 480-hour study, with recovery in individual subjects ranging from 68.6% to 91.3%. Faecal excretion was the predominant route of elimination. The overall mean recovery of radioactivity in faeces was 63.1% of the dose, with values for individual subjects ranging from 53.5% to 68.7%. 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%. Most of the administered radioactivity was recovered in the first 120 hours postdose (77.9%).

In faeces, unchanged crizotinib accounted for 53% (average) of the administered dose, and no other drug-related components accounted for an average of > 1% of the administered dose in the radio-HPLC profiles of faecal homogenate.

In urine, unchanged crizotinib accounted for 2.34% of the administered dose. The major drug-related component observed in radio-HPLC profiles of urine was a sulfate conjugate of the *O*-desalkyl lactam metabolite representing an average of 4.5% of the administered dose. No other metabolites accounted for > 1% of the total administered dose in the urine.

#### 3.2.4.2. Mass balance studies

**Study 1009** was Phase I, single-centre (Pfizer CRU, USA), open-label, single-dose (radiolabelled) study to evaluate the mass-balance and PKs of crizotinib in 6 healthy male subjects after a single oral 250 mg dose containing approximately 100 µCi of [<sup>14</sup>C]crizotinib. The dose was administered after an 8 hour overnight fast, and subjects remained fasting until 4 hours after dosing. Serial blood, urine and faecal samples were collected at specified times or over specified intervals up to 21 days postdose. The results for the PK parameters in plasma and whole blood are summarised below in Table 12. Relevant metabolic profiling and mass-balance data from this study has previously been referred to in this CER.

**Table 12: PK parameters <sup>a</sup> of crizotinib and radioactivity; single oral 250 mg dose of crizotinib containing approximately 100 µCi of [<sup>14</sup>C]crizotinib.**

Parameter	Plasma Crizotinib	Plasma Radioactivity	Whole Blood Radioactivity	RBC Radioactivity
N, n	6, 6	6, 2	6, 6	6, 6
AUC <sub>inf</sub> (ng.hr/mL) <sup>b</sup>	2777 (38)	29000, 29600 <sup>c</sup>	NC	NC
AUC <sub>last</sub> (ng.hr/mL) <sup>b</sup>	2686 (40)	22830 (11)	7032 (18)	3641 (23)
C <sub>max</sub> (ng/mL) <sup>b</sup>	109 (46)	436 (19)	312 (20)	175 (26)
T <sub>max</sub> (hr) 2.99	2.99 (1.98-6.00)	5.00 (2.98-6.00)	4.00 (2.98-6.00)	5.00 (2.98-8.00)



Parameter	Plasma Crizotinib	Plasma Radioactivity	Whole Blood Radioactivity	RBC Radioactivity
$t_{1/2}$ (hr)	94.0 (15)	134, 178 <sup>c</sup>	NC	NC
CL/F (L/hr)	90.1 (26)	8.61, 8.44 <sup>c</sup>	NC	NC

N = number of subjects; n = number of subjects contributing to the mean for AUC<sub>inf</sub>,  $t_{1/2}$ , and CL/F; NC = not calculated; CV = coefficient of variation.

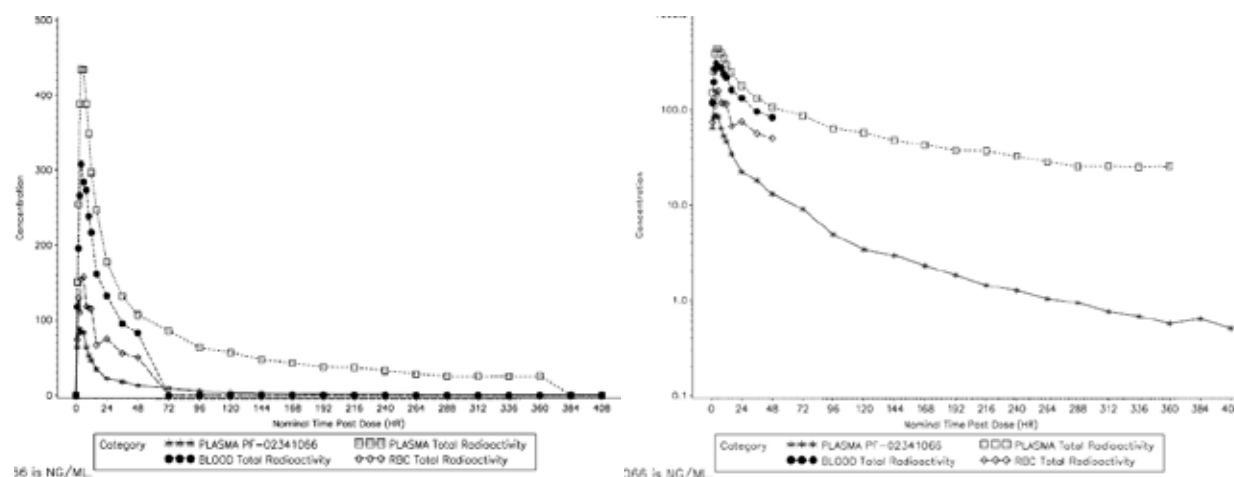
a = Geometric mean (% CV) for AUC<sub>inf</sub>, AUC<sub>last</sub>, C<sub>max</sub>, CL/F; arithmetic mean (% CV) for  $t_{1/2}$ ; median (range) for T<sub>max</sub>; individual values for AUC<sub>inf</sub>,  $t_{1/2}$ , and CL/F of plasma radioactivity due to the limited number of subjects.

b = Units for radioactivity parameters are ng-eq/mL (C<sub>max</sub>) or ng-eq·hr/mL (AUC).

c = Individual values for the 2 evaluable subjects.

Median concentration-time profiles for crizotinib (PF-02341066) in plasma and total radioactivity in plasma, whole blood and red blood cells are presented below in Figure 7.

**Figure 7: Study 1009 - Median concentration-time profiles for crizotinib (PF-02341066) in plasma and radioactivity in plasma, whole blood, and red blood cells (linear scale, left panel; log-linear scale, right panel).**



Note: For both panels, units for crizotinib (PF-02341066) are ng/mL and units for total radioactivity are ng-eq/mL.

The median crizotinib plasma T<sub>max</sub> was 3 hours, and the range was 2 to 6 hours. The geometric mean C<sub>max</sub> was 109 ng/mL. The mean  $t_{1/2}$  was 94 hours, and quantifiable plasma concentrations were measured up to 408 hours post-dose, probably accounting for the long  $t_{1/2}$  estimate. The intersubject variability (CV) was 38% for AUC<sub>inf</sub> and 46% for C<sub>max</sub>. The median plasma total radioactivity T<sub>max</sub> was 5 hours, and the range was 3 to 6 hours. The plasma exposure for crizotinib was considerably lower than that for plasma exposure for total radioactivity, with the crizotinib to radioactivity AUC<sub>last</sub> ratio of 0.12, indicating the presence of circulating metabolic products in plasma. The amount of total radioactivity in whole blood paralleled the profile for total radioactivity in plasma up to 48 hours, with peak radioactivity occurring at similar times (3 to 6 hours after dosing). The radioactivity in RBCs was low, compared with that in plasma and whole blood, indicating that the amount of radioactive products partitioning into RBCs was relatively small.

#### 3.2.4.2.1. Renal clearance

Following single oral doses of crizotinib (250 mg) to patients with advanced cancer the apparent mean terminal half life of crizotinib was 42.4 hours (%CV = 21). In Study 1009 (mass balance study), the original study report included erroneous values for the urinary excretion

parameters due to not all the data being loaded into the analysis tool (eNCA). However, the submission included a report providing the corrected data. The new data indicate that geometric mean excretion ( $A_e$  [%]) of unchanged crizotinib was 2.34% (%CV = 54), with the geometric mean excretion ( $A_e$  [mg]) of unchanged crizotinib being 5.85 mg (%CV = 54). The geometric mean renal clearance ( $CL_R$  [L/hr]) was estimated to be 2.11 L/hr (%CV = 14). The renal clearance (2.11 L/hr) is greater than the  $fu \cdot GFR$  (L/hr) (i.e.,  $0.09 \times 7.5$  L/hr = 0.675 L/hr), indicating that the drug definitely undergoes renal secretion and may be absorbed by the renal tubules.

### 3.2.5. Intra- and inter-individual variability of pharmacokinetics

In patients with advanced cancer (RP2D cohort [all]), the PKs of crizotinib showed “moderate” inter-subject variability with the %CV following multiple oral dosing of 250 mg BID crizotinib being 36% to 38% for the  $AUC_\tau$  and 38% to 44% for the  $C_{max}$ . No data could be identified in the submission assessing the intra-subject variability of crizotinib.

### 3.2.6. Population pharmacokinetic report (PMAR-01192)

The submission included a population modelling analysis report (PMAR-00192) issued on 26 January 2011. The report included a population pharmacokinetic analysis of the recommended Phase II dose of crizotinib (i.e., 250 mg BID). The objectives of the analysis were: (1) to describe the structural pharmacokinetic model; quantify the population variability in clearance and volume of distribution of crizotinib; and (2) to describe the effects of demographic factors and concomitant medications chronically used to reduce gastric pH on the PKs of crizotinib.

The analysis was performed using nonlinear mixed-effects modelling (NONMEM® Version 7.1.2). The analyses were conducted, and the final model was evaluated, using the first-order conditional estimation with  $\eta$  -  $\epsilon$  interaction (FOCEI) method. During model building, the goodness of fit of different models to the data were evaluated using the following criteria: change in the objective function, visual inspection of different scatter plots, precision of the parameter estimates, as well as decreases in both inter-individual variability and residual variability. A covariate modelling approach emphasizing parameter estimation rather than stepwise hypothesis testing was implemented. Predefined covariate-parameter relationships were identified based on exploratory graphics, scientific interest, and mechanistic plausibility of prior knowledge, and then a full model was constructed aimed to avoid correlation or colinearity in predictors. The performance of the final model was evaluated by simulating data using final parameter estimates from the final model (fixed and random effects) and conducting a predictive check. The report of the population PK analysis was comprehensive and complied with the requirements outlined in the relevant TGA adopted guideline (Guideline on Reporting the Results of Population Pharmacokinetic Analyses, CHMP/EWP/185990/06).

The population PK model was developed from a dataset from the two efficacy and safety studies (1001, 1005) in patients comprising 3184 crizotinib plasma concentrations from 250 patients with advanced cancer treated with crizotinib 250 mg BID. Of these 250 patients, 165 came from Study 1001 in the RP2D cohort with 2849 concentrations, and 85 came from Study 1005 with 335 concentrations. The 250 patients included 125 males and 125 females, with weights ranging from 36 kg to 117 kg. Weight was higher in males than females, and weight decreased with increasing disease severity. The majority of subjects in the analysis were Caucasian (65%) with the next highest percentage being Korean (15%) followed by Japanese (8%), African American (3%), Chinese (3%), Hispanic (2%), Other Asian (2%) and Other (2%). Weight was generally lower in Asian patients than in non-Asian patients.

#### 3.2.6.1. Results

The population pharmacokinetics of crizotinib were described by a two-compartment model with first-order absorption, a lag time, and a decrease in apparent (oral) clearance ( $CL/F$ ) after Cycle 1 Day 2 (i.e., after multiple dosing).



The pre-defined primary covariates of interest included:

- weight, sex, race, and ECOG status as predictors of  $CL/F$ ;
- weight as a predictor of apparent (oral) central volume of distribution ( $V2/F$ ), apparent (oral) intercompartmental clearance ( $Q/F$ ), and apparent (oral) peripheral volume of distribution ( $V3/F$ ); and
- the presence of proton pump inhibitors or H2 antagonists as a predictor of the absorption rate constant ( $ka$ ) for crizotinib.

For the effect of covariates on  $CL/F$ , the results were presented as the effect on the crizotinib area under the concentration-time curve for a dosing interval at steady-state ( $AUC_{ss}$ ) following multiple dosing of 250 mg BID. Additional covariate effects (tumour type and ALK mutation status) were investigated for their effects on  $CL/F$  via exploratory graphics following the development of the full model (this portion of the analysis was considered hypothesis generating).

The typical estimates (95% CI) of PK model parameters for the reference covariate effects (Caucasian, Male, 70 kg, ECOG status=0, no proton pump inhibitors or H2 antagonists) were:

- $CL/F = 102$  (95%CI: 91.6, 112) L/hr;
- $V2/F = 2390$  (95%CI: 2170, 2580) L;
- $Q/F = 44.4$  (95%CI: 35.7, 54.4) L/hr,
- $V3/F = 2200$  (95%CI: 1820, 2580) L;
- $CL/F_{chg} = 0.682$  (95%CI: 0.633, 0.737) – i.e., typical  $CL/F$  at steady state was estimated to decrease to 68.2% (95%CI: 63.3%, 73.7%) of the  $CL/F$  following single dose administration-
- $ka = 0.817$  (95%CI: 0.625, 1.16) hr<sup>-1</sup>; and
- $lag = 0.652$  (95%CI: 0.566, 0.759) hr

The model described that the variability in crizotinib  $CL/F$ , as demonstrated by changes in  $AUC_{ss}$ , was primarily affected by weight with typical  $AUC_{ss}$  decreasing with increasing body weight. Distributions for typical  $AUC_{ss}$  values indicated that the probability for the typical  $AUC_{ss}$  to fall outside the 80% to 125% reference range is minimal over the weight range of 50–110 kg. However, there is an 85% probability of having a typical  $AUC_{ss}$  greater than 125% of the value for the reference 70 kg individual when body weight is < 30 kg, and an approximately 30% probability of falling outside the reference range when body weight is > 130 kg. A trend towards increasing crizotinib  $CL/F$  with increasing body weight was estimated, with an effect typical estimate (95% CI) of 0.402 (0.156, 0.652). Distributions for relative typical  $CL/F$  values indicated that the probability for the typical  $CL/F$  to fall outside the 80 to 125% reference range was minimal over the weight range of 50–110 kg, and for weights < 50 kg or > 110 kg, the probability that the typical  $CL/F$  will fall outside the reference range was > 65%.

The remaining covariate effects (sex, race, and ECOG status) 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 (25% probability that the typical  $AUC_{ss}$  would be greater than 125% of the reference  $AUC_{ss}$  value for Caucasians), and ECOG performance status of 2, 3, or 4 (42% probability that typical  $AUC_{ss}$  would be greater than 125% of the reference value for ECOG status of 0 or 1). In Korean patients, a typical decrease in  $CL/F$  of ~ 16% or an increase in typical  $AUC_{ss}$  of ~ 16% was observed. However, the addition of all covariates resulted in only a small decrease in unexplained variability in  $CL/F$  (~ 6% relative change between base and final models), suggesting that the tested covariates explained only a small portion of the variability in  $CL/F$ .

The effects of H2 receptor antagonists demonstrated probability distributions for relative  $ka$  that were wide and were not entirely enclosed within the 80% to 125% reference range. This indicated that the current data set did not contain enough information to determine the relevance of this covariate effect. Probability distributions for relative typical  $ka$  values in the presence of concomitant protein pump inhibitors (PPIs) esomeprazole, omeprazole, and lansoprazole indicated there is a 98%, 92%, and 85% probability, respectively, that the typical  $ka$  would be less than 80% of the reference value. This suggests that the concomitant administration of these medications decreases the  $ka$  of crizotinib, and might reduce the bioavailability of crizotinib following oral administration. For the PPI pantoprazole, the probability distribution demonstrated results similar to those of H2 receptor antagonists indicating the current data set did not contain enough information to determine the relevance of this concomitant medication on  $ka$ .

### **3.2.7. Pharmacokinetics in other special populations**

#### **3.2.7.1. Pharmacokinetics in subjects with impaired hepatic function**

There was no formal PK study in patients with hepatic impairment. This is a deficiency in the submission as the data suggests that crizotinib is extensively cleared by hepatic metabolism.

#### **3.2.7.2. Pharmacokinetics in subjects with impaired renal function**

There was no formal PK study in subjects with impaired renal function. In urine, the percent of the dose excreted as unchanged crizotinib was 2.34% (%CV = 54%). However, 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% [Study 1009]. Consequently, it appears that renal mechanisms have an important role in the excretion of the metabolites of crizotinib. Consequently, it is considered that the absence of a formal PK study in patients with renal impairment is a deficiency in the submission.

#### **3.2.7.3. Pharmacokinetics according to age**

There were no formal PK studies investigating the effect of age on the PKs of crizotinib. Exploratory analyses (Box plots) in the Summary of Clinical Pharmacology Studies (Module 2.7.4) on patients with advanced cancer from Study 1001 showed no obvious effect of age on the PKs of crizotinib in the RP2D (all) cohort following single doses of crizotinib at Day -7 ( $AUC_{inf}$  and  $C_{max}$ ) and at C1D1 ( $C_{max}$ ), or following multiple doses of crizotinib at C1D15 ( $C_{max}$ ,  $AUC_T$ ).

#### **3.2.7.4. Pharmacokinetics related to genetic factors**

There was a small amount of PK data in the RP2D cohort in ALK-positive NSLC patients (n=39) and ALK-negative NSLC patients (n=4) following multiple dose administration of crizotinib 250 mg BID (Study 1001). The data showed similar  $C_{max}$  concentrations and  $T_{max}$  times in both groups, but no other PK parameters were determined in ALK-negative NSCLC patients.

#### **3.2.7.5. Pharmacokinetics in other special populations**

##### **3.2.7.5.1. Race**

**Study 1001** included a PK comparison between Asian and non-Asian patients with advanced cancer in the RP2D cohort (42 Asian and 125 non-Asian consisting of White, Black, and other). A total of 41 Asian and 104 non-Asian patients had crizotinib concentration-time data that were evaluable for the PK analysis. The median steady state crizotinib plasma  $C_{trough}$  (ng/mL) concentrations for Asian and Non-Asian patients following crizotinib 250 mg BID were summarised the study report. The PK parameters for crizotinib in Asian and non-Asian patients (including BSA adjusted and BW adjusted PK parameters) were provided the study report. The median plasma concentration time-profiles for Asian and non-Asian patients were provided in the study report.

**Comment:** In Study 1001, the median concentration - time profiles and systemic exposure parameters ( $AUC_{inf}$  and  $C_{max}$ ) following a single 250 mg crizotinib dose on Day -7 were similar in Asian and non-Asian patients. No marked differences in single-dose PK parameters between the two groups were evident, with the exception of a longer median  $T_{max}$  in Asian patients (6 hours) compared with non-Asian patients (4 hours). After multiple crizotinib doses (250 mg BID),  $AUC_{\tau}$ ,  $C_{max}$ , and  $C_{trough}$  on C1D15 and C2D1 were generally higher in Asian patients than in non-Asian patients. Following multiple dosing (250 mg BID), at C1D15, crizotinib  $C_{max}$  and  $AUC_{\tau}$  values in Asian patients were 1.57-fold [90% CI: 1.16, 2.13] and 1.50-fold [90% CI: 1.10, 2.04] greater than the corresponding values seen in non-Asian patients. Following multiple dosing (250 mg BID), at C2D2, crizotinib  $C_{max}$  and  $AUC_{\tau}$  values in Asian patients were 1.40-fold [90% CI: 0.994, 1.98] and 1.22-fold [90% CI: 0.859, 1.74] greater than the corresponding values observed in non-Asian patients.

The major differences in the demographic characteristics between the two groups were lower mean BW and BSA in Asian patients compared with non-Asian patients. When individual PK parameter data were adjusted for overall mean BW or BSA, the observed differences at C1D15 in the  $AUC_{\tau,ss}$  and the  $C_{max,ss}$  between Asian and non-Asian tended to be smaller than the corresponding uncorrected values. For BW, the Asian to non-Asian ratios for  $AUC_{\tau,ss}$  and  $C_{max,ss}$  changed from 1.50 and 1.57, (unadjusted) to 1.14 and 1.25 (BW adjusted), respectively. Similarly for BSA, the Asian to non-Asian ratios for  $AUC_{\tau,ss}$  and  $C_{max,ss}$  changed from 1.50 and 1.57 (unadjusted) to 1.30 and 1.38 (BSA adjusted). These results suggest that BW and BSA may be factors that influence the PK difference seen between Asian and non-Asian patients following multiple oral administrations.

In the population-PK analysis (PMAR-00192) the  $AUC_{ss}$  in Korean patients was ~ 16% higher than in Caucasian patients, but no other effects of race were observed on the population pharmacokinetics of crizotinib. In Study 1001 the comparison was between Asian and non-Asian patients, while in the population analysis the comparisons were between Caucasian patients and patients from separate racial groups (e.g., Korean or Japanese) and there was no comparison between pooled Asian and non-Asian patient groups. In Study 1001, after adjusting for weight, the  $AUC_{\tau,ss}$  at steady state (day 15) was ~ 14% higher in Asian patients compared with non-Asian patients. The steady-state results from Study 1001 were in good agreement with the results from the comparable analysis for Korean patients in the population-PK report (PMAR-00192) which showed an increase in typical  $AUC_{ss}$  of ~ 16% compared with Caucasians.

#### 3.2.7.5.2. Sex

There were no formal PK studies investigating the effect of sex on the PKs of crizotinib. However, the *population-PK analysis (PMAR-00192)* found that sex did not affect the  $AUC_{ss}$  of crizotinib. Exploratory analyses (Box plots) in the Summary of Clinical Pharmacology Studies (Module 2.7.4) in patients with advanced cancer from Study 1001 in the RP2D (all) cohort showed no notable difference between males and females for  $C_{max}$  values following single oral administration crizotinib (Day -7 and C1D1), however,  $AUC_{\tau}$  and  $C_{max}$  values were marginally lower in males following multiple oral administration of crizotinib (C1D15).

### 3.2.8. Pharmacokinetic interactions

#### 3.2.8.1. *Pharmacokinetic interactions demonstrated in human studies*

##### 3.2.8.1.1. *Study 1015 – Ketoconazole (CYP3A inhibitor) – healthy subjects*

**Study 1015** was a Phase I, single-centre (USA), open-label, 2-period, 2-treatment, 1-sequence, crossover interaction study that investigated the effect of co-administration of ketoconazole (a potent CYP3A inhibitor) and crizotinib on the PKs of crizotinib in healthy volunteers. Treatment

A (Reference) consisted of a single 150 mg dose of crizotinib administered in the fasted state on Day 1. Blood samples for the determination of plasma concentrations of crizotinib and its lactam metabolite (PF-06260182) were collected up to 144 hours post crizotinib dosing. Treatment B (Test) consisted of ketoconazole 200 mg BID (approximately 12 hours apart) administered orally on an empty stomach from Day 1 to Day 16, and a single 150 mg dose of crizotinib administered in the fasted state on Day 4. Blood samples for the determination of crizotinib and PF-06260182 plasma concentrations were collected up to 312 hours after crizotinib dosing. There was a washout period of at least 14 days between treatments. There were 15 healthy male volunteers assigned to study treatment (mean±SD age 36.5±7.6 years, range 22-49 years), and all 15 subjects completed the study. The statistical analysis of crizotinib exposure is summarised below in Table 13.

**Table 13: Study 1015 – Statistical analysis of crizotinib exposure; 15 healthy male subjects.**

Parameter	Test (criz + ket) <sup>a</sup>	Reference (criz) <sup>b</sup>	Ratio (Test/Reference) <sup>c</sup>	90% CI for Ratio
AUC <sub>inf</sub> (ng·hr/mL)	3986	1260	316.36 %	286.17, 349.73
AUC <sub>last</sub> (ng·hr/mL)	3929	1197	328.31 %	296.42, 363.63
C <sub>max</sub> (ng/mL)	94.47	65.54	144.13 %	126.42, 164.33

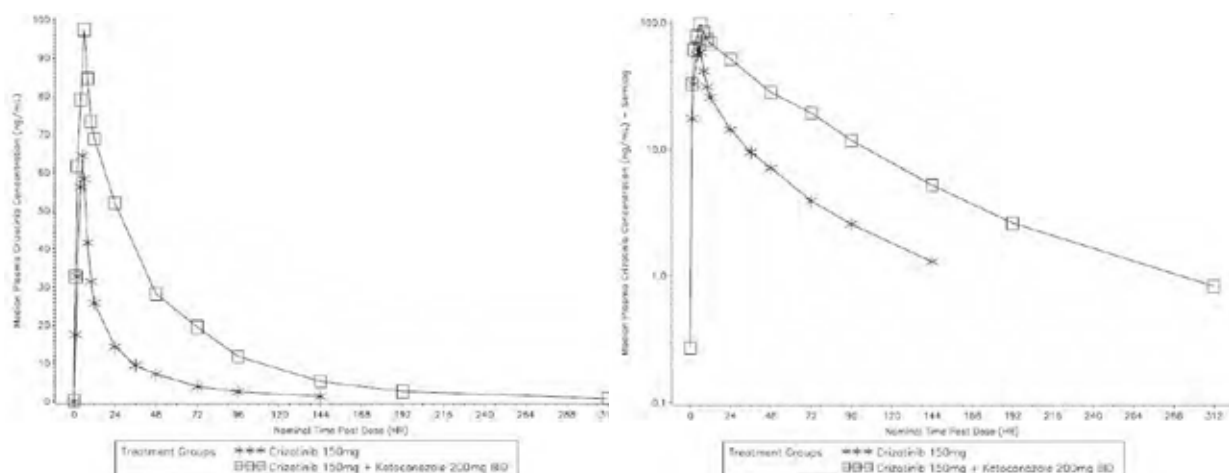
a = Test (single-dose crizotinib 150 mg [1x50 +1x100 mg IRT] + multiple-dose ketoconazole 200 mg BID);

b = Reference (single-dose crizotinib 150 mg [1x50 + 1x100 mg IRT]);

c = Ratio of adjusted geometric means and 90% CI expressed as percentages.

Median plasma crizotinib concentration-time profiles following crizotinib alone and after co-administration with ketoconazole are summarised below in Figure 8. The pharmacokinetics of crizotinib and its lactam its lactam metabolite (PF-06260182) with and without ketoconazole and the statistical analysis for the lactam metabolite were summarised in the study report.

**Figure 8: Study 1015 – Median crizotinib plasma concentration time-profiles for crizotinib alone and co-administered with ketoconazole (linear scale, left panel; semi-log scale, right panel).**



Following a single oral dose administration of crizotinib 150 mg with multiple oral doses of ketoconazole 200 mg BID, plasma exposures for both crizotinib and its lactam metabolite PF-06260182 were higher compared with exposure observed when crizotinib was administered alone. The geometric mean crizotinib  $AUC_{inf}$  and  $C_{max}$  values following co-administration of ketoconazole increased by 3.16-fold and 1.44-fold, respectively, compared with crizotinib administered alone. The geometric mean lactam metabolite (PF-06260182)  $AUC_{inf}$  and  $C_{max}$  values following co-administration of ketoconazole increased by 5.17-fold and 1.61-fold, respectively, compared with crizotinib administered alone.

When crizotinib was administered alone apparent oral crizotinib clearance (CL/F) was 3.2 fold higher than that when crizotinib was co-administered with ketoconazole. The median  $T_{max}$  for crizotinib increased from 5 hours (range 2 to 5 hours) when crizotinib was given alone to 6 hours (range 1 to 8 hours) when crizotinib was co-administered with ketoconazole. The mean  $t_{1/2}$  of crizotinib increased from 37.1 hours when crizotinib was given alone to 54.9 hours when crizotinib was co-administered with ketoconazole. The mean  $t_{1/2}$  of the lactam metabolite (PF-06260182) increased from 14.2 hours when crizotinib was administered alone to 41.8 hours when crizotinib was co-administered with ketoconazole.

Approximate increases in lactam metabolite (PF-06260182) to parent (crizotinib) ratios of 12% and 64% for  $C_{max}$  and  $AUC_{inf}$  were observed following co-administration of crizotinib and ketoconazole compared with crizotinib alone. The molar ratios of lactam metabolite (PF-06260182) to crizotinib for the  $C_{max}$  and  $AUC_{inf}$  were 0.247 and 0.137, respectively, following administration of crizotinib alone, and 0.277 and 0.224, respectively, following co-administration of crizotinib and ketoconazole.

**Comment:** This was a good quality PK drug-drug interaction study. Systemic plasma exposure to crizotinib was significantly higher following co-administration with ketoconazole (a potent CYP3A inhibitor). Crizotinib geometric mean  $AUC_{inf}$  and  $C_{max}$  values were 3.2-fold and 1.4-fold higher, respectively, following co-administration of crizotinib and ketoconazole compared with crizotinib alone. In addition, plasma exposure to the lactam metabolite (PF-06260182) of crizotinib was higher following co-administration of crizotinib with ketoconazole compared with crizotinib alone. The lactam metabolite (PF-06260182) mean  $AUC_{inf}$  and  $C_{max}$  values were 5.2-fold and 1.6-fold higher, respectively, following co-administration of crizotinib and ketoconazole compared with crizotinib alone. Systemic exposure to the lactam metabolite PF-06260182 increased to a greater extent than crizotinib following co-administration of crizotinib and ketoconazole, suggesting that the metabolism of PF-06260182 is more dependent on CYP3A than crizotinib.

#### 3.2.8.1.2. Study 1016 – Rifampin (CYP3A inducer) - healthy subjects

**Study 1016** was a Phase I, single-centre (USA), open-label, 2-period, 2-treatment, 1-sequence, crossover interaction study that investigated the effect of co-administration of rifampin (a potent CYP3A inducer) and crizotinib on the PKs of crizotinib in healthy volunteers. Treatment A (Reference) consisted of a single 250 mg dose of crizotinib administered in the fasted state on Day 1. Blood samples for the determination of plasma concentrations of crizotinib and its lactam metabolite (PF-06260182) were collected up to 144 hours post crizotinib dosing. Treatment B (Test) consisted of 600 mg QD doses of rifampin administered orally after overnight fasting from Day 1 to Day 14, and a single 250 mg dose of crizotinib administered in the fasted state on Day 9. Blood samples for the determination of crizotinib and PF-06260182 plasma concentrations were collected up to 144 hours post crizotinib dosing. The washout period between treatments A and B was at least 14 days. The study included 15 White patients (14 males, 1 female), and all 15 subjects were analysed following crizotinib treatment alone while 14 were analysed following crizotinib co-administered with rifampin. The mean $\pm$ SD age of the

15 patients was  $38.9 \pm 8.5$  years (range 30 to 55 years). The statistical analysis of crizotinib exposure is summarised below in Table 14.

**Table 14: Study 1016 – Summary of statistical analysis of crizotinib exposure; healthy subjects.**

Parameter	Test (criz + rifa) <sup>a</sup>	Reference (criz) <sup>b</sup>	Ratio (Test/Reference) <sup>c</sup>	90% CI for Ratio
AUC <sub>inf</sub> (ng·hr/mL)	399.2	2192	18.21 %	16.14, 20.54
AUC <sub>last</sub> (ng·hr/mL)	370.3	2103	17.60 %	15.48, 20.02
C <sub>max</sub> (ng/mL)	32.14	102.1	31.49 %	26.43, 37.51

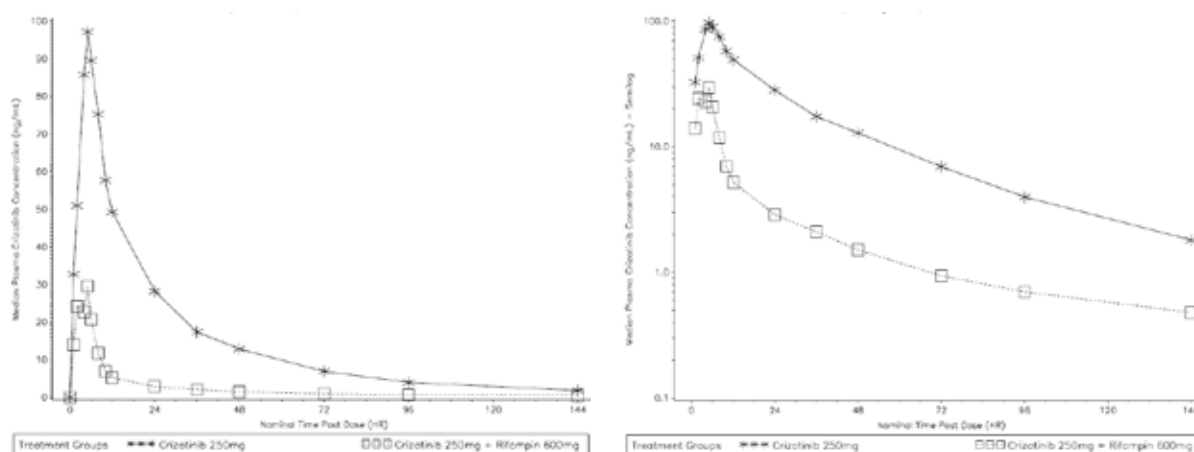
a = Test (single-dose crizotinib 150 mg [1x50 +2x100 mg IRT])+ multiple-dose rifampin 600 mg qd);

b = Reference (single-dose crizotinib 250 mg [1x50 mg + 2 x 100 mg IRT]);

c = Ratio of adjusted geometric means and 90% CI expressed as percentages.

Median plasma crizotinib concentration-time profiles following crizotinib alone and after co-administration with rifampin are summarised below in Figure 9. The pharmacokinetics of crizotinib and its lactam metabolite (PF-06260182) with and without rifampin and the statistical analysis for the lactam metabolite were summarised in the study report.

**Figure 9: Study 1015 – Median crizotinib plasma concentration time-profiles for crizotinib alone and co-administered with rifampin (linear scale, left panel; semi-log scale, right panel).**



Following co-administration of a single oral dose of crizotinib 250 mg with multiple oral doses of rifampin 600 mg QD, plasma exposures for both crizotinib and its lactam metabolite PF-06260182 were lower compared with values observed when crizotinib was administered alone. The geometric mean crizotinib AUC<sub>inf</sub> and C<sub>max</sub> values following co-administration of rifampin decreased by 81.8% and 68.5%, respectively, compared with crizotinib administered alone. PF-06260182 plasma exposure following co-administration of crizotinib and rifampin decreased by approximately 94.3% for AUC<sub>inf</sub> and 89.0% for C<sub>max</sub> compared to crizotinib administered alone.

When crizotinib was coadministered with rifampin the apparent oral crizotinib clearance (CL/F) was 5.5-fold higher than that seen when crizotinib was given alone. Following rifampin

co-administration, mean elimination  $t_{1/2}$  values for crizotinib increased from 33 hours to 48 hours, and the mean lactam metabolite (PF-06260182)  $t_{1/2}$  decreased from 22 hours to 2 hours.

Approximate decreases in lactam metabolite (PF-06260182) to parent (crizotinib) ratios of 65% and 68% for  $C_{max}$  and  $AUC_{inf}$  were observed following administration of crizotinib with rifampin compared with crizotinib alone. The molar ratios of lactam metabolite (PF-06260182) to crizotinib for the  $C_{max}$  and  $AUC_{inf}$  were 0.284 and 0.168, respectively, following administration of crizotinib alone, and 0.100 and 0.532, respectively, following the co-administration of crizotinib and rifampin.

**Comment:** This was good quality study. Systemic plasma exposure to crizotinib was significantly lower following co-administration with rifampin (a potent CYP3A inducer). The geometric mean crizotinib  $AUC_{inf}$  and  $C_{max}$  values following co-administration of rifampin decreased by approximately 82% and 69%, respectively compared with crizotinib administered alone. In addition, plasma exposure to the lactam metabolite (PF-06260182) of crizotinib was significantly lower following co-administration of crizotinib with rifampin compared with crizotinib alone. The geometric mean lactam metabolite (PF-06260182)  $AUC_{inf}$  and  $C_{max}$  values following co-administration of rifampin decreased by approximately 94% and 89%, respectively compared with crizotinib alone. Systemic exposure to the lactam metabolite PF-06260182 decreased to a greater extent than crizotinib following co-administration with rifampin, suggesting that the metabolism of PF-06260182 is more dependent on CYP3A than crizotinib.

#### 3.2.8.1.3. Study 1001 – Midazolam (CYP3A substrate) – patients

The effect of multiple administration of crizotinib on midazolam (MDZ) PKs was evaluated in 9 patients enrolled in the dose-escalation cohort of Study 1001 at crizotinib dose levels (100 mg QD and 300 mg BID), and in 14 patients from the RP2D cohorts administered 250 mg BID. Patients participating in the MDZ interaction substudy must not have taken any MDZ dose not specified in the protocol 7 days prior to the first dose of MDZ until 24 hours after the last dose of MDZ. In addition, these patients must not have taken medications, including herbal supplements, known to be CYP3A inhibitors or inducers for 7 days or 12 days, respectively, prior to the first dose of MDZ and until 24 hours after the last treatment of MDZ. The demographic characteristics of the patients in the study were summarised the study report.

The results for the 14 patients in the RP2D cohorts treated with multiple administration of crizotinib 250 mg BID are considered to be the most relevant as this is the crizotinib dosing regimen dose proposed for registration. A single 2 mg oral dose of MDZ was given on Day -7 (alone) and at C2D1 (co-administered with crizotinib). Blood samples were collected for the analysis of MDZ PKs on Day -7 and C2D1 at the following time points: 0 (predose), 0.5, 1, 2, 4, 6, 8, 9, and 24 hours post-dose. In addition, a blood sample was collected in C1D15 for exploratory metabolite profiling of crizotinib, but the results were not included in the CSR. Urine was collected for 24 hours after crizotinib dosing in C1D15 over the following intervals: 0 to 4 hours, 4 to 12 hours, and 12 to 24-hours postdose. All plasma and urine samples were analysed for MDZ concentrations using validated HPLC-MS/MS methods. The MDZ interaction analysis population included patients who had received at least 1 dose of MDZ and for which at least 1 MDZ PK parameter of interest ( $C_{max}$  or  $AUC_{inf}$ ) was available. The descriptive summary of the plasma MDZ PK parameters in the RP2D cohorts was provided in the study report. The statistical analysis of the results in the RP2D cohort are provided below in Table 15.



**Table 15: Study 1001 - Statistical comparisons of midazolam (MDZ) PK parameters between pre- and post-crizotinib co-administration in the RP2D cohorts.**

Parameter *	MDZ alone (n=14)	MDZ + Crizotinib (n=9)	Ratio (MDZ+CRI/MDZ) **	90% CI
AUC <sub>inf</sub> , ng.hr/mL	32.1	117	3.65	(2.63- 5.07)
C <sub>max</sub> , ng/mL	12.8	25.8	2.02	(1.39- 2.92)

\* Parameters = adjusted geometric means; \*\* Ratio = ratio of adjusted geometric mean.

**Comment:** In the RP2D cohort, after co-administration of MDZ (2 mg single dose) and crizotinib (250 mg BID for 28 days) the MDZ AUC<sub>inf</sub> and C<sub>max</sub> were 3.65-fold [90% CI: 2.63-5.07] and 2.02-fold [90% CI: 1.39-2.92], respectively, higher than those seen when MDZ (2 mg single dose) was administered alone. These findings suggest that crizotinib may be a moderate inhibitor of CYP3A as MDZ is metabolized by CYP3A. The AUC<sub>inf</sub> and C<sub>max</sub> ratios (MDZ+CRI/MDZ) in the dose-escalation cohort were lower with co-administration of the 100 mg QD dose (2.16 [90% CI: 1.61-2.90] and 1.32 [90% CI: 0.97-1.80], respectively) than with the 250 mg BID crizotinib dose. These findings suggest that the crizotinib mediated CYP3A inhibition might be dose-dependent.

### 3.2.8.2. *Clinical implications of in vitro findings*

#### 3.2.8.2.1. *Inhibition of CYP Enzymes*

**Study 153034** investigated the potential for crizotinib to inhibit human drug metabolizing enzymes *in vitro*. Crizotinib was evaluated at concentrations ranging from 0.1 to 30 µM (45 to 13,500 ng/mL) for inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A. The study demonstrated that crizotinib inhibited CYP3A with IC<sub>50</sub> values of 8.2 µM (3700 ng/mL) and 7.3 µM (3290 ng/mL) for felodipine oxidase and testosterone 6β-hydroxylase activities, respectively. Crizotinib also inhibited CYP2B6 and CYP2C9, with IC<sub>50</sub> values of 22 µM (9910 ng/mL) and 23 µM (10,400 ng/mL), respectively. Low inhibitor potency was observed for CYP1A2, CYP2C8, CYP2C19, CYP2D6, and CYP3A (midazolam 1'-hydroxylase) (IC<sub>50</sub> values >30 µM).

**Study PDM-017** investigated the time-dependent inactivation of CYP3A by crizotinib in human liver microsomes. The formation of 1'-hydroxy-midazolam from midazolam was used as a marker for CYP3A activity. The maximum rate of inactivation (k<sub>inact</sub>) and inhibitor concentration associated with the 50% maximal inactivation rate (K<sub>I</sub>) for CYP3A were estimated to be 0.11 min<sup>-1</sup> and 3.0 µM, respectively. In this study, the maximum free plasma concentration of crizotinib at steady-state (C<sub>max,free</sub>) was estimated to be approximately 20 nM at a clinical dose of 100 mg QD. The study estimated that, based on the Hall's equation using the predicted C<sub>max, free</sub>, K<sub>I</sub> and k<sub>inact</sub> (20 nM, 4.6 µM and 0.20 min<sup>-1</sup>, respectively), the potential *in vivo* drug interaction caused by crizotinib is predicted to be less than 2-fold in humans. Therefore, the authors conclude that clinically significant drug-drug interactions due to CYP3A inhibition by crizotinib would be unlikely to occur with co-administered CYP3A substrates.

**Comment:** The *in vitro* study 153034 data suggest that crizotinib inhibits CYP3A. The ratios of C<sub>max</sub>/IC<sub>50</sub> for CYP3A were > 0.1, based on the mean steady-state crizotinib C<sub>max</sub> of 411 ng/mL (0.91 µM) observed in patients with cancer (Study 1001), and crizotinib IC<sub>50</sub> values for the relevant substrate probes. The ratios of crizotinib C<sub>max</sub>/IC<sub>50</sub> were < 0.1 for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and



CYP2D6 suggesting that the possibility of interactions between drugs metabolized by these six enzymes and crizotinib are unlikely. The possibility of an interaction due to competitive inhibition is remote if the ratio of  $C_{max}/K_i$  (or  $C_{max}/IC_{50}$ ) is  $<0.1$ , possible if the ratio is between 0.1 and 1, and likely if the ratio is  $>1$  (Bjornsson et al., 2003).

In the *in vitro* study PDM-017, crizotinib demonstrated time-dependent inhibition of CYP3A4 in human liver microsomes. However, based on the *in vitro* data the authors predicted the potential *in vivo* drug inhibition on CYP3A4 caused by crizotinib to be less than 2-fold in humans, and considered this to be clinically insignificant. However, the  $C_{max}$  used in the calculation of Hall's equation was based on a crizotinib dose of 100 mg QD, which is significantly less than the proposed dose of 250 mg BID. Consequently, the estimated *in vivo* inhibitory effect of crizotinib on CYP3A4 based on the *in vitro* data is likely to be an underestimation.

The *in vivo* data from the midazolam interaction sub-study in patients with cancer (Study 1001) showed that multiple dose crizotinib 250 mg BID inhibited the single-dose (2 mg) PKs of midazolam. Following crizotinib administration, midazolam  $AUC_{inf}$  and  $C_{max}$  values were, respectively, 3.65-fold [90% CI: 2.63-5.07] and 2.02-fold [90% CI: 1.39-2.92] higher than those seen when midazolam was administered alone. These findings indicate that crizotinib is a moderate inhibitor of CYP3A.

#### 3.2.8.2.2. Induction of CYP3A4

**Study 153446** investigated the potential of crizotinib to induce CYP3A4 (testosterone as substrate) and CYP1A2 (ethoxyresorufin as substrate) *in vitro* using cryopreserved human hepatocytes. Treatment of the human hepatocytes with crizotinib caused marked induction of CYP3A4 mRNA levels at concentrations up to 7  $\mu$ M (3150 ng/mL), but did not show induction of testosterone 6 $\beta$ -hydroxylase. However, low cell viability was observed at concentrations of 7  $\mu$ M. The CYP3A4 induction kinetic parameters,  $EC_{50}$  and  $E_{max}$  could not be calculated on activity data since a true  $E_{max}$  could not be reached due to low cell viability at maximum crizotinib concentrations. Therefore, approximate estimations of  $EC_{50}$  and  $E_{max}$  induction parameters for CYP3A4 were calculated based on mRNA from three lots of human hepatocytes ( $EC_{50}$  and  $E_{max}$  = 0.47 and 6.4 [Lot HIE]; 0.79 and 23 [Lot Hu8020]; 3.1 and 29 [Lot Hu4026]). Treatment of human hepatocytes with crizotinib did not show induction of ethoxyresorufin-O-deethylation at the concentrations tested.

**Comment:** Study 153446 showed that crizotinib caused induction of CYP3A4 mRNA levels, but did not induce CYP3A4 activity. The sponsor speculated that this finding is likely due to crizotinib mediated time-dependent inhibition of CYP3A4. Crizotinib did not induce CYP1A2 activity, and would not be expected to reduce plasma concentrations of co-administered drugs metabolized by this enzyme. The sponsor comments that most drugs that induce CYP3A levels are believed to do so primarily via activation of the pregnane X receptor (PXR), and notes that activation of PXR can also result in upregulation of CYP2B and CYP2C genes, as well as other Phase II enzymes and transporters. There were no data in the submission on the risk of potential drug interactions mediated via induction of CYP2B or CYP2C enzymes. However, the sponsor states that *in vitro* studies are on-going with these two enzymes.

#### 3.2.8.3. Potential to inhibit efflux transporters

**Study 14187** investigated whether crizotinib is an inhibitor of P-glycoprotein (P-gp, also identified as Multi-Drug Resistance protein or MDR1) by measuring its effect on the flux of the clinically relevant probe substrate, digoxin, in Caco-2 cells. The maximal mean reduction of

digoxin efflux mediated by crizotinib at the highest concentration evaluated (20  $\mu\text{M}$ , 9000 ng/mL) was 31% of the control value, which represented an inhibition of 69%. In addition to showing that crizotinib was an inhibitor of P-gP, the study also showed that crizotinib is a P-gP substrate for efflux by exhibiting a BA/AB efflux ratio > 2.5 in Caco-2 cells (BA, the secretory direction; AB the absorptive direction). The  $\text{IC}_{50}$  of crizotinib was calculated to be 5.79  $\mu\text{M}$  in Caco-2 cells.

**Study 182103** investigated whether crizotinib is an inhibitor of the efflux transporter, BCRP (breast cancer resistance protein). The study showed that crizotinib did not fully inhibit BCRP efflux at the highest concentration that was tested (< 42 % inhibition at 30  $\mu\text{M}$ ), so determination of an  $\text{IC}_{50}$  value was not possible.

**Comment:** Based on the mean steady-state crizotinib  $C_{\text{max}}$  of 411 ng/mL (0.91  $\mu\text{M}$ ) in patients with cancer (1001) and the  $\text{IC}_{50}$  values in study 14187, the ratio of  $C_{\text{max}}/\text{IC}_{50}$  is 0.16 (i.e., > 0.1) suggesting that *in vivo* inhibition of the P-gp efflux transporter by crizotinib is possible. There were no clinical drug-drug PK interaction studies between crizotinib and P-gp substrates in the submission. The data from study 182103 showed that crizotinib was a weak inhibitor of BCRP-mediated efflux of topotecan *in vitro*, with less than 42% inhibition observed at 30  $\mu\text{M}$  (13,500 ng/mL).

#### 3.2.8.4. **Potential to inhibit selected hepatic uptake transporters**

**Study 181858** investigated the inhibitory potency of crizotinib against the human hepatic uptake transporter OATP 1B1 when expressed in HEK293 cells. The uptake of pravastatin was used as the probe substrate. The results showed at low concentrations (0.1  $\mu\text{M}$  to 5  $\mu\text{M}$ ), crizotinib causes an apparent increase in pravastatin uptake; 27% above the level of uptake observed in the absence of inhibitor. However, at higher concentrations, crizotinib exhibited an inhibitory effect on the uptake of pravastatin. When compared with the effect of positive control inhibitor rifamycin SV, which represents maximum inhibition, crizotinib reached a maximum inhibition of 70% when tested at 100  $\mu\text{M}$  (the limit of solubility in this assay). The  $\text{IC}_{50}$  was estimated by fitting the baseline uptake (i.e. the curve at 100% inhibition) using the rifamycin SV data. Using this method, the  $\text{IC}_{50}$  for crizotinib inhibition against OATP 1B1 was calculated at 47.8  $\mu\text{M}$ .

**Study 095303** investigated the inhibitory potency of crizotinib against the human hepatic uptake transporter OATP 1B3 when expressed in HEK293 cells. The uptake of rosuvastatin was used as the probe substrate. The results showed that the uptake of rosuvastatin was inhibited by crizotinib in a concentration-dependent manner. Complete inhibition was not observed at the highest test concentration achievable (100  $\mu\text{M}$ ) due to compound solubility limitations, as compared with uptake in the presence of 30  $\mu\text{M}$  rifampicin. The uptake in the presence of 30  $\mu\text{M}$  rifampicin data was therefore used as a fixed background level of uptake at 100% inhibition in order to determine an  $\text{IC}_{50}$  value. Using this method, the  $\text{IC}_{50}$  of crizotinib against OATP 1B3 was calculated at 44  $\mu\text{M}$ .

**Study 194244** investigated the hepatic uptake of crizotinib in human hepatocyte suspensions. Rosuvastatin was used as positive control for hepatic uptake. The results indicate that crizotinib enters hepatocytes by passive diffusion at both 1  $\mu\text{M}$  and 25  $\mu\text{M}$ . In contrast, the uptake of rosuvastatin (positive control) was fully inhibited by rifamycin.

**Comment:** Studies 181858 and 095303, showed that crizotinib had weak, dose-dependent *in vitro* inhibitory effects on OATP 1B1 and OATP 1B3, respectively. These findings are supported by the results from study 194244 that showed uptake of crizotinib into human hepatocytes *in vitro* is by passive diffusion. Based on the mean steady-state crizotinib  $C_{\text{max}}$  of 411 ng/mL (0.91  $\mu\text{M}$ ) in patients with cancer who received multiple oral doses of 250 mg BID (Study 1001), and the  $\text{IC}_{50}$  values for crizotinib determined in studies 181858 and 095393, the ratios

of  $C_{max}/IC_{50}$  were  $< 0.1$  suggesting that crizotinib is unlikely to be an *in vivo* inhibitor of substrates for the hepatic uptake transporters OATP 1B1 and OATP 1B3.

### 3.3. Evaluator's overall conclusions on pharmacokinetics

Overall, the pharmacokinetics of crizotinib were reasonably well characterized. 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 have the potential to increase systemic exposure to crizotinib.
- No drug-drug PK interaction study between crizotinib and 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 have the potential to increase systemic exposure to such substrates.
- No drug-drug interaction study between and drugs known to increase the gastric pH (e.g., antacids, H<sub>2</sub> 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 (i.e., 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 (e.g., ORR), and safety (e.g., ALT increased).

#### 3.3.1. 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  $AUC_{\tau}$  values following crizotinib 250 mg BID 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  $AUC_{\tau}$  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 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 BID in patients with advanced cancer, with the  $C_{max}$  and  $AUC_{\tau}$  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 BID 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 CV following multiple oral dosing of 250 mg BID crizotinib being 36-38% for the  $AUC_{\tau}$  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 indicates 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) (Module 2.4, 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  $\mu$ M (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). 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  $\mu$ M (study PDM-015).
- Following oral administration of a single radiolabelled dose of [ $^{14}$ C]crizotinib (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 (e.g., 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<sub>inf</sub> and C<sub>max</sub> 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 BID, repeat dose) decreased the crizotinib geometric mean AUC<sub>inf</sub> and C<sub>max</sub> 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 BID) co-administered with single dose midazolam (2 mg), a CYP3A substrate, increased midazolam AUC<sub>inf</sub> and C<sub>max</sub>

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 (i.e., AUC  $\geq$  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 metabolized 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 OATP1B1 and OATP1B3. 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 (e.g., OCT2, OAT1, OAT3). 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 status on AUCs demonstrated probability distributions for typical AUCs that fell within the 80% to 125% reference range for all categories except Korean race 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<sub>τ</sub> and C<sub>max</sub> values following 250 mg BID 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 BID) (a potent CYP3A inhibitor) markedly increased systemic crizotinib exposure compared with crizotinib administered alone. The crizotinib AUC<sub>inf</sub> and C<sub>max</sub> increased 3.16-fold and 1.44-fold, respectively, following co-administration, and the corresponding increases in the lactam metabolite (PF-06260182) AUC<sub>inf</sub> and C<sub>max</sub> 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 QD), a potent inducer of CYP3A, markedly reduced systemic crizotinib exposure compared with crizotinib administered alone. The crizotinib AUC<sub>inf</sub> and C<sub>max</sub> decreased 81.8% and 68.5%, respectively, following co-administration, and the corresponding decreases in the lactam metabolite (PF-06260182) AUC<sub>inf</sub> and C<sub>max</sub> 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.

## 4. Pharmacodynamics

### 4.1. Studies providing pharmacodynamic data

#### 4.1.1. Population modelling analysis report (PMAR-00224)

##### 4.1.1.1. 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 characterizing the effects of crizotinib exposure on the QT interval (QTc or heart rate corrected QT), evaluating Asian patients as a covariate on the concentration-QTc 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-QTc 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 data, 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 guideline (Guideline on Reporting the Results of Population Pharmacokinetic Analyses, CHMP/EWP/185990/06).

##### 4.1.1.2. 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%) Asian patients.
- **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 msec, 373 msec, 429 msec, 409 msec and 419 msec.
- **Crizotinib concentration data:** Crizotinib doses ranged from 50 mg QD to 300 mg BID, and the concentration data are summarised below in Table 16.



**Table 16: 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 msec/ng/mL [90% 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 BID (Study 1001 CSR) was 15.9 bpm (90% CI: 14.3, 17.5). Asian group (Asian vs. 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, 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 msec/ng/mL [90% CI: 0.0019, 0.0122]. Based on this model, an average QTcS increase of 0.7 msec (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 BID (Study 1001), a crizotinib induced increase in QTcS is predicted to be 3.4 msec [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 msec 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 msec/ng/mL (90% CI: -0.0163, -0.0051) for QTcB and for (non-Asian subjects) 0.0149 msec/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 (i.e., QTcS data) to interpret the clinical relevance of the observed concentration – QT data, rather than the standard correction factors used in clinical practice



(i.e., 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 msec (90% CI: 0.9, 5.8). The mean increase was < 5 ms and the upper bound of the 90% CI was < 10 msec. 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 (i.e., 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/m<sup>2</sup> (males) and 500 mg/m<sup>2</sup> (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 IC<sub>50</sub> of 1.1  $\mu$ 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 characterized 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" (CHMP/ICH/2/04).

## 5. 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 (i.e., 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<sub>24</sub>) exceeded 2.4  $\mu$ g-h/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 17.

**Table 17: Dose-limiting toxicities (DLTs).**

Toxicity Category	Toxicity/Grade
Hematologic	Prolonged Grade 4 neutropenia for >7 days
	<sup>a</sup> 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

<sup>a</sup> 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 NCI CTCAE (v3.0). 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 (eg, 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 BID, 300 mg BID, and 250 mg BID. The frequency of dosing was changed from QD to BID 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 **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 BID, 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 BID dose level. No DLTs were observed in the 3 patients initially treated with 250 mg BID, and the cohort was further expanded to have 6 evaluable patients (2 patients were not evaluable) with no DLTs reported. Therefore, 250 mg BID 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 BID dose level.

## 6. Clinical efficacy

### 6.1. Efficacy study (1001) – Designated pivotal by the sponsor

#### 6.1.1. Study design, objectives, locations and dates

##### 6.1.1.1. *Background*

The title of this ongoing study is – “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”.

The preliminary clinical study report (CSR) was generated to support Regulatory Market Authorization Applications. The first patient visit was on 19 April 2006 and the last patient visit for the purposes of the preliminary CSR occurred on 15 September 2010. There were snapshots of the active clinical database on 29 October 2010 and 1 November 2010. The study used electronic CRFs (eCRFs), which enabled continuous flow of data into the database.

In addition to the preliminary CSR, the submission also included a 60-day clinical data update report with the last patient visit for the purposes of the report being 01 February 2011. There was a snapshot of the active clinical database on 15 March 2011. All data entered in the electronic data capture system on the date of database snapshot were included in the serious adverse event (SAE), death, and Overall Survival (OS) summaries.

The data in the preliminary CSR were generated from the USA (6 centres), Australia (1 centre) and Korea (1 centre). There have been a number of publications based on this study and these were summarised in the study report.

##### 6.1.1.2. *Objectives*

1. Determine the safety profile of crizotinib including identification of dose-limiting toxicity (DLT) and maximum tolerated dose (MTD);
2. Determine the recommended Phase II dose (RP2D) and regimens of crizotinib;
3. Determine PK profile of crizotinib following oral administration including the effect of food;
4. Perform initial evaluation of crizotinib-related cytochrome P450 3A4 (CYP3A4) inhibition using midazolam (MDZ) as a probe;
5. Perform exploratory evaluation of c-Met/HGFR genotype and expression, pharmacodynamic (PD) endpoints, and biomarkers for crizotinib; and
6. Document any evidence of antitumour activity of crizotinib.

##### 6.1.1.3. *Design*

Study 1001 is a Phase I, multicentre, multinational, open-label, dose-escalation, safety, PK, PD, and antitumour activity study of crizotinib 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 study was originally designed as a Phase I, dose-escalation study in patients with any tumour type (except leukemia) followed by a **Recommended Phase II Dose (RP2D)** expansion cohort to include at least 8, but no more than 15 patients, to further evaluate the safety, PKs and MTD of crizotinib. However, there were numerous modifications to the original design with 15 amendments being made to the original protocol. As information about the safety and antitumour activity of crizotinib emerged, additional cohorts and sub-studies were introduced. In order to simplify the analyses, the study was divided into 3 parts:

1. Dose escalation for determination of MTD for BID dosing, which included all tumour types.

2. RP2D cohorts: ALK-positive NSCLC; ALK-negative NSCLC; and other (i.e., ALK-dependent tumours other than NSCLC and c-Met-dependent tumours).
3. Dose escalation for determination of MTD for QD dosing, which included patients with any tumour types, except for patients with ALK-negative or c-Met-dependent tumours. This segment of the study was initiated shortly before the database snapshot date for the preliminary CSR and was not included in the report.

In addition, midazolam (MDZ) interaction sub-studies were conducted in the dose-escalation and RP2D cohorts, and a food effect substudy was conducted in the enriched RP2D cohorts. These sub-studies have been reviewed in the relevant pharmacokinetic sections of this CER.

A treatment cycle was defined as 4 weeks of crizotinib treatment for all patient groups except for the ALK-negative NSCLC cohort, where a cycle was defined as 3 weeks.

**Comment:** In this CER, the review of the efficacy data centres on the ALK-positive NSCLC cohort (one of the RP2D cohorts) as this is the relevant cohort for the purposes of this submission. Study 1001 was designated by the sponsor as the pivotal efficacy and safety. However, the design features in Study 1001 considered to be unusual in a study designated as “pivotal” include: (a) the study was designed to gather initial information on the PKs, PDs, MTD, and safety of crizotinib which could be used in the design of subsequent Phase II and 3 studies; (b) the study was not specifically designed as a confirmatory Phase III therapeutic confirmatory study to establish the risk-benefit profile of crizotinib in patients with ALK-positive NSCLC; (c) efficacy objectives were not pre-specified as either primary or secondary study objectives; (d) the only efficacy objective listed for the study was “document any evidence of antitumour activity” (objective number 6); (e) the study specified a number of efficacy endpoints aimed at supporting objective number 6 but neither overall survival (OS) nor progression free survival (PFS)/disease free survival (DFS) were specified as primary or secondary endpoints; and (f) the study is open-label, and single-arm rather than randomised, controlled (placebo or active), and double-blind. The absence of data from a randomised, controlled-arm makes interpretation of “pivotal” efficacy data from an open-label, single-arm study problematic.

#### 6.1.1.4. ***Inclusion and exclusion criteria***

In addition to the inclusion and exclusion criteria, the study included standard criteria relating to patient withdrawal from oncology studies. In the case of patient withdrawal, every effort was required to document patient outcome.

**Comment:** The inclusion and exclusion criteria were extensive and are considered to be acceptable. In all cohorts, female or male subjects, 18 years of age or older were eligible for inclusion. Other important eligibility criteria in all cohorts included solid tumours with measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST, v1.1). Target lesions that had been previously irradiated were not considered measurable unless an increase in size was observed following completion of radiation therapy. In the investigator’s opinion, patients were required to be able to receive at least 2 cycles of treatment. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 was required. However, patients in the RP2D enriched population cohort or ALK-negative NSCLC cohort with an ECOG performance status of 2 may have been allowed to enter the study following agreement between the investigator and sponsor. Resolution of all acute toxic effects of prior therapy or surgical procedures to Grade  $\leq$  1 (except alopecia) was required. Adequate bone marrow, hepatic, and renal function were also required.

#### 6.1.1.5. **Study treatments**

Patients enrolled in the RPD2 cohorts received crizotinib 250 mg BID, with a cycle length of 4 weeks for all patient groups, except for the ALK-negative NSCLC cohort where a cycle was defined as 3 weeks. The crizotinib 250 mg BID dosing regimen was based on the data from the dose-escalation cohort (see *Dosage Selection for the Pivotal Studies*).

#### 6.1.1.6. **Efficacy variables and outcomes**

##### 6.1.1.6.1. **Methods used to assess efficacy**

1. **Tumour imaging assessments** at screening/baseline were to include computed tomography (CT) or magnetic resonance imaging (MRI) scans of the chest, abdomen, and pelvis, but brain and bone scans were to be performed at baseline only if disease was suspected. Scans were to be repeated every other cycle (i.e., every 8 weeks) at all sites of known or suspected disease; whenever disease progression was suspected; to confirm a partial or complete response (at least 4 weeks after initial documentation of response); and at the end/withdrawal from the study. In the ALK-positive NSCLC cohort, disease response was categorized using RECIST (v1.0) criteria.
2. **Follow-up survival data** were to be collected at least every 3 months after discontinuing study treatment for a minimum of 1 year after the last dose.

##### 6.1.1.6.2. **Efficacy endpoints**

The efficacy endpoints specified in the *Supplemental Statistical Analysis Plan (V1.1) for ALK-Positive NSCLC patients* dated 27 October 2011 were used to support study objective number 6 (i.e., document any evidence of anti-tumour activity of crizotinib for the subgroup of ALK positive, NSCLC patients). The specified efficacy endpoints are listed below:

- objective response rate (ORR);
- duration of response (DR);
- time to response (TTR);
- disease control rate (DCR) at weeks 8 and 16;
- progression free survival (PFS);
- 6 month PFS probability;
- overall survival (OS);
- 6 month and 1 year survival probability.

The efficacy endpoints of ORR, DR, TTR, DCR, and PFS were based on the investigator assessment of tumour response defined by RECIST criteria. However, an additional efficacy analyses based on independent radiology review (IRR) of tumour data (RECIST criteria) was also specified. The IRR was to be performed by an independent third-party core imaging laboratory in accordance with a review charter. It was to consist of sequential locked reads by two radiologists assessing images independently of Pfizer and of each other, and blinded to outside radiology reports, investigator assessments, and adverse events. The IRR appears to have been instigated at the request of the FDA.

For the purposes of the definitions of efficacy endpoints, the term “on study” includes the period from the date of the first dose until 35 days after the last dose of study medication (28 days + 1 week allowance). However, deaths were included in the PFS analysis if they occurred within 16 weeks (2 tumour assessment timeframes) from the last tumour assessment “on study”, and were included in the OS analysis irrespective of time of occurrence. In the definitions of efficacy endpoints, “first dose” refers to the Cycle 1, Day 1 (C1D1) dose.

The PFS for ALK-positive NSLC patients were evaluated in the **safety analysis (SA) set** which included all enrolled patients who received at least one dose of crizotinib on C1D1. The SA population is the primary population for all standard analyses (i.e., study conduct and patient disposition; baseline characteristics; treatment administration/compliance) and safety analyses.

The ORR, DCR, DR and TTR for ALK-positive NSLC patients were evaluated in the **response-evaluable (RE)** population, defined as all patients in the SA set who have an adequate baseline disease assessment (. The acceptable time window for baseline evaluations to be performed was 35 days prior to first dose of study treatment. However, the efficacy analysis included 6 patients with baseline data outside this window (36 days to 9 months) to prevent loss of important information contributing to the efficacy evaluation of crizotinib. In addition, for any interim reporting of the data, patients also needed to meet 1 of the following 2 criteria: (a) had at least one post-baseline disease assessment; (b) withdrew from the trial or experienced progression/death at any time on study.

**Comment:** Neither the preliminary CSR nor the Supplemental Statistical Analysis Plan (SAP) for ALK-positive NSCLC patients dated 27 October 2010 specified primary or secondary efficacy endpoints. This is inconsistent with the relevant TGA adopted clinical guideline on the evaluation of anticancer medicinal products (CPMP/EWP/205/Rev.3/Corr) which state that for Phase III therapeutic confirmatory trials, “acceptable primary endpoints include OS and PFS/DFS. If PFS/DFS is the selected primary endpoint then OS should be reported as secondary and vice versa”. The clinical overview (Module 2.5) stated that the primary efficacy endpoint was the ORR and the secondary endpoints included TTT, DR, and DCR at 8 and 16 weeks, PFS, and OS. However, this categorization appears to be a post hoc classification

#### 6.1.1.7. ***Randomization and blinding methods***

Not applicable. The study was open-label and single-arm. However, as noted above an additional efficacy analysis based on IRR of tumour data was specified.

#### 6.1.1.8. ***Analysis populations***

The relevant analysis populations for the assessment of efficacy and safety in ALK-positive NSLC have been referred to above (i.e., the RE population and SA set).

#### 6.1.1.9. ***Sample size***

There were no formal sample size calculations.

#### 6.1.1.10. ***Statistical methods***

- No formal statistical hypothesis testing was planned or undertaken.
- The primary analyses of tumour response were based on the investigator’s assessment of tumour data.
- The point estimate for ORR was provided along with the corresponding 2-sided 95% CI using the exact method based on the F-distribution. The best overall response was also summarised. For patients with a best response of stable disease (SD), the duration of SD was summarised using the following time intervals: 0 to < 3 months; 3 to < 6 months; 6 to < 9 months; 9 to < 12 months; and ≥ 12 months.
- Disease control rate (DCR) at Weeks 8 and 16 was summarised as for the ORR.
- Time-to-event endpoints (including DR, PFS, and OS) were summarised using the Kaplan-Meier (KM) method and displayed graphically. Median event times (and quartiles) and 2-



sided 95% CIs for the median were provided. Descriptive statistics were also provided for DR for the subgroup of responders who had an event (disease progression or death).

- TTR was summarised using descriptive statistics. In addition, the number and percent of patients with TTR in the following time intervals was provided: 0 to <8 weeks; 8 to <16 weeks; 16 to <24 weeks; and  $\geq 24$  weeks.
- The 6-month survival probability for both PFS and OS was estimated using the KM method, and 2-sided 95% CIs were calculated for the 6-month survival probabilities. The 1-year OS probability was estimated in a similar fashion.
- For ORR, additional multivariate analyses were performed to explore the influence of various baseline characteristics.
- Duration of follow-up for OS was summarised using the reverse KM method. The median event time (and quartiles) and 2-sided 95% CI for the median were provided.
- No values were imputed for missing data for the primary and secondary efficacy analyses, except for time-to-event endpoints where non-event observations were censored, and for ORR where patients with no post-baseline tumour evaluations were counted as non-responders.
- No formal interim analysis was planned. The final analysis will be performed after the last visit of the last subject. However, earlier analyses of the data may be performed for publication and regulatory reporting purposes.
- Descriptive statistics for agreement between investigator assessment of tumour response and IRR were provided.

#### 6.1.1.11. ***Participant flow***

The preliminary CSR included efficacy (and safety) data from snapshots of the active clinical database on 1 November 2011, and the 60-day clinical data update report included a snapshot of this database on 15 March 2011.

In the preliminary CSR, there were 119 patients with ALK-positive NSCLC in the SA population, and in the 60-day clinical data there were 136 patients in this population. The 60-day clinical update report included only updated efficacy results for OS.

In the preliminary CSR, of the 119 patients with ALK-positive NSCLC, 116 were included in the RE population and 3 were excluded due to absence of data at the 1 November 2010 snapshot. The median duration of follow-up at the time of the database snapshot of 1 November 2010 was 11.0 months (95% CI: 9.2, 12.8 months). Patient disposition for the 119 ALK-positive NSCLC patients in the preliminary CSR is summarised below in Table 18.



**Table 18: Study 1001 (preliminary CSR) – Disposition of patients with ALK-positive NSCLC treated with crizotinib 250 mg BID.**

Assigned to study treatment	119
Treated	119 (100%)
Ongoing at database snap shot date	77 (6.47%)
Discontinued	42 (33.5%)
Adverse event	3 (2.5%)
Progressive disease	25 (21.0%)
Patient died	8 (6.7%)
Patient no longer willing to participate in the study	1 (0.8%)
Other <sup>a</sup>	5 (4.2%)

<sup>a</sup> Other included patients with clinical progression not consistent with RECIST).

#### 6.1.1.12. **Major protocol violations/deviations**

Review of these deviations suggests that they are unlikely to significantly affect the efficacy and safety analyses of this study.

#### 6.1.1.13. **Baseline data**

The main baseline characteristics of the 119 patients with ALK-positive NSCLC included in the preliminary CSR are summarised below:

- The mean±sd age of the patients was 50.9±13.0 years (m = 59, 49.6%; f = 50.4%) and the range was 21 to 79 years. The majority of patients were White (74, 62.2%), followed by Asian (34, 26.6%), Other (8, 6.7%), and Black (3, 2.5%).
- Almost all patients had a histological classification of adenocarcinoma (97.5%, n=116).
- The majority of patients had Stage IV disease at baseline (95.8%, n=114), and the remainder had Stage III disease (4.2%, n=5). In addition, nearly all patients had measurable disease at baseline (96.6%, n=115) and adequate baseline assessment (98.3%, n=117). The most frequently reported conditions (medical history) at baseline were hypertension (24.4%) and gastroesophageal reflux disease (18.5%).
- ECOG status at baseline was 0 (34.5%, n=42), 1 (52.9%, n=63), 2 (11.8%, n=14), or 3 (0.8%, n=1). These results indicate that the majority of patients (ECOG 0 or 1) were fully active (ECOG = 0) or restricted in physical strenuous activity but ambulatory and able to carry out light work of a sedentary nature (ECOG = 1).
- Of the 119 patients, 118 had a positive ALK marker test by either non-Massachusetts General Hospital (MGH) Clinical Trial Assay (CTA) (52.9%, n=63) or MGH FISH-CTA (46.2%,

n=55), and 1 patient had an uninformative ALK marker test result locally, but was positive when retested by MGH. There were 3 major non-MGH CTAs:[information redacted].

- Of the 119 patients, most had received prior treatment for NSCLC (86.6%, n=103). Nearly all patients had been treated with prior surgery for NSCLC (98.3%, n=117), and prior radiation therapy had been received by more than half of all patients (57.1%, n=68). Of the 119 patients, most (86.6%, n=103) had received previous systemic therapy for their disease, while 16 (13.4%) had not received prior therapy for locally advanced or metastatic disease and were therefore in the first-line treatment setting at the time of enrolment. The most commonly reported prior systemic treatment regimen was platinum-based, administered to 92 (77.3%) patients for locally advanced or metastatic disease and 17 (14.3%) patients as adjuvant or neoadjuvant therapy.
- Of the 119 patients, 93.3% (n=111) received at least one drug treatment other than for NSCLC prior to the start of study treatment. The most common drug classes were analgesics (47.1%), followed by drugs for acid related disorders (42.9%), psycholeptics (41.2%), vitamins (33.6%), and ophthalmologicals (28.6%).

#### 6.1.1.14. *Concomitant treatments*

Of the 119 patients, 96.6% (n=115) received concomitant drug treatment during the study. The most common drug classes were drugs for acid related disorders (61.3%), psycholeptics (58.0%), analgesics (56.3%), anti-emetics and anti-nauseants (54.6%), and ophthalmologicals (47.1%).

#### 6.1.1.15. *Duration of exposure to crizotinib*

In the SA population (n=119), as of the database snapshot of 1 November 2010, for patients in the preliminary CSR the mean±SD duration of exposure was 31.9±22.7 weeks (range: 0.7 to 101.7 weeks), the mean±SD actual dose intensity was 491.5±25.5 mg/day, and the mean±SD relative dose intensity was 98.3±5.1%.

### 6.1.2. **Results for the efficacy outcomes in ALK-positive NSLC patients**

#### 6.1.2.1. *Objective Response Rate (ORR)*

The best overall response based on investigator assessed tumour data using RECIST criteria at the database snapshot (preliminary CSR) is summarised below in Table 19.

**Table 19: Study 1001 (Preliminary CSR) - Best Response <sup>a</sup> in ALK-positive cohort; RE population.**

Outcome	ALK-positive NSCLC cohort (n=116)
<b>Objective Response Rate (CR+PR)</b>	<b>61.2% (95% CI: 51.7, 70.1)</b>
Complete Response (CR)	2 (1.7%)
Partial Response (PR)	69 (59.5%)
Stable Disease (SD)	31 (26.7%)
Progressive Disease (PD)	6 (5.2%)
Early Death <sup>b</sup>	3 (2.6%)
Indeterminate <sup>c</sup>	5 (4.3)

a Best overall response was based on the investigator assessed tumour data

b Early death was death within 42 days (6 weeks) from first dose.

c 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 IRR (n=105), the ORR was 52.4% (55/105) [95%CI: 42.4, 62.2]. Best overall response results based on the IRR were summarised in the study report. Overall, 86 of the 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%.

#### 6.1.2.2. ***Duration of Response (DR)***

The preliminary median estimate for DR was 48.1 weeks (95%CI: 35.9, not reached) based on the KM method, but only 26 (36.6%) of the 71 patients with 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).

#### 6.1.2.3. ***Time to Tumour Response (TTR)***

Of the 71 patients with a confirmed objective response, the mean (SD) TTR was 11.2 (7.4) weeks and the median was 7.7 weeks (range: 4.3, 39.6 weeks). Of the 71 patients, 39 (54.9%) had a response in the period 0 to < 8 weeks, 18 (25.4%) had a response in the period 8 to < 16 weeks, 10 (14.1%) had a response in the period 16 to < 24 weeks, and 4 (5.6%) had a response at ≥ 24 weeks.

#### 6.1.2.4. ***Disease Control Rate (DCR)***

Of the 116 patients RE population, disease control (CR, PR, or SD) after the first dose of crizotinib was achieved by 92 patients at week 8 (79.3% [95%CI: 70.8, 86.3]), and 78 patients at week 16 (67.2% [95%CI: 57.9, 75.7]).

#### 6.1.2.5. ***Stable Disease (SD)***

Of the 31 patients with best response SD (i.e., ≥ 6 weeks from Cycle 1 Day 1), 29.0% (9/31) had SD duration of 0 to < 3 months, 48.4% (15/31) had SD duration of 3 to < 6 months, 19.4% (6/31) had SD duration of 6 to < 9 months, 3.2% (1/31) had SD duration of 9 to < 12 months, and no patients had SD duration of > 12 months.

#### 6.1.2.6. ***Overall Response in individual patients***

The waterfall plot of best percent change in target lesions from baseline by individual patient based on investigator assessment showed that about 90% of patients had at least some degree of tumour shrinkage during the study, based on assessment of PD, SD, PR or CR.

#### 6.1.2.7. ***Progression Free Survival (PFS)***

In the 119 patients in the SA population, the median PFS was 10.0 months (95%CI: 8.2, 14.7). The probability of being event free at month 6 was 71.9% (95%CI: 61.8, 79.7). Of the 119 patients, 40 (33.6%) had objective disease progression, 10 (8.4%) had died without objective disease progression, and 69 (58.0%) were censored.

#### 6.1.2.8. ***Overall Survival (OS)***

The 60-day clinical data update report included updated OS data for the SA population (n=136). In this update, the median OS had still not been reached for patients in the study population. Death had occurred in 40 (29.4%) patients, and 96 (70.6%) patients had been censored with 95 (69.6%) of these patients still being in follow-up for OS. The 6 and 12 month survival probabilities were 87.5% (95%CI: 80.4, 92.2) and 75.7% (95%CI: 66.8, 82.5), respectively.

### 6.1.2.9. *Efficacy (ORR) in special groups*

In baseline subgroup analyses the ORR was: (1) statistically significantly higher ( $p=0.003$ ) in Asians (82.4%, 28/34) compared with non-Asians (52.4%, 43/82), and remained statistically significantly higher after adjusting for baseline characteristics; (2) decreased with increasing number of prior treatments and ranged from 80.0% (12/15) with no prior treatments to 56.7% (17/30) with > 3 prior treatments; (3) surprisingly increased with higher ECOG performance status score ranging from 53.8% (21/39) with ECOG = 0 to 78.6% (11/14) with ECOG = 2; (4) was higher in patients aged  $\geq 65$  years 68.8% (11/16) compared with patients aged < 65 years 60.0% (60/100), but there was a marked imbalance in patient numbers between the two groups; and (6) was almost identical in males 61.0% (36/59) and females 61.4% (35/57).

## 6.2. **Efficacy study (1005) – Designated supportive by the sponsor**

### 6.2.1. **Study design, objectives, locations and dates**

#### 6.2.1.1. *Background*

The title of this study was – “Phase II, Open-Label Single Arm Study of the Efficacy and Safety of PF-02341066 in Patients with Advanced Non-Small Cell Lung Cancer (NSCLC) Harboring a Translocation or Inversion Involving the Anaplastic Lymphoma Kinase (ALK) Gene Locus”.

The preliminary clinical study report (CSR) was generated to support Regulatory Market Authorization Applications. The first patient visit was 7 January 2010 and the last patient visit for the preliminary CSR was 15 September 2010, with a database snapshot on 29 October 2010. The preliminary CSR for 1005 included only limited efficacy data compared with the preliminary CSR for Study 1001, which is the reason the sponsor designated the studies “supportive” and “pivotal”, respectively. However, the 60-day clinical data update report included additional efficacy data for Study 1005 with data cut-off date of 1 February 2011, and a database snapshot on 17 March 2011.

In the preliminary CSR, 57 centres had enrolled patients at the database snapshot of 29 October 2010 (Australia [2 centres], Canada [1 centre], France [4 centres], Germany [3 centres], Hong Kong [2 centres], Italy [3 centres], Japan [5 centres], Republic of Korea [3 centres], Poland [1 centre], Russian Federation [1 centre], Spain [5 centres], and United States [27 centres]).

#### 6.2.1.2. *Objectives*

##### 6.2.1.2.1. *Primary objectives:*

- To assess the antitumour efficacy (ORR) of oral single-agent crizotinib administered to patients with advanced ALK-positive NSCLC after failure of at least 1 line of chemotherapy; and
- To assess the safety and tolerability of oral crizotinib.

##### 6.2.1.2.2. *Secondary objectives:*

- To assess secondary measures of clinical efficacy including OS, DR, DCR at 6 and 12 weeks, and PFS;
- To determine PKs using population PK (POPPK) methods and to explore correlations between PK, response, and/or safety findings;
- To explore the relationship of ALK gene fusion to the presence of ALK protein and fusion transcript;
- To correlate changes from baseline in expression of biomarkers in signaling pathways (including Janus kinase [JAK]/signal transducers and activators of transcription [STAT],

mitogen-activated protein kinase [MEK]/extracellular signal-regulated kinases [ERK], and phosphatidyl inositol-3-kinase [PI3K]/AKT pathways) to PK and outcome measures; and

- To assess patient-reported outcomes (PRO) of health-related quality of life (HRQoL), disease/treatment-related symptoms of lung cancer, and general health status.

**Comment:** Phase II study (1005) was primarily established to assess the efficacy and safety of crizotinib in ALK-positive NSCLC patients. The primary study objective included assessment of crizotinib after failure of at least 1 line of chemotherapy. This contrasts with the proposed indication which does not restrict crizotinib to second-line treatment.

#### 6.2.1.3. *Design*

This is a Phase II, ongoing, multicentre, multinational, open-label, single-arm study of crizotinib in patients with locally advanced or metastatic ALK-positive NSCLC. The diagnostic test used to detect the ALK fusion events is an ALK break-apart FISH assay performed by a central laboratory.

The patient population included female or males aged 18 years of age or over with histologically or cytologically proven ALK-positive NSCLC that was locally advanced or metastatic. Patients enrolling in this study were either: (1) randomised into chemotherapy arm of the ongoing Phase III Study 1007 and discontinued from treatment due to RECIST criteria defined progression of disease as determined by independent radiology review; or (2) were ineligible for Study 1007 due to prior chemotherapy (as defined in inclusion criterion 3). Patients who were eligible for inclusion in Study 1007 were excluded from Study 1005. All patients were required to have measurable disease as per RECIST criteria and to have adequate organ function as defined in inclusion criterion 9. The study also included standard criteria relating to patient withdrawals. In cases of withdrawal, every effort was to be made to document the patient outcome.

Crizotinib 250 mg (administered as 2 x 100 mg tablets and 1x 50 mg tablet) was to be administered orally BID at approximately the same time each day on a continuous dosing schedule. Crizotinib could be taken without regard to meals. Cycles were defined in 21-day treatment periods to facilitate scheduling of visits and assessments.

Investigators were encouraged to employ best supportive care according to local institutional clinical practices, and according to pre-specified guidance for selected AEs relating to nausea and vomiting, and reductions in heart rate (<40 bpm). In addition, dose modifications were specified for non-haematological toxicity, ALT elevation with total bilirubin elevation < Grade 2 or ≥ Grade 2, left ventricular diastolic function, prolonged QTc interval, pneumonitis, visual disturbance, and haematologic toxicity (excluding lymphopenia).

Study treatment was to be continued until the occurrence of disease progression or clinical deterioration, unacceptable toxicity, patient withdrawal of consent, or protocol noncompliance. Crizotinib treatment could be continued after disease progression if the patient was considered to be deriving clinical benefit as judged by the investigator.

#### 6.2.1.4. *Efficacy variables and outcomes*

##### 6.2.1.4.1. *Efficacy evaluations*

###### a) Tumour assessments

Tumors must have measurable disease as per RECIST criteria. Tumour assessment at screening included computed tomography (CT) or magnetic resonance imaging (MRI) of the chest, brain, abdomen, and pelvis, and a bone scan was also required. Post-baseline tumour assessments were to be performed every 6 weeks from the date of the first dose of crizotinib (with the exception of bone scans to be performed every 12 weeks only if bone metastases were present at screening) until radiographic progressive disease (PD) had been documented. The date of the first dose of crizotinib was used as the point of reference to calculate the time of next tumour

assessment. CT or MRI scans were to be performed whenever disease progression was suspected (e.g., symptomatic deterioration). Antitumour efficacy was based on objective tumour assessments made according to RECIST criteria. CT scans were to be performed with contrast agents unless contraindicated for medical reasons. The same imaging modality was to be used throughout the study to measure disease. Tumor evaluation by positron emission tomography (PET) scan or by ultrasound may not have been substituted for CT or MRI scans. Post-baseline tumour assessment of the brain must have been included when brain metastases were noted at screening, otherwise, the brain was only evaluated when clinically indicated.

When new effusions or ascites were present and represented the only potential site of disease progression, cytological analysis was to be performed, and the results, malignant or nonmalignant, should have been recorded.

Measurable lesions that had been previously irradiated were not to be considered target lesions unless an increase in size had been observed following completion of radiation therapy.

All available images were to be sent to independent radiology laboratory for supplementary assessment of efficacy. Patient management decisions were based on the investigator's review of the CT or MRI scans.

b) Other efficacy evaluations – patient reported outcome assessments

Patient reported outcomes (PROs) of HRQoL, disease/treatment-related symptoms of lung cancer, and general health status were assessed using the European Organization for the Research and Treatment of Cancer Questionnaire (EORTC QLQ-C30), its corresponding module for lung cancer (QLQ-LC13), the EuroQoL (EQ-5D), and a newly developed visual symptom assessment questionnaire (VSAQ-ALK). Patients completed the self-administered questionnaires at Day 1 of each cycle and at the end of treatment/withdrawal. The EORTC QLQ-C30, the QLQ-LC13, the EQ-5D, and the VSAQ-ALK were to be completed by the patient prior to any testing, treatment, or discussion with the physician or clinic personnel.

6.2.1.4.2. *Efficacy endpoints*

Primary endpoints:

- ORR;
- Type, incidence, severity, seriousness, and relationship to study medications of AE and any laboratory abnormalities.

Secondary endpoints:

- OS, DR, TTR, DCR at 6 and 12 weeks, and PFS;
- Plasma concentrations of PF-02341066 (crizotinib);
- Types of EML4-ALK fusion variants and ALK protein expression;
- Protein expression of identified biomarkers in serial tumour samples from surgery or biopsy, when available;
- HRQoL, lung cancer disease/treatment-related symptoms, and general health status.

**Comment:** The primary efficacy analyses in the preliminary CSR and the 60-day clinical update report were based on the investigator's assessment of tumour data. The primary efficacy endpoint was ORR. As discussed previously in the CER, the ORR primary efficacy endpoint is inconsistent with relevant TGA adopted guidelines. Overall, the specified efficacy endpoints (ORR, OS, DR, TTT, DCR [weeks 6 and 12], and PFS) are consistent with those specified in the Phase I study (1001). The efficacy endpoint definitions are the same as those for the Phase I study (1001). Although OS and PFS were specified secondary efficacy endpoints, no data were



provided in either the preliminary CSR of 60-day clinical data update for Study 1005 on these endpoints.

#### 6.2.1.5. **Randomisation and blinding methods**

This was an open-label, single-arm study. Consequently, patients were not randomised nor were patients and investigators blinded to treatment. However, all available tumour scans were to undergo independent blinded radiological review.

#### 6.2.1.6. **Analysis populations**

- The **safety analysis (SA) population** included all patients who were enrolled and received at least 1 dose of crizotinib. The SA population was the primary population for evaluating patient characteristics, treatment administration, and safety endpoints, and will be used to summarize the efficacy endpoints of PFS and OS in the final CSR. In both the preliminary CSR and the 60-day clinical data update, the safety analysis population included 136 patients.
- The **response evaluable (RE) population** was defined as all patients in the SA population who had an adequate baseline tumour assessment. The RE population was the primary population for the efficacy endpoint analyses of ORR, DCR, DR and TTR. In addition, for any interim reporting of the data, patients also needed to meet 1 of the following 2 criteria: (1) had at least 1 post-baseline disease assessment ( $\geq 6$  weeks from the first dose of crizotinib); or (2) withdrew from the study or experienced progression/death at any time on study. Adequate baseline tumour assessments were defined as evaluations that were within 35 days prior to the first dose of crizotinib, included target and/or non-target disease with a corresponding measurement or assessment recorded, and were assessed with acceptable methods (as detailed in the SAP). Baseline tumour assessments were analysed in accordance with the SAP. In the preliminary CSR, the RE population included 76 of the 136 patients in the SA population, and in the 60-day update of clinical data the RE population included 133 of the 136 patients in the SA population.
- The **patient report outcome (PRO) evaluable population** was defined as the patients from the SA population who completed a questionnaire prior to dosing with study drug and at least 1 post-baseline PRO questionnaire. The PRO evaluable population is the primary population for determining change from baseline scores, and will also be used in the final CSR to assess the proportion of patients with scores that improved, worsened, or remained stable over treatment.

#### 6.2.1.7. **Sample size**

No specific hypothesis tests were planned or undertaken. The goal of the primary analysis was to estimate the ORR including the 95% CI. The 95% CI conditional on estimated sample sizes are summarised below in Table 20. For example, when the estimate ORR equals 40% and sample size equals 250, the 95% CI for the true ORR will be (34%, 46%).

**Table 20: Study 1005 – 95% CI conditional on estimated ORR.**

95% CI for ORR			
ORR	Sample Size		
	100	150	250
30%	(21%, 40%)	(23%, 38%)	(24%, 36%)
40%	(30%, 50%)	(32%, 48%)	(34%, 46%)
50%	(40%, 60%)	(42%, 58%)	(44%, 56%)

It was estimated that 250 enrolled patients would provide more than 90% power to detect any adverse events that occurred with a frequency of  $\geq 1\%$ . Furthermore, with 250 patients, the predicted 95% CI for the adverse event rate will be (0.3%, 3.5%) if three patients (1.2%) have the same adverse event.



### 6.2.1.8. *Statistical methods*

The SAP (Final) outlined the statistical analyses:

- The ORR and the 95% exact CI were to be provided. The best overall response results were to be summarised and SD was categorized according to duration in several time intervals. Subgroup analyses of the ORR were also to be provided.
- Time-to-event endpoints were to be summarised using the Kaplan-Meier method, and median event times with 2-sided 95% CIs were to be provided.
- The point estimates of the rates were to be provided along with the corresponding exact 2-sided 95% CIs using the exact method based on the F-distribution.
- Descriptive statistics, including mean, standard deviation, median, minimum, and maximum values, were to be provided for continuous endpoints.
- For the analyses of categorical data, the number and percentage of patients in each category were to be provided.

**Comment:** The statistical methods outlined in the SAP (Final) dated 27 October 2010 are considered to be acceptable. The analyses of the data in the preliminary CSR and the 60-day clinical data update did not differ significantly from those outlined in the SAP (Final). However, no data were provided on OS or PFS in the preliminary CSR or the 60-day clinical update data. It was stated in the preliminary CSR that analyses of the OS and PFS were not presented due to immaturity of the data, and in the 60-day clinical update it was stated that median OS and PFS are not yet available.

### 6.2.1.9. *Participant flow*

Enrolment in this study is still ongoing. In the preliminary CSR, 148 patients had been enrolled and 136 of these patients had received documented study treatment with crizotinb (including 13 who had crossed-over from the comparator arm of Study 1007), 3 were enrolled in error and did not receive study treatment, and 9 did not yet have documentation of study treatment administration at the time of the database snapshot. These 136 treated constituted the safety analysis (SA) population in the preliminary CSR, and these patients also constituted the SA population in the 60-day clinical data update.

In the preliminary CSR, of the 136 patients included in the safety analysis population at the date of the database snapshot, 119 (87.5%) were ongoing and 17 (12.5%) had discontinued from the study. In the 60-day clinical data update, of the 136 patients included in the safety analysis population at the database snapshot, 93 (68.4%) were ongoing and 43 (31.6%) had discontinued from the study. Patient disposition in the SA population at the two database snapshot dates is provided below in Table 21.

**Table 21: Disposition at the end of treatment; safety analysis population.**

	Prelim CSR (n=136) <sup>a</sup>	60-day update (n=136) <sup>b</sup>
Ongoing	119 (87.5%)	93 (68.4%)
Discontinuation – Total	17 (12.5%)	43 (31.6%)
Subject died	5 (3.7%)	6 (4.4%)
Completed	0	0

	Prelim CSR (n=136) <sup>a</sup>	60-day update (n=136) <sup>b</sup>
Global deterioration of health status	1 (0.7%)	2 (1.5%)
Adverse event	3 (2.2%)	6 (4.4%)
Objective progression or relapse	8 (5.9%)	26 (19.1%)
Protocol violation	0	0
Study terminated by sponsor	0	0
Lost to follow-Up	0	1 (0.7%)
Subject not willing to continue for reasons other than AE	0	2 (1.5%)
Other	0	0

a 29 October 2010 – date of database snapshot.

b 1 February 2011 – date of database snapshot.

In the preliminary CSR, the response evaluable (RE) population consisted of 76 of the 136 patients in the SA population, and in the 60-day clinical data update the RE population consisted of 133 of the 136 patients in the SA population. In the preliminary CSR, a total of 60 patients were excluded from the RE population due to: (1) post-baseline tumour assessment  $\geq$  6 weeks after the first dose was not available at the time of the database snapshot; and (2) patients did not progress, discontinue, or die during the study. The large number of patients excluded from the efficacy analysis in the preliminary CSR was mainly due to the high enrolment rate observed in the months immediately prior to the database snapshot. However, by the time of the 60-day clinical data update report, 57 of the 60 patients originally excluded from the RE population had become eligible for inclusion in the RE population.

#### 6.2.1.10. **Major protocol violations/deviations**

The sponsor identified 16 patients with “major and relevant” protocol deviations. The most commonly reported “major and relevant” protocols deviations were failure to obtain re-consent using an updated consent procedure (n=5), followed failure to perform all required screening safety laboratory tests (n=3). All other “major and relevant” protocol deviations occurred in only 1 patient. There were a total of 40 patients with protocol deviations (i.e., “major and relevant” plus others), and the most commonly reported deviations (n=22) related to the screening ophthalmological examination being either incomplete or not done.

**Comment:** Review of the “major and relevant” protocol deviations and the total protocol deviations suggests that that none of the deviations are likely to have invalidated the efficacy and safety analyses reported in this study.

#### 6.2.1.11. **Baseline data**

The main baseline characteristics of the 136 patients in the SA population are summarised below:

- The mean $\pm$ SD age was 52.7 $\pm$ 11.3 years (m/f = 47.1/52.9 %), and the age range was 29 to 82 years. The majority of patients were White (64.0%, n=87), followed by Asian (31.6%, n=43), black (3.7%, n=5), and other (0.7%, n=1).

- The majority of patients had a histological classification of adenocarcinoma (94.1%; n=129), and no patients had squamous cell carcinoma. The majority of patients had metastatic disease (94.1%, n=128), and the minority had locally advanced disease (5.9%, n=8). All tumours were identified as ALK-positive by FISH using the central laboratory.
- The mean duration between histopathological classification and date of first dose of crizotinib was 2.7 years (range 0.2 to 13.7 years). Measurable disease was present in 97.1% (n=132) of patients, not present in 1 (0.7%) patient and not reported in 3 (2.2%) patients; measurable disease was defined as at least 1 target lesion  $\geq$  2 cm or at least 1 target lesion  $>$  1 cm for spiral CT scan. Adequate baseline assessment was present in 97.8% (n=133) of patients and not reported in 3 (2.2%) patients. Baseline ECOG status was 0, 1, and 2 in 27.9% (n=29), 53.7% (n=73), and 18.4% (n=25) of patients, respectively.
- All patients had received at least 1 prior systemic treatment for NSCLC, nearly all patients had been treated with prior surgery (97.8%, n=133), and more than half of all patients had received prior radiation therapies (56.6% (n=77)).
- The majority of patients (93.4%, n=127) had received 2 or more prior systemic treatment regimens, and the number of prior systemic treatment regimens ranged from 1 to 11. The most commonly reported prior systemic therapy for advanced disease was platinum based therapies (86.8%, n=118), followed by EGFR TKI-containing therapies (53.7%, n=73).
- The best response to prior line of metastatic treatments was partial response (PR) reported in 17.7%, 15.5%, and 3.6% of patients with first-line chemotherapy, second-line chemotherapy, or prior single-agent metastatic EGFR tyrosine kinase inhibitor therapy, respectively. No patients had achieved a prior complete response (CR) with any treatments.
- Overall, 119 (87.5%) patients in the SA population reported any prior drug treatment, not including treatment for their primary disease prior to study treatment. The most commonly reported prior medications (i.e.,  $\geq$  25% of patients) were: analgesics (45.6%, n=62); drugs for acid-related disorders (34.6%, n=47); psycholeptics (32.4%, n=44), laxatives (29.4%, n=40); mineral supplements and ophthalmologicals (each in 26.5%, n=36); and corticosteroids (dermatological preparations) and vitamins (each in 25.0%, n=34).

#### 6.2.1.12. **Concomitant treatments**

Overall, 126 (92.6%) patients in the SA population reported concomitant drug treatments. The most commonly reported concomitant medications (i.e.,  $\geq$ 25% of patients) were: analgesics (50.7%, n=69); psycholeptics (47.1%, n=64); drugs for acid-related disorders (46.3%, n=63); laxatives (42.6%, n=59); mineral supplements (40.4%, n=55); anti-emetics and antinauseants (34.6%; n=47); ophthalmologicals (33.1%, n=45); antidiarrhoeal, intestinal anti-inflammatory/anti-infectious agents (31.6%, n=43); antithrombotic agents (28.7%, n=39); nasal preparations (29.4%, n=40); corticosteroids for systemic use (27.9%], n=38), vitamins (27.2%, n=37); drugs for functional gastrointestinal disorders (25.7%, n=35); and corticosteroids (dermatological preparations) and cough and cold preparations (each 25.0%, n=34).

Concomitant nondrug treatments were reported in 40 (29.4%) patients, including 16 (11.8%) patients with investigations (e.g., aspiration pleural cavity, chest x-ray, ultrasound Doppler), and 33 (24.3%) patients with surgical and medical procedures (e.g., oxygen supplementation, compression stockings, fluid replacement).

#### 6.2.1.13. **Exposure to crizotinib**

In the preliminary CSR, the mean $\pm$ SD duration of exposure in the SA population (n=136) was 10.7 $\pm$ 8.1 weeks (range: 0.1 to 36.1 weeks), the mean $\pm$ SD actual dose intensity was 483.4 $\pm$ 41.6 mg/day, and the mean $\pm$ SD relative dose intensity was 96.7 $\pm$ 8.3%. In 60-day clinical update data report, the mean $\pm$ SD duration of exposure in the SA population (n=136) was 23 $\pm$ 11.1 weeks

(range: 0.9 to 53.1 weeks), the mean±SD actual dose intensity was 466.9±63.1 mg/day, and the mean±SD relative dose intensity was 93.4±12.6%.

#### 6.2.1.14. Results for the primary efficacy outcome

The results for the primary efficacy endpoint of ORR in the preliminary CSR and the 60-day clinical data update are summarised below in Table 22. The best response outcomes were based on investigator assessment of tumour data using RECIST criteria.

**Table 22: Study 1005 – Best Response (investigator assessed); RE population.**

Outcome	Preliminary CSR (RE=76)	60-day updated (RE = 133)
Objective Response Rate (CR+PR)	30.3% (95%CI: 20.2, 41.9]	51.1% (95%CI: 42.3%, 59.9%)
Objective response (CR + PR) confirmed	23 (30.3%)	68 (51.1%)
Complete Response (CR) confirmed	0	1 (0.8%)
Partial Response (PR) confirmed	23 (30.3%)	67 (50.4%)
Stable Disease (SD) for at least 6 weeks	38 (50.0%)	45 (33.8%)
Progressive Disease (PD)	7 (9.2%)	10 (7.5%)
Early Death <sup>a</sup>	5 (6.6%)	5 (3.8%)
Indeterminate <sup>b</sup>	3 (3.9%)	5 (3.8%)

<sup>a</sup> Early death was death within 42 days (6 weeks) from first dose of crizotinib.

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

The results for duration of stable disease (SD) based on the number of patients with best overall response of SD are summarised below in Table 23.

**Table 23: Study 1005 – Stable disease duration.**

SD duration	Preliminary CSR (n=38) <sup>a</sup>	60-day update (n=45) <sup>a</sup>
0 to < 3 months	25 (65.8%)	9 (20.0%)
3 to < 6 months	12 (31.6%)	29 (64.4%)
6 to < 9 months	1 (2.6%)	5 (11.1%)
9 to < 12 months	0	2 (4.4%)
≥ 12 months	0	0

<sup>a</sup> number of patients with best overall response of SD

The waterfall plot of best percent change in target lesion from baseline by patient based on investigator assessment in 123 RE patients in the 60-day clinical data shows that over 90% had at least some degree of tumour shrinkage.

In the 60-day clinical data update, IRR resulted in an ORR of 41.9% (95% CI: 32.3%, 51.9%); the evaluable patient population included 105 patients of whom 43 had a confirmed PR and 1 had a CR. Overall, 75 of 102 patients were assessed in the same best overall response category by both investigators and IRR for a total agreement rate of 73.5%.

**Comment:** The ORR was higher in the 60-day clinical data update than in the preliminary CSR, and was derived from a larger number of patients included in the RE population. The ORR assessed by the IRR was about 10% lower than the ORR in the 60-day clinical data update assessed by investigators. In the 60-day clinical data update, the overall agreement rate between the IRR and investigators as regards best overall response category was 73.5%.

#### 6.2.1.15. *Results for other efficacy outcomes*

##### 6.2.1.15.1. *Secondary efficacy endpoints of DR, TTR, and DCR*

The results for the secondary efficacy endpoints of DR, TTR, and DCR (at weeks 6 and 12) in the preliminary CSR, and the 60-day clinical update in the RE populations are summarised below in Table 24.

**Table 24: Study 1005 – Efficacy results for DR, TTR, and DCR; RE populations.**

Outcome	Preliminary CSR	60-day clinical data updated
Duration of Response, median (range) <sup>a</sup>	NA (range 7.1 to 13.1 weeks)	12.8 weeks (range 7.1 to 41.9)
Time to Tumour Response, median (range) <sup>b</sup>	6.0 weeks (range 5.1 to 11.6)	6.1 weeks (range 5.1, 24.3)
Disease control rate (CR + PR +SD) at 6 weeks <sup>c</sup>	80.3% (95% CI: 69.5, 88.5); n=61	85.0% (95%: 77.7, 90.6); n=113
Disease control rate (CR + PR + SD) at 12 weeks <sup>c</sup>	44.7% (95%CI: 33.3, 56.6); n=34	73.7% (95%: 65.3, 80.9); n=98

<sup>a</sup> Duration of response assessed in patients with confirmed objective response in who disease had progressed or death had occurred at the database snap shot. In the preliminary CSR, only 2 of the 23 patients experienced subsequent disease progression or death. In the 60-day clinical data update, 14 of the 68 patients experienced subsequent disease progression or death.

<sup>b</sup> TTR based on the number of patients who experienced a confirmed objective tumour response (n=23 in the preliminary CSR and n=68 in the 60-day clinical data update).

<sup>c</sup> Disease control rate based on total number of patients in the RE population (n=76 in the preliminary CSR and n=133 in the 60-day clinical data update).

##### 6.2.1.15.2. *Secondary efficacy endpoints of OS and PFS*

No data were provided on OS or PFS in either the preliminary CSR or the 60-day clinical data update. This appears to be due to the immaturity of the data. The 60-day clinical data update report stated that that the median OS and PFS were not yet available.

##### 6.2.1.16. *Patient reported outcomes (PROs)*

Preliminary results from PROs were provided in Study 1005 (preliminary CSR), but no updated results were provided in the 60-day clinical data update report. Only 19% (26/136) of the

treated patients had completed the questionnaires through Cycle 8, and only preliminary summary statistics of the mean and mean change from baseline scores were reported for the EORTC QLQ-C30 and the QLQ-LC13. At the date of the data snapshot for the preliminary CSR, data were not robust enough for additional analysis of score proportions or analysis of the EQ-5D and VSAQ-ALK questionnaires. Overall, it is considered that the results for the EORTC QLQ-C30 and the QLQ-LC13 are too immature to meaningfully interpret, particularly in the absence of a control arm.

#### 6.2.1.17. *Efficacy in special groups*

There were no analyses of data in special patient groups in Study 1005 (i.e., race, sex, elderly).

### 6.3. **Analyses performed across trials (pooled analyses and meta-analyses)**

#### 6.3.1. **Technical report for historical control and other retrospective analyses**

##### 6.3.1.1. *Background*

The submission included a report titled – “Technical report for historical control and other retrospective analyses in advanced NSCL using data from Study A8081001 and data from control arms of three Pfizer-sponsored studies (A8501001, A8501002 and A6181087)”. The report was identified as “version final 1.1) and was dated 8 June 2011.

The report described the methods and results of two retrospective analyses supporting the New Drug Application (NDA) to the FDA for the use of crizotinib in patients with ALK-positive NSCLC. The report focused on the data from Study 1001 (preliminary CSR) as the response data from Study 1005 (preliminary CSR) were considered to be still too immature for this type of analysis.

The aim of the retrospective analyses was to provide evidence of treatment effect for crizotinib versus the agents in the control arms of three Pfizer sponsored studies. Imbalances were observed for known prognostic factors in NSCLC across Study 1001, the control arms of the three Pfizer-sponsored studies, and studies reported in the literature. Consequently, potential selection bias and confounding were controlled by covariate-matching or covariate-adjustment on baseline characteristics from Study 1001. The historical control arms from the three Pfizer studies were paclitaxel/carboplatin (Study 1); gemcitabine/cisplatin (Study 2); and erlotinib (Study 3).

The two retrospective analyses were:

- Covariate-matched analyses - Covariate-matched analyses were performed to compare the efficacy outcomes of ALK-positive NSCLC patients from Study 1001 with those from matched patients drawn from the control arms of the three Pfizer-sponsored advanced NSCLC studies.
- Covariate-adjusted modelling analyses – Covariate-adjusted modelling analyses were performed to retrospectively predict the ORR, PFS and OS of the 116 response evaluable ALK-positive NSCLC patients from Study 1001 as if these patients had been treated with the medicines from the control arms of the three Pfizer studies.

##### 6.3.1.2. *Study populations*

The study population included patients from Study 1001 (preliminary CSR), and patients from the control arms of three Pfizer-sponsored studies (identified as 1, 2, and 3):

- Study 1 (Pfizer study A8501001) - An international, randomised, open-label, Phase III trial of paclitaxel/carboplatin plus PF-3512676 versus paclitaxel/carboplatin alone as first-line treatment of patients with advanced NSCLC.



- Study 2 (Pfizer study A8501002): An international, randomised, open-label Phase III trial of gemcitabine/cisplatin plus PF-3512676 versus gemcitabine/cisplatin alone as first-line treatment of patients with advanced NSCLC.
- Study 3 (Pfizer study A6181087): A multicentre, randomised, double-blind, controlled Phase III efficacy and safety study of sunitinib in patients with advanced/metastatic NSCLC treated with erlotinib.

### 6.3.1.3. **Statistical methods**

#### 6.3.1.3.1. *Baseline characteristics in the three Pfizer studies*

The baseline characteristics (and efficacy outcomes) of patients enrolled in Study 1001 and the control arms of studies 1, 2, and 3 were summarised and compared with those reported from studies in the literature with similar agents. The relevant studies selected by the sponsor from the literature by were Herbst et al (2004), Herbst et al (2005), Kelly et al (2001), Sandler et al (2006), Scagliotti et al (2002), Schiller et al (2002) and Shepherd et al (2005). The baseline characteristics (and efficacy outcomes) in the control arms of Study 1, 2, and 3 were similar to those from the published studies.

#### 6.3.1.3.2. *Covariate-matched analysis*

Baseline characteristics for matching were based primarily on the known prognostic factors for NSCLC and the observed imbalances in distribution of baseline characteristics among the studies. Imbalances between Study 1001 and studies 1, 2 and 3 were observed for age, smoking, race (Asian/non-Asian), histological classification (adenocarcinoma/nonadenocarcinoma), and prior chemotherapy. Patients in Study 1001 were matched with patients from the control arms of studies 1, 2, and 3 by one or more of following baseline characteristics: adenocarcinoma histology, smoking classification, age and race (Asian/non-Asian). Due to limited data in the cross classification of these matching variables, simultaneous, exact matching on all variables was not achievable. The baseline characteristics used in the analysis were histology (adenocarcinoma versus non-adenocarcinoma); race (Asians versus non-Asians); smoking classification (ex/current smoker versus never smoker); and age by quartiles ( $\leq 43$  years;  $> 43$  to  $\leq 51$  years;  $> 51$  to  $\leq 61$  years;  $> 61$  years).

Because patients in Study 1001 have predominantly adenocarcinoma (97.5%), exact matching was performed for this variable by sub-setting to patients with this histology in Pfizer studies 1, 2, and 3. For other characteristics, matching was performed using random sampling with replacement (bootstrap technique). Based on 500 replications for each covariate (i.e. adenocarcinoma + smoking; adenocarcinoma + Asian; adenocarcinoma + age; and adenocarcinoma + Age + Asian), point estimates for the ORR with 95%CI, median PFS and median OS were calculated for each control treatment from Pfizer studies 1, 2, and 3. Hazard ratios (HR) were also calculated for PFS and OS for crizotinib versus each of the three historical control arms from each of the Pfizer studies 1, 2, and 3. For the sampling procedure, exact matching was used for categorical variables such as smoking classification and race, and quartile matching was used for continuous variables such as age. The report stated that covariate-matching with the bootstrap technique is a useful tool because it allows for parameter estimation, adjusting for confounding factors, without any distributional assumptions.

#### 6.3.1.3.3. *Covariate-adjusted analysis for ORR based on logistic regression*

In addition to the covariate-matched analysis, logistic regression modelling was performed to obtain a covariate-adjusted estimate for the ORR in Study 1001 patients as if they had received control regimens from Pfizer studies 1, 2, and 3. The 8 baseline characteristics used in the analysis were: histology (adenocarcinoma vs. non-adenocarcinoma); race (Asians vs. non-Asians); smoking classification (ex/current smoker vs. never smoker); age by quartiles ( $\leq 43$  years;  $> 43$  to  $\leq 51$  years;  $> 51$  to  $\leq 61$  years;  $> 61$  years); sex (male versus female); disease stage



(stage IIIA/B versus stage IV); ECOG performance status (0;  $\geq 1$ ; not-reported); and weight by quartiles ( $\leq 60$  kg;  $> 60$  to  $\leq 68$  kg;  $> 68$  to  $\leq 82$  kg;  $> 82$  kg).

A logistic regression model was fitted to each of the control arms in Pfizer studies 1, 2, and 3, and the fitted model was then used to estimate the probability of response for every patient in Study 1001 as if the patient had received the control arm treatment (i.e., paclitaxel/carboplatin; gemcitabine/cisplatin; or erlotinib). The four steps for the analysis algorithm were: (1) Fit a logistic regression model to each of the control studies 1, 2, and 3. Obtain the covariate estimate vector and its variance-covariance matrix. (2) Apply each of the three predictive models to the Study 1001 covariate data and obtain the estimated probability of response for each patient as if the patient had received the control regimen. (3) Calculate the average of the estimated probabilities of response. (4) Calculate the standard error of the estimated probabilities of response, and obtain the 95% CI.

#### 6.3.1.3.4. *Covariate adjusted analysis for PFS/OS based on Cox proportional hazard modelling*

In order to compare the time-to-event data in Study 1001 with historical control data, the expected PFS and OS curves for each control regimen from Pfizer studies 1, 2 and 3 were estimated using covariate adjusted modelling for time-to-event endpoints by adjusting for imbalances in prognostic covariates. Cox proportional hazard modelling was used for each of the three Pfizer control arms, including the same relevant covariates as used for the logistic regression model. The baseline hazard function was estimated from the semi-parametric model. The expected PFS and OS curves for the cohort of patients in Study 1001 as if the patients had received the control intervention were estimated as the weighted average of all the individual expected PFS or OS curves.

#### 6.3.1.4. **Results**

##### 6.3.1.4.1. *Covariate-matched ORR, PFS, OS - studies 1, 2, and 3 compared with Study 1001*

The baseline characteristics of patients in Study 1001 compared with the adenocarcinoma subset of patients and the covariate-matched patients from Pfizer studies 1, 2, and 3 were summarised in the study report.

The ORRs in Study 1001 for crizotinib and control arms in studies 1, 2, and 3 (unmatched; adenocarcinoma subset; and covariate matching) were summarised in the study report.

The time-to-event endpoints (PFS and OS) in Study 1001 and control arms in studies 1, 2, and 3 (unmatched; adenocarcinoma subset; and covariate matching) were summarised in the study report.

**Comment:** The mean ORR for crizotinib from Study 1001 (61.2%) was notably higher than the ORRs from the historical control arms from Pfizer studies 1, 2, and 3 for all analyses (i.e., unmatched; subset of adenocarcinoma; and matching on various covariates). Covariate-matched ORRs ranged from 12.0% to 21.5% with paclitaxel/carboplatin, 20.7% to 24.1% with gemcitabine/cisplatin, and 10.0% to 13.8% with erlotinib.

The observed preliminary median PFS for patients treated with crizotinib is 10 months compared with the observed covariate-matched median PFS values, which ranged from 4.6 to 5.9 months with first-line treatment with paclitaxel/carboplatin, 5.0 to 5.3 months, with first-line treatment with gemcitabine/cisplatin and 1.9 to 3.1 months with second/third-line treatment with erlotinib. The hazard ratios for PFS of crizotinib versus any of the three control regimens ranged from 0.28 to 0.38.

The covariate-matched median OS ranged from 10.6 to 14.6 months with first-line treatment with paclitaxel/carboplatin, from 12.0 to 15.9 months with first-

line treatment with gemcitabine/cisplatin and from 9.3 to 12.1 months with second/third-line treatment with erlotinib. OS data in Study 1001 (preliminary CSR) is still immature and the median OS has not yet been reached despite a median follow-up of 11 months (95% CI: 9.2, 12.8 months). The hazard ratios for OS of crizotinib versus any of the three control regimens ranged from 0.28 to 0.47 suggesting that patients treated with crizotinib could potentially have longer overall survival than those of the covariate-matched historical controls with reported median OS values ranging from 9.3 to 15.9 months.

#### 6.3.1.4.2. ORR covariate-adjusted analysis

After simultaneously adjusting for eight baseline characteristics (histology, gender, race, smoking classification, disease stage, ECOG performance status, age and weight), the results were:

- estimated predictive ORR for first-line treatment with paclitaxel/carboplatin (Study 1) for the 116 response evaluable patients in Study 1001 was 17.5% (95% CI: 11.3, 23.6);
- estimated predictive ORR for first-line treatment with gemcitabine/cisplatin (Study 2), for the 116 response evaluable patients in Study 1001 was 21.4% (95% CI: 13.8, 28.9); and
- estimated predictive ORR to for second/third-line treatment with erlotinib (Study 3) for the 116 response evaluable patients in Study 1001 was 15.0% (95% CI: 7.2, 22.8).

**Comment:** The estimated predictive ORRs for the 116 response evaluable patients in Study 1001 for the three historical regimens (15.0% to 21.4%) were markedly lower than the observed ORR for the 119 response evaluable patients in Study 1001 (61.2%). The result for the estimated predictive ORR from covariate-adjusted modelling was similar to the ORRs obtained from covariate-matching.

#### 6.3.1.4.3. PFS/OS covariate-adjusted analyses

The observed and expected PFS/OS curves for the 119 response-evaluable patients from Study 1001 based on the direct adjusted method were summarised in the study report.

**Comment:** The expected PFS/OS curves from the covariate-adjusted analysis for the three control treatments were below the observed PFS/OS Kaplan-Meier curves from Study 1001. The expected PFS/OS curves for the three control treatments were generally below the lower 95% Haller Wellner confidence bands for the observed PFS and OS (immature) curves from Study 1001.

## 6.4. 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 BID 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 Clinical Overview (Module 2.5) and the Summary of Clinical Efficacy (Module 2.7.3) based their favourable assessments of the efficacy of crizotinib primarily on the ORR results from Studies 1001 and 1001. 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/2 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 criteria. 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/2 studies translate into clinically meaningful benefits such as improved overall survival (OS) and/or progression-free survival (PFS). The relevant TGA adopted guideline which relates 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 date 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 (i.e., 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 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 Meeting (Buyse et al., 2008) 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, “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 (i.e., 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 (i.e., 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 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/2 studies (1001/1005) translate into meaningful clinical benefits. Study 1014 is comparing crizotinib with premetrexed/cisplatin and premetrexed/carboplatin in previously untreated patients with ALK-positive NSCLC. Study 1007 is comparing crizotinib with standard of care chemotherapy (premetrexed 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.

## 7. Clinical safety

### 7.1. Studies providing evaluable safety data

#### 7.1.1. 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 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, 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.

### **7.1.2. Initial data**

The submission included an integrated Summary of Clinical Safety (Module 2.7.4) 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 BID 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.

### **7.1.3. 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;
- information on 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;
- information on 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;
- information on 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.

### **7.1.4. 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 this 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 this CER.

## **7.2. Primary safety population (Studies 1001 and 1005)**

### **7.2.1. 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 (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)%.

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.

### 7.2.2. Disposition of the safety analysis population

Of the 119 patients enrolled in Study 1001, 77 (64.7%) were ongoing at the database snapshot and 42 (35.3%) had discontinued, primarily due to progressive disease (n=25; 21.0%). Of the 136 patients enrolled in Study 1005, 93 (68.4%) were ongoing at the database snapshot and 43 (31.6%) had discontinued, primarily for objective disease progression or relapse (n=26; 19.1%)

## 7.3. Adverse events

### 7.3.1. Overview of the AE data

#### 7.3.1.1. Study 1001

An overview of the AE profile for the preliminary CSR safety analysis population (n=136), and the preliminary CSR 60-day update safety analysis population (n=136) from Study 1001 are summarised below in Table 25. The preliminary CSR included comprehensive reporting of safety, while the preliminary CSR 60-day clinical data update report included limited safety data relating to SAEs and deaths only.

**Table 25: Study 1001 - Overview of the AE profile.**

	Study 1001 (preliminary CSR)		Study 1001 (preliminary CSR 60-day update)	
	All causality	Treatment related	All causality	Treatment related
Patients evaluable for AEs	119	119	136	136
Patients with AEs (all grades), N (%)	117 (98.3%)	114 (95.8%)	NR	NR
Grade 3 or 4 AEs, N (%)	43 (36.1%)	19 (16.0%)	NR	NR
SAEs (all grades), N (%)	33 (27.7%)	7 (5.9%)	50 (36.6%)	8 (5.9%)
SAEs Grade 3 or 4, N (%)	15 (12.6%)	5 (4.2%)	24 (17.6%)	5 (3.7%)



	Study 1001 (preliminary CSR)		Study 1001 (preliminary CSR 60-day update)	
	All causality	Treatment related	All causality	Treatment related
Discontinued due to AEs, N (%)	8 (6.7%)	3 (2.5%)	NR for all AEs	NR for all AEs
Temporary discontinuations due to AEs, N (%)	39 (32.8%)	14 (11.8%)	NR for all AEs	NR for all AEs
Dose reductions due to AEs, N (%)	7 (5.9%)	6 (5.0%)	NR for all AEs	NR for all AEs
Deaths – Total, N (%)	23 (19.3%)	0	40 (29.4%)	1 (0.7%)
Deaths within 28 days of last dose, N (%)	13 (10.9%)	0	19 (14.0%)	1 (0.7%)

Abbreviations: AE=adverse event; SAE=serious adverse event; N =number of patients; SAEs - according to the investigator's assessment

#### 7.3.1.2. Study 1005

An overview of the AE profile for the preliminary CSR 60-day update safety analysis population (n=136), and the 60-day safety analysis population (n=261) for Study 1005 are summarised below in Table 26. The safety data from the 60-day update report on 136 patients included in the preliminary CSR was comprehensive and included information on deaths, SAEs, AEs, laboratory abnormalities, ECGs, vital signs, and ophthalmological assessments. However, the safety data on the 261 patients from the 60-day safety analysis were limited and included information on SAEs and deaths only.

**Table 26: Study 1005 – Overview of the AE profile.**

	Study 1005 (preliminary CSR 60-day update)		Study 1005 (safety analysis)	
	All causality	Treatment related	All causality	Treatment related
Patients evaluable for AEs, N	136	136	261	261
Patients with AEs (all grades), N (%)	136 (100%)	131 (96.3%)	NR	NR
Grade 3 or 4 AEs, N (%)	50 (36.8%)	32 (23.5%)	NR	NR
SAEs (all grades), N (%)	43 (31.6%)	10 (7.4%)	62 (23.8%)	12 (4.6%)
SAEs Grade 3 or 4, N (%)	25 (18.4%)	6 (4.4%)	32 (12.3%)	8 (3.1%)
Discontinued due to AEs, N (%)	15 (11.0%)	8 (5.9%)	NR	NR

	Study 1005 (preliminary CSR 60-day update)		Study 1005 (safety analysis)	
	All causality	Treatment related	All causality	Treatment related
Temporary discontinuations due to AEs, N (%)	47 (34.6%)	25 (18.4%)	NR	NR
Temporary dose reductions due to AEs, N (%)	17 (12.5%)	16 (11.8%)	NR	NR
Deaths – Total, N (%) <sup>1</sup>	21 (15.4%)	2 (1.5%)	32 (12.3%)	2 (0.8%)
Deaths within 28 days of last dose, N (%)	16 (11.8%)	2 (1.5%)	26 (10.0%)	2 (0.8%)

Abbreviations: AE=adverse event; SAE=serious adverse event; N =number of patients. SAEs - according to the investigator's assessment

### 7.3.2. Commonly occurring adverse events

#### 7.3.2.1. Study 1001 (preliminary CSR)

The most commonly occurring all causality and treatment-related adverse events ( $\geq 5\%$  of patients) in the ALK-positive data set from Study 1001 (preliminary CSR) coded by MedDRA v13.0 were summarised in the CER.

##### 7.3.2.1.1. All causality adverse events

In the ALK-positive NSCLC patient population (n=119), all causality AEs (all grades) were reported in 98.3% (n=117) of patients, and Grade 3 or 4 AEs were reported in 27.7% (n=33) of patients.

All causality AEs (all grades) occurring in  $\geq 10\%$  of patients were nausea (49.6%), diarrhoea (47.9%), visual impairment (47.9%), vomiting (40.3%), constipation (37.8%), oedema peripheral (31.9%), dizziness (27.7%), fatigue (25.2%), decreased appetite (23.5%), ALT increased (17.6%), rash 21 (17.6), dyspnoea (16.0%), pyrexia (16.0%), AST increased (14.3%), cough (12.6%), headache (11.8%), dyspepsia (11.8%), nasopharyngitis (11.8%), arthralgia (10.9%), back pain (10.9%), upper respiratory tract infection (10.9%), abdominal pain upper (10.1%), and insomnia (10.1%).

All causality AEs (Grade 3 or 4) occurring in  $\geq 1\%$  of patients were ALT increased (6.7%), AST increased (4.2%), pneumonia (4.2%), dyspnoea (4.2%), pulmonary embolus (4.2%), neutropenia (3.4%), lymphopenia (2.5%), fatigue (2.5%), anaemia (2.5%), hypophosphataemia (1.7%), and arthralgia (1.7%).

##### 7.3.2.1.2. Treatment-related adverse events

In the ALK-positive NSCLC patients (n=119), treatment-related AEs (all grades) were reported in 95.8% (n=114) of patients, and Grade 3 or 4 AEs were reported in 16.0% (n=19) of patients.

Treatment-related AEs (all grades) occurring 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 AEs (Grade 3 or 4) occurring 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%).

### 7.3.2.2. Study 1005 (preliminary CSR 60-day update)

#### 7.3.2.2.1. All causality adverse events

All causality AEs by MedDRA (v13.0) preferred terms and maximum CTC grade occurring in  $\geq 1\%$  of patients in the preliminary CSR 60-day update safety analysis population (n=136) were summarised in the CER.

All causality AEs (any grade) were reported in 100% (n=136) of patients, and Grade 3 or 4 AEs were reported in 36.8% (n=50) of patients.

All causality AEs (all grades) occurring in  $\geq 10\%$  of patients were nausea (63.2%), vomiting (50.0%), diarrhoea (49.3%), visual impairment (44.1%), constipation (39.0%), fatigue (36.6%), oedema peripheral (33.1%), decreased appetite (30.1%), cough (25.7%), dyspnoea (23.5%), dizziness (18.4%), dysgeusia (16.9%), headache (14.7%), insomnia (13.2%), ALT increased (12.5%), arthralgia (11.8%), back pain (11.0%), and rash (10.3%).

All causality AEs (Grade 3 or 4) reported in  $\geq 1\%$  of patients were dyspnoea (7.3%), ALT increased (6.6%), neutropenia (4.2%), hypoalbuminaemia (3.6%), hyponatraemia (3.0%), lymphopenia (2.9%), fatigue (2.2%), hypokalaemia (2.2%), dysphagia (1.5%), vomiting (1.5%), cellulitis (1.5%), infection (1.5%), AST increased (1.5%), appetite decreased (1.5%), syncope (1.5%), deep vein thrombosis (1.5%), and hypophosphataemia 1.4%.

#### 7.3.2.2.2. Treatment related adverse events

Treatment-related AEs by MedDRA (v13.0) preferred terms and maximum CTC grade occurring in  $\geq 1\%$  of patients in the preliminary CSR 60-day update safety analysis population (n=136) were summarised in the CER.

Treatment related AEs (any grade) were reported in 96.3% (n=131) of patients, and Grade 3 or 4 AEs were reported in 23.5% (n=32) of patients.

Treatment related AEs (all grades) occurring 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 AEs (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%).

### 7.3.3. Deaths and other serious adverse events

#### 7.3.3.1. Deaths

Assessment of deaths “on study” included all deaths that occurred during the safety evaluation period from first dose of crizotinib through to 28 days after administration of the last dose of crizotinib. Patients were followed-up for long-term survival for at least 12 months after their last dose of crizotinib in Study 1001 or until 12 months after the last patient has discontinued crizotinib treatment in Study 1005. The 60-day clinical data update report included updated data on deaths from Study 1001 and Study 1005 (see Table 27, below).

**Table 27: Deaths in patients with ALK-positive NSCLC.**

Number of patients, n	Study 1001 (n=136)	Study 1005 2 (n=261)
Total	40 (29.4%)	32 (12.3%)

Number of patients, n	Study 1001 (n=136)	Study 1005 2 (n=261)
Within 28 days of last dose	19 (14.0%)	26 (10.0%)
> 28 days after last dose	21 (15.4%)	6 (2.3%)
Due to disease progression	31 (22.8%)	26 (10.0%)
Related to study drug	1 (0.7%)	2 (0.8%)

Of the 45 deaths occurring in Studies 1001 and 1005 within 28 days of the last dose, the majority (35) 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, 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.

#### 7.3.3.1.1. Deaths in Study 1001 ALK-positive NSCLC cohort (preliminary CSR 60-day update)

There were a total of 40 deaths (29.6%) reported in 136 patients in the ALK-positive NSCLC cohort. Of these 40 deaths, 19 (29.4%) occurred “on study”, and the majority of deaths (n=31; 22.8%) were considered to be due to disease progression. Of the 40 deaths, 1 (0.7%) was considered to be related to treatment with crizotinib (disseminated intravascular coagulation).

#### 7.3.3.1.2. Deaths in Study 1001 in other disease cohorts (preliminary CSR 60-day update)

Among the 25 patients with ALK-negative NSCLC in the R2PD cohort, there were 4 (16.0%) deaths (all within 28 days of the last dose of crizotinib treatment). Of the 4 deaths, 2 were due to disease progression, 1 was due to the disease under study, and 1 was considered to be due to pneumonia. None of the 4 deaths were considered to be treatment related.

Among the 56 patients in the RP2D cohort with tumours other than NSCLC, there were 30 deaths (12 within 28 days of the last dose of study drug). Of the 30 deaths, 25 were due to disease progression, and none were related to crizotinib treatment.

Among the 36 patients in the dose-escalation cohort, there were 25 deaths (4 within 28 days of the last dose of study drug). Of the 25 deaths, 22 were due to disease progression, and none of the deaths were related to crizotinib treatment.

#### 7.3.3.1.3. Deaths in Study 1005 (SA population 60-day update)

There were a total of 32 deaths (12.3%) reported in the safety analysis population (n=261). Of these 32 deaths, 26 (10.0%) occurred “on study”, and the majority of deaths (n=26; n=10.0%) were considered to be due to disease progression. Of the 32 deaths, 2 (0.8%) were considered to be related to treatment with crizotinib (1 case of pneumonitis and 1 due to unknown cause).

#### 7.3.3.1.4. Deaths in Study 1007 (preliminary CSR 60-day update)

In the 71 patients included in the 60-day clinical data update, 6 crizotinib treated patients had SAEs with a fatal outcome. Of these 6 deaths, 5 occurred within 28 days of the last dose of study 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). In addition to these deaths, 1 additional death due to treatment-related pneumonitis occurred after the data cut-off date for the 60-day update.

### 7.3.3.2. **Other serious adverse events (SAEs)**

SAE were defined as any untoward medical occurrence at any dose that resulted in death, was life-threatening (immediate risk of death), required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, or resulted in congenital anomaly/birth defect. Other important medical events were considered SAEs if they jeopardized the patient or required medical or surgical intervention to prevent one of the outcomes listed in the definition.

SAEs (all causality and treatment-related) for all grades and for Grade 3 or 4 from the 397 patients in the 60-day clinical data updates for Studies 1001 and 1005 are summarised below in Table 28.

**Table 28: SAEs from Studies 1001 and 1005; 60-day clinical data update.**

Number of patients, n	Study 1001 (n=136)	Study 1005 2 (n=261)
All causality SAEs (all grades)	50 (36.8%)	62 (23.8%)
Treatment related SAEs (all grades)	8 (5.9%)	12 (4.6%)
All causality SAEs (Grade 3 or 4)	24 (17.6%)	32 (12.3%)
Treatment related SAEs (Grade 3 or 4)	5 (3.7%)	8 (3.1%)

#### 7.3.3.2.1. *Study 1001 (preliminary CSR 60-day update)*

All causality SAEs (all grades) were reported in 50 (36.8%) patients, and all causality SAEs (Grade 3 or 4) were reported in 24 (17.6%) patients.

All causality SAEs (all grades) reported in  $\geq 1\%$  of patients were disease progression (n=13; 9.6%), pneumonia (n=6; 4.4%), pulmonary embolism (n=5; 3.7%), syncope (n=4; 2.9%), dyspnoea (n=4; 2.9%), convulsion (n=3; 2.2%), pneumonitis (n=2; 1.5%), anaemia (n=2; 1.5%), atrial fibrillation (n=2; 1.5%), constipation (n=2; 1.5%), pyrexia (n=2; 1.5%), and deep vein thrombosis (n=2; 1.5%).

All causality SAEs (Grade 3 or 4) reported in  $\geq 1.0\%$  of patients were pulmonary embolism (n=5; 3.7%), syncope (n=4; 2.9%), dyspnoea (n=4; 2.9%), pneumonia (n=3; 2.2%), convulsion (n=2; 1.5%), and deep vein thrombosis (n=2; 1.5%).

Treatment-related SAEs (all grades) were reported in 8 (5.9%) patients, and SAEs (Grade 3 or 4) were reported in 5 (3.7%) patients.

Treatment related SAEs (all grades) reported in the 8 patients with an event were pneumonitis (n=2; 1.5%), intravascular coagulation (n=1; 0.7%), constipation (n=1; 0.7%), oesophageal ulcer (n=1; 0.7%), renal abscess (n=1; 0.7%), ALT increased (n=1; 0.7%), and liver function test abnormal (n=1; 0.7%).

Treatment-related SAEs (Grade 3 or 4) reported in 5 patients with an event were pneumonitis (n=2; 1.5%), constipation (n=1; 0.7%), ALT increased (n=1; 0.7%), and liver function test abnormal (n=1; 0.7%).

### 7.3.3.2.2. Study 1005 (safety analysis population 60-day update)

All causality SAEs (all grades) were reported in 62 (23.8%) patients, and all causality SAEs (Grade 3 or 4) were reported in 32 patients (12.2%).

All causality SAEs occurring (all grades) reported in  $\geq 1\%$  of patients were disease progression (n=14; 5.4%), pneumonia (n=8; 3.1%), dyspnoea (n=8; 3.1%), and pyrexia (n=3; 1.1%).

All causality SAEs (Grade 3 or 4) occurring in  $\geq 1.0\%$  of patients were pneumonia (n=6; 2.3%), and dyspnoea (n=3; 2.7%).

Treatment-related SAEs (all grades) were reported in 12 (4.6%) patients, and treatment-related SAEs (Grade 3 or 4) were reported in 8 (3.1%) patients.

Treatment-related SAEs (all grades) reported in the 12 patients with an event were pneumonitis (n=2; 0.8%), febrile neutropenia (n=1; 0.4%), supraventricular tachycardia (n=1; 0.4%), death (n=1; 0.4%), oedema peripheral (n=1; 0.4%), infection (n=1; 0.4%), pneumonia (n=1; 0.4%), hepatic enzyme increased (n=1; 0.4%), hypokalaemia (n=1; 0.4%), hyponatraemia (n=1; 0.4%), haematuria (n=1; 0.4%), renal cyst (n=1; 0.4%), dyspnoea (n=1; 0.4%), and haematoma (n=1; 0.4%).

Treatment-related (Grade 3 or 4) SAEs reported in the 8 patients with an event were febrile neutropenia (n=1; 0.4%), infection (n=1; 0.4%), pneumonia (n=1; 0.4%), hepatic enzyme increased (n=1; 0.4%), hypokalaemia (n=1; 0.4%), hyponatraemia (n=1; 0.4%), haematuria (n=1; 0.4%), renal cyst (n=1; 0.4%), dyspnoea (n=1; 0.4%), and pneumonitis (n=1; 0.4%).

### 7.3.3.2.3. Study 1007 (preliminary CSR 60-day update)

Of the 71 crizotinib treated patients in the updated analysis, 19 (26.8%) had at least 1 SAE. Of these 19 patients, 10 (14.1%) had SAEs considered to be treatment-related (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).

## 7.3.4. Permanent treatment discontinuations due to AEs

### 7.3.4.1. Study 1001

In Study 1001 (preliminary CSR) (n=119), all causality and treatment-related AEs resulting in permanent treatment discontinuation were reported in 8 (6.7%) and 3 (2.5%) patients, respectively. The 3 patients with treatment-related AEs resulting in permanent treatment discontinuation included 2 patients with pneumonitis and 1 patient with ALT increased.

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).

### 7.3.4.2. Study 1005

In Study 1005 (preliminary CSR 60-day update), all causality and treatment-related AEs resulting in permanent treatment discontinuation were reported in 15 (11.0%) and 8 (5.9%) patients, respectively. The most commonly reported treatment-related AEs resulting in permanent treatment discontinuation were ALT increased (3 patients; 2.2%) and pneumonitis (2 patients; 1.5%). Other treatment-related AEs resulting in permanent discontinuation were AST increased (1 patient; 0.7%), death (1 patient; 0.7%), dyspnoea (1 patient; 0.7%), and nausea (1 patient; 0.7%).



### **7.3.5. Temporary treatment discontinuations and dose reductions due to AEs**

#### **7.3.5.1. Study 1001 (preliminary CSR)**

Temporary treatment discontinuations associated with causality AEs and due to treatment-related AEs occurred in 39 (32.8%) and 14 (11.8%) patients, respectively. All causality AEs resulting in temporary treatment discontinuation and occurring in  $\geq 2\%$  of patients were ALT increased (n=7; 5.9%), pneumonia (n=5; 4.2%), pyrexia (n=5; 4.2%); neutropenia (n=4; 3.4%); and AST increased (n=4; 3.4%).

Dose reductions associated with all causality AEs and due to treatment-related AEs occurred in 7 (5.9%) and 6 (5.0%) patients, respectively. The all causality AEs resulting in dose reduction were ALT increased (5 patients; 4.2%), AST increased (2 patients; 1.7%), fatigue, and arthralgia (1 patient [0.8%] each). All of these events were considered treatment-related, except for arthralgia in 1 patient.

#### **7.3.5.2. Study 1005 (preliminary CSR 60-day update)**

Temporary treatment discontinuations associated with all causality AEs and due to treatment-related AEs occurred in 47 (34.6%) and 25 (18.4%) patients, respectively. All causality AEs resulting in temporary treatment discontinuation occurring in  $\geq 2\%$  of patients were ALT increased (n=7; 5.1%); dyspnoea (n=6; 4.4%); neutropenia (n=6; 4.4%), pneumonia (n=5, 3.7%), and fatigue (3 patients; 2.2%).

Dose reductions associated with all causality AEs and due to treatment-related AEs occurred in 17 (12.5%) and 16 (11.8%) patients, respectively. The most common all causality AEs resulting in dose reduction and occurring in  $\geq 2$  patients were ALT increased (6 patients; 4.4%) and ECG QT prolonged (2 patients; 1.5%).

### **7.3.6. Laboratory tests**

#### **7.3.6.1. Overview**

Blood and urine samples were evaluated as specified in the study protocols. Investigators may have requested additional tests for the purposes of planning treatment administration, modifying doses, or following up on AEs.

In Studies 1001 and 1005, haematology and blood chemistry were evaluated at screening, on Days 1 and 15 of Cycle 1, on Day 1 of each cycle thereafter, and at the end of treatment. Coagulation parameters were evaluated at screening in both studies and, for Study 1001 only, on Days 1 and 15 of Cycle 1 and Day 1 of Cycle 2. Urinalysis by dipstick evaluation was performed in Study 1001 at screening and on Day 1 of each cycle. Urinalysis was not performed in Study 1005.

Laboratory test abnormalities were graded in accordance with NCI CTCAE Version 3.0 for both studies. The number and percent of patients with abnormal laboratory test results were summarised by maximum NCI CTCAE grade. Summaries of shifts in laboratory test results between baseline (prior to morning dosing on Cycle 1 Day 1) and post-baseline times of testing were provided.

Abnormal laboratory test results were considered adverse events if they were associated with symptoms, required additional diagnostic testing, led to 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 as specified for each study.

#### **7.3.6.2. Haematology**

The data summarised in this section are from the revised tables for Studies 1001 (preliminary CSR) and 1005 (preliminary CSR and 60-date update) provided with the sponsor's Note to Reviewers (Module 1.0.1). In these two studies, clinical laboratory results were primarily



evaluated by laboratory shift tables. The shift tables for haematology parameters from CTC Grade  $\leq 2$  at baseline to CTC Grade 3 or 4 post-baseline were summarised in the CER.

In both studies, the highest frequency of shifts from Grade  $\leq 2$  at baseline to Grade 3 or 4 post-baseline in haematology parameters were observed for lymphopenia with shifts of 11.6% (n=13) and 11.3% (n=15) in Studies 1001 and 1005, respectively.

In Study 1001, decreases from baseline Grade  $\leq 2$  to post-baseline Grade 3 or 4 neutrophils, leukocytes, platelets and haemoglobin were each observed in patients at frequencies of 3.5% (n=4), 1.8% (n=2), 0.9% (n=1), and 0.9% (n=1), respectively. In Study 1005, decreases from baseline Grade  $\leq 2$  to post-baseline Grade 3 or 4 neutrophils, leukocytes, platelets and haemoglobin were observed in patients at frequencies of 6.8% (n=9), 3.0% (n=4), 0%, and 0.8% (n=1), respectively.

### 7.3.6.3. **Biochemistry**

The data summarised in this section are from the revised tables for Studies 1001 (preliminary CSR) and 1005 (preliminary CSR and 60-date update) provided with the sponsor's Note to Reviewers (Module 1.0.1). In Studies 1001 and 1005, clinical laboratory results were primarily evaluated by laboratory shift tables.

Biochemical laboratory parameters with shifts from Grade  $\leq 2$  at baseline to Grade 3 or 4 post-baseline with an incidence of  $\geq 5\%$  in the pooled population for the two studies were ALT (6.0%; 15/248), and hyponatraemia (5.2%; 12/249).

### 7.3.7. **Adverse events of special interest**

#### 7.3.7.1. **Overview**

The sponsor identified safety AEs of special interest in patients with ALK-positive NSCLC selected *post-hoc* on the basis of clinical significance or frequency of observation in the clinical trials, and possible attribution to treatment with crizotinib. The selected AEs were analysed as individual PTs, clustered terms, or laboratory values. The PTs included within each clustered term are summarised below in Table 29.

**Table 29: PTs reported within each clustered term.**

Clustered Term	MedDRA Preferred Term(s) Actually Reported
Alanine aminotransferase increased	Alanine aminotransferase increased
Anemia	Anaemia, Haemoglobin decreased
Bradycardia	Bradycardia, Sinus bradycardia
Edema	Localized oedema, Oedema, Oedema peripheral
Esophageal-related disorder	Dysphagia, Epigastric discomfort, Gastrooesophageal reflux disease, Odynophagia, Oesophageal obstruction, Oesophageal pain, Oesophageal spasm, Oesophageal ulcer, Oesophagitis, Reflux oesophagitis
Fatigue	Asthena, Fatigue
Neuropathy	Burning sensation, Hypoaesthesia, Hypoaesthesia facial, Neuralgia, Neuropathy peripheral, Paraesthesia, Peripheral motor neuropathy, Peripheral sensory neuropathy, Sensory disturbance
Neutropenia	Neutropenia
Seizure	Convulsion
Thrombocytopenia	Platelet count decreased, Thrombocytopenia
Vision disorder	Diplopia, Photopsia, Vision blurred, Visual field defect, Visual impairment, Vitreous floaters

For selected AEs, time to first onset and duration of event were also presented for both Studies 1001 (preliminary CSR) and 1005 (preliminary CSR), and prevalence during different cycles was presented for Study 1001. Time to first onset of the event, but not duration was summarised for Study 1005 (preliminary CSR 60-day update).

The sponsor also identified those AEs (individual PTs and clustered terms) considered to be adverse drug reactions (ADRs) related to treatment with crizotinib from Study 1001 (preliminary CSR), Study 1005 (preliminary CSR), and Study 1005 (preliminary CSR 60-day update). The results from the tables for Study 1001 (preliminary CSR) and Study 1005

(preliminary CSR 60-day update) were used to create Table 3 (Adverse Reactions Reported in Studies A and B) in the proposed PI.

#### 7.3.7.2. *AEs of special interest (clustered term)*

The most commonly occurring treatment-related clustered term was vision disorder, which was reported in 62.2% (n=74) of patients. Other treatment-related AEs clustered terms occurring in  $\geq 10\%$  of patients were oedema 27.7% (n=33), ALT increased 14.3% (n=17), fatigue 14.3% (n=17), neuropathy 10.9% (n=13), and oesophageal related disorder 10.9% (n=13).

The most commonly occurring treatment-related clustered term was vision disorder, which was reported in 58.8% (n=80) of patients. Other treatment-related AEs clustered terms reported in  $\geq 10\%$  of patients were oedema 28.7% (n=39), fatigue 27.2% (n=37), neuropathy 15.4% (n=21); and ALT increased 12.5% (n=17).

##### 7.3.7.2.1. *Time to first onset*

The shortest median time to onset in Study 1001 was observed for diarrhoea (2 days), nausea (2 days) and vomiting (2 days) and the longest for neutropenia (197 days). Median time to first onset of within 7 days was reported for diarrhoea (2 days), nausea (2 days) and vomiting (2 days); from 7 to 14 days for vision disorder (13 days); from 15 to 28 days for ALT increased (22 days); and from 29 to 197 days for all other AEs of special interest.

The shortest median time to onset in Study 1005 was observed for nausea (2 days) and vomiting (2 days) and the longest for neutropenia (64 days). Median time to first onset of within 7 days was reported for nausea (2 days) and vomiting (2 days); from 7 to 14 days for vision disorder (7 days), oesophageal related disorder (10.5 days), pneumonitis (12 days), and diarrhoea (14.5 days); from 15 to 28 days no events; and from 29 to 64 days for all other AEs of special interest.

##### 7.3.7.2.2. *Duration of events*

The shortest median duration in Study 1001 was 14.5 days (pneumonitis) and the longest was 188 days (neuropathy). Median durations of up to 28 days were reported for pneumonitis (14.5 days), neutropenia (16.5 days), vomiting (17.5 days); 29 to 56 days for oesophageal-related disorder (48 days); 57 to 86 days for ALT increased (74 days); and 87 to 188 days for all other special AEs of special interest.

##### 7.3.7.2.3. *Pneumonitis*

Treatment-related pneumonitis was reported in 4 (1.6%) patients in the pooled population (n=255) from Studies 1001 (preliminary CSR) and 1005 (preliminary CSR 60-day update). All 4 cases were SAEs (Grade  $\geq 3$ ), all were associated with permanent treatment discontinuation, and 1 was fatal. The median time to first onset of treatment related pneumonitis was 12.5 days in Study 1001 (2 cases) and 12 days in Study 1005 (2 cases), and the median duration of the event was 14.5 days (2 cases) in Study 1001.

An independent review committee (IRC) consisting of a respiratory physician, oncologist, and radiologist was convened by the sponsor to review the frequency of all possible drug induced cases of pneumonitis from Studies 1001 and 1005. Of the 4 cases of pneumonitis considered to be treatment-related by investigators, 3 were confirmed to be drug-induced pneumonitis by the IRC. In summary, the IRC identified 3 cases of pneumonitis/interstitial lung disease out of 340 subjects (i.e., incidence of 0.9%), and 1 fatality due to the disease out of the 3 cases (i.e., fatality rate of 33.3%).

In the 60-day clinical date update for Study 1007, interstitial lung disease with a fatal outcome was reported in 1 (1.4%) out of 71 patients, and this event was considered by the investigator to be treatment related. In addition, there was 1 additional death due to treatment-related pneumonitis reported after the data cut-off for the Study 1007 update.

**Comments:** The IRC identified treatment-related pneumonitis in 3 (0.9%) of 340 subjects from Studies 1001 and 1005, and considered that death due to the disease occurred in 1 of the 3 subjects. The 3 cases occurred at a mean of 11.3 days after starting crizotinib. These 3 cases were identified from 46 respiratory AEs/SAEs, 11 determined to be due to progressive disease and 35 to be true respiratory AEs/SAEs.

The IRC noted that although the sample size was relatively large, the incidence of pneumonitis was small and firm conclusions were difficult to draw. Nevertheless, the IRC commented that the incidence of pneumonitis/ILD in their review is consistent with that reported for gefitinib and erlotinib. In addition, the IRC commented that 1 fatal case out of 3 events, a 33% fatality rate, is also consistent with the literature relating to drug-induced pneumonitis. The IRC commented that the mean time to development of pneumonitis (11.3 days) is shorter than has been observed with erlotinib and gefitinib. The IRC also noted that at least two patients had received prior chemotherapy, an identified risk factor for the development of TKI-induced pneumonitis. The IRC also commented that cessation of the suspected agent and administration of systemic corticosteroids appear to have a positive effect on survival. The IRC also identified 2 cases of typical radiation pneumonitis (1 case developed while on crizotinib and 1 case worsened while on crizotinib). The IRC commented that it is unknown whether the cases of radiation pneumonitis represent merely an association or whether “crizotinib predisposed these patients to worsening radiation pneumonitis or recall radiation pneumonitis”. The IRC concludes that pneumonitis/interstitial disease associated with crizotinib therapy deserves further study.

#### 7.3.7.2.4. QTc prolongation

Information on the potential for QTc interval prolongation with crizotinib treatment was collected from routine ECG assessments, as AEs, and as part of a correlative assessment of plasma concentration versus QTc. The sponsor considered that Fridericia's correction (QTcF) provided the best correction for most studies. The QTcF results from Studies 1001 (preliminary CSR) and 1005 (preliminary CSR 60-day update) are summarised below in Table 30.

**Table 30: QTcF by maximum value and by maximum change from baseline in patients with ALK-positive NSCLC.**

	Parameter	Study 1001 <sup>1</sup>	Study 1005 <sup>2</sup>
Maximum QTcF	< 450 ms	104 (88.1%)	119 (88.1%)
	450 to < 480 ms	12 (10.2%)	12 (8.9%)
	480 to < 500 ms	1 (0.8%)	3 (2.2%)
	≥ 500 ms	1 (0.8%)	1 (0.7%)
Maximum change in QTcF	< 30 ms	93 (87.7%)	114 (87.0%)
	30 to < 60 ms	9 (8.5%)	12 (9.2%)

Parameter	Study 1001 <sup>1</sup>	Study 1005 <sup>2</sup>
≥ 60 ms	4 (3.8%)	5 (3.8%)

1 = Study 1001 (preliminary CSR) – n=118 and n=106 for maximum QTcF and maximum change in QTcF, respectively. 2 = Study 1005 (60-day update of preliminary CSR) – n=135 and n=131 for maximum QTcF and maximum change in QTcF, respectively.

Treatment-related EGG QT prolongation was reported as an AE in 1 (0.8%) patient in Study 1001, and in 3 (2.2%) patients in Study 1005 (Grade 3/4 in 2 of these patients). There were no permanent discontinuations, and there were 0 and 1 (0.7%) temporary discontinuations due to ECG QT prolongation in Studies 1001 and 1005, respectively. There were no deaths attributed to QT interval prolongation.

There were no reports of seizure, ventricular tachycardia, or ventricular arrhythmia in Studies 1001 (preliminary CSR) and 1005 (preliminary CSR). Syncope or presyncope was reported in 5 (4.2%) and 3 (2.2%) patients, from Studies 1001 and 1005, respectively, and the respective reports of convulsion were 4 (3.4%) and 0 patients. Review of the case narratives for the 8 patients with syncope or presyncope, and the 4 patients with convulsions does not suggest primary cardiac causes.

In Study 1007 (60-day update report), no new AE events categorized as ECG QT prolonged were reported (1 event had been reported in the initial data). Consequently, in Study 1007 (60-day update) ECG QT prolonged AEs have been reported in 1.4% (1/71) of patients.

**Comment:** The data show that there is a risk of QTcF prolongation associated with crizotinib treatment. However, no cases of ventricular tachycardia, ventricular arrhythmia or torsades de pointes were reported in Studies 1001 and 1005, but there has been 2 cases of QT prolongation reported as Grade 3/4 events. Central tendency analysis for the QTcF data (preliminary CSRs) showed that mean changes from baseline at steady state ranged from 2.0 to 5.0 ms in Study 1001 with the highest upper bound of two-sided 90% CI being 8.2 ms across the measured time points, and the corresponding figures for Study 1005 were mean range of 7.2 to 10.3 ms, and highest upper bound of two-sided 90% CI of 13.3 ms. The central tendency result from Study 1005 is a matter of regulatory concern.

#### 7.3.7.2.5. Hepatic enzyme elevation and treatment-related hepatic impairment

Information on hepatic enzyme elevations was collected as laboratory abnormalities and as AEs. The shift results for total bilirubin, ALT and AST from Grade ≤ 2 at baseline to Grade 3 or 4 post-baseline for Study 1001 (preliminary CSR) and Study 1005 (preliminary CSR 60 day update) are summarised below in Table 31.

**Table 31: Studies 1001 and 1005 – Laboratory shifts from CTC Grade ≤ 2 at baseline to Grades 3 or 4 post-baseline in patients with ALK-positive NSCLC.**

	Study 1001 – Data cut-off 15 September 2010			Study 1005 – Data cut-off 1 February 2011		
	n	Grade 3	Grade 4	n	Grade 3	Grade 4
Bilirubin (total)	111	0	0	135	1 (0.7%)	0
AST	113	3 (2.7)	0	135	4 (3.0%)	0
ALT	113	5 (4.4%)	1 (0.9%)	135	7 (5.2%)	2 (1.5%)

In Study 1005 (preliminary CSR 60-day update), increased ALT and increased AST were reported as AEs (all causality) in 12.5% (n=17) and 8.8% (n=12) of patients, respectively, and the corresponding results for AEs (treatment-related) were 12.5% (n=17) and 8.1% (n=11). Treatment-related increased ALT and increased AST were reported as Grade 3/4 AEs in 6.6% (n=9) and 0.7% (n=1) of patients, respectively. ALT increased was the most common treatment-related AE resulting in permanent treatment discontinuation and was reported in 3 patients (2.2%). There were no Hy's law cases, hepatic failure, or fatal hepatotoxicity reported in Study 1005 (preliminary CSR 60-day update).

In Study 1001 (preliminary CSR), increased ALT and increased AST were reported as AEs (all causality) in 17.6% (n=21) and 14.3% (n=17) of patients, respectively, and the corresponding results for AEs (treatment-related) were 14.3% (n=17) and 10.9% (n=13). Treatment-related increased ALT and increased AST were reported as Grade 3/4 AEs in 4.2% (n=5) and 2.5% (n=4) of patients, respectively. Five patients (4.2%) had a dosing interruption due to treatment-related ALT increased. Treatment-related ALT increased was associated with permanent discontinuation from study treatment in 1 patient. There were no cases of hepatic failure or fatal hepatotoxicity reported in Study 1001 (preliminary CSR), although there was 1 patient who experienced hepatic dysfunction possibly meeting Hy's Law criteria for drug-induced liver injury.

In Study 1001 (preliminary CSR), the patient meeting Hy's law criteria for drug-induced liver injury was a 64-year-old male with ALK-positive advanced NSCLC without metastatic liver disease who had been treated with crizotinib 250 mg BID for approximately 1 month prior to experiencing lip swelling and sharp upper abdominal pain. Study treatment was interrupted, and treatment with dexamethasone and diphenhydramine was instituted. The following day, the symptoms persisted or worsened and following laboratory parameters were elevated, ALT 592 U/L, AST 401 U/L, alkaline phosphatase 82 U/L, total bilirubin 2.1 mg/dL, and lipase 713 U/L. Abdominal ultrasound revealed cholelithiasis with gallbladder sludge and a moderately distended gallbladder without wall thickening; no scintigraphic evidence of acute cholecystitis was seen. Abdominopelvic CT scan revealed increased size of right lower lobe lung mass without metastatic liver disease. ALT and AST peaked the following day at 803 U/L and 580 U/L, respectively, and total bilirubin peaked 2 days after admission at 3.6 mg/dL. Alkaline phosphatase remained in the normal range throughout the event. The patient's abdominal pain steadily decreased, and he was discharged 2 days after admission. This event was considered possibly related to treatment with crizotinib. The patient was permanently withdrawn from the study due to clinical disease progression.

Subsequent to the submission to register crizotinib for the treatment of ALK-positive NSCLC, the sponsor informed the TGA of 2 new cases fulfilling Hy's law criteria (with fatal hepatic failure in 1 patient) and 2 cases of hepatic impairment (with fatal hepatic failure in 1 patient). These 4 patients all came from Study 1005 and have been reported to relevant health authorities as SAEs related to crizotinib treatment. Consequently, there have now been 3 cases meeting Hy's law criteria for drug-induced liver injury (including 1 case of fatal hepatic failure), and 2 cases of hepatic impairment (including 1 case of fatal hepatic impairment) related to crizotinib treatment. The 5 events have occurred in more than 1400 patients treated with crizotinib in clinical trials. In these 5 cases, 2 patients presented with anorexia, 2 patients presented with weakness and fatigue, and 1 patient presented with abdominal pain. Of the 5 cases, 4 (including the 2 fatal cases) were observed within the first 2 months of starting treatment with crizotinib, while in the fifth case significant transaminase elevation was observed 6 months after starting crizotinib treatment.

The sponsor provided the CIOMS form (suspect adverse drug reaction) for each of the 4 patients. The report of the potential Hy's law case in a 58 year old Korean male concluded that "based on a plausible temporal relationship, on the compatibility with the known safety profile of the drug, and on the lack of alternative explanations, there is a reasonable possibility that this

potential Hy's law case is related to study medication crizotinib". The report indicates that the patient was recovering. The report of the potential Hy's law case in a 57 year old Taiwanese male concluded "there is a reasonable possibility that the...drug-induced liver injury is related to study medication crizotinib. The event occurred in a plausible temporal relationship with study drug administration and might be compatible with the known adverse profile of this drug. The reasonable possibility that the event is related also to concomitant drugs phenazopyrine, amoxicillin and clindamycin cannot be excluded". This patient is reported to have died due to "drug-induced liver injury".

The report of the case of hepatotoxicity in a 30 year old German male concluded "based on a plausible temporal relationship, on the compatibility with the known safety profile of the drug, and on the lack of alternative explanations, there is a reasonable possibility that the reported event is related to study medication crizotinib". The report indicated that the event abated after stopping crizotinib. The reported case of fatal liver failure and bloody diarrhoea in a 40 year old German female concluded "that there is not an obvious explanation for the clinical event reported in this case, however, the observed laboratory values and clinical course are also consistent with disseminated intravascular coagulation. The recent administration of amoxicillin/clavulanic acid, as well as of oxycodone, and the evolution of underlying malignancy might have played a causative role for hepatic failure. Nadroparin administration and coagulation alteration induced by progressive liver failure may have played a contributory role in hemorrhagic evolution of diarrhoea. However, based on a plausible temporal relationship, there is also a reasonable possibility that both events are related to study drug crizotinib".

**Comment:** The 5 cases of treatment related hepatic impairment associated with crizotinib are of concern, particularly against a background of commonly occurring increased ALT levels reported as treatment-related AEs.

#### 7.3.7.2.6. *Vision disorder*

MedDRA PTs contributing to the clustered term vision disorder were diplopia, photopsia, vision blurred, visual field defect, visual impairment, and vitreous floaters.

In Study 1001 (preliminary CSR), treatment-related vision disorder (clustered term) was reported in 74 (62.2%) patients, and all events were Grade 1 in severity. The patient incidence of the individual treatment-related eye disorders AEs contributing to the clustered term was 47.9% (n=57) visual impairment, photopsia 9 (7.6%), 1.7% (n=2) vitreous floaters, 1.7% (n=2) vision blurred and 0.8% (n=1) diplopia. The prevalence of treatment-related vision disorder (clustered term) ranged from 41% to 51% over the first 6 cycles of treatment.

In Study 1005 (preliminary CSR 60-day), treatment related vision disorder (clustered term) was reported in 58.8% (n=80) of patients, and all events were Grade 1 apart from three Grade 2 events. The patient incidence of the individual treatment-related eye disorders AEs contributing to the clustered term was 42.6% (n=58) visual impairment, 6.6% (n=9) photopsia, 5.9% (n=8) vision blurred, 3.7% (n=5) vitreous floaters, and 3.3% (n=3) diplopia.

In Study 1005 (preliminary CSR 60-day update), there were a limited number of ophthalmological investigations and these showed a small number of abnormalities.

**Comment:** Vision disorder (clustered term) occurred very commonly in association with crizotinib treatment with the most common individual AE contributing to the clustered term being visual impairment Grade 1. There was only one report of temporary treatment discontinuation due to vision disorder (clustered term) in a patient with diplopia Grade 2. Limited ophthalmological data have not identified a potential cause for the high incidence of visual disorders. No SAEs, permanent discontinuations or deaths due to vision disorder (clustered term) have been reported in Studies 1001 or 1005.

### 7.3.7.2.7. *Gastrointestinal disorders*

Gastrointestinal events of special interest, including nausea, vomiting, and diarrhoea, were among the most commonly reported AEs for patients in Studies 1001 and 1005, and the clustered term esophageal-related disorder was also a commonly reported event.

#### 7.3.7.2.8. *Nausea*

In Study 1001 (preliminary CSR), treatment-related nausea was reported in 58 (48.7%) patients, and all events were Grade 1 or 2 in severity. Treatment-related nausea most often began in Cycle 1 (42% prevalence), and prevalence decreased after the first cycle of treatment (27% to 32%). There were no SAEs or permanent treatment discontinuations due to nausea.

In Study 1005 (preliminary CSR 60-day update), treatment-related nausea was reported in 57.4% (n=78) of patients, and Grade 1 and 2 events were reported in 68 (50.0%) and 10 (7.4%) of patients, respectively. There was 1 report of permanent treatment discontinuation, and 2 (1.5%) reports of temporary treatment discontinuation due to nausea. There were no reports of SAEs associated with nausea.

#### 7.3.7.2.9. *Vomiting*

In Study 1001 (preliminary CSR), treatment-related vomiting was reported in 42 (35.3%) patients, and all events were Grade 1 or 2 in severity. Treatment-related vomiting most often began in Cycle 1 (32% prevalence), and prevalence decreased substantially after the first cycle of treatment (9% to 14%). There were no reports of SAEs, or permanent or temporary discontinuations for vomiting.

In Study 1005 (preliminary CSR 60-day update), treatment-related vomiting was reported in 43.4% (n=59) of patients, and Grade 1 and 2 events were reported in 39.0% (n=53) and 4.4% (n=6) of patients, respectively. There were no reports SAEs or permanent treatment discontinuation for vomiting, but there were 4 (2.0%) reports of temporary treatment discontinuation for nausea.

#### 7.3.7.2.10. *Diarrhoea*

In Study 1001 (preliminary CSR), treatment-related diarrhoea was reported in 51 (42.9%) patients, and all events were Grade 1 or 2 in severity. Treatment-related diarrhoea most often began in Cycle 1 (36% prevalence), and prevalence decreased after the first cycle of treatment (22% to 30%). There were no reports of SAEs or permanent or temporary treatment discontinuations associated with diarrhoea.

In Study 1005 (60-day clinical date update), treatment-related diarrhoea was reported in 42.6% (n=58) of patients, and Grade 1 and 2 events were reported in 39.7% (n=54) and 2.9% (n=4) of patients, respectively. There were no reports of SAEs or permanent or temporary treatment discontinuations associated with diarrhoea.

#### 7.3.7.2.11. *Oesophageal-related disorder (clustered term)*

MedDRA PTs contributing to the clustered term oesophageal-related disorder were dysphagia, epigastric discomfort, gastrooesophageal reflux disease, odynophagia, oesophageal obstruction, oesophageal pain, oesophageal spasm, oesophageal ulcer, oesophagitis, and reflux oesophagitis.

In Study 1001 (preliminary CSR), treatment-related PTs in the clustered term oesophageal-related disorder were reported in 13 (10.9%) patients, and all events were Grade 1 or 2 in severity. One (0.8%) AE of oesophageal ulcer was reported as a treatment-related SAE. The prevalence of oesophageal-related disorder (clustered term) was relatively stable across treatment cycles (4% to 7%). There were no permanent treatment discontinuations or deaths attributed to esophageal-related disorder (clustered term).



In Study 1005 (preliminary CSR 60-day update), treatment-related oesophageal-related disorder (clustered term) was reported in 6 (4.4%) patients, with Grade 1 and 2 events being reported in 4 (2.9%) and 2 (1.5%) patients, respectively. There were no treatment-related SAEs.

#### 7.3.7.2.12. *Oedema*

MedDRA PTs contributing to the clustered term oedema were localized oedema, oedema, and oedema peripheral.

In Study 1001 (preliminary CSR), treatment-related oedema (clustered term) was reported in 33 (27.7%) patients, and all events were Grade 1 or 2 in severity. The prevalence of treatment-related oedema (clustered term) increased between Cycle 1 (6%) and subsequent cycles (8% to 17%). Treatment-related peripheral oedema was the most commonly reported individual AE contributing to the clustered term. Treatment-related peripheral oedema occurred in 24.4% (n=29) of patients, and the majority of cases were Grade 1 (n=24) with remainder being Grade 2 (n=5). There were no SAEs, permanent treatment discontinuations or deaths attributed to edema (clustered term).

In Study 1005 (preliminary CSR 60-day update), treatment-related oedema (clustered term) was reported in 39 patients (28.7%), and the majority of events were Grade 1 in severity (n=27; 19.9%) with the remainder being Grade 2 (n=12; 8.8%). Treatment-related peripheral oedema was reported in 27.5% (n=35) of patients, and the majority of cases were Grade 1 (n=26; 19.1%) with the remainder being Grade 2 (n=9; 6.6%). There was 1 (0.7%) case of peripheral oedema (Grade 2) reported as a treatment-related SAE. There were no cases of permanent or temporary treatment discontinuation due to oedema (clustered term).

#### 7.3.7.2.13. *Neuropathy*

MedDRA PTs contributing to the clustered term neuropathy included burning sensation, hypoaesthesia, hypoaesthesia facial, neuralgia, neuropathy peripheral, paraesthesia, peripheral motor neuropathy, peripheral sensory neuropathy, and sensory disturbance.

In Study 1001 (preliminary CSR), treatment-related neuropathy (clustered term) was reported in 13 (10.9%) patients, and the majority of events were Grade 1 (n=12; 10.1%) with the remainder being Grade 3 (1 event; 0.8%). The prevalence of treatment-related neuropathy increased between Cycle 1 (1%) and subsequent cycles (5% to 8%). No SAEs or permanent discontinuations were reported for treatment-related neuropathy, and temporary discontinuation was reported in 1 (0.8%) patient for treatment-related hypoaesthesia.

In Study 1005 (preliminary CSR 60-day update), treatment-related neuropathy (clustered term) was reported in 21 (15.4%) patients, and the majority of events were Grade 1 (n=16; 11.8%) with the remainder being Grade 2 (n=5; 3.7%). There were no SAEs and no permanent or temporary treatment discontinuations reported for treatment-related neuropathy (clustered term).

#### 7.3.7.2.14. *Neutropenia*

In Study 1001 (preliminary CSR), shift from normal pre-treatment neutrophil count, to Grade 1, 2, 3, or 4 on-treatment occurred in 13 (11.4%), 21 (18.4%), 3 (2.6%), and 1 (0.9%) patients, respectively.

In Study 1005 (preliminary CSR 60-day update), shift from normal pre-treatment neutrophil count to Grade 1, 2, 3 or 4 on-treatment occurred in 25 (18.8%), 19 (14.3%), 7 (5.3%), and 2 (1.5%) of patients, respectively.

In Study 1001 (preliminary CSR), treatment-related neutropenia (clustered term) was reported in 5.0% (n=6) of patients, with Grade 1, 2 and 3 events reported in 0.8% (n=1), 0.8% (n=1) and 3.4% (n=4) of patients, respectively. The prevalence of treatment-related neutropenia was relatively stable across treatment cycles (1% to 2%). No events of neutropenia were considered

to be SAEs, or associated with permanent discontinuation. There were no reports of febrile neutropenia. No deaths were attributed to neutropenia.

In Study 1005 (preliminary CSR 60-day update), treatment-related neutropenia (clustered term) was reported in 8.8% (n=12) of patients, and Grade 1, 2, 3, and 4 events were reported in 0.7% (n=1), 2.2% (n=3), 4.4% (n=6), and 1.5% (n=2) of patients, respectively. There were no cases of neutropenia reported as SAEs, but there was 1 (0.7%) case of treatment-related febrile neutropenia reported as a SAE (Grade 4 severity). There were no permanent treatment discontinuation due to neutropenia, but temporary treatment discontinuations were reported in 6 (4.4%) patients and dose reductions in 2 (1.5%) patients. There were no deaths attributed to neutropenia.

### **7.3.8. Other safety issues of interest**

#### **7.3.8.1. Infections and infestations**

##### *7.3.8.1.1. Study 1001*

In Study 1001 (preliminary CSR), all causality infections and infestations (SOC) were reported in 42.0% (n=50) of patients, and Grade 1, 2, 3, 4 and 5 (death) events reported in 21.8% (n=26), 11.8% (n=14), 5.0% (n=6), 2.5% (n=3) and 0.8% (n=1) of patients, respectively. Individual PT AEs occurring in  $\geq 5\%$  of patients were nasopharyngitis (11.8%; n=14), pneumonia (8.4%; n=10) and URTI (10.9%; n=13).

SAEs (all causality) infections and infestations were reported in 10 (8.4%) patients (all  $\geq$  Grade 2), and included 1 (0.8%) death due to pneumonia. The only SAE occurring in  $\geq 5\%$  of patients was pneumonia which was reported in 6 (5.0%) patients. Permanent discontinuations due to infections and infestations were reported in 1 (0.8%) patient due to pneumonia. Temporary discontinuations due to infections and infestations were reported in 10 (8.4%) patients, and the only event contributing more than 1 patient was pneumonia (n=5; 4.2%). No infections and infestations were associated with dose reductions.

##### *7.3.8.1.2. Study 1005*

In Study 1005 (preliminary CSR 60-day update report), all causality infections and infestations (SOC) were reported in 33.8% (n=46) patients, and Grade 1, 2, 3, 4, and 5 (death) events were reported in 10.3% (n=14), 11.8% (n=16), 8.1% (n=11), 0.7% (n=1), and 2.0% (n=4) of patients, respectively. Individual PT AEs occurring in  $\geq 5\%$  of patients were nasopharyngitis (8.1%; n=11), pneumonia (6.6%; n=9) and URTI (6.6%; n=9).

SAEs (all causality) infections and infestations were reported in 15 (11.0%) patients (all  $\geq$  Grade 3 severity), and these events included 4 deaths (pneumonia x1 [0.7%]; pyothorax x1 [0.7%]; sepsis x1; [0.7%], and septic shock x1 [0.7%]). Individual AEs occurring in  $\geq 1\%$  of patients were pneumonia (5.1%; n=7) and infection (1.5%; n=2).

Despite 4 deaths being reported there was only 1 report of permanent discontinuation due to infection and infestations (1x sepsis). Temporary discontinuations were reported in 10 (7.4%) patients due to infections and infestations, and no event contributed more than 1 patient. No infections and infestations were associated with dose reductions.

### **7.3.9. Other safety issues**

#### **7.3.9.1. Vital signs**

The most notable change in vital signs in Studies 1001 (preliminary CSR) and 1005 (preliminary CSR) was related to reductions in pulse rate. In the pooled population (n=255), 9.8% (n=25) of patients had a maximum pulse rate on study of  $< 50$  bpm, compared with 3.1% (n=8) of patients with a maximum pulse rate on study of  $> 120$  bpm, and 37.6% (n=96) of patients had a maximum decrease from baseline of  $\geq 30$  bpm compared with 1.6% (n=4) of patients who had a maximum increase from baseline of  $\geq 30$  bpm. In the pooled population (n=255) from Study

1001 (preliminary CSR) and Study 1005 (preliminary CSR 60-day update), there were 12 (4.7%) patients with treatment-related AEs of bradycardia (10x Grade 1 and 2x Grade 2). The only other change of note in vital signs was maximum decrease from baseline of  $\geq 20$  mmHg in 25.0% (n=64) of patients in the pooled population (n=255). In the pooled population (n=255) from Study 1001 (preliminary CSR) and Study 1005 (preliminary CSR 60-day update), there were 3 (1.2%) patients with a treatment-related AE of hypotension (all Grade 1).

### **7.3.10. Safety in special populations**

#### **7.3.10.1. Elderly patients**

There was no marked difference in the AE profile between patients aged < 65 years and patients aged  $\geq 65$  years in Studies 1001 (preliminary CSR) and 1005 (preliminary CSR). However, in both studies there was a marked imbalance in patient numbers in favour of patients aged < 65 years compared with patients aged  $\geq 65$  years.

#### **7.3.10.2. Sex**

In the pooled data from Studies 1001 (preliminary CSR) and 1005 (preliminary CSR), the overall incidence of treatment-related AEs was similar in male (88.6%; [109/123]) and female patients (90.9%; [120/132]). However, review of treatment-related AEs occurring in  $\geq 10\%$  of patients showed that there were a number of events that occurred  $\geq 2\%$  more frequently in females than males in both studies. These events were: nausea; vomiting; constipation; oedema peripheral; dizziness; ALT increased; and dysgeusia. There were no treatment-related AEs occurring more commonly than  $\geq 10\%$ , and  $\geq 2\%$  more frequently in males than in females in both studies. The comparisons between males and females for treatment AEs occurring in  $\geq 10\%$  of patients were summarised in the study report.

#### **7.3.10.3. Race**

In the pooled data from Studies 1001 (preliminary CSR) and 1005 (preliminary CSR), the overall incidence of treatment-related AEs (all grades) was similar in non-Asian (89.3%; [159/178]) and Asian (90.9%; [70/77]) patients. However, review of treatment-related AEs occurring in  $\geq 10\%$  of patients showed that there were a number of events that occurred  $\geq 2\%$  more frequently in Asians than in non-Asians in both studies. These events were: nausea; vomiting; diarrhoea; visual impairment; dizziness; and decreased appetite. Grade 3/4 AEs occurred more frequently in non-Asian (16.9%; [30/178]) than in Asian (10.3%; 8/77), and most Grade 3/4 events appeared to occur more commonly in non-Asian than in Asian patients. The comparisons between non-Asian and Asian patients for treatment AEs (all grades) occurring in  $\geq 10\%$  of patients were summarised in the study report.

#### **7.3.10.4. Drug interactions**

There are no specific safety data on drug-drug interactions in patients with ALK-positive NSCLC. The proposed PI includes a comprehensive section on potential interactions between crizotinib and other medicines.

## **7.4. Postmarketing experience**

No post-marketing safety data were submitted.

## **7.5. Evaluator's conclusion on clinical safety**

### **7.5.1. 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 BID 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 this section of the CER relating to the safety of crizotinib (250 mg BID) 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 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 (i.e., 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.

#### 7.5.2. 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 ≥ 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 ≥ 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 ≥ 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%).

### 7.5.3. 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 (i.e., “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, 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.

### 7.5.4. 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%).

### 7.5.5. 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  $\geq 2$  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  $\geq 2$  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.

#### 7.5.6. 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%), 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%).

#### 7.5.7. Laboratory tests

- In both studies the highest frequency of shifts from Grade  $\leq 2$  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  $\leq 2$  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 WBC from baseline Grade  $\leq 2$  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  $\leq 2$  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  $\leq 2$  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 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.

#### 7.5.8. 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 100 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 14.5 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 (≥ 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  $\geq 500$  ms were reported in 0.8% (2/251) of patients, and maximum change in QTcF of  $\geq 60$  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 msec, and the highest upper bound of the two-sided 90% CI was 13.3 msec. These central tendency results are of regulatory concern as the mean increases in QTcF were greater than 5 msec, and the highest upper bound 95% CI was greater than 10 msec.
- *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 hypoesthesia.
- *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 (i.e., incidence of 0.9%), and that 1 of these cases had been fatal (i.e., 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, G3=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).

## 7.6. First round benefit-risk assessment

### 7.6.1. 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 criterium 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 (i.e., 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.

#### **7.6.2. First round assessment of risks**

Nearly all patients with ALK-positive NSCLC exposed to crizotinib 250 mg BID 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 localized 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 (i.e., incidence of 0.9%), and confirmed that 1 of these cases has been fatal (i.e., 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 (i.e., 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 (Camidge et al., 2012).

### **7.6.3. 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 (i.e., OS and/or PFS). The information from the retrospective analyses in the Technical Report (covariate-matched and covariate-adjusted analyses) suggest 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.

### **7.6.4. 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 (i.e., 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.

### 7.7. Clinical questions

See *Second Round Evaluation of clinical data submitted in response to questions* below.

## 8. Second round evaluation of clinical data submitted in response to questions

The second round data package was dated 27 April 2012 and provided the sponsor's "response to section 31 request for information" from the Therapeutic Goods Administration (TGA) relating to the first round evaluation of the submission. The relevant clinical data were included in Module 1 and Module 5 of the data package. The relevant hard copy clinical documentation consisted of Module 1 (2 volumes; 250 pages), Module 5 (2 volumes; 820 pages), and Module 5.3.1 (1 volume, 4 pages). The complete response was also provided in European CTD format for Modules 2-5 and Australian specific format for Module 1. The clinical evaluation of the submitted response is based on the relevant clinical data provided on the CD. The electronic copies of the relevant data were comprehensive and facilitated clinical evaluation of the submission. The new and updated Module 1 and Module 5 data directly relevant to this review and evaluation are summarised in this report.

This second round clinical review and evaluation report provides comment on the sponsor's s31 response to the clinical questions raised following the first round clinical evaluation, the second round benefit-risk assessment, the second round recommendation regarding authorization, and the second round comments on the product documentation.

The first and second round clinical evaluation reports have been prepared by the same clinical evaluator and the two reports are complementary and should be considered together. However, it should be noted that the second-round benefit-risk assessment differs from the first-round benefit-risk assessment. In particular, the second-round benefit-risk balance for crizotinib for the proposed indication is now considered to be **favourable**, in contrast with the first-round unfavourable assessment. Furthermore, the second-round recommendation regarding authorization is now to **approve** the application to register crizotinib for the proposed indication, in contrast with the first-round recommendation which was to reject authorization. The revised benefit-risk assessments and recommendation regarding authorization are due to favourable evaluation of the updated and new clinical efficacy and safety data provided with the sponsor's s31 response to the first-round clinical questions.

### 8.1. Questions on Pharmacokinetics

#### 8.1.1. Question a

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.

##### 8.1.1.1. *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.

#### 8.1.1.2. **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.

#### 8.1.2. **Question b**

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.

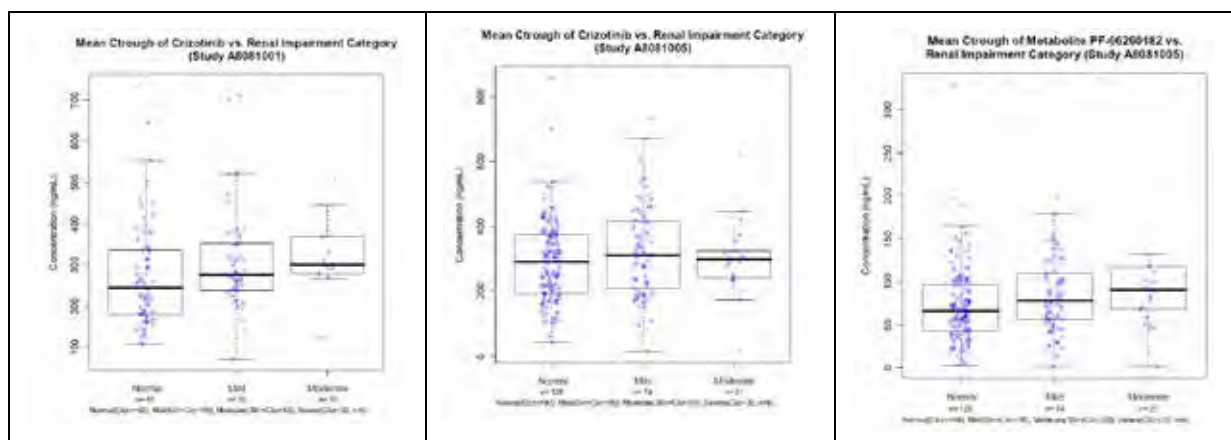
##### 8.1.2.1. **Sponsor's response**

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 [<sup>14</sup>C]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 (CL<sub>cr</sub>) and mean steady-state trough concentration (C<sub>trough,ss</sub>) 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 (CL<sub>cr</sub> greater than 90 mL/min), mild (CL<sub>cr</sub> 60 to 90 mL/min), moderate renal impairment (CL<sub>cr</sub> 30 to 60 mL/min) and severe renal impairment (CL<sub>cr</sub> <30 mL/min, no PK data available for this group). Results of the analysis indicated that C<sub>trough,ss</sub> 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 10).



**Figure 10. Box-Plots of Trough Concentrations of Crizotinib and its Metabolite PF-06260182 vs. 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 realizes 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 (CTD Section 2.7.2). 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<sub>cr</sub> 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 TG.

#### 8.1.2.2. *Clinical evaluator’s comment*

The sponsor’s response is satisfactory. The sponsor provided data summarizing crizotinib and metabolite PF-06260182 C<sub>trough,ss</sub> 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<sub>max,ss</sub> and AUC<sub>ss</sub> levels, or on C<sub>trough,ss</sub> 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<sub>cr</sub> effect on crizotinib PK”.

The new data summarised the ANCOVA results of steady state crizotinib (PF-02341066) and steady state crizotinib metabolite (PF-06260182) C<sub>trough,ss</sub> 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<sub>trough,ss</sub> are summarised below in Table 32 (Study 1001), and Table 33 (Study 1005). The analyses showed that mild and moderate renal impairment had no

marked effects on Ctrough.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, Ctrough.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 32: 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 33: 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) Ctrough 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.

### 8.1.3. Question c

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 have 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.

#### 8.1.3.1. 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) resulting from alterations of either absorption or systemic clearance following coadministration of crizotinib with a P-gp inhibitor/inducer for the following reasons:

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

Categorization 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. Crizotinib (0.1 to 50 µM [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. 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 µM [22,500 ng/mL]). The gastrointestinal concentration of crizotinib after oral administration of 250 mg (I2) is calculated to be 2220 µM (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% indicating a moderate to high fraction absorbed (Fa >43%). Based on these observations, it is unlikely that absorption of crizotinib will be limited by this efflux transporter at therapeutic doses.

##### 8.1.3.1.2. *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. 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-fold [Johnson et al. (2011)], consistent with that observed in the clinical study with ketoconazole, 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. 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 [<sup>14</sup>C]crizotinib. 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).

**8.1.3.1.3. 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 [<sup>14</sup>C]crizotinib, crizotinib-derived radioactivity was below the limit of quantitation in the brain and spinal cord. A low crizotinib concentration in CSF was reported in 1 ALK-positive NSCLC patient in Study A8081001 treated with crizotinib (250 mg BID) who developed metastatic brain disease (Costa et al., 2011). 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 (Ayrton & Morgan, 2001). Moreover, in examples where interactions were observed, the effects were relatively modest, with less than 2-fold increase in CNS penetration (Ayrton & Morgan, 2008). There are currently no consistent clinical examples in which inhibition of P-gp on the BBB resulted in adverse effects (Eyal, et al. 2009).

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.

**8.1.3.2. Clinical evaluator's comment**

The sponsor's response is satisfactory.

**8.1.4. Question d**

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.

**8.1.4.1. 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) (Pfizer report PF-02341066\_11May10\_141847). The IC<sub>50</sub> of crizotinib inhibition of P-gp-mediated digoxin efflux was 5.8 µM (2610 ng/mL). Based on the mean unbound crizotinib plasma C<sub>max</sub> (38 ng/mL, 0.085 µM) at the 250 mg BID therapeutic dose, crizotinib is unlikely to have systemic interaction with substrates of P-gp. Crizotinib demonstrated time-dependent inhibition of CYP3A *in vitro* and was shown to be a moderate inhibitor of CYP3A in clinical trial. Many P-gp substrates are also metabolized 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 (Lin et al., 2007). In contrast to CYP-mediated changes, DDIs related to changes in P-gp activity are generally not clinically significant (PK ratios ≤2) (Fenner et al., 2009). 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 (Giacomini et al., 2010). 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.

#### 8.1.4.2. *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  $\mu$ M) and the  $IC_{50}$  of crizotinib inhibition of P-gp mediated digoxin efflux (2610 ng/mL, 5.8  $\mu$ 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  $\mu$ 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 (Zhang et al, 2009; Bjornsson et al., 2003; FDA Guidance for Industry, Drug Interaction Studies, 2012). 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 (Giacomini et al., 2010). 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.

#### 8.1.5. **Question e**

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 (i.e., 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 H<sub>2</sub> inhibitors. If not please provide a justification for not providing such data.

#### 8.1.5.1. **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, Randomised, Cross-Over Study to Estimate the Effect of Esomeprazole on the Pharmacokinetics of Crizotinib in Healthy Volunteers".

#### 8.1.5.2. **Clinical evaluator's comment**

The sponsor's response is satisfactory.

### 8.1.6. **Question f**

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.

#### 8.1.6.1. **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 utilized 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.

#### 8.1.6.2. **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 non-clinical 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  $\mu\text{M}$ , with rifampin (10  $\mu\text{M}$ ) 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 (Fahmi et al., 2010). 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.

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 (i.e., > 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 utilized 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.

### 8.1.7. Question g

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.

#### 8.1.7.1. Sponsor's response

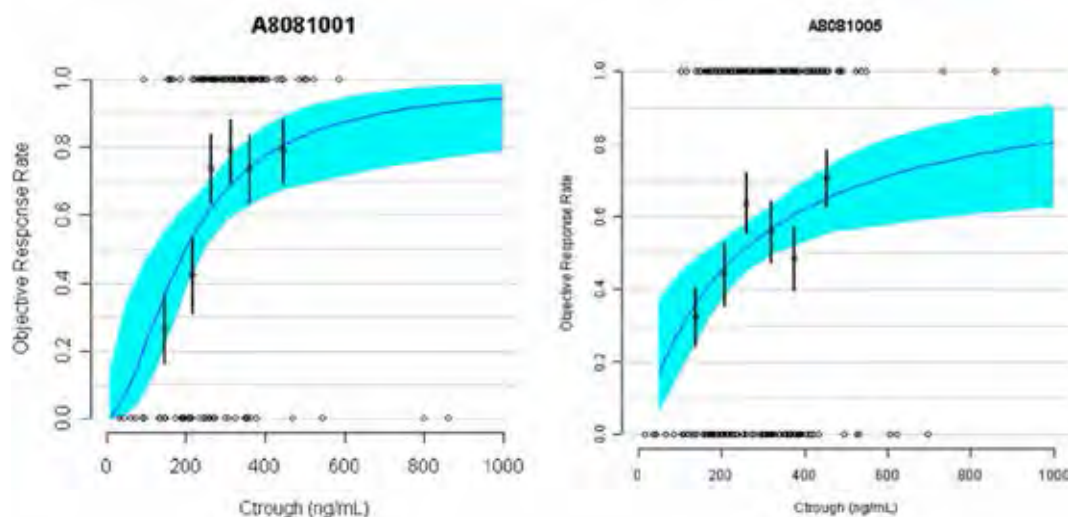
The sponsor has completed preliminary exposure-response analyses using data from Studies A8081001 and A8081005 which are summarised in PMAR-0242 and PMAR-0266, respectively. These studies included exposure-response analyses for objective response rate (ORR),

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  $\geq 3$  in severity and had the 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.

#### 8.1.7.1.1. 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 11). 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 11. 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.

#### 8.1.7.1.2. 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.

#### 8.1.7.1.3. 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  $\geq 450$  mg were not likely to have a low exposure (C<sub>trough</sub>), and the ORR for these patients was  $>50\%$ .

#### 8.1.7.1.4. 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 BID 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 BID dosing regimen for ALK-positive advanced NSCLC patients.

#### 8.1.7.2. Clinical evaluator's comment

The sponsor's response is satisfactory. The exposure-response analysis showed a statistically significant relationship between C<sub>trough</sub> 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.

#### 8.1.8. Question h

*In vivo* data in patients with advanced cancer showed that multiple dose crizotinib (250 mg BID) co-administered with single dose midazolam (2 mg), a CYP3A substrate, increased midazolam AUC<sub>inf</sub> and C<sub>max</sub> 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 (i.e., AUC increase  $\geq 2$ -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?

##### 8.1.8.1. 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.

#### **8.1.8.2. Clinical evaluator's comment**

The sponsor's response is satisfactory.

#### **8.1.9. Question i**

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: i.e., 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.

#### **8.1.9.1. 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 interaction is 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 (01 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, antidiarrhoeal, 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.

#### 8.1.9.2. *Clinical evaluator's comment*

The sponsor's response is acceptable.

### 8.2. Questions on pharmacodynamics

#### 8.2.1. Question a

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). 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.

##### 8.2.1.1. *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 BID 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 enrolment). 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).

##### 8.2.1.2. *Clinical evaluator's comment*

The sponsor's response is acceptable.

### 8.3. Questions on safety

#### 8.3.1. Questions a (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.



**8.3.1.1. Sponsor's response**

The requested ALT data were provided.

**8.3.1.2. Clinical evaluator's comment**

The updated ALT data from the Day 120 CDA (01 June 2011 cut-off): Maximum increases in ALT  $\geq 3$  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  $\geq 3$ xULN and all but 1 of these patients had baseline levels  $< 3$ xULN, and 7.5% (n=30) had ALT levels  $\geq 5$ xULN with all patients having baseline levels  $\leq 5$ xULN.

**8.3.2. Question b (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.

**8.3.2.1. Sponsor's response**

The requested total bilirubin data were provided.

**8.3.2.2. Clinical evaluator's comment**

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

**8.3.3. Question c (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.

**8.3.3.1. Sponsor's response**

The requested alkaline phosphatase (ALP) data were provided.

**8.3.3.2. Clinical evaluator's comment**

The alkaline phosphatase (ALP) data from the Day 120 CDA (01 June 2011 cut-off): Maximum increases in ALP  $\geq 1.5$ 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  $\geq 1.5$ xULN.

**8.3.4. Questions d and e (genetic mutations)**

Please comment on the potential for resistance to crizotinib to develop due to genetic mutations in the EML-ALK gene (question d). Please comment on the potential for resistance to crizotinib to develop due to genetic mutations in the EML-ALK gene (question e).

**8.3.4.1. 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 (Doebele et al. 2012; Katayama et al., 2012; Sasaki et al., 2010; Sasaki et al., 2011). 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.

#### 8.3.4.2. **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.

#### 8.3.5. **Question f**

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 (i.e., 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 (i.e., Studies 1007 and 1014).

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

##### 8.3.5.1. **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

### 8.3.5.2. *Clinical evaluator's comment*

#### 8.3.5.2.1. *Updated efficacy and safety data - study A8081001 (1001)*

##### 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 antitumour activity study of crizotinib (250 mg BID) 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 included updated clinical efficacy and safety data from patients in the ALK-positive NSCLC cohort as of 01 June 2011 (i.e., 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 34. 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 34: 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
<b>Safety Analysis Population</b>	<b>125</b>	<b>149</b>
Ongoing as of data cutoff	64 (51.2)	82 (55.0)
Completed	0	0
<b>Discontinued</b>	<b>61 (48.8)</b>	<b>67 (45.0)</b>
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 *	5 (4.0)	5 (3.4)

<sup>a</sup> Other included patients who had clinical progression not consistent with RECIST.

- The demographic characteristics were similar for the previously treated (n=125) and all patient (n=149) groups. 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 in the two groups, 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.

#### 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 35, 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 35: 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)
<b>Best Response, n (%)</b>			
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 <sup>a</sup>	3 (2.6)	4 (3.3)	4 (2.8)
Indeterminate <sup>b</sup>	5 (4.3)	2 (1.7)	3 (2.1)
<b>ORR (CR + PR), % (n)</b>	<b>71 (61.2)</b>	<b>73 (60.3)</b>	<b>88 (61.5)</b>
<b>[95% CI]</b>	<b>[51.7, 70.1]</b>	<b>[51.0, 69.1]</b>	<b>[53.0, 69.5]</b>
<b>PD or Death after Response n/N of responders (%)</b>	26/71 (36.6)	40/73 (54.8)	45/88 (51.1)
<b>TTR Median, weeks (Range)</b>	7.7 (4.3 – 39.6)	7.9 (2.1 – 39.6)	7.9 (2.1 – 57.3)
<b>DR, Median weeks (Kaplan- Meier estimate)</b>	48.1	48.1	49.1
<b>[95% CI]</b>	[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) (i.e., 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) (i.e.,  $\geq 6$  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  $\geq 12$  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 that were  $\geq 65$  years (72.2%) than in those < 65 years (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. The results of the sub-group analyses were summarised in the study report.
- 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 (i.e., 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 a were summarised in the study report.
- 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 the study report.

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 36.

**Table 36: 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)
<b>Duration of Treatment</b>			
Median (Range) in weeks	31.9 (0.7-101.7)	42.3 (0.1-138.4)	43.1 (0.1-138.6)
<b>Deaths, n (%)</b>			
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*
<b>Serious Adverse Events, n (%)</b>			
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)
<b>Grade 3 or 4 Adverse Events, n (%)</b>			
All-causality	43 (36.1)	70 (56.0)	77 (51.7)
Treatment-related	19 (16.0)	30 (24.0)	36 (24.2)
<b>Treatment-Related, Adverse Events, n (%)</b>			
<b>Associated With:</b>			
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 (i.e., 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. Total deaths within 28 days of the last dose of crizotinib were summarised in the study report.
- 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  $\geq 20\%$  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 (all causality, all cycles) by MedDRA preferred term and maximum CTC occurring in  $\geq 10\%$  of patients in the cohort were summarised in the study report.
- *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 37.

**Table 37: Study 1001 - Treatment-related adverse events with frequency  $\geq 5\%$  in either group of ALK-positive NSCLC patients; safety analysis population at 1 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%). Clustered terms in the all patient group (all causality and treatment-emergent) were summarised in the study report.

- *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  $\leq 2$  at baseline to Grade  $\geq 3$  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  $\leq 2$  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 BP of  $\geq 40$  mmHg and diastolic BP of  $\geq 20$  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  $\geq 40$  mmHg and diastolic BP  $\geq 20$  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  $\geq 30$  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  $\geq 500$  msec 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  $< 30$ ,  $\geq 30$  to  $< 60$ , and  $\geq 60$  msec 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.



## 8.3.5.2.2. Updated efficacy and safety data – study A8081005 (1005)

## 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 BID) 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 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, and 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 38. 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 38: 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 <sup>a</sup>	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 <sup>b</sup>	1 (0.4)	1 (0.2)

<sup>a</sup> Two patients from Study 1005 were incorrectly reported as “Completed” at the time of analysis for this Day 120 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.

<sup>b</sup> Other included patients who had clinical progression not consistent with RECIST.

- The baseline demographics were similar for patients in both safety analysis populations (mature safety [n=261], and all patients [n=439]). 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 were similar for patients in both safety analysis populations (mature safety [n=261], and all patients [n=439]). 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.

### 8.3.5.2.3. 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 39. 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 39: 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*
<b>Best Response, n (%)</b>		
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 <sup>a</sup>	12 (4.7)	11 (4.2)
Indeterminate <sup>b</sup>	9 (3.5)	6 (2.3)
<b>ORR (CR + PR), n (%)</b>	136 (53.3)	153 (59.1)
<b>[95% CI]</b>	[47.0, 59.6]	[52.8, 65.1]
<b>DR Median weeks, Kaplan-Meier Estimate, [95% CI]</b>	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 01 June 2011 (n=255), and the Day 120 CDA “all RE” population (n=340) were summarised in the study report. With additional crizotinib treatment and patient follow-up through 02 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 were summarised in the study report. 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.

#### 8.3.5.2.4. *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 40. 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 40: 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)
<b>Duration of Treatment</b>			
Median (Range) in weeks	22.3 (0.9-53.1)	24.6 (0.9-68.4)	15.7 (0.1-68.4)
<b>Deaths, n (%)</b>			
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)
<b>Serious Adverse Events, n (%)</b>			
All-causality	43 (31.6)	89 (34.1)	126 (28.7)
Treatment-related	10 (7.4)	15 (5.7)	29 (6.6)
<b>Grade 3 or 4 Adverse Events, n (%)</b>			
All-causality	61 (44.9)	115 (44.1)	152 (34.6)
Treatment-related	33 (24.3)	64 (24.5)	82 (18.7)
<b>Treatment-Related, Adverse Events, n (%), Associated With:</b>			
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  $\geq 4$  (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  $\geq 4$  (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=231), 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). In the “all SA” population (n=439), treatment-emergent all causality AEs reported in  $\geq 1\%$  of patients were summarised in the study report.
- **Adverse events (treatment-related):** In the “mature SA” population (n=231), 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 41.

**Table 41: Study 1005 – Treatment-emergent, treatment-related AEs in  $\geq 5\%$  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  $\geq 2\%$  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  $\geq 2\%$  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 42. Treatment-emergent all causality clustered AE terms in the “all SA” population and treatment-emergent, treatment-related clustered AE terms in the “mature SA” population were summarised in the study report.

**Table 42: 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  $\geq 2$  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  $\geq 2$  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  $\leq 2$  at baseline to Grade  $\geq 3$  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  $\leq 2$  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  $\geq 40$  mmHg and diastolic BP of  $\geq 20$  mmHg were reported in 5.2% (N=13/250) and 8.4% (N=21/250) of patients, respectively; maximum decreases from baseline in SBP  $\geq 40$  mmHg and diastolic BP  $\geq 20$  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  $\geq 30$

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  $\geq 500$  msec 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,  $\geq 30$  to < 60, and  $\geq 60$  msec 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  $\geq 2$  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  $\geq 2$  lines (5 [8.2%] for right eye, 6 [9.7%] for left eye).

#### 8.3.5.2.5. 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).

#### 8.3.5.2.6. 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 3<sup>rd</sup> 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 ( $\geq 10$ -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 ( $\geq 10$ -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 ( $\geq 10$ -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  $\leq 1$  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.

#### 8.3.5.2.7. *New retrospective analyses - study A8081005 and historical controls*

- The sponsor's s31 response 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 (i.e., 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/m<sup>2</sup> 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 (i.e., 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/m<sup>2</sup> (day 1, day 8) and cisplatin 75 mg/m<sup>2</sup> (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 the study report. 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 the study report.
- **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 (i.e., 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).

#### 8.3.5.2.8. 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 43 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 43: 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 <sup>st</sup> line combination	112(39%)				
	2 <sup>nd</sup> line single agent	117(41%)	2 <sup>nd</sup> line single agent	117	2 <sup>nd</sup> line single agent	117
	2 <sup>nd</sup> line combination	58 (20%)				
Crizotinib	2 <sup>nd</sup> line single agent	37 (13%)	3 <sup>rd</sup> line single agent	76(65%)	2 <sup>nd</sup> line single agent	62
	≥3 <sup>rd</sup> line single agent	250(87%)[3,9]†	≥4 <sup>th</sup> 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 44. 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 enrolment. 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 44: 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#	
<b>TTP</b>						
<b>Treatment</b>	Criz	Pem/Doc	Criz	Pem/Doc	Criz	Pem/Doc
<b>Median (months)</b>	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]
<b>HR Criz vs. Pem/Doc [95% CI]</b>	0.451 [0.341, 0.595]		0.464 [0.317, 0.678]		0.242 [0.113, 0.522]	
<b>HR* Criz vs. Pem/Doc [95% CI]</b>	0.431 [0.310, 0.550]		0.428 [0.290, 0.631]		0.285 [0.131, 0.620]	
<b>PFS</b>						
<b>Treatment</b>	Criz	Pem/Doc	Criz	Pem/Doc	Criz	Pem/Doc
<b>Median (months) §</b>	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]
<b>HR Criz vs. Pem/Doc [95% CI]</b>	0.595 [0.461, 0.767]		0.631 [0.443, 0.899]		0.311 [0.157, 0.615]	
<b>HR* Criz vs. Pem/Doc [95% CI]</b>	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 enrolment 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 versus 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) versus 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). This result indicates 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 TTP 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 (Hanna et al., 2004 [TPP]; Scagliotii et al., 2009 [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) versus 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 TPP 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 versus prior pemetrexed/docetaxel TTP, after adjustment for ECOG performance status, was 0.369 (95% CI: 0.185, 0.738).

#### 8.3.5.2.9. *New retrospective analysis – saligia et al; 2012*

The original submission (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 included a report (Salgia et al., 2012) 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 enrolment. 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.

#### 8.3.5.2.10. *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 met 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 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.

#### 8.3.5.2.11. *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 (i.e., 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); see original CER.

#### **8.4. Second round benefit-risk assessment**

##### **8.4.1. Second round assessment of benefits**

###### **8.4.1.1. 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 1001<sup>1</sup> 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.

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<sup>1</sup> Erratum: Study 1005

Furthermore, the retrospective analyses consistently showed that crizotinib was more efficacious than standard first-line systemic treatment regimens for NSCLC.

#### 8.4.1.2. **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 (Day120 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  $\geq 3$  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 ( $\geq 10$ -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.

#### 8.4.1.3. *Data from the new retrospective analyses*

The sponsor's s31 response 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 (i.e., 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 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 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). 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 enrolment 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.

#### **8.4.2. 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 (i.e., treatment-emergent, treatment-related adverse events) from Studies 1001 (n=149, SA) and 1005 (n=261, "mature SA") were summarised in the submission. The sponsor has included the data from this table in the amended Adverse Effects section of the revised PI provided with its s31 response.

##### **8.4.2.1. *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).

##### **8.4.2.2. *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).



#### 8.4.2.3. **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%).

#### 8.4.2.4. **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, R eye; 62, L 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  $\leq 2$  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.

#### 8.4.2.5. **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).

#### 8.4.2.6. **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 (i.e., 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.

#### 8.4.2.7. **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  $\geq 4$  (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  $\geq 4$  (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.

#### 8.4.2.8. **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  $\geq 2$  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 (i.e., 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).

#### 8.4.2.9. ***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  $\geq 2$  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.

#### 8.4.2.10. ***Laboratory results***

In both Study 1001 (SA) and Study 1005 ("mature SA"), shifts in laboratory values from CTCAE severity Grade  $\leq 2$  at baseline to Grade  $\geq 3$  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/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  $\leq 2$  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  $\leq 2$  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%).

#### 8.4.2.11. ***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  $\geq 500$  msec 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 msec 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 TdP 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.

#### 8.4.2.12. *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.

#### 8.4.2.13. *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.

#### 8.4.2.14. *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.

### 8.4.3. **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<sup>2</sup>, the ORR was 68.2% ([95% CI: 45.1, 86.1]; n=15/22), which was marginally higher than for the sub-groups 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: 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

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<sup>2</sup> Erratum: Study 1001

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, the sponsor provided statements supporting its position from [information redacted] participating in Studies 1001, 1005, 007, and 1014, [information redacted] participating in Studies 1005, 1007, and 1014, and [information redacted] participating in Study 1005, [information redacted].

[information redacted] stated that, in [information redacted] opinion, “*there are few anticancer drugs with as favourable a risk benefit ratio as crizotinib in ALK positive NSCLC*”. [information redacted] 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*”.

[information redacted] stated that [information redacted] “*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.*

### **8.5. 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:

- the final reports from ongoing Studies 1001 and 1005 should be submitted to the TGA for evaluation;
- the final reports from ongoing Phase III Studies A8081007 and A8081014 should be submitted to the TGA for evaluation;
- the final report from 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 should be submitted to the TGA for evaluation on completion;
- 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 real-world settings should be submitted to the TGA for evaluation on completion;
- the final report from Phase I Study A8081020 designed to evaluate the safety and single-dose PKs of crizotinib in subjects with severely impaired renal function should be submitted to the TGA for evaluation on completion;
- the final report of the planned updated population PK analysis to definitively assess the CL<sub>Cr</sub> effect on crizotinib PKs using pooled data from clinical trials, including but not limited to Studies A8081001 and A8081005, should be submitted to the TGA for evaluation on completion;
- the final report of 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 should be submitted to the TGA for evaluation on completion;
- 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 PKs of crizotinib should be submitted to the TGA for evaluation on completion;
- the final report of Study A8081035 designed to study the actions of proton pump inhibitors or H<sub>2</sub> antagonists on the PKs of crizotinib should be submitted to the TGA for evaluation on completion.

## **9. References**

### **9.1. First round evaluation**

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