19 July 2012
EMA/CHMP/497137/2012
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

XALKORI

International non-proprietary name: **crizotinib**

Procedure No. **EMEA/H/C/002489**

Note

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

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Product information

Name of the medicinal product:	XALKORI
Applicant:	Pfizer Ltd. Ramsgate Road Sandwich Kent CT13 9NJ United Kingdom
Active substance:	crizotinib
International Nonproprietary Name/Common Name:	crizotinib
Pharmaco-therapeutic group (ATC Code):	Protein kinase inhibitors (L01XE16)
Therapeutic indication:	XALKORI is indicated for the treatment of adults with previously treated anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC).
Pharmaceutical form:	Capsule, hard
Strengths:	200 mg, 250 mg
Route of administration:	Oral use
Packaging:	Blister (PVC/alu), Bottle (HDPE)
Package size:	60 capsules

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List of abbreviations

AEs	Adverse Events
ALT	ALanine AminoTransferase
ALK	Anaplastic lymphoma kinase
ANC	Absolute neutrophil count
AST	ASpartate aminoTransferase
AUC	Area under plasma concentration-time curve
BID	Twice daily
BSA	Body surface area-
BW	Body weight
CHMP	Committee for Medicinal Products for Human Use
%CV	Coefficient of variation
CYP	Cytochrome P450
CYP3A	Cytochrome P450 3A
CYP3A4	Cytochrome P450 3A4
CTCAE	Common Terminology Criteria for Adverse Events
CR	Complete response
CT	Computed tomography
DCR	Disease Control Rate
DLT	Dose-Limiting Toxicities
DOR	Duration Of Response
ECGs	Electrocardiograms
EGFR	Epidermal Growth Factor Receptor
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FISH	Fluorescence in situ hybridization
GCP	Good clinical practices
HR	Hazard ratio
ICH	International Congress on Harmonization
IRR	Independent radiology review
ITT	Intent to treat
MAA	Marketing Authorisation Application
MDZ	Midazolam
MRI	Magnetic resonance imaging
MTD	Maximum Tolerated Dose
N/A	Not Applicable
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association
ORR	Objective Response Rate
OS	Overall survival
PD	Pharmacodynamic
PFS	Progression free survival
PK	Pharmacokinetic
PP	Per protocol
PR	Partial response
PRO	Patient reported outcome
QoL	Quality of life
RECIST	Response Evaluation Criteria in Solid Tumor
RP2D	Recommended Phase 2 dose
RTK	Receptor tyrosine kinase
QD	Once daily
QTc	QT interval corrected
QTcB	QT interval corrected – Bazett's conversion
QTcF	QT interval corrected – Fridericia's conversion
QTcS	QT interval corrected by study-specific method
SAE	Serious adverse event
SAWP	Scientific Advice Working Party
SD	Standard Deviation
SmPC	Summary of product characteristics
TKI	Tyrosine kinase inhibitor
ULN	Upper limit of normal
VEGF	Vascular Endothelial Growth Factor
VEGFR	Vascular Endothelial Growth Factor Receptor
WBC	White blood count

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Pfizer Ltd. submitted on 28 July 2011 an application for Marketing Authorisation to the European Medicines Agency (EMA) for XALKORI, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 21 December 2010.

The applicant applied for the following indication:

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

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

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

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision EMA/304142/2010 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

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

Applicant's request for consideration

Conditional Marketing Authorisation

The applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14(7) of the above mentioned Regulation based on the following claims:

- The risk-benefit balance of the medicinal product, as defined in Article 1(28a) of Directive 2001/83/EC, is positive.

Based on the data presented to date, crizotinib has promising evidence of clinical effectiveness as shown by ORR of 61.2% (95% CI: 51.7%, 70.1%). The preliminary estimate of mPFS was 10.0 months (95% CI: 8.2 months, 14.7 months; N=119), with a 1-year survival probability of 80.5%. The compelling crizotinib antitumor activity observed in Study A8081001 is supported by preliminary data from Study A8081005, an ongoing, multicenter, multinational, open-label, single-arm, Phase 2 study in patients with previously treated ALK-positive advanced NSCLC, with an ORR of 51.1%. The most common AEs were vision disorder and gastrointestinal events, including nausea, diarrhoea, vomiting, and constipation, plus oedema and fatigue, all of which were generally mild to moderate in severity.

The incidence of severe and serious AEs and laboratory abnormalities reported on crizotinib treatment was relatively low and generally manageable in this patient population. The clinical results obtained to date support the clinical benefit of single-agent crizotinib in patients with ALK-positive advanced NSCLC and overall, crizotinib has successfully addressed a high unmet medical need for a relatively rare NSCLC subtype. This favourable benefit/risk assessment was supported by an impressive rate of objective tumor responses that were rapid, durable, and clinically meaningful together with an AE and laboratory profile demonstrating that crizotinib was generally safe and well-tolerated.

- It is likely that the applicant will be in a position to provide comprehensive clinical data.

Randomized Phase 3 studies are ongoing in second-line NSCLC (Study A8081007) and in first-line non-squamous NSCLC (Study A8081014). As of June 2011, Study A8081007, which will confirm the clinical benefit of crizotinib in previously treated patients with ALK-positive advanced NSCLC ,was 70% enrolled at the time of filing, and has since completed.

- Unmet medical needs to be fulfilled.

Although there are treatments available for NSCLC, there is very limited information on the efficacy of anticancer therapies in ALK-positive NSCLC. Data to date from 5 retrospective analyses of small cohorts have suggested that 1) ALK status is not predictive of improved standard chemotherapy outcomes, 2) ALK status is predictive of poor response to EGFR TKI therapy, and 3) ALK positivity is not a favourable prognostic factor in NSCLC (Shaw et al, 2009; Yang C-H et al, 2010; Koh et al, 2011; Kim et al, 2011; Shaw et al, 2011). Controlled or case-matched analyses have suggested that ALK positivity may represent a negative prognostic factor in NSCLC (Yang et al, 2011; Kim et al, 2011).

- The benefits to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required.

To date, there are no therapies specifically indicated for the treatment of patients with ALK-positive NSCLC. Molecularly targeted therapies such as crizotinib may offer patients an alternative therapeutic option with a positive benefit/risk profile. Crizotinib will not be administered to all patients with NSCLC. Patients are required to have ALK-positive NSCLC prior to receiving treatment with crizotinib, as confirmed by the use of a validated ALK assay, which will be available on the European market with the approval of crizotinib. This should avoid potential concern for misuse of the drug.

New active substance status

The applicant requested the active substance crizotinib contained in the above medicinal product to be considered as a new active substance in itself.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 24 September 2009 and a follow-up Scientific Advice on 20 May 2010. The Scientific Advice pertained to non-clinical and clinical aspects of the dossier.

Licensing status

XALKORI has been given a Marketing Authorisation in the United States, Korea, Israel, and Switzerland on 26 August 2011, 29 December 2011, 21 February 2012, and 5 March 2012, respectively.

A new application was filed in the following countries: Japan, Canada, Mexico, Philippines, Australia, India, Morocco, Taiwan, Thailand, Venezuela, Russia, Singapore, Argentina, El Salvador, Malaysia, China, Panama, Guatemala, Honduras, and Saudi Arabia.

1.2. Steps taken for the assessment of the product

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

Rapporteur: **Pierre Demolis** Co-Rapporteur: **Daniela Melchiorri**

- The application was received by the EMA on 28 July 2011.
- The procedure started on 17 August 2011.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 08 November 2011 (Annex 1). The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 06 November 2011 (Annex 2)
- During the CHMP meeting on 15 December 2011, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 15 December 2011 (Annex 3).
- The applicant submitted the responses to the CHMP consolidated List of Questions on 22 March 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 7 May 2012 (Annex 4).
- During the CHMP meeting on 24 May 2012, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant (Annex 5).
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 18 June 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 3 July 2012 (Annex 6).
- During the meeting on 19 July 2012, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a conditional Marketing Authorisation to XALKORI.

2. Scientific discussion

2.1. Introduction

Disease

Lung cancer is the most common and lethal cancer worldwide. In 2008, the number of new lung cancer cases was estimated at 1.61 million, or 12.7% of all new cancers, and the number of deaths at 1.38 million, or 18.2% of the total cancer deaths. In Europe, estimates for the year 2008 were 391,000 cases and 342,000 deaths.

The majority of lung cancers (85%) are NSCLC. Most patients with NSCLC are diagnosed at advanced stages, and the 5-year survival rate for NSCLC in the US for the period 1999-2006 was 18%.

Treatment

- Standard first-line treatment of patients with advanced NSCLC of any histological subtype normally consists of platinum-based chemotherapy, which has been shown to have modest impact on efficacy outcomes, as ORRs in the range of 15% to 32% have been reported with a median PFS of 3-6 months and a median OS of 8-12 months (1-year OS of 34% to 44%).

- After disease progression on first-line treatment, standard second-line treatment of advanced NSCLC consists of single-agent chemotherapy (pemetrexed or docetaxel), which has been associated with an ORR of approximately 9%, a median PFS of approximately 3 months, and a median OS of approximately 8 months (1-year OS of 30%).

- More recently, pemetrexed use has been restricted to patients with non-squamous histology as in the first-line treatment setting, with a reported ORR of 11.5%, median PFS of 3.1 months, and a median OS of 9.3 months (1-year OS of 41% assuming exponential distribution).

- When given to unselected patients with advanced NSCLC who have received 1 or 2 prior lines of chemotherapy, the EGFR TKI erlotinib has reported ORR of 8.9%, median PFS of 2.2 months, and median OS of 6.7 months (1-year OS of 31%).

- Recently, advances in the understanding and treatment of NSCLC have been made based on the identification of molecular alterations specific to tumor cells. Results of randomized Phase III studies analyzed retrospectively in selected advanced NSCLC patients harbouring activating EGFR mutations have recently shown that first-line treatment with gefitinib or erlotinib increases ORR and prolongs PFS compared to standard chemotherapy doublets (ORR 62%-83% vs. 31%-47%; median PFS range: 9-13 months vs. 5-6 months).

Advanced NSCLC remains a highly symptomatic and incurable disease, more effective and safer agents including those that target key oncogenic drivers of lung cancer, are still needed.

About the product

Crizotinib is a selective small-molecule inhibitor of the ALK receptor tyrosine kinase and its oncogenic variants (i.e., ALK fusion events and selected ALK mutations). Crizotinib is also an inhibitor of the hepatocyte growth factor receptor (HGFR, c-Met) RTK is currently under development for the treatment of ALK-positive advanced NSCLC.

The applicant claimed the approval for the following indication:

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

The final indication following CHMP review of this application is:

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

2.2. Quality aspects

2.2.1. Introduction

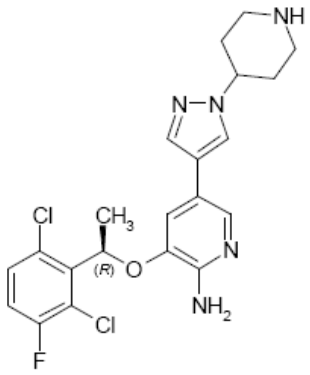
The drug product Xalkori contains the active substance crizotinib. The composition is described in section 6.1. of the SmPC. The two dosage strengths 200 mg and 250 mg are dose/weight proportional and the size/colour/printing of the capsules adequately differentiate between one another. Xalkori capsules will be packaged in HDPE bottles with child-resistant caps or PVC/Alu foil blisters.

2.2.2. Active Substance

The active substance, crizotinib is qualified as a new active substance, it is a white to pale yellow powder, non-hygroscopic. Crizotinib has one asymmetric center of R configuration. It is considered as a class IV compound as per the BCS classification (low permeability, low solubility substance). Only

one crystalline form has been found, this is the thermodynamically stable form A, no other crystalline form has been found.

The corresponding molecular formula is $C_{21}H_{22}Cl_2FN_5O$ and the relative molecular mass 450.34.



*The chemical name of the active substance is (*R*)-3-[1-(2,6-Dichloro-3-fluorophenyl)ethoxy]-5-[1-(piperidin-4-yl)-1*H*-pyrazol-4-yl]pyridin-2-amine*

Manufacture

The synthetic process of the active substance Crizotinib is using well characterised and commercially available starting materials. The batch size is based on input of starting materials.

The description of the manufacturing process is sufficiently detailed. The applicant has used risk assessments and design of experiments to identify the critical process parameters and adequate in process controls have been put in place. Proven acceptable ranges have been established and normal operating ranges for critical parameters have been provided.

The justification of the starting materials and their specification is based on their manufacturing process, the impurities that can be generated and their fate in the crizotinib synthesis. .

The analytical procedures are described and validated.

Specification

The specification of the active substance contains tests with suitable limits for appearance (visual), identification (FTIR) spectrum, assay (HPLC), specified, unspecified and total Impurities (HPLC), residue on Ignition (Ph. Eur), Heavy Metals (Ph. Eur), Residual Solvent (GC), Particle Size (laser light diffraction) and palladium (ICP-MS or ICP-OES). The palladium limit in the drug substance specification assures patient safety and is well within the safety limit of EMA/CHMP/SWP/4666/2000 Option 2a. However based on the available batch data, the CHMP recommends to review and possibly restrict the palladium limit, when more experience is gained on the commercial process.

Based on the antimicrobial properties of the drug substance and crizotinib formulated capsules, microbial enumeration testing will not be performed for routine batch release. These batches have been used for toxicology studies, for manufacture of drug product for clinical studies and for stability studies. In all cases that batch analysis results met the predefined specifications for the active substance.

Stability

Stability studies were performed using samples from four batches manufactured according to the commercial route and packaged in the commercial packaging. Stability results have been provided for up to 12 months at 25°C/60%RH and 6 months at 40°C/75%RH. They show a good stability for the active substance.

The parameters tested were the same as those included in the release specification. Stress studies were performed at high temperatures and no significant degradation was observed after 14 days stored at 100°C. Minor degradation was observed when crizotinib was exposed to strongly acidic, strongly basic, intense light and oxidative conditions.

2.2.3. The stability results indicate that the drug substance is sufficiently stable and justify the proposed retest period. Finished medicinal product

Pharmaceutical development

The aim of the development was to obtain an immediate release hard gelatin capsule to deliver 200 mg and 250 mg crizotinib as a single unit dose.

The initial dosage form used during early Phase 1 clinical studies was a powder in capsule (PIC), consisting of crizotinib in a hard gelatin capsule shell. Then a tablet dosage form was developed containing 50 mg and 100 mg crizotinib (drug substance loading of 12.5%), to meet increased clinical demand for Phase 3 clinical studies. In vitro dissolution profiles for both the clinical tablet and PIC dosage forms demonstrated rapid release within 30 minutes in 0.1N HCl. In vivo performance was subsequently shown to be bioequivalent between the clinical tablet and PIC. However for manufacturability reasons, the crizotinib capsule form was developed and it was designed to be qualitatively similar to the clinical tablet formulation. The pharmaceutical development was based on the Quality by Design concept. No design space has been claimed by the applicant in the manufacturing process of the finished product.

Multivariate experimental design studies were executed to evaluate and determine criticality of process parameters and their effect on manufacturing and performance of the final formulated capsule

The excipients used in the formulation comply with compendial requirements. Appropriate in-house specifications are provided for the capsule shells.

The primary packaging proposed is stated in the SmPC and it is adequate to support the stability and use of the product.

Adventitious agents

Valid TSE CEP certificates have been provided for the gelatin of capsules.

Manufacture of the product

The manufacturing process is considered as standard, and adequate information has been provided. The main critical steps have been studied in detail andthe critical process parameters (CPPs) have been described adequately. . The target normal operating ranges and proven for these CPPs are considered acceptable. A satisfactory validation protocol was filed.

All batches manufactured using the process ranges described have produced drug product of acceptable quality and performance showing that this product can be manufactured reproducibly

according to the agreed finished product specification, which is suitable for control of this oral preparation.

Product specification

The drug product specifications have been developed in line with ICH guidelines Q3B (R2) and Q6A. They are based on the data ranges from three 150 mg, one 200 mg, and three 250 mg batches manufactured by the commercial manufacturing process. Batch analysis data confirm the consistency and uniformity of manufacture and indicate that the process is capable and under control.

The specification include appropriate tests for appearance (visual inspection), identity (HPLC and UV), assay (HPLC), impurities (HPLC), dissolution (UV),uniformity of dosage units (Ph.Eur. 2.9.40).

Stability of the product

Crizotinib capsules were evaluated for appearance, assay, degradation products, dissolution, water content and microbiological quality. The analytical procedures used are the same as those used for release. Water content is monitored on stability using Ph. Eur. 2.5.12, method A. The microbial quality test is monitored on stability using Ph. Eur. 2.6.12. Results are provided for up to 12 months at 25°C/60%RH and 30°C/75%RH and 6 months at 40°C/75%RH in both packaging systems.

Samples stored in PVC/aluminium foil blisters showed some caking of the capsule contents at the 6 month time point at 30°C/75%RH and from the 2 month time point onwards at 40°C/75%RH. Brittleness of the capsule shells was also seen at the 6 month time point at 40°C/75%RH. These observations were not associated with changes in degradation product levels, assay or dissolution results. Also, they were not been observed through 9 months at the 25°C/60%RH or 30°C/75%RH storage conditions.

For samples stored in PVC/aluminium foil blisters, the water content increased by about 0.5% at 25°C/60%RH and by about 1.5% at 30°C/75%RH and 40°C/75%RH through 6 months. The water content did not increase at the 9 month time point. This increased water content has not led to any changes in degradation product levels, assay or dissolution results.

A photostability study in ICH conditions was also run. Besides water uptake and changes in appearance of capsules that did not affect assay, degradation products or dissolution, no trends have been evidenced. The capsules are also stable to light. Also in use stability of capsules packed in the HDPE bottle has been demonstrated. Based on available stability data, the proposed shelf-life with no special storage conditions as stated in the SmPC are considered acceptable.

2.2.4. Discussion on chemical, and pharmaceutical aspects

The quality of Xalkori is adequately established. In general, satisfactory chemical and pharmaceutical documentation has been submitted for marketing authorisation. Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

At the time of the CHMP opinion, there was a minor unresolved quality issue having no impact on the Benefit/Risk ratio of the product. The CHMP recommended that these issues are addressed in the future development of the product (see section 2.2.6)

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product (see section 2.2.6 below).

2.2.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- The CHMP recommends the applicant to review and tighten, if possible, the palladium limit when more data from testing of the active substance manufactured at commercial scale is available.

2.3. Non-clinical aspects

2.3.1. Introduction

The goal of the nonclinical studies was to support the registration of crizotinib for the proposed indication.

2.3.2. Pharmacology

Primary pharmacodynamic studies

The applicant submitted 9 *in vitro* and 14 *in vivo* primary pharmacodynamic studies.

Crizotinib demonstrated *in vitro* inhibition of tyrosine kinase in biochemical enzymatic assays and in cell-based assays against EML4-ALK, NPM-ALK, c-Met/HGFR and RON enzyme in several human cell lines. Crizotinib major metabolites were also tested and crizotinib lactam metabolites showed relevant inhibitory activity in the nanomolar range, thus close to crizotinib potency. When tested to its selectivity for different kinases, crizotinib was relatively specific to c-Met/HGFR and ALK fusion proteins.

Crizotinib inhibited cell proliferation, migration, invasion and motility in tumour or endothelial cells expressing EML4-ALK, NPM-ALK or c-Met/HGFR. These data suggest that crizotinib has an effect on both tumour cell growth and survival and on angiogenesis.

In vivo, Crizotinib demonstrated a dose-dependent cytoreductive antitumour activity in several tumour models expressing EML4-ALK, NPM-ALK or c-Met/HGFR. PK/PD modelling indicated that the extent and duration of the inhibition of target kinase phosphorylation is directly related to the level of anti-tumour efficacy. Near complete inhibition of ALK or c-Met/HGFR activity for the duration of treatment is necessary to get the maximal anti-tumour efficacy (tumour regression). There is a correlation between inhibition of ALK or c-Met/HGFR phosphorylation and modulation of key signalling pathways involved in cancer cell survival, growth, proliferation and apoptosis. Crizotinib also exhibited an antiangiogenic effect when administered for a long time. This effect was not seen in every tumour type.

Secondary pharmacodynamic studies

Crizotinib demonstrated the ability to bind with a series of off-target receptor or channel such as adrenergic, muscarinic, nicotinic or serotonin receptors, calcium or sodium channels, dopamine or serotonin transporters, for some of them at concentrations close to therapeutic concentrations. It was a functional agonist of 5-HT4e and 5-HT7 serotonin receptors and an antagonist of the rat adrenergic α_{1A} receptor. It was an inhibitor of dopamine and 5-HT uptake.

It also inhibited the activity of PDE4 and p55fyn kinase. This large binding ability can induce undesirable effects. No such data is available for the major metabolite, crizotinib lactam that was demonstrated to be active on the target kinases.

Safety pharmacology programme

Crizotinib demonstrated adverse cardiac effects in safety pharmacology studies. *In vitro*, it inhibited hERG, sodium and calcium currents. The antagonist effect on calcium channel was confirmed in the isolated rat aorta model and in a Purkinje fiber assay. *In vivo*, crizotinib induced a decrease in heart rate and an increase in PR-interval, QRS and QT-interval.

The *in vivo* study has been conducted in anesthetised animals. This is not the appropriate method to detect predictive haemodynamic and ECG effects to humans because anaesthesia prevents from a correct interpretation of cardiac effects.

QTc prolongation has been observed in humans following crizotinib administration and a warning has been included in section 4.4 of the SmPC.

Regarding neurofunctional effects, decreased locomotor activity has been observed. It is correlated with a transitory decrease in respiratory rates.

Pharmacodynamic drug interactions

Crizotinib and cytochromes

In vitro studies with human liver microsomes and recombinant enzymes demonstrated that crizotinib was mainly metabolised by CYP3A4, which also mediated the formation of crizotinib lactam and the *O*-desalkyl metabolites. *In vitro* data indicated that the most pronounced inhibitory potential of crizotinib was observed with respect to CYP3A-mediated drug metabolism. Crizotinib showed a time-dependent inhibition of CYP3A enzymes in human liver microsomes.

Clinically relevant interactions with substrates of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6 are unlikely to occur considering the low potential of crizotinib to inhibit these enzymes and at crizotinib plasma concentrations achieved following therapeutic doses.

Crizotinib caused marked induction of CYP3A4 based on mRNA levels in human cryopreserved hepatocytes. However, a corresponding induction of CYP3A4 enzyme activity was not observed. This finding is likely due to the crizotinib-mediated time-dependent inhibition of CYP3A4. Crizotinib did not induce CYP1A2. Therefore, crizotinib would not be expected to reduce plasma concentrations of coadministered CYP1A2 substrates *in vivo*.

Results from an induction study show an increase ARNm level at concentrations of crizotinib up to 7 µM, but this effect is limited by the time-dependent inhibition of crizotinib on CYP3A4.

However, although the CYP3A4 induction is compensated by the time-dependent inhibition of crizotinib, the inducing potency of crizotinib on other enzymes or transporters PXR-dependent is likely even if the magnitude of induction is lesser than those observed with CYP3A4.

Crizotinib and protein transporters

In vitro experiments showed a saturable involvement of P-glycoprotein (P-gp, ABCB1) in a transfected Madin-Darby Canine Kidney (MDCK) cell line. Crizotinib was not found to be a substrate for the breast cancer resistance protein gene (BCRP, ABCG2) efflux transporter. *In vitro* studies showed that crizotinib inhibited P-gp.

Furthermore, as regards the inducing effect of crizotinib on transporters, the Applicant provided a clear discussion on the inducing effect of crizotinib on PXR-regulated drug transporters with particular relevance of P-gp mediated interactions.

Even if multidrug resistance-associated proteins [MRP]2, MRP3, organic anion-transporting polypeptide [OATP]1B1 could be considered potential target of inducing effect of crizotinib, the clinical relevance of interaction involving such mechanism is unlikely.

In vitro, the uptake of crizotinib into human hepatocytes is not OATP-dependent and occurred via passive diffusion.

Although crizotinib was determined to be a weak inhibitor of (OATP) 1B1 and 1B3 *in vitro*, clinical interactions with substrates of these hepatic uptake transporters are unlikely at crizotinib therapeutic concentrations.

2.3.3. Pharmacokinetics

Absorption

In vitro studies demonstrated that crizotinib is a substrate for P-gp but not for BCRP and that it enters hepatocytes by passive diffusion.

Pharmacokinetics studies after a single administration were conducted in rats, dogs and monkeys. Plasma clearance was moderate in every tested species (9 to 47 mL/min/kg). The volume of distribution was large (2.9 to 24 L/kg in rats, 11 to 13 L/kg in dogs and 13 L/kg in monkeys, indicating an extensive distribution into body tissues. The bioavailability was variable, ranging from 38 to 66% for the same dose in dogs and from 26 to 63% in rats depending on the dose.

The half-life after oral administration ranged from 5.8 to 13 hours in rats, 12 to 13 hours in dogs and 14 hours in monkeys. Repeat dose studies demonstrated that accumulation of crizotinib after repeat administration in rats (after a period longer than 1 month), dogs and monkeys.

There was no sex-related difference in dogs and monkeys while higher exposure in male rats than in females was observed.

Distribution

In vivo, crizotinib was widely distributed with a C_{max} occurring between 4 to 8 hours. Concentration in tissues was generally higher than blood concentration. Crizotinib does not seem to distribute across the blood-brain barrier. It demonstrated a high affinity for pigmented tissues (eyes, skin) where the elimination was slow due to a reversible binding to melanin. Crizotinib-derived radioactivity was retained in several other tissues (including pituitary gland and testis) and that elimination was not yet complete by 168 hours postdose.

In vitro, Crizotinib was highly bound to protein. Mean unbound fractions of crizotinib were 0.036, 0.057, 0.070, 0.043, 0.072, and 0.093 for the mouse, rat, rabbit, dog, monkey, and human,

respectively. The extent of protein binding was similar for crizotinib lactam and its diastereoisomers. In mice, rats, dogs, and humans, crizotinib did not preferentially distribute into red blood cells.

Metabolism

In vivo, metabolism was studied in rats, dogs and human. Unchanged crizotinib was the main component in plasma and faeces in rats, dogs and humans.

The major metabolic pathway was oxidation of the piperidine ring to form critonib lactam M10 (in rats, and humans and to a lesser extent, dogs) and crizotinib nitrone M21 (in rats and dogs).

In rats, direct sulphate conjugation to form M19 was a major pathway in females but not in males, this could explain a lower exposure to crizotinib in females.

Even if M10 was not as abundant is rat plasma as in human plasma, a comparison of exposure to M10 indicated that rats are equally or more exposed than humans.

Some human metabolites were not detected in animal *in vivo* studies. The Applicant has clarified that M10 was the only active metabolite in human.

CYP3A enzymes are the main enzymes involved in crizotinib metabolism. The major metabolite M10 is formed in a 2-step reaction. An oxidation catalysed by CYP3A4/5 and to a lesser extent CYP2C8, 2C19 and 2D6 leading to an imine intermediate is followed by an AO- or CYP-catalysed oxidation resulting in M10. Dealkylation of crizotinib (leading to M4) or of M10 (leading to M2) is also catalysed by CYP3A4.

The involvement of CYP450 in crizotinib metabolism has been confirmed in humans.

Excretion

The major route of excretion was the faeces in rats and dogs (after 168h: ~99% in non-canulated rats and 62% and 85% in male and female dogs, respectively). In canulated rats, bile excretion amounted to 38% and 62% after 48h in males and females, respectively. Urinary excretion was minor (generally below 3%).

2.3.4. Toxicology

Crizotinib underwent a non clinical testing compliant with the guideline ICH S9 on non clinical for anticancer pharmaceuticals.

Single dose toxicity

No single dose studies were conducted.

Repeat dose toxicity

Table 1 Summary of repeat dose toxicity studies

Report No GLP compliance	Species/ Number/ group	Test article	Dose (mg/kg/ day) Route	Duration	NOAEL (mg/kg/ day)	Major findings
04HGF003 Not GLP	C57BL6 Mouse 5 F/group	2-HCl salt form of crizotinib	0, 40, 200 Oral	1 month	< 40	**≥ 40 mg/kg**: ↑ ALAT and ASAT **200 mg/kg**: ↑ liver weight, ↓ TG
05HGF006 Not GLP	SD Rats 3/sex/group	Mono-HCl salt of crizotinib	0, 2000 Oral	2 days	< 2000	**2000 mg/kg:** 1 dead F (with lethargy, dyspnea, prophyrin staining on the forelimbs) Lethargy, stress leukogram (neutrophilia and lymphopenia), ↑ ALAT and ASAT, ↑ creatinine kinase ↑ heart weight Minimal hepatocyte necrosis Bone marrow myeloid and erythroid cells necrosis Minimal to mild bone marrow hypocellularity
04HGF004 Not GLP	SD Rats 3/sex/group	Mono-HCl salt of crizotinib	0, 50, 150, 500 Oral	7 days	< 50	**≥ 50 mg/kg**: Diarrhea, lethargy, oral discharge, gurgled and raspy breathing **500 mg/kg:** 1 dead M Body weight loss, ↓ food consumption, ↑ urine output Stress leukogram (neutrophilia, lymphopenia and monocytosis), ↑ RBC count, ↑ ALAT and ASAT, ↓ sodium and chloride. Bone marrow hypocellularity (erythroid and myeloid) and lymphoid depletion in GALT and thymus. Decreased splenic extramedullary hematopoiesis. Ovaries single cell necrosis. Salivary gland single cell necrosis and secretory material depletion. Stomach mucosal edema. Gene expression profiling suggested for renal tubular toxicity at 500 mg/kg and potential for liver toxicity at ≥ 150 mg/kg.

05137 GLP	SD Rats 10/sex/group TK: 3/sex/group	Crizotinib	0, 10, 50, 150 Oral	1 month	10 (M) 50 (F)	**≥ 50 mg/kg**: ↑ salivation ↑ALAT and ASAT (M) ↓ urinary pH (M) Renal cortical tubule vacuolation (M) Testicular pachytene spermatocyte degeneration ↓ spleen and thymus weights, thymic atrophy, splenic, GALT and peripheral lymph nodes lymphoid depletion (M) ↓ prostate weights and prostate atrophy ↓ liver, kidney and epididymal organ weights. **150 mg/kg**: ↓ body weight and ↓ food consumption (M) ↑ALAT and ASAT (F) ↓ urinary pH (F) Vacuolated lymphocytes (M) ↑ GGT (M) Bone marrow hypocellularity (erythroid and myeloid) (M) Decreased long bones formation and reduction of diaphyseal trabecular bone (M)
09GR347 GLP	SD Rats 15/sex/group	Crizotinib	0, 10, 30, 100 (M) 0, 10, 50, 250 (F) Oral	3 months + 2 months of recovery	10	**≥ 10 mg/kg**: ↑ALAT and ASAT (M) **≥ 30 mg/kg**: Phospholipidosis (cellular vacuolation and foamy macrophages in bile duct, intestine, pituitary gland, prostate, lung, mesenteric lymph node) (partially reversible) Exacerbation of cardiac myofiber necrosis (M) Myeloid cell debris in the bone marrow (M) **≥ 100 mg/kg**: ↓ body weight and food consumption (reversible) ↑ ALP (reversible) Slight ↓ in Hb, Ht, MCV (reversible) ↑ Platelet and neutrophil counts (reversible) ↑ WBC, monocytes and large unstained cell (F) (reversible) ↑ALAT and ASAT (F) Myeloid cell debris in the bone marrow (F) Swelling of submandibular salivary gland (partially reversible) ↓ thymus weight and lymphocytolysis in the thymus Dilatation of the small intestine ↓ spleen, kidney, liver and epididymis weights (partially reversible)

05079 Not GLP	Beagle dogs 1/sex/group	Crizotinib	0, 10, 25, 40 Oral	Single dose on D1, D5 and D8	NA	**≥ 10 mg/kg**: ↑ salivation (F) **≥ 25 mg/kg**: ↑ salivation (M) and emesis **40 mg/kg**: Termination of both dogs at D8. Bloody emesis and bloody diarrhea ↓ WBC, neutrophils and lymphocytes (M) Diffuse mucosal congestion with neutrophilic infiltrate and mucus un the lumens of the intestine. Hepatocellular rarefaction (F)
05079 Not GLP	Beagle dogs 1/sex/group	Crizotinib	0, 20 Oral	7 days	20	↑ salivation, emesis (↓ incidence during the study) and diarrhea (only on D1). ↓ WBC, neutrophils and lymphocytes
05162 GLP	Beagle dogs 3/sex/group	Crizotinib	0, 1, 6, 20 Oral	1 month	20	**≥ 6 mg/kg**: Emesis (↓ incidence during the study), ↑ salivation and occasional diarrhea. Slight ↓ albumin (1 F) ↓ Thymus weights **20 mg/kg**: High variability in QT/QTc values but no consistent trend => considered not toxicologically significant ↓ neutrophil peroxidase activity ↓ RBC, HB and Ht and ↑ WBC, neutrophils and lymphocytes (1 F) ↓ thymic cellularity
09GR346 GLP	Beagle dogs 5/sex/group	Crizotinib	0, 1, 5, 25 Oral	3 months + 2 months of recovery	5	**≥ 1 mg/kg**: ↑ ALP **≥ 5 mg/kg**: Abnormal stools, emesis. ↑ predose QTc but no changes in postdose QTc (M) (reversible) ↑ ALAT, ASAT and GGT ↑ heart weight (F) **25 mg/kg**: ↓ RBC, HB and Ht ↑ eosinophils ↑ WBC, neutrophils, lymphocytes and/or monocytes ↑ platelets ↑ fibrinogen (F) ↓ Total protein, albumin and A/G ratio ↓ Calcium *All hematological effects and clinical chemistry changes were reversible.* ↑bone marrow eosinophils and precursors ↑ predose QTc but no changes in postdose QTc (F) (reversible)

3584 Not GLP	Cynomolgus monkeys 2/sex/group	Crizotinib	0, 50	1 month	< 50	1 F euthanized at D21 (changes in fecal excretion, hunched posture, hypoactivity, ↓ body weight, ↓ RBC parameters, ↓ P, ↑ ALAT/ASAT, ↓ albumin, marked multifocal erosion or ulceration of the cecum, hypercellularity of bone marrow) In surviving animals: diarrhea, soft feces, ↓ body weight and absent food consumption ↓ reticulocytes and ↑ neutrophils, monocytosis, ↓ granulation of neutrophilic precursors Vacuolation of lymphocytes and macrophages cytoplasm ↓ P and ↑ ASAT and ALAT Hypocellularity in bone marrow (myeloid and erythroid cells) Signs of bone marrow necrosis and cytotoxicity Presence of immature neutrophils in peripheral blood ↑ percentage of bone marrow proliferating myeloid cells Absence of granulation in neutrophilic precursors ↓ Peroxidase activity => Drug-related effect on WBC differentiation

Crizotinib was tested in mice and monkeys for 1 month and in rats and dogs for up to 3 months.

The main target organs were:

- the hematopoietic system : increased white blood count (WBC), monocytes and neutrophils in rats and in dogs, bone marrow hypocellularity or necrosis in rats and monkey and presence of immature neutrophils in monkeys indicating effects on WBC proliferation, decreased red blood count (RBC) parameters including reticulocytes suggesting a suppression of erythroid production in bone marrow.

- the cardiovascular system: mixed ion channel blocker, decreased heart rate and blood pressure, increased LVEDP, QRS and PR intervals, and decreased myocardial contractility

- the liver: increased liver weight in mice, decreased liver weight in rats, increased ALAT and ASAT in mice, rats, dogs and monkeys, increased APL and GGT in rats and dogs rarely correlated with microscopic findings. The only histological finding was a minimal hepatocyte necrosis in rats given 2000 mg/kg for 2 days.

- the gastrointestinal system : diarrhea in rats, dogs and monkeys, emesis, congestion and dilatation of intestines in dogs.- the reproductive organs: ovaries single cell necrosis in the rat 7-day study and spermatocyte degeneration and decreased epipidymis weight in the 1-month rat study.

Phospholipodosis observed in rats and monkeys (vacuolated lymphocytes and macrophages in several organs in rats and monkeys and vacualoation in cortical tubules in rats) can be seen with amphiphilic molecules such as crizotinib.

In an electroretinography study, oral administration of crizotinib at 100 mg/kg/day to Long-Evans rats for 15 or 29 days resulted in significant reductions in the rate of retinal dark adaptation.

Genotoxicity

Table 2 Summary of genotoxicity studies

Type of test/study ID/GLP	Test system	Concentrations/ Concentration range/ Metabolising system	Results
Ames test 3565 GLP	*S. typhi* TA98, TA100, TA1535, TA1537 *E. coli* WP2 *uvr*ApKM1010	31.3, 62.5, 125, 250, 500 and 1000 µg/plate +/- S9	Negative
Chromosome aberration test 3554 GLP	Human peripheral lymphocytes	1, 5 and 10 µg/mL for 3 hours with metabolic activation (S9) 2.5, 5. and 7.5 µg/mL for 3 hours without metabolic activation 1, 1.5 and 2.5 µg/mL for 24 hours without metabolic activation	Positive <u>In the 3-hour trial with metabolic activation</u> Statistically significant increase in chromosome aberration at 10 µg/mL. Dose dependant increase in numerical aberration at all doses (polyploidy). <u>In the 3-hour trial without metabolic activation</u> Statistically significant increase in chromosome aberration at 2.5 and 7.5 µg/mL. Dose dependant increase in numerical aberration at all doses (polyploidy). <u>In the 24-hour trial without metabolic activation</u> No statistically significant increase in chromosome aberration. Dose dependant increase in numerical aberration at all doses (polyploidy).
In vitro micronucleus assay with kinetochore analysis PG0135 Not GLP	CHO-WBL cells Immunostaining using anti-centromeric antibodies	0.15, 0.20, 0.27 and 0.30 µg/mL Treatment for 24 hours without metabolic activation	Positive Induction of micronuclei at ≥ 0.20 µg/mL with the presence of kinetochore staining indicating aneugenicity
In vivo micronucleus assay in rats 3665 GLP	SD rats (5/sex/group)	0, 250, 500 and 1000 mg/kg orally for 2 days Positive control control group treated with cyclophosphamide	Positive Adverse clinical signs and body weight loss at ≥ 100 mg/kg. Significant bone marrow toxicity Induction of micronuclei at ≥ 250 mg/kg in males. No genotoxic effects in females (they had lower exposure than males)
In vivo micronucleus assay in rats 3746 GLP	SD rats (5 M/group)	0, 25, 100, 250 mg/kg orally for 2 days Positive control control group treated with cyclophosphamide	Positive Adverse clinical signs and body weight loss Changes in bone marrow at 250 mg/kg Induction of micronuclei at 250 mg/kg (AUCtotal = 38.9 µg.hr/mL and Cmaxtotal = 2.06 µg/mL) No genotoxic effects at ≤ 100 mg/kg (AUCtotal = 22.2 µg.hr/mL and Cmaxtotal= 1.42 µg/mL)

Crizotinib was tested in a conventional genotoxicity battery. It was negative in the Ames test, suggesting that it was not mutagenic. It was positive in the chromosome aberration test where it induced polyploidy. In an *in vitro* micronucleus test, crizotinib induced micronuclei with the presence of kinetochore staining suggesting an aneugenic potential. In the *in vivo* micronucleus test, crizotinib was

positive at 250 mg/kg and higher but had no effect at 100 mg/kg (representing 3.5-fold human AUC or 2-fold human C_{max}).

Carcinogenicity

No studies were performed. This is acceptable according to the guideline ICH S9 on Non Clinical Evaluation for Anticancer Pharmaceuticals.

Reproduction toxicity

No fertility studies were performed. According to ICH S9, fertility and early embryonic development studies are not warranted for marketing authorisation. For crizotinib, effects on reproductive organs were seen in repeat-dose toxicity indicating a potential impairment of male and female fertility.

Table 3 Summary of embryo-foetal development studies

Study type/ Study reference / GLP	Species; Number/ sex/group	Dose (mg/ kg/day) Route	Study design	NOAEL (mg/kg/day)	Major findings
Dose range-finding embryofetal development study 09GR345 Not GLP	SD Rats 6F/group	0, 50, 250, 500 Oral	GD6 to GD17	NOAEL (maternal) < 50 NOAEL (development) = 500	50 mg/kg: ↓ body weight gain 250 mg/kg: Maternal body weight loss or reduced body weight gain; ↓ food consumption. ↓ fetal body weight 500 mg/kg: All animals were euthanized on GD12 due to clinical signs, declining maternal body weight and reduced food consumption
Embryofetal development study 10GR072 GLP	SD Rats 20F/group	0, 10, 50, 200 Oral	GD6 to GD17	NOAEL (maternal) = 50 NOAEL (development) = 10	≥ 50 mg/kg: ↑ postimplantation loss 200 mg/kg: 1F euthanized on GD12 due to clinical signs, declining maternal body weights and reduced food consumption. ↓ body weight, body weight gain and food consumption, ↓ gravid uterine weight ↓ fetal body weight No teratogenic effect.
Dose range-finding embryofetal development study 09GR350 Not GLP	NZW Rabbits 6F/group TK: 5F/sex	0, 25, 75, 175, 350 Oral	GD7 to GD19	NOAEL (maternal) = 25 NOAEL (development) ≥ 75	75 mg/kg: 1 F euthanized moribund, ↓ body weight and food consumption ≥ 175 mg/kg: Early termination due to ↓ body weight and food consumption and clinical signs
Embryofetal development study 10GR073 GLP	NZW Rabbits 20F/group TK: 5F/sex	0, 10, 25, 60 Oral	GD7 to GD19	NOAEL (maternal) = 60 NOAEL (development) = 25	60 mg/kg: ↓ fetal body weight No teratogenic effect.

In rats, decreased foetal body weight was observed at 200 mg/kg in the presence of maternotoxicity and increased postimplantation loss at 50 mg/kg in the absence of maternotoxicity. In rabbits, crizotinib had no effect on dams but a decrease in body weight was recorded in foetus at 60 mg/kg. Crizotinib did not demonstrate teratogenic effects in both species.

No pre- and postnatal studies were performed. According to ICH S9, the absence of study is acceptable.

Toxicokinetic data

Table 4 Exposure margin based on AUC and Cmax

Type of study	Species	Duration	NOAEL (mg/kg/day)	AUC tafamidis (ng.h/mL) at NOAEL[a]	Cmax tafamidis (ng/mL) at NOAEL[a]	Exposure margin[b] based on	
						AUC	**Cmax**
Repeated dose	**Rat**	**3 months**	10	137.2	13.2	**0.4**	**0.3**
	Dog	**3 months**	5	382.5	23.4	**1.0**	**0.6**
Reproductive toxicity	**Rat**	**Segment II**	10	38.2	6.1	**0.1**	**0.2**
	Rabbit	**Segment II**	25	191	30.5	**0.5**	**0.8**

[a:] AUC and Cmax on the last time point. Unbound average values are given.
[b] Animal/human exposure ratios calculated from crizotinib human values of $C_{max\ unbound}$=**38 ng/mL** and $AUC_{unbound}$= **361 ng·h/mL** after administration of 250 mg BID (based on an unbound fraction of 0.093)

The safety margins were around 1 based on phospholipidosis and effects on bone marrow in rats, effects on haematological parameters, clinical chemistry and bone marrow in dogs and decreased fetal body weight in the absence of maternotoxicity in rabbits.

Other toxicity studies

Impurities

Four impurities are specified above the level of qualification in the drug substance.

The adverse effects in the impurity qualification study were consistent with those observed in the other repeat-dose toxicity studies.

Phototoxicity

Crizotinib showed affinity with eyes and skin and absorbs light in the 290-700 nm range. According to the *in vitro* 3T3 NRU assay, crizotinib is a probable phototoxicant (see SmPC section 5.3). This is also addressed in the RMP as a potential risk.

Electroretinography (ERG)

In an electroretinography study, oral administration of crizotinib at 100 mg/kg/day to Long-Evans rats for 15 or 29 days resulted in significant reductions in the rate of retinal dark adaptation.

2.3.5. Ecotoxicity/environmental risk assessment

Table 5 Summary of main study results

Substance (INN/Invented Name): Crizotinib			
CAS-number (if available):877399-52-2			
PBT screening		Result	**Conclusion**

Bioaccumulation potential- log K_{ow}	OECD107	Log D = 0.169 (pH 4) = 1.83 (pH 7) = 3.88 (pH 9)	No Potential PBT
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	ND	B/not B
	BCF	ND	B/not B
Persistence	DT50 or ready biodegradability	ND	P/not P
Toxicity	NOEC or CMR	ND	T/not T
PBT-statement :			
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$ refined *Fpen = 0.000064*	0.016	µg/L	> 0.01 threshold
Other concerns (e.g. chemical class)	ND		(Y/N)

Crizotinib log D does not exceed 4.5. Therefore, no PBT screening is required. Crizotinib is not expected to bio-accumulate in the environment

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

To perform all studies necessary to complete the Phase II of the ERA in compliance with the EMA guidelines and agreed to submit an updated environmental risk assessment with the studies recommended during the Q1 2013.

2.3.6. Discussion on non-clinical aspects

No solid data are available at present showing that the anticancer activity of crizotinib in preclinical models of NSCLC is substantially dependent on the inhibition of ALK and its variants. Thus, no sound conclusion on the main molecular mechanism underlying crizotinib anticancer activity in NSCLC may be drawn from pre-clinical studies.

Crizotinib was also active against a wide range of enzymes and transporters at concentrations close to therapeutic concentrations, possibly leading to undesirable effects.

Regarding safety pharmacology, non-clinical evaluation for the potential delay of ventricular repolarisation was conducted according to guideline ICH S7B, however the effect on I_{Kr} was not tested following GLP as recommended by the guideline but this study was proven to have been performed with the same rigor of quality addressed by GLP.

Pharmacokinetic and toxicokinetic studies were conducted in mice, rats, rabbits, dogs and monkeys in order to investigate absorption, plasma kinetics, distribution, metabolism and excretion of crizotinib. Most of these studies were conducted using the oral route, some of them using the IV route.

Pharmacokinetic studies after a single administration were conducted in rats, dogs and monkeys. Plasma clearance was moderate in every tested species. The volume of distribution was large indicating an extensive distribution into body tissues. The bioavailability was variable. The half-life after oral administration ranged from 5.8 to 13 hours in rats, 12 to 13 hours in dogs and 14 hours in monkeys.

Due to the large volume of distribution and the evidence that apparent half-life of crizotinib in organs or tissues significantly exceeds the apparent half-life of the elimination phase in plasma, repeated dose

tissue distribution studies should have been performed according to the ICH topic S3B but the Applicant provided convincing justification for not performing such studies.

According to the Applicant, the long-lived radioactivity in tissues and human plasma and the incomplete extraction recovery of total radioactivity from human plasma suggest the potential for some degree of binding of crizotinib-derived radioactivity to plasma proteins and/or tissue macromolecules. The Applicant did not discuss the incomplete extraction recovery of total radioactivity from human plasma considering it potentially due to the low levels of radioactivity in plasma in the ADME study and to technical limitations. The justification was considered acceptable, with monitoring of the potential clinical effects, which can be derived from the product accumulation after repeated administration.

Repeat dose studies demonstrated accumulation of crizotinib after repeated administration in rats (after a period longer than 1 month), dogs and monkeys.

Regarding, drug-drug interactions

Although the CYP3A4 induction is compensated by the time-dependent inhibition of crizotinib, the inducing potency of crizotinib on other enzymes or transporters PXR-dependent is likely even though the magnitude of induction is lesser than those observed with CYP3A4.

Crizotinib and UGTs (UDP-glucuronyl transferase)

The effect of crizotinib on glucuronidation enzymes was not assessed. Even though the phase II enzymes such as UGT are not mainly involved in crizotinib metabolism, its inhibitory effect of the latter as well as its inducing effect should be investigated. During the procedure, the Applicant proposed an interesting simulation giving a range of at risk concentrations however without the calculation of the Ki value of crizotinib for UGTs, it is difficult to know whether crizotinib is or not an UGT inhibitor at therapeutic concentrations. Of note, a drug can be an UGT inhibitor whilst it is not metabolised by this enzyme. Therefore, caution should be exercised when crizotinib and substrates of UGTs, such as paracetamol, morphine, or irinotecan, are combined, see section 4.5 of the SmPC.

The effect of crizotinib as a substrate and inhibitor of BSEP and renal secretory transporters like OCT2 and OATs, initially missing, has been discussed by the Applicant during the procedure. On renal transporters, the Applicant did not estimate the Ki or IC50 value of crizotinib and chose to make deduction based on clinical data. It is agreed that clinically relevant interactions involving renal transporters were rare but the applicant is recommended to further investigate this potential effect.

On BSEP, the high metabolism of crizotinib by CYP3A4, makes the biliary secretion a minor elimination pathway, therefore an *in vitro* study assessing the effect of crizotinib as a substrate of BSEP is not warranted. Regarding the potential for crizotinib to be a BSEP inhibitor, it was recommended to the applicant to conduct an *in vitro* study assessing the inhibitory potency of crizotinib on BSEP.

Crizotinib underwent a non clinical testing compliant with the guideline ICH S9 on non clinical evaluation for anticancer pharmaceuticals.

The main target organs were related to the gastrointestinal (emesis, fecal changes, congestion), hematopoietic (bone marrow hypocellularity), cardiovascular (mixed ion channel blocker, decreased heart rate and blood pressure, increased LVEDP, QRS and PR intervals, and decreased myocardial contractility), or reproductive (testicular pachytene spermatocyte degeneration, single-cell necrosis of ovarian follicles) systems. The No Observed Adverse Effect Levels (NOAEL) for these findings were either subtherapeutic or up to 5-fold human clinical exposure based on AUC. Other findings included an effect on the liver (elevation of liver transaminases) and retinal function, and potential for phospholipidosis in multiple organs without correlative toxicities.

Crizotinib was not mutagenic in vitro in the bacterial reverse mutation (Ames) assay. Crizotinib was aneugenic in an in vitro micronucleus assay in Chinese Hamster Ovary cells and in an in vitro human lymphocyte chromosome aberration assay. Small increases of structural chromosomal aberrations at cytotoxic concentrations were seen in human lymphocytes. The NOAEL for aneugenicity was approximately 4-fold human clinical exposure based on AUC.

Carcinogenicity studies with crizotinib have not been performed.

No specific studies with crizotinib have been conducted in animals to evaluate the effect on fertility; however, crizotinib is considered to have the potential to impair reproductive function and fertility in humans based on findings in repeat-dose toxicity studies in the rat. Findings observed in the male reproductive tract included testicular pachytene spermatocyte degeneration in rats given ≥ 50 mg/kg/day for 28 days (approximately 2-fold human clinical exposure based on AUC). Findings observed in the female reproductive tract included single-cell necrosis of ovarian follicles of a rat given 500 mg/kg/day for 3 days.

Crizotinib was not shown to be teratogenic in pregnant rats or rabbits. Postimplantation loss was increased at doses ≥ 50 mg/kg/day (approximately 0.8 times the AUC at the recommended human dose) in rats, and reduced foetal body weights were considered adverse effects in the rat and rabbit at 200 and 60 mg/kg/day, respectively (approximately 2-fold human clinical exposure based on AUC).

Decreased bone formation in growing long bones was observed in immature rats at 150 mg/kg/day following once daily dosing for 28 days (approximately 7 times human clinical exposure based on AUC). Other toxicities of potential concern to paediatric patients have not been evaluated in juvenile animals.

The results of an *in vitro* phototoxicity study demonstrated that crizotinib may have phototoxic potential.

Four impurities are specified above 0.15%, the level of qualification in the drug substance. The adverse effects in the impurity qualification study were consistent with those observed in the other repeat-dose toxicity studies. No specific genotoxicity studies were conducted to qualify these impurities. However, the Applicant provided QSAR analysis demonstrating that these impurities do not carry supplementary alerts compared to crizotinib.

2.3.7. Conclusion on the non-clinical aspects

The non-clinical studies submitted in support of this MAA have been performed in accordance with the requirements of the guideline ICH S9 "Nonclinical evaluation for anticancer pharmaceuticals".

2.4. Clinical aspects

2.4.1. Introduction

The initial dossier for marketing authorisation of crizotinib in previously treated ALK positive advanced NSCLC included:

- Six Phase 1 biopharmaceutics and clinical pharmacology studies in healthy volunteers. The effect of crizotinib on the pharmacokinetics of a CYP3A substrate (midazolam) and the effect of food on the pharmacokinetics of crizotinib were also evaluated.

- Study 1001 (pivotal), is a phase I-II multicenter, multinational, open-label, single-arm study evaluating the safety, pharmacokinetics, pharmacodynamics, and antitumor activity of oral crizotinib in patients with advanced cancers. Study 1001 was comprised of a dose escalation component, plus

cohorts of patients receiving the recommended Phase 2 dose (RP2D) of 250 mg BID, including a large cohort of patients having ALK-positive advanced NSCLC.

- Study 1005 an ongoing multicenter, multinational, open-label, single arm, Phase 2 study evaluating the safety and efficacy of oral crizotinib at 250 mg BID in patients with ALK-positive advanced NSCLC after failure of at least 1 line of chemotherapy for advanced disease.

This regulatory submission included preliminary CSRs for Studies 1001 (pivotal), and 1005 (supportive).

GCP

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

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

- Tabular overview of clinical studies

Study ID	Population and N treated/analysed	Design	Route , dose and duration of treatment	Objective
A8081008 Biopharmaceutic study	Healthy volunteers N= 24	A relative bioavailability study comparing Crizotinib 250 mg powder in capsule (PIC) and Crizotinib 250 mg immediate release tablet (IR)	Oral ; 250 mg, single dose	Safety, tolerability, PK
A8081009 Pharmacology study	Healthy volunteers N= 6	^{14}C Radiolabeled Crizotinib ADME study (extemporaneously prepared oral suspension)	Oral ; 250 mg, single dose	Safety, tolerability, PK
A8081010 Biopharmaceutic study	Healthy volunteers N = 14	Absolute bioavailability study comparing Crizotinib 50 mg IV and Crizotinib 250 mg IR tablet	IV, 50 mg Oral, 250 mg Single dose	Safety, tolerability, PK
A8081011 Biopharmaceutic study	Healthy volunteers N = 36	Bioequivalence study of commercial formulated capsule (FC) vs IR tablet and PIC, Food effect study with FC capsule	Oral; 250 mg FC (fed and fasted); 250 mg IR ; 250 mg PIC; Single dose	Safety, tolerability, PK
A8081015 Pharmacology study	Healthy volunteers N = 15	Drug-Drug interaction (DDI) study comparing Crizotinib 150 mg IR w/wo Ketoconazole 200 mg BID (16 days)	Oral ; Crizotinib 150 mg IR ; single dose Oral ; Ketoconazole 200 mg BID ; 16 days	Safety, tolerability, PK, inhibiting DDI
A8081016 Pharmacology study	Healthy volunteers N = 15	Drug-Drug interaction (DDI) study comparing Crizotinib 250 mg IR w/wo Rifampin 600 mg QD (14 days)	Oral ; Crizotinib 250 mg IR ; single dose Oral ; Rifampin. 600 mg QD ; 14 days	Safety, tolerability, PK, inducing DDI
A8081001 Part 1 Dose escalation cohorts	Cancer patients ; N = 38	All doses with Crizotinib PIC 50 mg QD, n = 3 100 mg QD, n = 4 200 mg QD, n = 9 200 mg BID, n = 7 250 mg BID, n = 9 300 mg BID, n = 6	Part I : Oral ; Crizotinib PIC, 50, 100, 200, 250, 300 mg ; single or multiple doses ; 4-week cycle	Efficacy, tolerability, PK, PD

A8081001 Part 2 RP2D Cohorts	Cancer patients ; N = 171	All doses with Crizotinib 250 mg BID, PIC or IR tablet ALK-positive NSCLC, n = 119 ALK-negative NSCLC, n = 5 Other, n = 47 Midazolam DDI sub-study, n = 14 Food effect sub-study, n = 13	Oral ; 250 mg BID, multiple doses ; 4-week cycle	Efficacy, tolerability, PK, PD
A8081005	Cancer patients ; N = 136	Phase 2 efficacy and safety study Crizotinib 250 mg BID, IR tablet	Oral ; 250 mg BID, continuous 21-day cycles	Efficacy, tolerability, PK, PD

The applicant claimed the approval for the following indication:

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

The final indication following CHMP review of this application is:

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

2.4.2. Pharmacokinetics

Absorption

After a single-dose of 250 mg given orally, crizotinib is slowly absorbed at a median t_{max} of 4 to 6 hours, with mean Cmax and AUC_{inf} reaching 100-130 ng/mL and 2100 – 2900 ng*hr/mL, respectively

The absolute bioavailability of a single oral 250 mg crizotinib dose administered in the fasted state as the IR tablets relative to a 50 mg IV crizotinib dose administered over 2 hours was assessed in healthy adult volunteers in Study 1010. It shows that crizotinib is slowly absorbed in fasting subjects with median t_{max} of 5.0 h. This seems compatible with *in vitro* findings allowing to consider crizotininib as a class 4 compound (low solubility, low permeability) under the Biopharmaceutical Classification System. The absolute bioavailability is moderate, 43 % on average (90% CI: 39.68%-47.56%). Taking into account this value of 43%, linear kinetics can be proposed between 50 mg IV and 250 mg oral, single-dose, based on extent of systemic exposure. The apparent volume of distribution is very large, suggesting high tissue penetration. Based on the results observed with the lactam metabolite, metabolite ratios indicate extensive pre-systemic biotransformation of crizotinib.

Bioequivalence between the different formulations used was demonstrated according to standard procedures for bioequivalence assessment. Results were very consistent between studies and following a single oral administration of 250 mg crizotinib to healthy volunteers at fasting state, C_{max} occurred 5 to 6 h post dosing, reaching around 120 ng/mL while the extent of systemic exposure was about 2800 hxng/mL. . Full bioequivalence can be acknowledged between the formulated capsule to be marketed and previous oral formulations such as simple powder in capsule or immediate release tablet. This allows the bridging of data obtained in the whole clinical program.

Regarding the pharmacokinetic profile of the lactam metabolite PF-06260182, no difference exists between the three oral formulations. On average, Cmax is 4-fold less and AUC is 6 to 7-fold less than the corresponding values measured for unchanged crizotinib.

Crizotinib PK parameters demonstrated moderate variability (CV: 36-45% for C_{max} and AUC) in both healthy subjects and patients with advanced solid tumours: : in the 1010 study, CV values in AUC_{inf}

and C_{max} range from 28% to 34% for oral administration compared to 18% to 19% following IV infusion. In the pivotal study, the CV is 36-38% for AUC_T and 38-44% for C_{max}, respectively.

On average, when crizotinib is given with high-fat meal, there is approximately 14% decrease in C_{max} and in AUC, with a moderate delay in T_{max}. Since the point estimate is the same in healthy subjects and in cancer patients, it can be concluded that crizotinib can be administered irrespective of food intake, even if the lower limit of the 90% confidence interval in Study A8081001, is 69.23% for C_{max} and 65.11% for AUC, respectively. This finding provided the basis for the removal of food restrictions with regards to crizotinib dosing.

Distribution

Crizotinib is highly bound to plasma proteins (>90% in humans: 91% for crizotinib and 94-95 % for the main metabolite).. A relatively equal distribution into the blood cell and plasma compartments is shown. Crizotinib is very largely distributed in the body with apparent volume of distribution V/F around 5000 L (Vss being measured at 1772 L following a single 50 mg IV dose) indicating extensive distribution into tissues from the plasma.

The available data on systemic exposure to crizotinib and active metabolites suggested that steady-state was achieved within 15 days of continuous administration of crizotinib 250 mg twice daily. The steady state plasma concentrations exceeded the target efficacious concentrations (23 nM free drug or 111 ng/mL total drug) of ALK inhibition predicated from preclinical tumour models.

Elimination

Crizotinib undergoes extensive hepatic metabolism, likely pre-systematically by CYP3A, leading to numerous metabolites amongst which the lactam compound PF-06260182 could be active. Crizotinib is primarily metabolised by CYP3A4/5. A 216% increase and an 81.8% decrease in crizotinib plasma exposure was noted in clinical drug-drug interaction studies conducted with ketoconazole (strong CYP3A inhibitor) and rifampin (strong CYP3A inducer), respectively.

The primary metabolic pathways in humans were oxidation of the piperidine ring to crizotinib lactam and O-dealkylation, with subsequent Phase 2 conjugation of O-dealkylated metabolites.

The lactam metabolite of crizotinib (PF-06260182, M10) is the most abundant metabolite in circulation. Trough concentrations of the metabolite PF-06260182 are 50% lower in Study 1005 compared with Study 1001. The applicant plans to conduct a clinical PK/PD study with the main lactam metabolite (PF-06260182) which exhibits inhibitory activity in vitro against ALK and c-Met/HGFR.

Some other metabolites have been detected in man (less than 10%) in addition to the lactam metabolite, and elimination is mostly renal.

Following single doses of crizotinib, the apparent plasma terminal half life of crizotinib was 42 hours in patients.

Following the administration of a single 14C-radiolabeled crizotinib 250 mg dose, 63% and 22% of the drug-related radioactivity was recovered in the faeces and urine, respectively. Non-metabolic elimination such as biliary excretion cannot be excluded. Unchanged crizotinib represented approximately 53% and 2.3% of the administered dose in feces and urine, respectively.

Renal excretion of unchanged crizotinib is a minor route of elimination; however, the kidney appears to play an important role in the elimination of metabolites. It is agreed that no dose adjustment is required in patients with mild and moderate renal insufficiencies. No data are available in patients with severe and end-stage renal impairment. The applicant will perform such investigation following a step-

wise approach as reflected in the RMP (see section 2.7). First a single dose is planned in patients with severe renal impairment. The need for further investigations (steady-state study or SIM-CYP simulation) will be decided based on the findings of the single dose study.

Dose proportionality and time dependencies

Crizotinib demonstrated somewhat non-linear pharmacokinetics in humans.

- Single-dose PK of crizotinib has been evaluated in healthy subjects (Studies 1008, 1009, 1010, 1011, 1015, and 1016) and in patients with advanced tumours (Study 1001). After a single 250 mg crizotinib dose in patients, peak crizotinib plasma concentrations (C_{max}) were achieved at a median T_{max} of 4.0 hours. Following attainment of C_{max}, plasma crizotinib concentrations declined in a multi-exponential manner with a long mean terminal half life of 42 hours.

Single-dose crizotinib systemic exposures in cancer patients were similar to those observed in healthy subjects, indicating that there are no inherent differences in PK between healthy subjects and cancer patients. Systemic exposure of crizotinib increases with dose in a less-than-proportional manner after single dose (over the range 50-300 mg QD).

- Greater than dose proportional increases in crizotinib AUC and C_{max} were observed over the 50 to 100 mg QD dose range and over the 200-300 mg BID in patients. Multiple-dose pharmacokinetics of crizotinib can therefore not be precisely predicted by single-dose. However, no significant changes in steady-state trough concentrations following 250 mg BID have been observed during repeated treatment cycles. In order to better elucidate the systemic exposure to crizotinib and active metabolites, the applicant was recommended to investigate further this aspect and will submit the outcome as soon as it becomes available.

Special populations

Renal impairment

Renal excretion of unchanged crizotinib is a minor route of elimination; however, the kidney appears to play an important role in the elimination of metabolites. It is agreed that no dose adjustment is required in patients with mild (CLcr 60 to 90 mL/min) and moderate (CLcr 30 to 60 mL/min) renal insufficiencies. The steady-state trough concentrations in these two groups were similar to those in patients with normal renal function (CLcr greater than 90 mL/min) in studies 1001 and 1005. There is no specific study in renal impairment and serum creatinine > 2 x ULN was an exclusion criteria for the main studies (1001 and 1005). No data are available in patients with severe and end-stage renal impairment. The applicant has committed to perform an investigation following a step-wise approach in planned study A8081020 "A Phase I, Single-Dose, Parallel-Group Study to Evaluate the Pharmacokinetics of Crizotinib in Subjects with Impaired Renal Function" (as reflected in section 2.7) and the available data have been adequately reflected in section 4.2 of the SmPC. The need for further investigations (steady-state study or SIM-CYP simulation) will be decided based on the findings of the single dose study.

Liver impairment

There is also no specific study in hepatic impairment. Clinical trials 1001 and 1005 excluded patients with ALT or AST >2.5 x ULN, or if due to underlying malignancy, > 5.0 x ULN or with total bilirubin >1.5 x ULN. Hepatic impairment is likely to alter the kinetics of crizotinib as it is primarily hepatically eliminated and the lack of data has been adequately reflected in section 4.2 of the SmPC. Population PK analysis did not select transaminases as significant covariates influencing crizotinib. The influence of liver insufficiency on the disposition of crizotinib remains to be established and no recommendations of

use could be made yet in this sub-group of patients with mild or moderate hepatic impairment. The Applicant has committed to perform adequate investigations (planned study A8081012 and post authorisation safety study to evaluate multiple dose (due to the non-linear pharmacokinetics of crizotinib) and determine the PK profile of crizotinib and metabolites in patients with various degrees of hepatic impairment (see section 2.7). A contra-indication has been added in section 4.3 of the SmPC in patients with severe hepatic impairment.

Elderly patients

Age was not identified as a significant co-variate for crizotinib in the population PK analysis and the characteristics of patients with ALK-positive status (younger patients) seem to differ from unselected NSCLC patients. Only a small proportion (12-14 %) of the patients included in the main studies (1001-1005) were over 65 years. No formal dosing recommendation can be made until additional data become available. The PKs of crizotinib have not been formally investigated in elderly patients and the Applicant has committed to investigate further this issue in the final popPK analysis report of the main studies (see section 2.7 RMP).

Race

After repeated administration of 250 mg BID, steady-state crizotinib C_{max} and $AUC\tau$ in Asian patients were higher than in Non-Asian: respectively, 1.57 (90% CI: 1.16-2.13) fold and 1.50 (90% CI: 1.10-2.04) fold those seen in non-Asian patients (also see section 2.4 with regard to differences in ORR). Bodyweight, size and BSA, appear to be factors partly contributing to the PK difference seen between Asian and non-Asian patients. Other potential mechanisms for this PK difference are unknown. Crizotinib ORR was much greater in Asian patients than in non-Asian patients with ALK-positive advanced NSCLC. As 45% of the population in study A8081007 was Asian, an additional comparative analysis of crizotinib vs. Pemetrexed/docetaxel according to race is expected as part of the A8081007 study report (as indicated in the specific obligations to conduct post-authorisation measures).

Pharmacokinetic interaction studies

In vitro studies

In vitro studies in human liver microsomes demonstrated that crizotinib is a time-dependent inhibitor of CYP3A (see section 4.5). In vitro studies indicated that clinical drug-drug interactions are unlikely to occur as a result of crizotinib-mediated inhibition of the metabolism of medicinal products that are substrates for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP2D6.

An in vitro study in human hepatocytes indicated that clinical drug-drug interactions are unlikely to occur as a result of crizotinib-mediated induction of the metabolism of medicinal products that are substrates for CYP1A2 or CYP3A.

An *in vitro* study in human hepatocytes indicated that crizotinib may induce pregnane X receptor (PXR)-regulated enzymes (e.g., CYP2B6, CYP2C8, CYP2C9, UGT1A1, with the exception of CYP3A4). Therefore, caution should be exercised in administering crizotinib in combination with medicinal products that are predominantly metabolized by these enzymes. Of note, the effectiveness of concomitant administration of oral contraceptives may be altered. (see section 4.5 of the SmPC).

Based on an *in vitro* study, crizotinib is predicted to inhibit intestinal P-gp. Therefore, administration of crizotinib with medicinal products that are substrates of P-gp (e.g., digoxin, dabigatran, colchicine, pravastatin) may increase their therapeutic effect and adverse reactions. Close clinical surveillance is recommended when crizotinib is administered with these medicinal products (see section 4.5 of the SmPC).

In vitro, crizotinib did not inhibit the human hepatic uptake transport proteins OATP1B1 or OATP1B3 at therapeutic concentrations. Therefore, clinical drug-drug interactions are unlikely to occur as a result of crizotinib-mediated inhibition of the hepatic uptake of medicinal products that are substrates for these transporters as the concentration of crizotinib that inhibits 50% of OATP-mediated transport greatly exceeds the mean unbound crizotinib plasma concentration at C_{max} (38 ng/mL, 0.085μM) and the estimated maximum crizotinib concentration in liver following therapeutic doses of 250 mg BID in patients with cancer (A8081001).

In vivo studies

Agents whose plasma concentrations may be altered by crizotinib

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

Despite a moderate effect at therapeutic dosage, with the dose of 300 mg QD of crizotinib, and regardless of the low number of subjects, the upper bound of the 90% CI, is equal to 8,68 thus suggesting that crizotinib might be a potent CYP3A4 inhibitor. This is particularly relevant for the population at risk of higher exposure such as Asian and low weight population. Indeed, of the 14 patients receiving crizotinib given at 250 mg BID, 6 did not complete the study and on the 8 remaining patients, 3 displayed an AUCi/ AUC ratio for midazolam > 5, making crizotinib a possible potent CYP3A inhibitor.

Therefore, coadministration of crizotinib with CYP3A substrates with narrow therapeutic indices, including but not limited to alfentanil, cisapride, cyclosporine, ergot derivatives, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus should be avoided (see sections 4.4 and 4.5 of the SmPC). If the combination is needed, then close clinical monitoring should be exercised.

Agents that may increase crizotinib plasma concentrations

In vitro, CYP3A4 was the main enzyme involved in crizotinib metabolism, notably in the formation of the lactam (or M10).

Coadministration of crizotinib with strong CYP3A inhibitors may increase crizotinib plasma concentrations. Coadministration of a single 150 mg oral dose of crizotinib in the presence of ketoconazole (200 mg twice daily), a strong CYP3A inhibitor, resulted in increases in crizotinib systemic exposure, with crizotinib AUCinf and Cmax values that were approximately 3.2-fold and 1.4-fold, respectively, those seen when crizotinib was administered alone. The reported adverse events suggest a likely activity from the metabolite M10. Eyes disorders, for example, were frequently reported and may be related to the combination rather than to crizotinib alone. In other clinical studies, these AEs were observed after repeated-dose of crizotinib administered at 250 mg BID and not after a single dose. Hence, the explanation behind this effect might be the consequence of the active fraction crizotinib + M10 circulating levels, reaching sufficient concentrations to penetrate the ocular system.

Therefore, the concomitant use of strong CYP3A inhibitors (certain protease inhibitors like atazanavir, indinavir, nelfinavir, ritonavir, saquinavir, and, certain azole antifungals like itraconazole, ketoconazole, and voriconazole, certain macrolides like clarithromycin, telithromycin, and troleandomycin) should be avoided. Grapefruit or grapefruit juice may also increase plasma concentrations of crizotinib and should be avoided (see sections 4.2 and 4.4 of the SmPC). Furthermore, the effect of CYP3A inhibitors on steady-state crizotinib exposure has not been established.

Agents that may decrease crizotinib plasma concentrations

Coadministration of a single 250 mg crizotinib dose with rifampicin (600 mg QD), a strong CYP3A4 inducer, resulted in 82% and 69% decreases in crizotinib AUCinf and Cmax, respectively, compared to when crizotinib was given alone.

PF-06260182 plasma exposure following coadministration of crizotinib and rifampicin decreased by approximately 94.3% for AUCinf and 89.0% for Cmax compared to when crizotinib was administered alone. When co administered with rifampicin the apparent oral clearance of crizotinib was 5.5-fold that seen when crizotinib was given alone. The apparent terminal t1/2 of crizotinib was longer than that seen when crizotinib was given alone (48 vs. 33 hours), even though CL/F of crizotinib increased due to rifampin-mediated induction of CYP3A

Coadministration of crizotinib with strong CYP3A inducers may therefore decrease crizotinib plasma concentrations. The concurrent use of strong CYP3A inducers, including but not limited to carbamazepine, phenobarbital, phenytoin, rifabutin, rifampicin, and St. John's wort, should be avoided (see section 4.4). Furthermore, the effect of CYP3A inducers on steady-state crizotinib exposure has not been established.

The solubility of crizotinib is pH dependant (level 4 of BPS) with solubility decreasing at higher pH. Despite the results from the PK-pop analysis, a clinically relevant impact of these drugs on crizotinib absorption cannot be excluded. Therefore, the applicant is recommended to perform a DDI study with PPI and H2 antagonists in order to assess the magnitude of this interaction and to anticipate a recommendation for dose adjustment.

The CL/F after multiple dosing was lower than that observed after single dosing of crizotinib. Since crizotinib is primarily metabolized via CYP3A and is a moderate CYP3A inhibitor, CYP3A auto inhibition may likely be the mechanism for the decrease in CL/F after multiple dosing.

2.4.3. Pharmacodynamics

Mechanism of action

No clinical studies on the mechanism of action were submitted. For in vitro and in vivo results, see non-clinical pharmacodynamics.

Primary and Secondary pharmacology

PF-06260182 (with two constituent diastereomers PF-06270079 and PF-06270080), is the only identified metabolite accounting for > 10% of circulating radioactivity and is approximately 3- to 8-fold less potent against ALK and 2.5- to 4-fold less potent against c-Met/HGFR *in vitro*. The other metabolites (M1, M2, M3, M4, M8) that are present in man but not in animal are not active.

Clinical relevance/activity of crizotinib lactam (M10, PF-06260182) and its constituent diastereomers (PF-06270079 and PF-06270080), is still not clear. The Applicant was recommended to collect additional PK/PD data regarding crizotinib lactam metabolite.

In order to definitively assess the CLcr effect on crizotinib PK/PD, the applicant was recommended to complete an updated population PK analysis using pooled data from clinical trials including but not limited to Studies A8081001 and A8081005.

Genetic differences (CYP 3A4/5) may affect the metabolism of crizotinib in humans. It is unlikely that genetic differences on CYP2C19 and CYP2D would significantly influence the metabolism of crizotinib in humans.

It is not known whether crizotinib is only effective in patients with ALK positive status. The enrolment of ALK-negative NSCLC patient as a new cohort in Study A8081001 has been requested as Post-Marketing Commitment related to US-NDA approval and the applicant agreed to provide results from this cohort as soon as available.

Resistance

Clinical collaborations involving crizotinib resistance have identified ALK secondary mutations after demonstrating evidence of (radiographic) disease progression in a total of 11 of 36 cases (31%) of NSCLC (including L1196M, G1269A, C1156Y, L1152R, and F1174L mechanistically characterized in in vitro cell-based assays and demonstrated to confer resistance to crizotinib). Additional studies of ALK-positive tumors suggested involvement of alternative pathways as potential mechanisms of ALK mutation-independent resistance. The Applicant will continue to address this issue and provide another analysis of crizotinib resistance after an additional significant amount of new data becomes available.

RR and QTc prolongation:

Crizotinib induces a dose-dependent increase of the RR-interval (decrease in heart rate expected around 4 bpm decrease for a 100 ng/mL increase in crizotinib concentration).

There is a marked estimated decrease in heart rate at the average steady-state C_{max} of 478 ng/mL after 250 mg BID dosing of crizotinib (A8081001) of 15.9 bpm (90% CI: 14.3, 17.5).

Table 6 Summary of drug effects for concentration-RR modelling

Concentration Increase (ng/mL)	Mean Drug Induced Change in RR (SE) (msec)	90% Conf. Limits (msec)	Mean Change in Heart Rate (bpm)
100	38.8 (3.02)	33.8, 43.8	-3.96
200	77.6 (6.05)	67.7, 87.6	-7.54
300	116.4 (9.07)	101.5, 131.3	-10.80
400	155.2 (12.09)	135.3, 175.1	-13.78

SE = standard error of the estimate; Artifact ID: 4101144

In addition to the mean changes, of main interest are the dispersion and the individual RR values as shown above overall and also according to race and sex.

Individual values for concentration-RR final according are given overall in Figure 1 of Pop PK and according to sex and Race in Figure 2 and 3 of Pop PK:

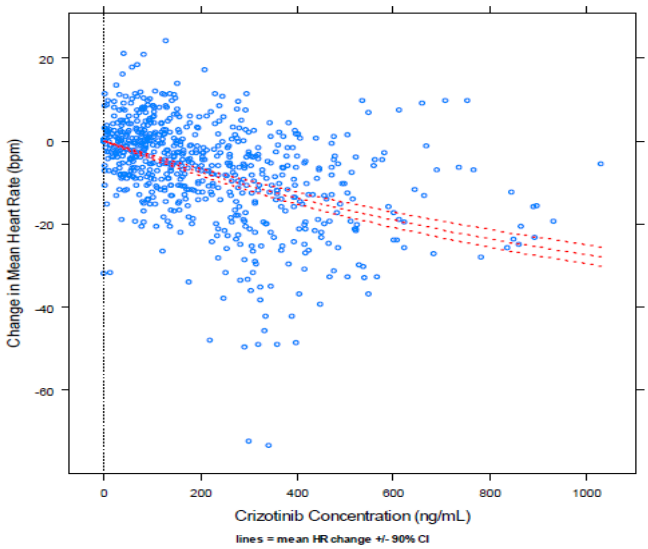


Figure 1 Observed/predicted change in mean heart rate for all subjects

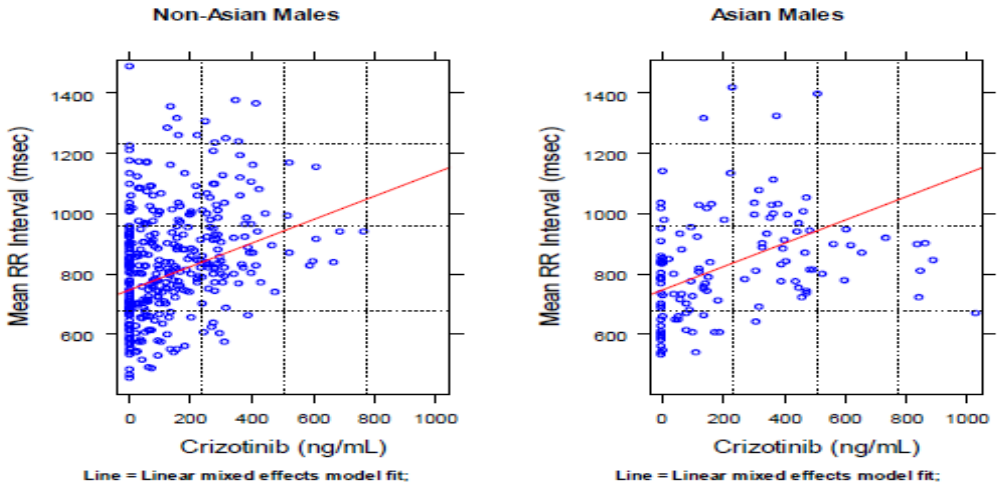


Figure 2 Concentration-RR relationship for males and Asian group

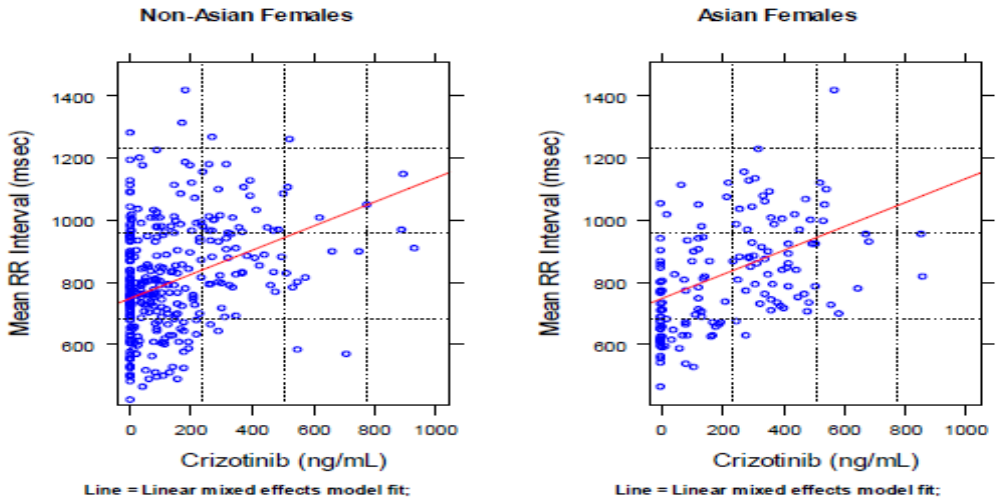


Figure 3 Concentration-RR relationship for females and Asian group

QTc prolongation is a pharmacological class effect/safety concern for TKI.

The QT interval prolongation potential of crizotinib was assessed in all patients who received crizotinib 250 mg BID. Serial ECGs in triplicate were collected following a single dose and at steady-state to evaluate the effect of crizotinib on QT intervals. Four of 382 patients (1.0%) were found to have QTcF (corrected QT by the Fridericia method) ≥500 msec, and 15 of 364 patients (4.1%) had an increase from baseline QTcF ≥60 msec by automated machine-read evaluation of ECG. A central tendency analysis of the QTcF data demonstrated that the highest upper bound of the two-sided 90% CI for QTcF was <15 msec at the protocol pre-specified time points.

Automatic reading of ECGs is not the optimal way to best detect QT prolongations and study specific "most appropriate correction method" (QTcS) is not likely to be used in clinical practice.

Of interest is the concentration-QTcF relationship provided (figure 4 and 5 of the Pop PK):

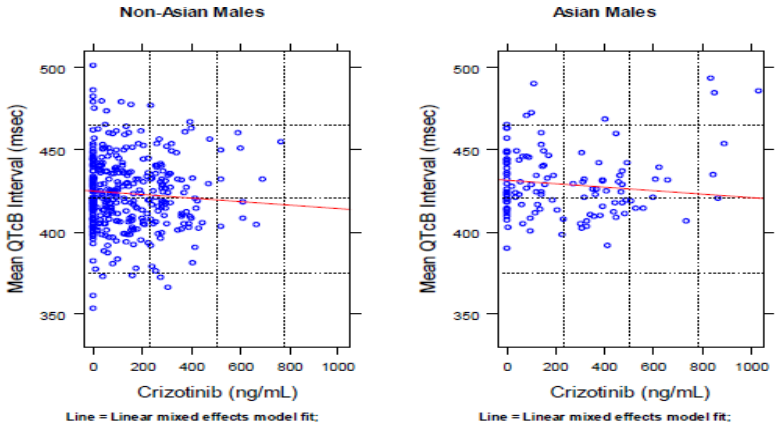


Figure 4 Concentration-QTcB relationship for males and Asian group

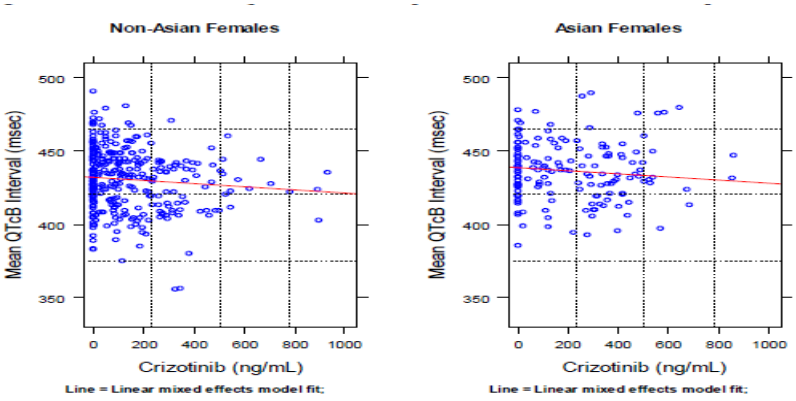


Figure 5 Concentration-QTcB relationship for females and Asian group

Of main interest is the dispersion and the individual QTcF values overall and also according to race and sex as outliers QTcF values as well as marked individual increases in QTcF compared with baseline values could allow proper evaluation of risk of occurrence of clinical events.

Automatic reading QTcF was over 500 msec on at least one post baseline assessment in 4/308 patients (1.3%) and maximum change in QTcF was ≥60 msec in 3.5 %(10/289), from preliminary data of studies 1001-1005. QTcF prolongation from 389 msec to 578 msec was observed in a 24-year old Asian in one ongoing phase II study.

2.4.4. Discussion on clinical pharmacology

Crizotinib lactam (M10) was the only metabolite observed in humans known to possess pharmacological activity against ALK or c-Met/HGFR. Although it was the major metabolite in human plasma, it was not detected in urine following oral crizotinib administration. Therefore, a marked increase in the plasma exposure of this metabolite in patients with impaired renal function is not anticipated. The other following metabolites observed in humans are considered inactive (M1, M2, M3, M4, M5, M6, and M8).

The contribution of c-Met/HGFR inhibition to crizotinib anti-cancer activity will be further elucidated given that c-MET is often over-expressed in NSCLC patients, c-MET over-expression in NSCLC is associated with a poor prognosis, and no information has been submitted on the prevalence of co-expression of high levels of c-MET and ALK mutation in NSCLC. However, the enrolment of ALK-negative NSCLC patient as a new cohort in Study A8081001 has been requested as Post-Marketing Commitment related to US-NDA approval. The applicant agreed to provide results from this cohort as soon as available.

While crizotinib is a class 4 compound within the BCS, the coadministration of food does not seem to enhance solubility or permeability of this compound.

Available data do not allow to definitively conclude whether or not crizotinib may cross the BBB; the absence of metastatic brain disease response does not necessarily imply the crizotinib inability to cross the BBB; moreover, additional information in patients with brain metastatses will be discussed in the efficacy section.

Because of extensive pre-systemic metabolism, hepatic impairment is likely to cause accumulation of crizotinib. Clinical trials 1001 and 1005 excluded patients with ALT or AST >2.5 x ULN, or if due to underlying malignancy, >5.0 x ULN or with total bilirubin >1.5 x ULN. Exclusion criteria therefore prevented exploring the relationship between signs of hepatic toxicity and exposure (see CPMP/EWP/205/95/Rev.3/Corr.2). Considering that lung cancer most often spreads to the liver and safety issues have been raised insufficient information is still available on the effect of hepatic impairment on PK/PD of crizotinib and active metabolite. In order to address this issue, the Applicant will conduct both Study A8081012 ("A Phase 1 Study to Evaluate the Effect of Hepatic Impairment on the Pharmacokinetics of Crizotinib in Advanced Cancer Patients") and 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 (see section 2.7).

Insufficient information is available on the effect of severe renal impairment on crizotinib PK/PD and safety. Therefore, no valid dosing recommendation could be made in this subgroup and additional information is required. The Applicant will 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 in Subjects with Impaired Renal Function") with the final clinical study report expected in Q2 2013 (see section 2.7).

In addition, it was recommended to the applicant to complete an updated population PK analysis to definitively assess the CLcr effect on crizotinib PK using pooled data from clinical trials (including but not limited to Studies A8081001 and A8081005).

The PK/PD of crizotinib has not been adequately evaluated in patients over 65 years of age and this information has been adequately reflected in sections 4.2, 4.4 and 5.1 of the SmPC. The Applicant will complete an updated popPK analysis to definitively assess the effect of age on crizotinib PK using pooled data from clinical trials (including but not limited to Studies A8081001 and A8081005), with the final report to be submitted second half of 2013 (see section 2.7).

In addition, the applicant is recommended to further investigate the influence of body weight and mainly lean body weight in order to validate dosing recommendations in obese and underweighted patients.

Although the long apparent elimination half-life is supportive of a once-daily dosing regimen, the Applicant selected a twice-daily dosing schedule for the RP2D to better manage the frequency and severity of gastrointestinal events. The other pharmacokinetic reason could be the large volume of distribution and the possibility of a deep compartment in very slow equilibrium with the central compartment, although the amount of crizotinib in this deep compartment is likely small.

PK/PD analysis suggested that the patients at the lower end of the exposure range obtained with the normal clinical dose had doubled risk for increase in tumour size from baseline at the end of treatment, compared with medium and high exposure categories (data not shown). In order to better understand these results, the CHMP recommended the applicant to conduct a definitive Exposure-Response (ER) analyses for each of the main studies A8081001, A8081005, and the two Phase 3 randomised studies (A8081007 and A8081014) when final data are available, as summarised in the Population Modelling Analysis Plan with PFS and OS (if applicable) as efficacy endpoints and the race factor (Asian vs. non-Asian) will be included as one of the covariates in the modelling. A final ER analyses could be conducted at the end of each study, using a similar approach.

A pharmacokinetic/pharmacodynamic analysis suggested a relationship between crizotinib plasma concentration and QTc. However, a reliable estimation of QTcF effect size is not possible at present, and large increases in QT interval (20 ms or over) cannot be reliably excluded because of limited data, and ECG interpretation issues. Additional data and analyses are required in order to have a reliable estimation of the size of the HR and QTc effect and potential clinical consequences. The Applicant has committed to amend study A8081014 in order to include additional ECG time points and central blinded manual review and to present bradycardia and QT potentially related AEs/SAEs/deaths (such as arrhythmias, syncope, seizure and sudden death cases, bradycardias, QT increase) and draw reliable conclusions about their associations with HR reduction and QTcF prolongation (see section 2.7).

During the procedure, the applicant was requested to specifically investigate the occurrence of enantiomeric conversion of R-enantiomer as the R enantiomer of Form A is reported to be the active form of crizotinib. It could be agreed, that conversion following identified and thus expected mechanisms is not likely. Nevertheless, it could not be excluded that isomerisation through unknown mechanism may occur. It was therefore recommended to the applicant to investigate the potential for crizotinib to undergo chiral inversion using an in vitro human system.

Drug-Drug interactions

CYP3A4 is moderately involved in crizotinib metabolism but the study performed with rifampicin exhibits outstanding results. The results from the planned DDI study with multiple doses of rifampin are therefore considered of primary importance in terms of clarification and definition of the need for dose modifications (see section 2.7).

The solubility of crizotinib is pH dependant (level 4 of BPS) with solubility decreasing at higher pH. Furthermore, preliminary results of the popPK analysis do not allow discarding a clinically relevant impact of PPI and H2 antagonists on crizotinib absorption. The CHMP recommended the applicant to conduct a single-dose study since the potential effect of gastric pH-elevating agents on crizotinib PK, if any, would be mediated via altered drug absorption and not post-absorptive processes (e.g., drug metabolism).

The planned DDI studies with ketoconazole or rifampin at steady-state will provide more evidence for the correct crizotinib dose adjustment in case of co-administration with CYP3A inhibitors and inducers in NSCLC patients. In the mean time, the proposal that concomitant use of strong CYP3A inhibitors and inducers should be avoided is endorsed (see section 4.5 of the SmPC).

The effect of crizotinib on glucuronidation enzymes was not assessed. Even though the phase II enzymes such as UGT are not mainly involved in crizotinib metabolism, it was recommended to the applicant to further investigate the inhibitory effect of the latter as well as its inducing effect.

The CHMP recommended the conduct of an *in vitro* study assessing the inhibitory potency of crizotinib on BSEP.

2.4.5. Conclusions on clinical pharmacology

The data submitted by the applicant are considered appropriate. However, additional PK studies are proposed to address some deficiencies: effect of hepatic or renal impairment, reason for differences in exposure in Asian and drug-drug interaction. The long half-life, however, is likely to reduce the day-to-day variability in exposure related to variable bioavailability. The lack of data is reflected in the SmPC.

The CHMP considers the following measures necessary to address the issues related to pharmacology and pharmacokinetics:

- to submit DDI studies with ketoconazole or rifampin at steady-state in order to allow defining dosing adjustments in case of co-administration.

- To submit the CSR of Study A8081012 "A Phase 1 Study to Evaluate the Effect of Hepatic Impairment on the Pharmacokinetics of Crizotinib in Advanced Cancer Patients." and the Post-Authorisation Safety Study (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).

- To present the results of a step-wise investigation in patients with severe renal impairment.

- To submit a definite assessment of the effect of age for the main studies A8081001, A8081005, A8081007 according to Population Modelling Analysis Plan at the time of submission of the study report for the pivotal study A8081007.

- To amend study A8081014 to include additional ECG time points and central blinded manual review. Furthermore, events such as sudden death, cardiac disorders, arrhythmias, syncope, dizziness, bradycardia, electrocardiogram QT prolonged, should be further presented and discussed together with the assessment potential QT prolongation (and the risk of electrolyte unbalances linked to important frequency of diarrhoea and vomiting).

2.5. Clinical efficacy

The MAA for crizotinib is based on 2 ongoing clinical trials, the pivotal phase I/II A8081001 study (referred to as study 1001) and the supportive phase 2 A8081005 study (referred to as study 1005), in patients with ALK-positive advanced NSCLC.

Two phase III trials of crizotinib in the treatment of ALK-positive NSCLC are ongoing*:*

Study A8081007 (referred to as study 1007): *Phase 3, Randomized, Open-Label Study Of The Efficacy And Safety Of crizotinib Versus Standard Of Care Chemotherapy (Pemetrexed Or Docetaxel) In Patients With Non-Small Lung Cancer Harboring A Translocation Or Inversion Event Involving The ALK Gene Locus*

Study A8081014: *Phase 3, Randomized, Open-Label Study Of The Efficacy And Safety Of crizotinib Versus Pemetrexed/Cisplatin Or Pemetrexed/Carboplatin In Previously Untreated Patients With Non-Squamous Carcinoma of The Lung Harboring A Translocation Or Inversion Event Involving The ALK Gene Locus*

Protocol	Setting	Trial Design	Endpoints	Stratification
A8081001	All Lines Solid Tumors ALK-Positive NSCLC	Multicenter, Multinational, Single-Arm, Open-Label	Primary: Safety, PK, ORR, Secondary: DR, OS, PFS, TTR, DCR	
A8081005	≥2nd-Line ALK-Positive NSCLC	Phase 2, Multicenter, Multinational Single-Arm, Open-Label	Primary: ORR, Safety Secondary: OS, DR, DCR, PFS, QoL	
A8081007	2nd-Line ALK-Positive NSCLC	Phase 3, Multicenter, Multinational, Crizotinib vs. Pemetrexed or Docetaxel, Open-Label	Primary: PFS Secondary: 6- and 12-month-OS, OS, ORR, DCR, DR, Safety, QoL, Biomarkers	ECOG PS (0/1 vs. 2) Previous anti-EGFR TKI treatment Brain metastases
A8081014	1st-Line ALK-Positive NSCLC	Phase 3, Multicenter, Multinational Crizotinib vs. Pem/Carbo or Pem/Cis, Open-Label	Primary: PFS Secondary: 6- and 12-month-OS, OS, ORR, DCR, DR, Safety, QoL, Biomarkers, Health care resource utilization (HCRU)	ECOG PS (0/1 vs. 2) Ethnicity (Asian vs. non-Asian) Brain metastases

During the evaluation procedure, efficacy updates from the 2 uncontrolled studies (1001 and 1005) were provided as well as top-line summary results from the comparative Study A8081007.

2.5.1. Dose response study(ies)

In the dose escalation phase of study 1001, 38 patients with different types of tumours were assigned to study treatment, and 36 patients were treated with at least 1 dose of crizotinib beginning on Cycle 1 Day 1: 35 (97.2%) patients discontinued from treatment, mainly for progressive disease (22 [61.1%] patients).

Progressive disease was noted in 66.7%, 50.0%, 62.5%, patients treated with daily dosing of respectively 50, 100 and 200 mg who did not experience AEs, and in 42.9 %, 75.0%, 66.7% of patients treated with BID dosing of respectively 200, 250 and 300 mg BID for whom AEs frequency was respectively 14.3%, 25.0%, 16.7%.

The Applicant selected the 250 mg BID dosing because of the absence of DLTs in 8 patients treated at this dose level and the occurrence of 2 DLTs of Grade 3 fatigue in 2 out of 6 patients treated at the 300 mg BID dose.

2.5.2. Main study(ies)

A8081001: Phase 1 Safety, Pharmacokinetic and Pharmacodynamic Study of PF-02341066, a c-Met/HGFR Selective Tyrosine Kinase Inhibitor, Administered Orally to Patients with Advanced Cancer

Methods

Study Participants

Female or male patients, 18 years of age or older, signed informed consent

Key inclusion criteria

1. Tumour eligibility:

- All cohorts, except RP2D-enriched population cohort:

Histologically confirmed advanced malignancies (except for leukaemias) refractory to standard of care therapy, or for whom no standard of care therapy was available.

- RP2D-enriched population cohort:

Histologically confirmed advanced malignancies that met one of the following criteria:

- Positive for c-Met amplification by FISH (excluding polysomy).
- Positive for ALK chromosomal translocations or gene amplification.
- Positive for known c-Met kinase domain activating mutations.
- Chromosomal translocations/fusions that lead to altered transcriptional regulation of c-Met and/or hepatocyte growth factor (HGF) including metastatic alveolar soft part sarcoma, clear cell sarcoma, rhabdomyosarcoma, or translocation associated renal cell carcinoma.
- Positive for chromosomal translocations at ROS gene in glioblastoma.

- ALK-negative NSCLC cohort:

Histologically or cytologically proven diagnosis of NSCLC that was locally advanced or metastatic and of the adenocarcinoma subtype (including mixed adenosquamous histology). All patients must have either been non smokers, former smokers, or light smokers (≤10 pack-years). Patients must have received only 1 prior chemotherapy treatment and this regimen must have been platinum-based. Patients who had been treated with an EGFR tyrosine kinase inhibitor were also allowed to enter the study. However, on a case-by-case basis and in agreement between the sponsor and investigator, patients who had more than 1 prior chemotherapy treatment were allowed to enter the study.

2. At least 1 measurable tumour lesion according to the RECIST version 1.0
3. ECOG 0 or 1 (ECOG 2 possible if agreed by investigator and sponsor for patients in the RP2D-enriched population cohort or ALK-negative NSCLC)
4. Able to receive at least 2 cycles of treatment (investigator's opinion)
5. Adequate organ (bone marrow, hepatic and renal) function (defined as: AST and ALT ≤2.5 x ULN), or AST and ALT ≤5 x ULN if liver function abnormalities were due to underlying malignancy, Total

serum bilirubin ≤1.5 x ULN (except for patients with documented Gilbert's syndrome), ANC ≥1500/microL, Platelets ≥100,000/microL, Hemoglobin ≥9.0 g/dL, Serum creatinine ≤2.0 x ULN.)

6. - Resolution of all acute toxic effects of prior therapy or surgical procedures to Grade ≤1 (except alopecia).

7. - Signed and dated informed consent document (Disease assessment at baseline was to include imaging of the chest, abdomen, and pelvis; brain and bone scans were to be performed if disease at these sites was suspected).

Key exclusion criteria

Included major surgery, radiation therapy, or systemic anticancer therapy within 4 weeks, forbidden prior or concomitant medications (see thereafter), brain metastases, spinal cord compression, carcinomatous meningitis, or leptomeningeal disease (unless appropriately treated and neurologically stable for at least 4 weeks),

- any of the following within the 12 months: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, congestive heart failure, or cerebrovascular accident including transient ischemic attack , pulmonary embolus within 6 months.

- ongoing cardiac dysrhythmias of National Cancer Institute (NCI) CTCAE Version 3.0 Grade ≥2, uncontrolled atrial fibrillation of any grade, or QT interval, corrected (QTc) interval >470 msec.

- uncontrolled hypertension (>150/100 mm Hg despite optimal medical therapy), known (HIV) infection, patients with known interstitial fibrosis or interstitial lung disease.

Treatments

Treatment allocated

Crizotinib 250 mg was to be administered orally BID in continuous 4-week cycles. Doses were to be taken approximately 12 hours apart and at approximately the same times each day.

A substudy evaluated crizotinib taken with or without food.

A 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.

Duration /Discontinuation

Crizotinib was to be continued until the occurrence of PD or clinical deterioration, unacceptable toxicity that did not improve with dosing interruption, dose reduction, and/or standard medical therapy, patient's withdrawal of consent, investigator's determination that it was in the patient's best interest to discontinue therapy, or initiation of treatment with another anticancer therapy.

Crizotinib treatment could be continued beyond RECIST-defined PD if, in the opinion of the investigator, the benefit/risk assessment justified continuation of treatment.

Interruption

Dosing interruption with or without dose reduction (by 1 or 2 dose levels) was allowed for treatment-related toxicity. Crizotinib treatment could be interrupted to allow surgery and/or palliative radiation therapy to localized sites of disease progression.

Authorised Concomitant medications

At screening, all concomitant medication had to be approved by the sponsor.

Supportive care (such as analgesics, antiemetics, antidiarrheals, and hematopoietic growth factors) was to be administered at the discretion of the treating physician.

Palliative radiotherapy and surgery were allowed.

Unauthorised Concomitant medications

- Other anticancer treatments were not permitted during the study (except palliative radiotherapy and surgery)

- Concurrent use of potent CYP 3A inhibitors (including, but not limited to ketoconazole, itraconazole, miconazole, clarithromycin, erythromycin, ritonavir, indinavir, nelfinavir, saquinavir, amprenavir, delavirdine, nefazodone, diltiazem, verapamil, and grapefruit juice)was not allowed for 7 days prior to the first dose of crizotinib and for the duration of crizotinib treatment.

- Concurrent use of potent CYP 3A inducers (including, but not limited to carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, tipranavir, ritonavir, and St John's Wort) was not allowed for 12 days prior to the first dose of crizotinib and for the duration of crizotinib treatment.

- Concurrent use of drugs that were CYP3A4 substrates with narrow therapeutic indices (including, but not limited to pimozide, aripiprazole, triazolam, ergotamine, and halofantrine)

Objectives

The objectives of the study were:

1. Determine the safety profile of crizotinib including identification of dose-limiting toxicity (DLT) and maximum tolerated dose (MTD);

2. Determine the recommended Phase 2 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;

6. Document any evidence of antitumor activity of crizotinib.

Outcomes/endpoints

The evaluation of antitumor efficacy for ALK-positive advanced NSCLC was based on objective tumour response according to RECIST (version 1.0).

The primary efficacy endpoint in this cohort was ORR: ORR was defined as the percent of patients in the Response Evaluable (RE) population achieving a confirmed CR or confirmed PR according to RECIST.

Other efficacy endpoints included: time to response (TTR), duration of response (DR), disease control rate (DCR), progression free survival (PFS), and overall survival (OS).

The primary analyses of tumour response used the investigator's recorded measurements and assessments for target, non target, and new lesions to programmatically evaluate response using rules based on RECIST (called "investigator assessment").

The secondary analysis of tumour response was based on an independent radiology review (IRR) ("independent assessment") as available scans were also retrospectively reviewed by an independent radiology laboratory. Overall response evaluations were also noted by the investigator ("investigator-noted assessment").

Tumour Evaluations

Disease assessment at baseline (screening) was to include a CT or MRI scan of the chest, abdomen, and pelvis; brain and bone scans were to be performed if disease at these sites was suspected.

Scans were to be repeated at all sites of known disease every 2 cycles (i.e., every 8 weeks unless treatment delayed), whenever disease progression was suspected, and at the end of or withdrawal from study treatment. Sites where disease was not present at baseline were not required to be re-imaged on-study unless new disease was suspected. Disease responses (partial response (PR) or complete response (CR)) were to be confirmed at least 4 weeks after initial documentation of response. Brain and bone scans were repeated as appropriate or if PD was suspected. The same imaging modality was to be used throughout the study to evaluate tumour burden. Scans were to be repeated at all sites of known or suspected disease every 2 cycles (i.e., every 8 weeks unless treatment was delayed), whenever disease progression was suspected, and at the end of or withdrawal from study treatment. Response Evaluation Criteria in Solid Tumours (RECIST) version 1.0 was used to evaluate disease response and progression.

Sample size

RP2D Cohorts

Following identification of the RP2D of crizotinib, patients were enrolled to address questions in molecularly defined disease and to conduct PK, MDZ interaction, food effect, positron emission tomography (PET) imaging, and other PD markers.

At least 25 patients were planned; the number was increased as a result of the antitumor activity observed in the initial ALK-positive NSCLC patients.

A minimum of 25 to a maximum of 40 ALK-negative NSCLC patients were planned.

Randomisation

Not applicable as it was a non-comparative single-arm study.

Blinding (masking)

Not applicable as it was an open-label study.

Statistical methods

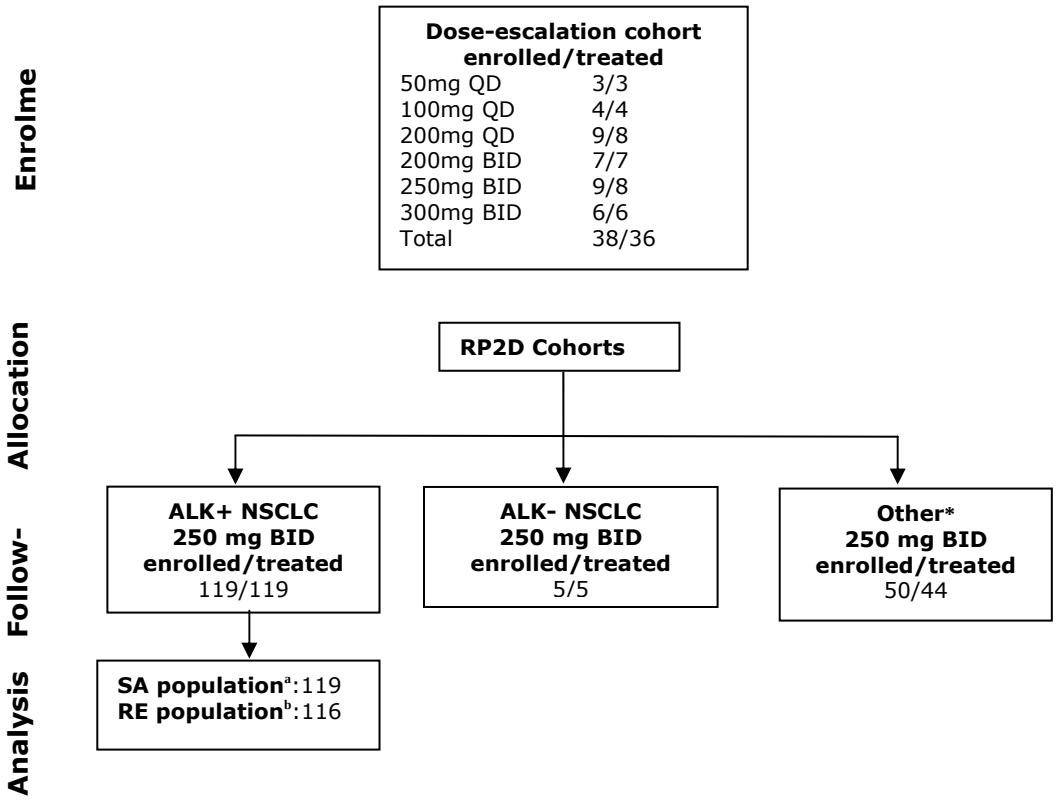
Analysis of ORR, DR, TTR, and DCR was performed for the RE population, the Safety Analysis (SA) population was used for the analysis of PFS and OS (see participant flow).

The planned statistical analyses and methods used to access the efficacy endpoints included:

- Exact method based on F-distribution with 95% confidence intervals (CI) for ORR, DCR at weeks 8 and 16

Results

Participant flow



*** ALK-dependent tumors other than NSCLC and c-Met-dependent tumors**
[a] Safety Analysis population: all enrolled patients who received at least 1 dose of crizotinib starting on cycle 1 day 1
[b] Response-Evaluable population: all patients in the SA population who had an adequate baseline disease assessment and also met 1 of the following 2 criteria: a) had at least one post-baseline disease assessment at least 6 weeks from first dose, or b) withdrew from the trial or experienced progression/death at any time on study.; 3 patients excluded because they were enrolled close to the target last patient (15 September 2010) visit and did not have post-baseline disease assessment recorded.

Recruitment

The first patient visit was on 19 April 2006; while the last patient visit date is not available considering that the study is still ongoing.

Conduct of the study

There were 15 main amendments to the study, and main amendments are as follows :

- Amendment 3 added 2 RP2D cohorts: 1 to evaluate the effect of an MDZ drug-drug interaction and 1 to evaluate clinical activity in an enriched population (patients with tumors harboring c-Met gene amplification or mutation, or anaplastic large cell lymphoma cases with ALK translocation). [18F] FLT-PET was evaluated in a small subset of patients in the RP2D-enriched cohorts (N=6) as a noninvasive measure of tumor inhibition. The fed/fasted study was added.

- Amendment 4: EML4-ALK-positive NSCLC patients were allowed to enter, QTc eligibility criteria were modified from to >470 msec for both males and females, "prior radiotherapy to >25% of bone marrow" was removed from exclusion criteria.

- Amendment 8: allowed patients with stable brain metastases

- Amendment 9, patients with pulmonary embolism within 6 months prior to starting study treatment were allowed

- Amendment 12: Increased the number of patients, added an ALK-negative NSCLC cohort, reopened the dose-escalation cohort to determine a QD MTD, widened creatinine eligibility criteria to ≤2 x ULN, replace tablets by capsules , added a screening ophthalmology examination and follow-up as clinically indicated was, treatment allowed without regard to meals after Cycle 2 Day 1, added patients with tumors having an ROS gene translocation to the RP2D-enriched cohort.

- Amendment 13: excluded only uncontrolled atrial fibrillation criteria, removed coumadin dosing restriction, modified PK sampling time points

- Amendment 14: modified survival monitoring period, removed food restriction criteria, added evaluation of active metabolites

- Amendment 15: added safety monitoring for pneumonitis, excluded patients with interstitial fibrosis or interstitial lung disease, added treatment guidelines of selected crizotinib-related AEs.Baseline data

Baseline data

Table 7 Demographic and disease characteristics for previously-treated ALK-positive NSCLC patients

Characteristics	**N=125**
Sex, n (%)	
Male	63 (50)
Female	62 (50)
Age (years), n (%)	
Median (range)	51 (21-79)
<65 years	107 (86)
≥65 years	18 (14)
Race, n (%)	
White	76 (61)
Black	5 (4)
Asian	37 (30)
Other	7 (6)
Smoking status, n (%)	
Never smoked	90 (72)
Former smoker	34 (27)
Current smoker	1 (1)
Disease Stage	
Locally advanced	7 (6)
Metastatic	118 (94)
Histological classification	
Adenocarcinoma	122 (98)
Large cell carcinoma	1 (1)
Squamous cell carcinoma	1 (1)
Adenosquamous carcinoma	0 (0)
Other	1 (1)
ECOG PS at baseline, n (%)	
0	40 (32)
1	69 (55)
2 – 3[a]	16 (13)
Prior Radiation Therapy	
No	51 (41)
Yes	74 (59)
Not Reported	0 (0)
Prior Systemic Therapy for Advanced Disease	
Number of Advanced/Metastatic Regimens	
0	0 (0)
1	47 (38)
2	31 (25)
≥3	47 (38)

[a] Includes 1 patient with an ECOG PS of 1 at screening but was 3 at baseline

Table 8 Overall summary of diagnostic ALK marker testing

	ALK-Positive NSCLC 250 mg BID (N=119)			
	Positive n (%)	Negative n (%)	Uninformative n (%)	Total n (%)
CTA tested	118 (99.2)	0	1 (0.8)	119 (100)
MGH CTA	55 (46.2)	0	0	55 (46.2)
Non-MGH CTA	63 (52.9)	0	1 (0.8)	64 (53.8)
Retested by MGH CTA[a]	41 (64.1)	1 (1.6)	3 (4.7)	45 (70.3)

Source: Table 13.12.1
Abbreviations: CTA=Clinical Trial Assay, n=number of patients; MGH=Massachusetts General Hospital; CRF=Case Report Form; ALK=anaplastic lymphoma kinase; BID=twice daily; N=number of patients; NSCLC=non-small cell lung cancer
Non-MGH is based on the CTA-local and other test collected from the CRF.
Note: MGH results for 5 patients were reported directly by the laboratory (Appendix B13.12.2) rather than on the CRF.
[a]Includes the number of patients tested by non-MGH CTA that were retested by MGH CTA (% is based on number of patients with non-MGH CTA of any result).

Numbers analysed

The SA population consisted of: 125 patients of the ALK-positive pre-treated NSCLC cohort, the 35 patients of the ALK-negative NSCLC cohort and 48 out of 63 patients of the RP2D Other cohort assigned to treatment and treated.

Assessment of PFS and OS for the ALK-positive pre-treated NSCLC cohort was performed on the SA population.

The RE population consisted of: 121 patients out of the 125 patients of the ALK-positive NSCLC cohort (4 patients were excluded as they did not meet the Response-Evaluable criteria). The Response-Evaluable population is defined as all patients in the Safety Analysis dataset who had an adequate baseline disease assessment and also met 1 of the following 2 criteria: a) had at least one post-baseline disease assessment at least 6 weeks from first dose, or b) withdrew from the trial or experienced progression/death at any time on study.

Assessment of ORR, DR, TTR for the ALK-positive pre-treated NSCLC cohort were performed on the RE population.

Outcomes and estimation

At the time of the initial database snapshot for this application, 119 ALK-positive NSCLC patients were included in the SA population (updated to 125). Patients with ALK positive NSCLC were evenly distributed with regard to sex (50% female), young (mean/median age of 51 years, 21-79, 86% <65 years), mostly White (61%), and included 30% Asian, and were mainly (99%) never or only former smoking (72% never smokers, 27% ex-smokers). Most of the patients had metastatic disease at baseline and had a primary diagnosis of NSCLC with an histology of mostly adenocarcinoma (122/125, 98%) and all had an ECOG performance status of mainly 0 or 1 (87%). Most (70%) of these patients were previously pre-treated and most of them had received ≥2 prior systemic treatment regimens for metastatic disease.

ORR:

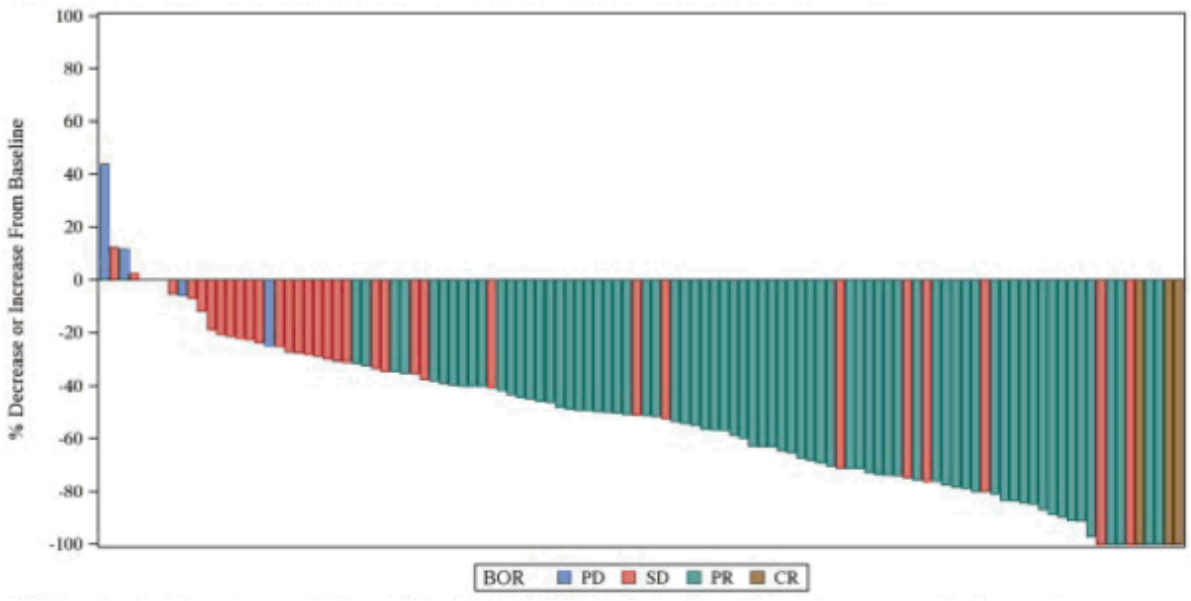
The (initial database snapshot) ORRs from prior first-line and second-line for these patients of 16.3% and 9.7%, respectively, were similar to those reported in the literature in unselected advanced NSCLC patients.

Of the 121 ALK-positive patients in the RE population treated with crizotinib 250 mg BID, 3 patients had confirmed CRs, and 70 patients had confirmed PRs, for an investigator-assessed ORR of 60.3% (95% CI: 51.0%, 69.1%). Best overall response in patients included in the RE population and best change in target lesions are provided below.

Table 9 Objective response related endpoints – ALK positive NSCLC (Response-evaluable population)

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

[a] Early death was death within 42 days (6 weeks) from first dose of crizotinib
[b] Indeterminate = patients having available on-study scans that could not be evaluated or patients who discontinued prior to obtaining adequate scans to evaluate response
Abbreviations: ALK = Anaplastic lymphoma kinase; CI = Confidence interval; CR = Complete response; CSR = Clinical Study Report; DR = Duration of response (a descriptive statistic); N/n = Number of patients; NSCLC = Non-small cell lung cancer; ORR = Objective response rate; PD = Progressive disease; PR = Partial response; RE = Response evaluable; RP2D = Recommended Phase 2 dose; SD = Stable disease; TTR = Time to tumor response



N=112 (Response Evaluable, excluding patients with early death, indeterminate response, and non-measurable disease). One additional patient (10061087) was excluded due to missing assessments for one or more target lesions after baseline.
Abbreviations: ALK = Anaplastic lymphoma kinase; BOR = Best Overall Response, CR = Complete response, NSCLC = Non-small cell lung cancer; PD = Progressive disease, PR = Partial response, RP2D = Recommended Phase 2 dose; SD = Stable disease

Figure 6 Waterfall plot of best percent change in target lesions from baseline by patient based on investigator assessment (ALK-Positive NSCLC)

These responses were rapid with a median TTR of less than 8 weeks and durable with a preliminary median DR estimate of 48.1 weeks (95% CI: 35.7 weeks, 64.1 weeks).

Table 10 Time to tumour response – ALK-positive NSCLC (response-evaluable population; objective responders only)

	ALK-Positive NSCLC 250 mg BID (N=116)
Time to tumor response (weeks)	
N	71
Mean (sd)	11.2 (7.4)
Median	7.7
Range	4.3 - 39.6
Time to tumor response category (weeks), n (%)	
0 to <8	39 (54.9)
8 to <16	18 (25.4)
16 to <24	10 (14.1)
≥24	4 (5.6)

Source: Table 13.4.4.2
Abbreviations: ALK=anaplastic lymphoma kinase; NSCLC=non-small cell lung cancer; N/n=number of patients; CR=complete response; PR=partial response; BID=twice daily; sd=standard deviation
Time to tumor response was the time from the date of the first dose to the first documentation of objective tumor response (CR or PR) that was subsequently confirmed.

The ORR was independent of age gender, and number of prior metastatic treatment regimens. In addition, best overall response appeared to be independent of percent ALK positivity.

There was a higher ORR in Asian (82.4%) than in non-Asian patients (52.4%).

Table 11 Objective response rate by baseline characteristics – ALK positive NSCLC (response-evaluable population)

Subgroup	Objective Response Rate (N=116) % (n/N)
No. of prior metastatic treatment regimens	
0	80.0 (12/15)
1	57.1 (16/28)
2	61.9 (13/21)
3	59.1 (13/22)
>3	56.7 (17/30)
ECOG Performance status	
0	53.8 (21/39)
1	62.9 (39/62)
2	78.6 (11/14)
3	0 (0/1)
Age	
<65 years	60.0 (60/100)
≥65 years	68.8 (11/16)
Gender	
Male	61.0 (36/59)
Female	61.4 (35/57)
Race	
Asians	82.4 (28/34)
Non-Asians	52.4 (43/82)

Source: Tables 13.4.1.2, 13.4.1.3, 13.4.1.4, 13.4.1.5, 13.4.1.6.1, and 13.4.1.6.2
Abbreviations: ECOG=Eastern Cooperative Oncology Group; n/N=number of patients; ALK=anaplastic lymphoma kinase; NSCLC=non-small cell cancer; No.=number

These results on ORR were even higher in the patients' subgroup that was retested by a central lab MGH CTA especially when compared with patients not retested: ORR was 63.6% (95% CI: 53.4%, 73.1%) in the retested MGH CTA subgroup vs. 47.1% (95% CI: 23.0%, 72.2%, and no CR), i.e. 16.5% difference, with however overlapping CI (small number of not retested patients).

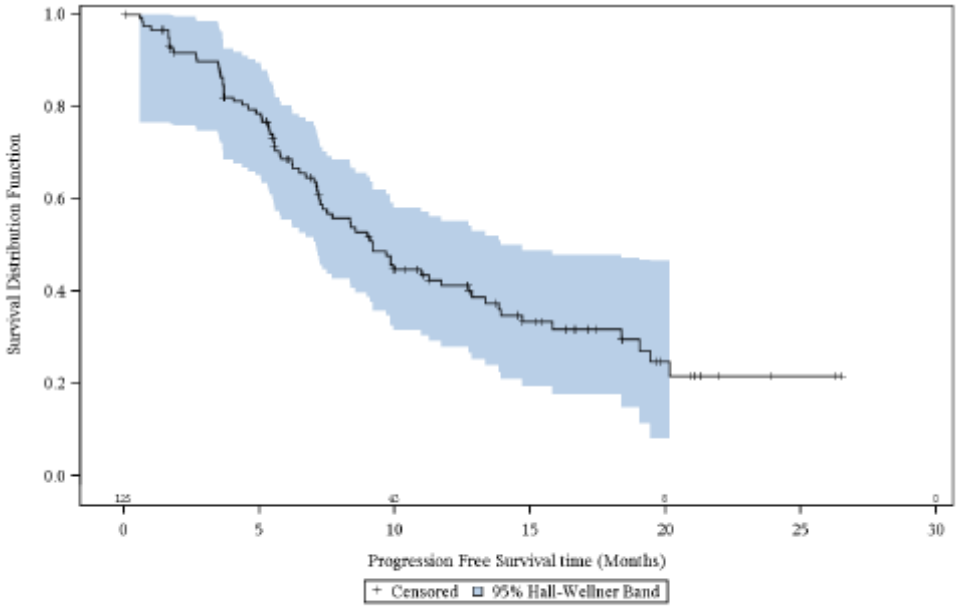
PFS:

The initial preliminary estimate of median PFS was 10.0 months (95% CI: 8.2 months, 14.7 months).

Table 12 Progression free survival – ALK-positive NSCLC (safety analysis population; objective responders only)

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

[a] Progression-free survival status of Patient 10021084 was unknown at the time of the preliminary Study 1001 CSR; this patient was reported as death (cause unknown) at the time of analysis for this Day 120 Clinical Data Addendum
[b] Includes Patient 10051009 who withdrew from treatment without PD
[c] Estimated from the Kaplan-Meier curve.
[d] Derived from the CI for the log-transformed cumulative hazard function.
[e] Based on the Brookmeyer and Crowley method.
Abbreviations: ALK=Anaplastic lymphoma kinase; CI=Confidence interval; CSR=Clinical study report; N/n=Number of patients; NSCLC=Non-small cell lung cancer; PD=Progressive disease; RP2D=Recommended Phase 2 dose



Tumor assessment is based on the Investigator Tumor Assessment
Abbreviations: ALK = Anaplastic lymphoma kinase; NSCLC = Non-small cell lung cancer; RP2D = Recommended Phase 2 dose

Figure 7 Kaplan-Meier plot of progression-free survival for previously treated ALK-positive NSCLC patients in the RP2D cohort – Safety analysis population

At the data cut-off of 2 January 2012, the updated median PFS was 9.9 months (95% CI: 7.7, 13.4) in the overall population. In the 125 previously treated patients subgroup, 74 (59.2%) events occurred with a median PFS of 9.2 months (95% CI: 7.3, 12.7).

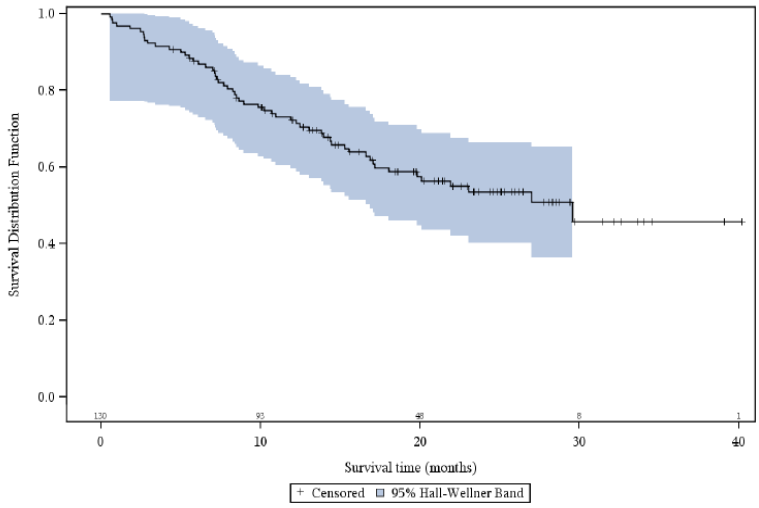
OS:

At the cut-off date of 2 January 2012, , median OS was 29.6 months (18.0, NA) with crizotinib in study 1001 to be compared with median OS (preliminary estimates) in study 1007 of 20.3 months for crizotinib vs. 22.8 months for chemotherapy respectively.

Table 13 Overall survival results for ALK-positive NSCLC patients in the RP2D cohort of study 1001 – safety analysis populations – preliminary clinical study report, Day 120 clinical data addendum, and update as of 02 January 2012.

	Preliminary CSR (N=119)	Day 120 Clinical Data Addendum Previously Treated Patients (N=125)	As of 02 January 2012 Previously Treated Patients (N=130)
Number of deaths, n (%)	23 (19.3)	43 (34.4)	55 (42.3)
Number censored, n (%)	96 (80.7)	82 (65.6)	75 (57.7)
Patient remains on follow-up	94 (79.0)	80 (64.0)	64 (49.2)
Patient no longer being followed	2 (1.7)[a]	2 (1.6)	11 (8.5)
Median OS, months (95% CI)	NR	NR	29.6 [18.0, NA]
6-month Survival Probability, % (95% CI)	90.0 (82.7, 94.4)	87.5 (80.1, 92.3)	87.7 (80.6, 92.3)
1-year Survival Probability, % (95% CI)	80.5 (70.9, 87.2)	72.3 (62.9, 79.7)	72.3 (63.5, 79.2)

[a] Includes Patient 10021084, who was lost to follow-up at the time of the preliminary Study 1001 CSR; this patient's death was subsequently reported and included in this update.
Abbreviations: ALK = Anaplastic lymphoma kinase; CI = Confidence interval; CSR = Clinical study report; N/n = Number of patients; NA = Not available; NR = Not reached; NSCLC = Non-small cell lung cancer; OS = Overall survival; RP2D = Recommended Phase 2 dose
Source: 02 Jan 2012, Table 13.4.3.1.e; Day 120 Clinical Data Addendum Appendix 1A, Table 13.4.3.1.e; Study 1001 Preliminary CSR, Table 13.4.3.1



Abbreviations: ALK = Anaplastic lymphoma kinase; NSCLC = Non-small cell lung cancer; RP2D = Recommended Phase 2 dose

Source: 02 Jan 2012, Figure 14.3.e

Figure 8 Kaplan-Meier plot of overall survival for ALK-positive NSCLC patients in the RP2D cohort of study 1001 – previously treated population – as of 02 January 2012

Summary of main study

The following table summarises the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 14 Summary of Efficacy for Trial A8081001

Title: Phase 1 Safety, Pharmacokinetic and Pharmacodynamic Study of PF-02341066, a c-Met/HGFR Selective Tyrosine Kinase Inhibitor, Administered Orally to Patients with Advanced Cancer

Study identifier	Study A8081001, EudraCT N/A ISRCT N/A		
Design	open-label, multicenter, multinational, dose escalation, safety, PD, PK, and antitumor activity study of crizotinib administered as a single oral agent to patients with advanced malignancies.		
	Duration of main phase:		Study treatment was to be continued until the occurrence of disease progression or clinical deterioration, unacceptable toxicity, patient's withdrawal of consent, or protocol noncompliance. Treatment could be continued after disease progression if the patient was considered to be deriving clinical benefit as judged by the investigator.
Hypothesis	Exploratory		
Treatments groups	ALK-positive NSCLC Cohort		Crizotinib 250 mg BID as a starting dose was to be administered orally continuously in 28-day cycles.
Endpoints and definitions	Objective Response Rate	ORR	ORR was defined as the percent of patients with a confirmed complete response (CR) or confirmed partial response (PR) according to RECIST version 1.0, relative to the response-evaluable (RE) population.
	Duration of Response	DR	Duration of Response (DR) is defined as the time from the first documentation of objective tumor response (CR or PR) that is subsequently confirmed, to the first documentation of objective tumor progression or to death on study due to any cause, whichever occurs first.
	Progression Free Survival	PFS	Progression Free Survival (PFS) is defined as the time from the date of the first dose to the date of the first documentation of objective tumor progression or death on study due to any cause, whichever occurs first.
	Overall Survival	OS	OS is defined as the time from the first dose to the date of death due to any cause.
Database lock	Initial CSR Database Snapshot: November 1, 2010 60 Day Clinical Data Addendum Database Snapshot: March 15, 2011 Day 120 clinical data addendum: June 1, 2011 OS update: January 2, 2012		

Results and Analysis

Analysis description	**Primary Analysis**	
Analysis population and time point description	Response Evaluable Population for ORR	
Descriptive statistics and estimate variability	Treatment group	Crizotinib ALK-positive NSCLC Cohort
	Number of subjects	125 (3 patients not evaluable for response)
	ORR (%)	60%
	95% CI	51%, 69%
Effect estimate per comparison	Not Applicable	
Analysis description	**Secondary Analysis**	

Analysis population and time point description	Response Evaluable (RE) Population for DCR and the subgroup of patients with a confirmed objective tumor response in RE for TTR and DR. Safety Analysis Population for PFS, OS TTR, DR, DCR, PFS, OS analyses were pre-specified.	
Descriptive statistics and estimate variability	Treatment group	Crizotinib ALK-positive NSCLC Cohort
	PFS (median)	9.2 months
	95% CI	7.3 months, 12.7 months
	Updated median OS	Median OS : 29.6 months
	95% CI	18.0 months, not available

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

Indirect comparison versus other treatment was provided (data not shown). These analyses were regarded as exploratory and to be confirmed by the results of the prospective randomized comparison (phase 3 study 1007):

The initial application included comparisons but most were based on small series and only phase III comparative studies can provide a definite answer with regard to respective efficacy of crizotinib and other therapies.

Clinical studies in special populations

Until now available studies enrolled mainly middle aged (patient population younger compared with unselected NSCLC patients), white (25-30 % Asian), otherwise essentially healthy patients with good performance status and essentially normal organ functions.

Severe renal impairment and hepatic impairment: Additional data have been requested and the Applicant agreed to provide additional data/studies in special populations including severe renal impairment, hepatic impairment and elderly (see section 2.7).

Elderly patients: Few elderly patients were included in the studies as most ALK+ NSCLC patients appear younger. Of the 125 patients in study 1001, 18 (14%) were 65 years or older. Of the 261 patients in study 1005, 30 (12%) were 65 years or older. No patients in Studies 1001 or 1005 were 85 years or older. Clinical studies did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from younger patients.

Histology: Information is available from only 29 response-evaluable patients with non-adenocarcinoma NSCLC in Studies 1001 and 1005. Partial responses were observed in 10 of these patients for an ORR of 31%, which was less than the ORRs reported in Study 1001 (60%) and Study 1005 (53%). Comparisons with ORR in this subgroup of NSCLC patients treated with standard chemotherapy are not yet available. As most of the efficacy data is obtained in patients with ALK+ NSCLC/adenocarcinoma, it was considered critical to review additional data/analyses, including comparative data from study 1007 in order to address the benefit/risk of crizotinib (PFS/OS/ORR/safety) versus chemotherapy in ALK positive NSCLC patients according to histology (adenocarcinoma versus other).

Patients with brain metastases

Pivotal study A8081001 did not require baseline brain imaging prior to patient enrolment, and therefore no data were provided from that study. The comparison of the clinical outcome according to the presence of brain metastasis has been provided only for patients enrolled in study 1005, which required baseline brain imaging.

Brain metastases were present in nearly 25% of the patients included in study A8081005.. The ORR is similar in the 61 patients with baseline brain metastases and in the 194 patients without brain involvement, but the rate of early deaths is more than twice in patients with CNS involvement at baseline: ORR of 57.4% [95% CI 44.1%, 70.0%]) versus 52.1% [95% CI: 44.8%, 59.3%] respectively, with however 6 deaths in each subgroup (6/61, 9.8% versus 6/194, 3.1% respectively).

Twenty patients in study 1005 were enrolled with asymptomatic brain metastases that were not irradiated, 17 of whom were evaluable for both brain metastasis and systemic tumour responses. Eight (47%) of these 17 patients had responses in the brain that matched or exceeded the systemic tumour responses, 2 (25%) of whom had complete brain metastasis responses. Nine (53%) of these 17 patients had systemic tumour responses that exceeded the brain metastasis responses, 8 (89%) of whom had stable brain disease for at least 3 tumour reassessments. The limited number of patients included in the analysis should be taken in consideration.

Table 15 Brain Metastasis and Systemic Responses by RECIST in Evaluable[+] Study A8081005 Patients with Asymptomatic (Non-Irradiated) Brain Metastases*

	Systemic Response n (%)				
	N=17	CR	PR	SD	PD
Brain Metastasis Response n (%)	CR	–	2 (12%)	–	–
	PR	–	1 (6%)	–	–
	SD	–	8 (47%)	4 (24%)	–
	PD	–	–	1 (6%)	1 (6%)

[+]Defined as best overall brain metastasis responses and best overall systemic responses of CR, PR, SD, or PD
[*]Excluding 3 patients (1 with indeterminate brain metastasis response, 1 without systemic disease, and 1 who died prior to the first tumor reassessment)

Supportive study(ies)

1- Study 1005

Study 1005 is an ongoing multicenter, multinational, open-label, single-arm, Phase II study of crizotinib in patients with advanced (locally advanced or metastatic) "ALK-positive NSCLC" who have received at least 1 prior chemotherapy regimen.

It evaluates the efficacy and safety of crizotinib in patients with previously treated ALK-positive advanced NSCLC and provides additional supportive efficacy data.

In the initial submission of data relevant to this study it was considered supportive as not all patients had been included and only preliminary results were available on selected efficacy criteria not including PFS. Further updates have been made available during the course of the procedure.

Table 16 Demographic and disease characteristics

Characteristics	N=261
Sex, n (%)	
Male	119 (46)
Female	142 (54)
Age (years), n (%)	
Median (range)	52 (24-82)
<65 years	231 (89)
>65 years	30 (11)
Race, n (%)	
White	152 (58)
Black	8 (3)
Asian	96 (37)
Other	5 (2)
Smoking status, n (%)	
Never smoked	176 (67)
Former smoker	73 (28)
Current smoker	12 (5)
Disease Stage	
Locally advanced	21 (8)
Metastatic	240 (92)
Histological classification	
Adenocarcinoma	242 (93)
Large cell carcinoma	4 (2)
Squamous cell carcinoma	3 (1)
Adenosquamous carcinoma	3 (1)
Other	9 (3)
ECOG PS at baseline, n (%)	
0	67 (26)
1	147 (56)
2 – 3a	47 (18)
Prior Radiation Therapy	
No	107 (41)
Yes	153 (59)
Not Reported	1 (1)
Prior Systemic Therapy for Advanced Disease	
Number of Advanced/Metastatic Regimens	
0	0 (0)
1	27 (10)
2	90 (35)
≥3	144 (55)

Crizotinib was administered 250 mg orally BID in patients with ALK-positive, mostly metastatic (94.1%) adenocarcinoma (94.1%) of the lung, and ECOG performance status of 0-3 and who had at least 1 prior systemic treatment, including mostly platinum based for advanced disease (86.8%) and to a lesser extend EGFR TKI therapies.

The Objective-Response Related endpoints are reported in the table below.

Table 17 Investigator-assessed objective response related endpoints – Study 1005

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

[a] Early death was death within 42 days (6 weeks) from first dose of crizotinib
[b] Indeterminate = patients having available on-study scans that could not be evaluated or patients who discontinued prior to obtaining adequate scans to evaluate response
[c] DR from the first Clinical Data Addendum is the median duration and range of observed values (a descriptive statistic); DR for this Day 120 Clinical Data Addendum is the Kaplan-Meier estimate.
Abbreviations: CI = Confidence interval; CR = Complete response; CSR = Clinical study report; DR = Duration of response (a descriptive statistic); DCR = Disease control rate; N/n = Number of patients; ORR = Objective response rate; PD = Progressive disease; PR = Partial response; RE = Response evaluable; SA = Safety Analysis; SD = Stable disease; TTR = Time to tumor response
Source: First Clinical Data Addendum Appendix 2, Tables 13.4.1.1, 13.4.2.1, 13.4.4.1, 13.4.4.2
Appendix 2, Tables 13.4.1.1, 13.4.2.1, 13.4.4.1, 13.4.4.2, Appendix 2A, Tables 13.4.1.1b, 13.4.2.1b, 13.4.4.1b, 13.4.4.2b

Results according to previous treatments were provided: response to crizotinib seems higher (indirect unplanned subjective comparison) than those reported to prior treatment regimens, regardless of the line of treatment and the previous agent used. In particular, the response to crizotinib seems higher to that retrospectively evaluated for prior 1st line, second line chemotherapy, single agent TKI (17.5%, 13.9%, and 3.5%, respectively), or pemetrexed and docetaxel (ORR was, however, lower for the latter with a wide CI) and seem larger than ORR obtained with prior chemotherapy. This analysis, not pre-specified and lacking of independent adjudication of response to prior treatment, must be regarded as exploratory and needs to be confirmed by the results from the prospective randomized phase 3 study (study 1007).

The median PFS was 8.5 months in both the Overall (439 pts, 28.2% PFS events occurred, 95% CI 6.2, 9.9) and in the Mature Safety population (261 pts, 41.8% PFS events occurred 95% CI 6.5, 9.9). An updated PFS of 8.1 months (95% CI 6.8, 9.7), as of 2 January 2012, was reported for the Mature Safety population (261 pts, 65.5% PFS events occurred).

The probability of survival at 12 months was estimated as 61% (95% CI: 49%, 71%).

2- <u>"top-line summary" of study 1007</u>

The Applicant provided a "top-line summary" of study 1007 (including data from visits through 30 March 2012 of an Open-label, multicenter, randomised Phase 3 efficacy and safety study of crizotinib (starting dose of 250 mg BID, same dose as in the previously submitted uncontrolled studies) vs second-line standard of care chemotherapy, pemetrexed (500 mg/m^2, on Day 1 of every cycle) or

docetaxel (75 mg/m^2, on Day 1 of every cycle), in ALK-positive, advanced NSCLC patients who received only one prior platinum-based chemotherapy regimen.

This is the first controlled trial in ALK-positive NSCLC patients.

The primary study objective was to demonstrate the superiority of crizotinib vs standard chemotherapy (pemetrexed or docetaxel) in terms of PFS, based on Independent Radiology Review (IRR). This primary objective is adequate. Comparison of ORR, OS, safety and tolerability were secondary objectives. Efficacy secondary objectives of mainly OS and to a lesser extent ORR are adequate.

Three-hundred and eighteen patients (318) were planned to be randomised 1:1 to Arm A (crizotinib) or Arm B (pemetrexed or docetaxel) with stratification by ECOG performance status, brain metastases, and prior (yes, no) EGFR TKI treatment.

Pemetrexed was the first option, unless patients had already received this drug in the context of a first-line chemotherapy or had a squamous histology. As the vast majority of ALK-positive NSCLC has a non-squamous histology (>90% of the patients in Study 1007 had adenocarcinoma), pemetrexed might in principle be more active in these patients. This is supported by published retrospective analyses, in small series of ALK-positive NSCLC patients, in which a good activity of pemetrexed was reported. In study A8081007, 58% of patients received pemetrexed and 42% docetaxel.

PFS and ORR were tested at the 1-sided 0.025 level while OS was tested at the 1-sided 0.0004 level corresponding to the number of OS events observed at the final PFS analysis. From available data, 347 patients (173 in the crizotinib arm and 174 in the chemotherapy group) were randomised, from February 2010 to February 2012, in 105 sites in 21 countries. The reason for the inclusion of these extra-patients has not been provided. The Full Analysis (FA) population is the primary set for evaluating patient characteristics / disposition and efficacy endpoints and includes all patients who were randomized (n=347, 173 to crizotinib, 174 to the chemotherapy arm (99 pemetrexed [58%] and 72 [42%] docetaxel)with study drug assignment according to the actual randomization.

Similar to the phase I-II uncontrolled studies 1001 and 1005, most patients were young (median 50 years), evenly distributed with regard to sex (56% women), never-smokers (63%) or light smokers, had an histology of adenocarcinoma (92-94%)had an ECOG 0 or 1 (92%);12% had received prior EGFR TKI.. A surprisingly quite higher proportion were Asian (45%) which should be further discussed when the CSR will be provided, as results of the previous studies had shown a much higher response rate in Asian.

With regard to histology, non-adenocarcinoma histology NSCLC was less than 8% (similar to the low rate in Studies A8081001 and A8081005) and none of the crizotinib patients had squamous cell carcinoma. A quite large proportion of patients had brain metastases (35%) at baseline. There were more cycles started (10.5 vs. only 4) and more dose reductions in the crizotinib arm. A total of 85 (49%) patients in the crizotinib arm and 28 (16%) patients in the chemotherapy arm were on treatment at the time of data cutoff. The difference in treatment duration/FU and possible cross-over make assessment of OS and safety more difficult.

Primary efficacy criteria (PFS)

According to the preliminary data presented by the Applicant, a statistically significant difference in median PFS was observed, with 7.7 (95% CI: 6.0, 8.8) and 3.0 (95% CI: 2.6, 4.3) months in crizotinib and chemotherapy arm, respectively: HR 0.487 (95% CI: 0.371, 0.638, p-value <0.0001).

This was consistent both with PFS based on investigator's assessment in study 1007 (HR : 0.416 (95% CI: 0.314, 0.552), p<0.0001) and with PFS with crizotinib in the previous uncontrolled studies (1001 and 1005).

Secondary Efficacy criteria

OS:

OS data showed no difference (nor trend) between treatment groups; OS data are not mature yet and the high rate of cross-over (62%) should be taken into account.

In Study 1007, patients progressing in the control arm were allowed to cross-over to crizotinib and were enrolled in Study 1005. Actually, at the data cut-off of this analysis, 108 patients (meaning 62% of the total patients enrolled in the control arm) crossed over to receive crizotinib in study A8081005. Therefore, OS data will be confounded by the cross-over, do not allowing a direct comparison between the two arms.

ORR:

According to the data presented by the Applicant, the ORR (assessed by IRR) was 65.3% (95%CI: 57.7%, 72.4%) for crizotinib and 19.5% (95% CI: 13.9%, 26.2%) for chemotherapy.

2.5.3. Discussion on clinical efficacy

Initial available data came from 2 single-arm/uncontrolled multicenter, multinational, open-label, ongoing phase I-II studies (study 1001 and 1005) of crizotinib in patients with advanced (locally advanced or metastatic) "ALK-positive NSCLC" (NSCLC harboring a translocation or inversion event involving the ALK gene locus) with primarily a histology of adenocarcinoma who have received at least 1 prior chemotherapy regimen (84% in 1001, , all in study 1005). Study 1001 was originally designed as a phase 1 dose escalation trial for the definition of the RP2D. The crizotinib MTD, 250 mg BID, was selected on the basis of 2 DLTs of Grade 3 fatigue in 2 out 6 patients treated at 300 mg BID dose level.

ORR, DR and PFS are now mature for both studies. Response rates and PFS are concordant between studies and durable, with an updated ORR of 60% and 53% for previously treated ALK-positive advanced NSCLC RE population in Studies A8081001 and A8081005, respectively, and updated median DRs of 48.1 weeks and 42.9 weeks, respectively.

Median PFS reported in previously treated patients is slightly different between the two studies, being longer in Study A8081001 [9.2 months (95% CI: 7.3, 12.7)] compared with Study A8081005 [8.5months (95% CI: 6.5, 9.9)] but this (small) difference seems mainly due to a larger variability in the former study rather than differences between studies.

Mature data for OS are not yet available. The 1-year survival probability is now estimated as 72% (95% CI: 63%, 80%) in study 1001 and 61% (95% CI: 49%, 71%) in study 1005. Median OS is now 29.6 months (95% CI: 18.0 months, NA) with crizotinib in study 1001. The applicant also provided selected top-line results of the randomised controlled phase III trial in pre-treated ALK-positive NSCLC (1007). According to the data presented by the Applicant, a statistically significant difference in median PFS was observed, with 7.7 (95% CI: 6.0, 8.8) and 3.0 (95% CI: 2.6, 4.3) months in crizotinib and chemotherapy arm, respectively and HR 0.487 (95% CI: 0.371, 0.638, p-value <0.0001). According to the preliminary data presented by the Applicant, the ORR (assessed by IRR) was 65.3% (95%CI: 57.7%, 72.4%) for crizotinib and 19.5% (95% CI: 13.9%, 26.2%) for chemotherapy.

The interim analysis for OS (with only 96 events, about 40% of the events required for the final analysis) did not show significant differences with a median OS of 20.3 months (95% CI: 18.1, NR) in the crizotinib arm and 22.8 (95% CI: 18.6, NR) months in the chemotherapy arm (HR 1.021 (95% CI: 0.677, 1.540), with a p-value of 0.5394). Consistent ORR and PFS has been observed with crizotinib in the phase I and II studies, supported by the preliminary results of the phase III study.

Impact of histology

Few available data (to date, very partial non comparative data provided on 32 patients only) seem to indicate a decreased benefit with crizotinib in patients with subtypes other than adenocarcinoma: ORR of 31 % for non adenocarcinoma patients; this ORR is half and outside of the 95% CI of that observed with crizotinib in the comparative study 1007: 65.3% (95%CI: 57.7%, 72.4%) for crizotinib and duration of response seems also shorter. This has been mentioned in section 4.4 and 5.1 of the SmPC. The benefit/risk of crizotinib and comparison with chemotherapy (especially pemetrexed) is unknown in these patients at present. As ALK+ was targeted and this subgroup of patients is also likely to be small in the real life and may benefit from crizotinib treatment, no mention was added in section 4.1.

Duration of treatment

With regard to duration of treatment, considering the lack of data showing a benefit from continuation upon progression, an appropriate text has been proposed in section 4.2 of the SmPC.

Effect of crizotinib on other mutations

The effect of crizotinib on other than ALK mutations is not known, and additional data have been required (PAC) but the effect on one mutation may not preclude approval on an other mutations whose efficacy has been demonstrated.

In addition, available data do not allow to definitively conclude whether or not crizotinib may cross the BBB; the absence of metastatic brain disease response does not necessarily imply the crizotinib inability to cross the BBB.

Design and conduct of clinical studies

Initial available data came from 2 single-arm/uncontrolled multicenter, multinational, open-label, ongoing phase I-II studies (study 1001 and 1005) of crizotinib in patients with advanced (locally advanced or metastatic) "ALK-positive NSCLC" (NSCLC harbouring a translocation or inversion event involving the ALK gene locus) with primarily a histology of adenocarcinoma who have received at least 1 prior chemotherapy regimen (70% in 1001, all in study 1005). The absence of direct comparative study was the most important drawback: indirect comparison with historical controls from different controlled studies in NSCLC and retrospective analyses of response to previous treatments in patients enrolled in Study 1005 were presented but of limited value.

Additional efficacy data needed in the context of a conditional MA

There is a need to provide confirmatory data (full study report) from the comparative study A8081007 and updated (OS) data from the 2 uncontrolled studies A8081001 and A8081005.

2.5.4. Conclusions on the clinical efficacy

A concordant high ORR and PFS has been observed with crizotinib in the 2 phase I/II uncontrolled studies, and are supported by the preliminary Top-line results of the phase III comparative study (1007).

These results indicate that crizotinib has a positive clinically meaningful benefit as a single agent in previously treated patients with ALK-positive advanced NSCLC.

In all studies, the ORR and PFS are high, which might be supportive to a better OS. However, the premature OS data of the phase III study do not seem to indicate a better OS for patients treated with crizotinib compared with chemotherapy. This might be due to the immaturity of the data (40% of expected events), the high cross over rate (62%, also demonstrating the need for effective therapy), or a poor safety profile.

The observed effect of crizotinib in ALK-positive NSCLC patients with a histology other than adenocarcinoma is limited, but appeared to be smaller. This has been mentioned in sections 4.4 and 5.1 of the SmPC and the applicant was recommended to provide additional data.

At present, a positive benefit seems clearly established with crizotinib in anaplastic lymphoma kinase (ALK)-positive advanced pretreated NSCLC.

The efficacy results must be confirmed by more robust data (full study report) from the direct prospective comparative study (1007), the full study report of the 2 uncontrolled studies (including updated OS data), additional information on efficacy patients with histologies other than adenocarcinomas, .

The Applicant should also address some additional outstanding issues with regard to efficacy.

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

- To submit the CSR of study A8081007 including a detailed analysis of outcome on post-progression treatments in Study 1007 as well as efficacy and baseline data according to race (Caucasian/Asian) by treatment groups

- To submit an update of OS data for both studies (1001 and 1005) when the final study report of each study is available. To compare and explain potential differences in OS for crizotinib in the 3 studies (1001 and 1005 and 1007).

The CHMP considers the following measures necessary to address issues related to efficacy:

- To submit additional data/analyses, including comparative data from study A8081007 in order to address the benefit/risk of crizotinib (PFS/OS/ORR/safety) versus chemotherapy in ALK-positive NSCLC patients according to histology (adenocarcinoma versus other).

2.6. Clinical safety

Safety analysis focused on data from two ongoing open-label, single-arm studies: pivotal study (study A8081001) and supportive study (A8081005). All patients who received at least one dose of crizotinib have been included in the studied safety population. These two phase 2 studies (1001 and 1005) were the single-arm studies without any comparative data.

Top-line preliminary safety comparative results from the open-label, multicenter, randomised phase 3 trial (A8081007) were made available during the review procedure.

Safety experience from 6 Phase 1 biopharmaceutical and Clinical Pharmacology studies in healthy volunteer subjects receiving 1 to 4 single doses of crizotinib was briefly mentioned in the dossier.

Only data on SAEs and deaths for patients in the crizotinib arm from the ongoing first-line phase 3 study, A8081014 have been included in the submitted documentation.

Patient exposure

A total of 588 patients with ALK-positive advanced NSCLC received crizotinib 250 mg orally twice daily (BID) and were included in the safety analysis population dataset: 149 patients in study 1001 and 439 patients in study 1005, comprising the target population receiving the recommended dosing regimen for crizotinib treatment.

The baseline demographics were very similar between Study 1001 and Study 1005.

Both studies had an even distribution of men and women, most patients were relatively young with median age in their early 50's, and most patients had never smoked, although approximately one-quarter were former smokers and a few were current smokers. The majority of patients were white, and nearly one-third were Asian, primarily Korean or Japanese.

Table 18 Disease characteristics for ALK-positive NSCLC patients in RP2D cohort of study 1001 – All patients and previously treated patients – Safety analysis populations

	Previously Treated Patients N=125	All Patients N=149
Measurable Disease Present		
Yes	123 (98.4)	147 (98.7)
No	2 (1.6)	2 (1.3)
Disease Stage		
Locally advanced	7 (5.6) [a]	9 (6.0) [a]
Metastatic	118 (94.4)	140 (94.0)
Histological Classification		
Adenocarcinoma	122 (97.6)	144 (96.6)
Squamous cell carcinoma	1 (0.8)	2 (1.3)
Large cell carcinoma	1 (0.8)	1 (0.7)
Other	1 (0.8)	2 (1.3)
ECOG PS at baseline, n (%)		
0	40 (32.0)	56 (37.6)
1	69 (55.2)	75 (50.3)
2	15 (12.0)	17 (11.4)
3	1 (0.8) [b]	1 (0.7) [b]

[a] Includes Patient 10071062 reported as NSCLC Stage IIB at baseline at the time of analysis for this Day 120 Clinical Data Addendum, this has since been changed to Stage IIIA.
[b] Patient 10021042 had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 1 at screening and thus met the protocol inclusion criteria.
Abbreviations: ALK = Anaplastic lymphoma kinase; ECOG = Eastern Cooperative Oncology Group; N/n = Number of patients; NSCLC = Non-small cell lung cancer; PS = Performance status; RP2D = Recommended Phase 2 dose

Table 19 Disease characteristics of patients in study 1005 – All patients and mature safety population – Safety analysis populations

Characteristic	Mature Safety Population N=261	All Patients N=439
Measurable Disease Present		
Yes	260 (99.6)	430 (97.9)
No	1 (0.4)	9 (2.1)
Disease Stage		
Locally advanced	21 (8.0)	39 (8.9)
Metastatic	240 (92.0)	400 (91.1)
Histological Classification		
Adenocarcinoma	242 (92.7)	402 (91.6)
Squamous cell carcinoma	3 (1.1)	7 (1.6)
Large cell carcinoma	4 (1.5)	5 (1.1)
Adenosquamous carcinoma	3 (1.1)	6 (1.4)
Other	9 (3.4)	19 (4.3)
ECOG PS at baseline, n (%)		
0	67 (25.7)	116 (26.4)
1	147 (56.3)	250 (56.9)
2	43 (16.5)	62 (14.1)
3	4 (1.5)	11 (2.5)

Abbreviations: ECOG = Eastern Cooperative Oncology Group; N/n = Number of patients; PS = Performance status

The median duration of follow-up for the 149 ALK-positive NSCLC patients in Study 1001 was 16.6 months ([95% confidence interval (CI): 15.0 months, 18.6 months]. The median duration of treatment increased from 31.9 weeks in the preliminary CSR to 43.1 weeks for 149 ALK positive NSCLC patients

in this Day 120 Clinical Data Addendum; 65 out of the 149 patients (43,6%) were treated with crizotinib for more than 1 year.

The median duration of follow-up for the 439 patients in Study 1005 was 4.7 months ([95% CI: 4.2 months, 5.2 months]. The median duration of treatment decreased from 22.3 weeks in the first clinical data addendum (136 patients) to 15.7 weeks in this Day 120 Clinical Data Addendum (439 patients). However, considering the mature safety population (261 patients), median duration of treatment increased from 22.3 (0.9-53.1) weeks to 24.6 (0.9-68.4) weeks.

Adverse events

In Study 1001 and in Study 1005, the most commonly reported treatment-emergent all causality AEs were Nausea, Diarrhoea, Vomiting, Constipation, and Visual impairment.

Other events reported at frequencies ≥ 20% in one or both studies included Oedema peripheral, Dizziness, Fatigue, Rash, and Decreased appetite. In both Studies 1001 and 1005, hepatic events were reported frequently, and included Alanine aminotransferase (ALT) increased (17.4% and 13,2%, respectively) and Aspartate aminotransferase (AST) increased (14.1% and 9.3%, respectively). Four patients possibly met Hy's Law case criteria for potential drug-induced liver injury.

In study 1001, a total of 147 of the 149 evaluable patients with ALK-positive NSCLC cohort (98,7%), had at least 1 treatment-emergent all causality AE, and 144 patients (96.6%) had at least 1 treatment related AE. According to the provided data, a total of 58 patients (38.9%) experienced SAEs.

All causality Grade 3-4 AEs were reported in 77 (51.7%) patients and Grade 5 AEs in 23 (15.4%) patients. 19 patients (12.8%) had AEs leading to discontinuation of study treatment, 62 (41.6%) patients had AEs associated with a temporary discontinuation and 11 patients (7.4%) had dose reduction due to AEs.

Vision disorders including photopsia, diplopia, blurred vision, visual impairment and vitreous floaters occurred in 103 patients (69.1%). Majority of adverse events were assessed as treatment related by the investigators.

ALT increased was observed in 26 patients (17.4%). In addition, liver dysfunction could be suspected in patients with AST increased (21 patients-14.1%) or Alkaline phosphatase increased (11-7.4%) or blood bilirubine increased (1–0,7%), liver function test anormal (1–0,7%) or transaminases increased (2–1,3%).

Other common treatment-emergent all-causality AEs were anaemia, bradycardia, neutropenia, thrombocytopenia, seizure, edema, fatigue, neuropathy, and esophageal-related disorder.

In study 1005, 419 (95.4%) of 439 patients experienced a total of 3742 AEs, of which 2186 were considered treatment-related.

All causality Grade 3-4 AEs were reported in 152 (34.6%) patients and Grade 5 AEs in 51 (11.6%) patients. Fifty three (53) patients (12.1%) had AEs leading to discontinuation of study treatment, 110 (25.1%) patients had AEs associated with a temporary discontinuation and 43 patients (9.8%) had dose reduction due to AEs.

The most frequently observed TEAEs were as follows:

- Gastrointestinal disorders (356 – 81.1%) including nausea (217), vomiting (193) diarrhoea (173), constipation (145);

- Eye disorders (256 – 58.3%) including visual impairment (162), photopsia (41) vision blurred (25), vitreous floaters (14), visual acuity reduced (2);

- Hepatic disorders have been reported, including ALT increased (58 – 13.2%), AST increased (41 – 9.3%), alkaline phosphatase increased (19 – 4.3%),hepatic function abnormal (3 – 0.7%), , cytolytic hepatitis (2 – 0.5%), , GGT increased (2 – 0.5%), hepatic enzyme increased (2 – 0.5%), liver function test abnormal (2 – 0.5%), hepatotoxicity (1 – 0.2%), hyperbilirubinemia (1 – 0.2%), liver disorder (1 – 0.2%), blood bilirubin increased (1 – 0.2%), . Four additional cases of liver disorders from study 1005 have been reported after the data cut-off of 01 June 2011. Three of them are potential Hy's law cases: 30-old male patient (2011266525), 58-old male patient (2011288949), 57-old male patient (2011300243) and one case of liver failure in 40-old female patient (2011267823). Two patients died.

- Peripheral neuropathy (12), sensory (14), motor (2);

- Cardiac disorders including sinus bradycardia (6), QT prolonged (8), syncope (8), palpitation (2), tachycardia (5), supraventricular tachycardia (1), bradycardia (5), atrial fibrillation (1) and AV block (1) each).

Overall, in both the ALK-positive NSCLC cohort of Study 1001 and Study 1005, the AE profile of crizotinib was characterised by events that were primarily gastrointestinal, visual, neurological, constitutional, and hepatic in nature.

The table below (Table 20) summarises the adverse drug reactions considered associated with crizotinib in the 386 patients with previously treated ALK-positive NSCLC:

Table 20 Adverse drug reactions considered associated with crizotinib use for ALK-positive NSCLC previously treated patient populations as 01 June 2011 Data cut-off – Studies 1001 and 1005

Adverse Reaction, n (%)	**Frequency[b]**	**(N=386)**	
		All Grades	Grade 3/4
Blood and lymphatic system disorders			
Neutropenia	Very Common	39 (10)	26 (7)
Leukopenia	Common	17 (4)	2 (<1)
Lymphopenia	Common	9 (2)	8 (2)
Anemia	Common	6 (2)	1 (<1)
Metabolism and nutrition disorders			
Decreased Appetite	Very Common	73 (19)	0 (0)
Hypophosphatemia	Common	10 (3)	6 (2)
Nervous system disorders			
Neuropathy[c]	Very Common	44 (11)	2 (<1)
Dizziness	Very Common	59 (15)	0 (0)
Dysgeusia	Very Common	51 (13)	0 (0)
Eye disorders			
Vision Disorder[c]	Very Common	225 (58)	1 (<1)
Cardiac disorders			
Bradycardia[c]	Common	14 (4)	0 (0)
Respiratory, thoracic and mediastinal disorders			
Pneumonitis	Common	4 (1)	4 (1)[d]
Gastrointestinal disorders			
Vomiting	Very Common	157 (41)	3 (<1)
Nausea	Very Common	208 (54)	2 (<1)
Diarrhoea	Very Common	160 (42)	2 (<1)
Constipation	Very Common	111 (29)	0 (0)
Oesophageal-related disorder[c]	Common	24 (6)	0 (0)
Dyspepsia	Common	19 (5)	0 (0)
Skin and subcutaneous tissue disorders			
Rash	Common	35 (9)	0 (0)
Renal and urinary disorders			
Renal cyst[e]	Uncommon	2 (<1)	1 (<1)
General disorders and administration site conditions			

Fatigue[c]	Very Common	86 (22)	6 (2)
Oedema[c]	Very Common	104 (27)	0 (0)
Investigations			
Alanine aminotransferase increased	Very Common	53 (14)	20 (5)
Electrocardiogram QT prolonged	Common	4 (1)	2 (<1)
Aspartate aminotransferase increased	Common	38 (10)	7 (2)
Blood alkaline phosphatase increased	Common	9 (2)	0 (0)

[a] Study A used NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0, and Study B used NCI CTCAE version 4.0

[b] Based on highest frequency between Study A and Study B

[c] Includes cases reported within the clustered terms: oedema (oedema, oedema peripheral), oesophageal-related disorder (gastroesophageal reflux disease, odynophagia, oesophageal pain, oesophageal ulcer, oesophagitis, reflux oesophagitis, dysphagia, epigastric discomfort), neuropathy (neuralgia, neuropathy peripheral, paraesthesia, peripheral motor neuropathy, peripheral sensorimotor neuropathy, sensory disturbance), vision disorder (diplopia, photopsia, vision blurred, visual impairment, vitreous floaters), bradycardia (bradycardia, sinus bradycardia), and fatigue (asthenia, fatigue)

[d] Includes 1 Grade 5 event

[e] Includes complex renal cysts

Preliminary results of study 1007 (full study report not yet available)

In study 1007, 172 patient (100%) treated in the crizotinib arm experienced an AE, of which 164 patients (95.3%) experienced a treatment related AE, compared to respectively 168 of the 171 patients (98.2%) and 151 (88.3%) in the chemotherapy arm.

All causality AEs or Treatment related AEs preferred term or clustered term with a frequency of at least 2-fold greater in the crizotinib arm group compared with "chemotherapy" group included Gastrointestinal disorder (Diarrhoea, Vomiting, Dysgueusia), Vision disorder, Hepatic disorders (elevated transaminase, Hepatotoxicity), Respiratory disorders (Pulmonary embolism, Interstitial lung disease) and Bradycardia. It has to be noted that, the only All causality AEs PT reported with a frequency 2-fold greater in the chemotherapy arm compared with crizotinib was Alopecia and for the Treatment related AEs were Rash, Alopecia and Dyspnoea.

Frequency and grading of the AEs reported (Crizotinib vs Chemotherapy):

- All grade SAEs (37.2% vs 23.4%);

- Grade 3 /4 SAEs (19.8% vs 17%)

- all causality AE (100% vs 98.2%);

- treatment related AEs (95.3% vs 88.3%);

- all causality grade 3-4 AE (44.2% vs 42.1%)

- treatment related Grade 3/4 AEs (31.4% vs 31%);

- Treatment related SAEs were more frequently reported in the chemotherapy arm (14%) compared to crizotinib arm (11.6%). Given that the study 1007 was open-label study, it is questionable whether there was bias in the treatment-related consideration of the adverse events.

- Permanent discontinuation from treatment: more patients in the crizotinib arm (30;17%) had AEs associated with permanent discontinuation from treatment (23; 14%) than in the chemotherapy arm.

More patients in the crizotinib arm had AEs associated with permanent discontinuation from the treatment ((30 (17%) vs 23 (14%) in the chemotherapy arm). It is surprising that less discontinuations were considered related to crizotinib than to chemotherapy, 11 (6%) and 17 (10%), respectively. This could be due to bias, taking into account that study 1007 was an open label study.

Overall, the AE profile of crizotinib compare to the AE profile of Chemotherapy does not seem similar:

in terms of frequency and grading: more all causality and treatment related AEs and more all causality grade 3-4 AE and treatment related Grade 3/4 AEs have been reported with crizotinib, compare to chemotherapy. More patients with crizotinib discontinued the treatment due to AEs.

In terms of nature: AEs related to crizotinib as Bradycardia, QT prolongations, Syncope, ILD, Pulmonary Embolism, Hepatotoxicity, are unforeseeable and may be life threatening or fatal, whereas, AEs related to chemotherapy, mainly haematotoxicity, which may also be life threatening or fatal, seems more easy to monitor for the physician.

- From the available data, All causality AEs of elevated transaminases were more frequently reported in the crizotinib arm compared with the chemotherapy arm: 66 (38.4 %) versus 25 (14.6 %). Treatment related AES of elevated transaminases were more frequently reported in the crizotinib arm: 62 (36 %) versus 23 (13.5 %) respectively and treatment related Grade 3/4 SAES of elevated transaminases occurred in 2 patients with crizotinib (non in the chemotherapy arm). Three patients had permanent discontinuation from crizotinib due to 5 hepatic events (hepatic failure (1 G3), ALT increase (2 G3) and AST increase (2 G3)).

There were 6 events of Grade 4 increases in ALT and/or AST with crizotinib versus none in the chemotherapy arm; an additional fatal case of hepatic failure (Hy's Law case) considered as related to crizotinib has been reported after the date of data cut-off of the preliminary Topline Summary report.

AEs in Pharmacological healthy volunteer studies

There were 6 studies involving healthy volunteers in the crizotinib clinical development program (Studies A8081008, A8081009, A8081010, A8081011, A8081015, and A8081016). In these studies, 110 subjects were exposed to 1-4 single oral (150 or 250 mg) doses of crizotinib with at least a 14-day washout period between doses, or to 1 single intravenous (50 mg) dose crizotinib. The most common adverse events reported in healthy volunteer studies were Nausea and Diarrhoea, the majority of which were mild in severity. One subject in Study A8081011 experienced an AE of liver enzyme elevation without total bilirubin elevation and was discontinued from the study. This event was considered moderate in intensity and resolved 21 days after the last dose of crizotinib. There were no other permanent discontinuations due to an AE in these studies, and there were no SAEs or deaths reported.

Serious adverse event/deaths/other significant events

Deaths

The updated 30-day and 60-day all-cause mortality in the 588 patients in the all ALK-positive NSCLC across Studies 1001 and 1005 (Day 120 clinical data addendum) were 3.6% and 5.1% respectively. Seventy-one (71) of the 588 patients (12.1%) have died while on study (within 28 days of the last dose of study drug). For most of the deaths, the underlying cause was the disease under study. In Study 1001, one death was attributed to study drug toxicity (disseminated intravascular coagulation). In Study 1005, 3 deaths were considered treatment-related. One death was due to pulmonary embolism, 1 death of unknown cause and 1 death due to pneumonitis.

Ten (10) crizotinib treated patients who died in Study 1007 had SAEs with a fatal outcome. Of the 10 deaths reported, 3 were considered related to study drug: Cardiac arrest and Respiratory failure, Interstitial lung disease, and Pneumonitis.

Among the 63 patients in the RP2D cohort with tumours other than molecularly defined ALK-positive or ALK-negative NSCLC with data available for the updated report, there were 33 deaths (14 within 28

days of the last dose of study drug); 27 were considered due to disease progression, and none were considered related to crizotinib treatment.

For study 1007, a total of 96 deaths had been reported as of the date of data cutoff.

•32 Grade 5 AEs (25 in the crizotinib arm and 7 in the chemotherapy arm) and 32 deaths (23 in the crizotinib arm and 9 in the chemotherapy arm) occurred respectively on study and in the survival follow up in study 1007;

•18 Grade 5 AEs and 12 deaths occurred respectively on study and in the survival follow up in patients who crossed over from the chemotherapy arm to study 1005, to receive crizotinib;

•1 death occurred in a patients enrolled by mistake in the crizotinib arm and reported during survival follow up on study 1005

•1 Grade 5 AE (suicide) reported before treatment started in the chemotherapy arm.

The rate of death reported at the database snapshot was similar in both arms (a total of 49 (28.3%) and 47 (27%) deaths, respectively, had been reported in the crizotinib, and the chemotherapy arms) and mainly related to the underlying disease in similar proportions: (40/49: 81.6%) for crizotinib (15/17: 88.2%) for chemotherapy and (26/30: 86.6%) for chemotherapy with crossover to study 1005.

One death in the crizotinib arm was reported as related to study treatment toxicity (ILD) compared to none in the chemotherapy arm. . Considering the chemotherapy treatment, all the study treatment toxicity events were observed only in 2 patients after crossover to crizotinib (pneumonitis (1) and a non informative data as the cause of death reported as "docetaxel and PF1066 [crizotinib]").

Of note, in the previous results of study 1007 submitted: 3 deaths (2.3%) were considered related to crizotinib (Arrhythmia, Interstitial lung disease, pneumonitis), compared to one death (0.6%) considered related to chemotherapy (Sepsis). In addition, 2 deaths in the crizotinib arm (Death and Sudden death), initially considered non drug related are being re-evaluated for possible treatment relatedness. and an additional case of fatal heptotoxicity related to crizotinib was received at the French agency after date of data-cut-off of the top line summary. However, no difference is observed in global deaths reporting between crizotinib and chemotherapy arms.

Other Serious Adverse Events

In Study 1001, a total of 58 (38.9%) ALK-positive RP2D NSCLC patients experienced SAEs, of these, 9 (6.0%) had 10 SAEs considered related to crizotinib treatment.

In Study 1005, 126 (28.7%) patients experienced SAEs, of these, 29 patients (6.6%) had SAEs considered related to crizotinib.

In Study 1007, of the 172 patients treated with crizotinib, 64 (37.2%) had SAEs of whom, 20 (11.6%) had treatment related SAEs according to preliminary review by the Applicant.

Treatment related SAEs, were Interstitial lung disease (4), Pneumonia (2), pulmonary embolism (1), elevated transaminases (2), hepatotoxicity (1) and neutropenia (2) All other treatment-related SAEs, included but were not limited to Electrocardiogram QT prolonged, malaise, Renal cyst.

Of the 171 patients treated with chemotherapy, 40 (23.4%) had SAEs of whom, 24 (14%) had treatment related SAEs. These related SAEs were mainly related to haematological toxicity.

In Study 1014, 4 of the 19 patients treated with crizotinib had SAEs, of which 1 was considered treatment-related (oesophagitis).

Among the 63 patients in the RP2D cohort with tumours other than molecularly defined ALK-positive or ALK-negative NSCLC with data available for the updated report, there were 27 SAEs, 5 of which were considered related to crizotinib treatment, and 10 of which were associated with permanent discontinuation from crizotinib treatment.

Immunological events

One single case of autoimmune thyroiditis has been reported in patient treated with crizotinib for clear cell sarcoma. The event was considered treatment-related.

Laboratory findings

Lymphopenia, neutropenia, ALT elevation, and hyponatraemia were the most common Grade 3 or Grade 4 abnormalities. Neutropenia and ALT elevation have been identified previously as AEs commonly associated with crizotinib use. Two febrile neutropenia events were reported in study 1005.

Four additional cases of liver disorders from study 1005 have been reported after the data cut-off date: three of them were potential Hy's law cases.

In both studies, there was no evidence of clinically significant effects of crizotinib on vital signs, or on PR or QRS complex intervals. Decreases in pulse rate and diastolic blood pressure were not clinically meaningful as evidenced by low frequencies of Bradycardia and Hypotension reported as AEs.

Overall, lymphopenia, neutropenia, ALT elevation, and hyponatraemia were the most common Grade 3 or Grade 4 abnormalities.

Electrocardiogram abnormalities involved bradycardia and QT prolonged.

Safety in special populations

Experimental data did show reproductive toxicity (decrease in foetus body weight and increased postimplantation loss). In addition, even if according to ICH S9, fertility and early embryonic development studies are not warranted for marketing authorisation, effects on reproductive organs were seen in repeat-dose toxicity indicating a potential impairment of male and female fertility. Both men and women should therefore seek advice for fertility preservation before treatment.

Genotoxicity studies also suggest an aneugenic potential of crizotinib. Genotoxicity leads to a safety concern on embryo-foetal development in relation to effects on DNA gametes, including the case of male treated patients, as a partner of women of childbearing potential.

There is no clinical experience in pregnant women. However a treatment-emergent SAE of spontaneous abortion has been reported by the applicant (study 1001). Crizotinib should not be used during pregnancy unless the clinical condition of the mother requires treatment. Pregnant women, or patients becoming pregnant while receiving crizotinib, or treated male patients as partners of a pregnant women, should be apprised of the potential hazard to the foetus. Adequate contraceptive methods should be used during therapy, and for at least 90 days after completing therapy

It is not known whether crizotinib and its metabolites are excreted in human milk. Because of the potential harm to the infant, mothers should be advised to avoid breast-feeding while receiving crizotinib.

The applicant provided the analysis of safety data by age groups, sex and race. Overall, 308 patients were <65-year old and 48 ≥ 65 year-old. The rate of AEs is variable but the number of patients in two

groups is rather low to reveal specific crizotinib related safety issues in any of these age groups, especially elderly patients.

Oedema peripheral (30% vs 18.6), dizziness (25% vs 13.6%) and ALT increased (18.3% vs 10.2%) were more frequent in female compared to male. Some grade 1 or 2 AEs were reported more or less frequently in Asian patients (77) compared to non-Asian (178 patients). However, grade 3/4 events were more frequently reported in non-Asian population.

No clinically significant effect of food on crizotinib exposure has been reported.

There have been no known cases of crizotinib overdose. No information regarding abuse of crizotinib is available.

Crizotinib has minor influence on the ability to drive and use machines. However, caution should be exercised when driving or operating machines as patients may experience vision disorder, dizziness, or fatigue while taking crizotinib.

Safety related to drug-drug interactions and other interactions

Pharmacodynamic interactions

In clinical studies, prolonged QT interval was observed with crizotinib. Therefore, the concomitant use of crizotinib with medicinal products known to prolong QT interval or medicinal products able to induce Torsades de pointes (e.g., class IA [quinidine, disopyramide] or class III [e.g., amiodarone, sotalol, dofetilide, ibutilide], methadone, cisapride, moxifloxacine, antipsychotics, etc.) should be carefully considered. A monitoring of the QT interval should be made in case of combinations of such medicinal products as reflected in section 4.4 of the SmPC.

Bradycardia has been reported during clinical studies; therefore, use crizotinib with caution due to the risk of excessive bradycardia when used in combination with other bradycardic agents (e.g., non-dihydropyridine calcium channel blockers such as verapamil and diltiazem, beta-blockers, clonidine, guanfacine, digoxin, mefloquine, anticholinesterases, pilocarpine), as reflected in section 4.5 of the SmPC.

Discontinuation due to adverse events

In study 1001, 19 of the 149 ALK-positive NSCLC patients in the RP2D cohort (12.8%) had AEs that were associated with permanent discontinuation from treatment, of whom, 3 patients (2.0%) had treatment-related AEs associated with permanent discontinuation: Pneumonitis (2 patients, 1.6%) and ALT increased (1 patient, 0.8%).

In study 1005, 53 patients (12.1%) had AEs that were associated with permanent discontinuation from treatment. Fourteen (14) patients (3.2%) permanently discontinued treatment for AEs considered related to treatment: Pneumonitis (4 patients); ALT increased (3 patients); Nausea, Dyspnoea, Hypokalaemia, Colitis, Death, Pulmonary Embolism, and Cytolytic hepatitis (1 patient each).

In study 1007, 30 patients (17%) in the crizotinib arm and 23 (14%) in the chemotherapy arm had AEs associated with permanent discontinuation from treatment. The most common all causality AEs associated with permanent treatment (crizotinib vs chemotherapy) discontinuation were related to:

- respiratory, thoracic and mediastinal disorders: 9 (including ILD (3) and pulmonary embolism (2)) vs 3;

- general disorders and administration site conditions: 7 (including death (1), sudden death (1), disease progression (5) vs 3 (asthenia (2), fatigue (1));

- blood and lymphatic system disorders: 0 vs. 4 (anemia (1), febrile neutropenia (3));

- and cardiac disorders: 1 (Arrhythmia) vs. 4 (cardiomyopathy (1), left ventricular dysfunction (1) and pericardial effusion (2)).

In addition, 3 patients had permanent discontinuation from crizotinib due to 5 hepatic events compared to none in chemotherapy arm.

Less discontinuations were considered related to crizotinib than to chemotherapy, 11 (6%) and 17 (10%), respectively. This could be due to bias, as this study was an open label study.

2.6.1. Discussion on clinical safety

Clinical safety data are still mainly based on one pivotal study (1001) and one ongoing supportive phase 2 study (1005).

Top line preliminary efficacy and safety comparative results from the open-label, multicenter, randomized phase 3 trial (A8081007) were provided during the review procedure of the application.

Safety experience from 6 Phase 1 Biopharmaceutical and Clinical Pharmacology studies in healthy volunteer subjects receiving 1 to 4 single doses of crizotinib was briefly mentioned in the dossier.

Only data on SAEs and deaths for patients in the crizotinib arm from the ongoing first-line phase 3 study, A8081014, have been included in the submitted documentation.

Study A8081014 is a multicenter, multinational, randomized, open-label, Phase 3 study comparing oral crizotinib at a starting dose of 250 mg BID to pemetrexed/cisplatin or pemetrexed/carboplatin as first-line treatment of advanced ALK-positive NSCLC.

A total of 832 subjects have been treated with crizotinib in the studies included in the safety analysis: 588 patients with ALK-positive locally advanced or metastatic NSCLC (149 from pivotal study 1001; 439 from supportive study 1005), receiving the recommended dosage of crizotinib 250 mg orally BID; 134 patients with advanced cancer enrolled in Study 1001 but who did not represent the target population and/or did not receive the recommended dosing regimen; and 110 healthy volunteers enrolled in clinical pharmacology studies.

The median treatment duration was 43.1 and 15.7 weeks in studies 1001 and 1005, respectively with 82 patients (14%) treated for more than one year (65 patients in study 1001 and 17 patients in study 1005).

The updated 30-day and 60-day all-cause mortality in the 588 patients in the all ALK-positive NSCLC patient population at the RP2D across Studies 1001 and 1005 were 3.6% and 5.1% respectively. Seventy-one (71) of the 588 patients (12.1%) have died while on study (within 28 days of the last dose of study drug). Majority of deaths (83%) were related to disease progression.

A total of 7 deaths are considered as related to crizotinib (taking into account study 1007): pneumonitis (2), interstitial lung disease (1), cardiac arrest and respiratory failure (1), treatment toxicity (1), unknown cause (1), pulmonary embolism (1) while the applicant mentioned 2 cases of study treatment toxicity.

Moreover, 2 fatal cases of liver disorders, related to study drug, in study 1005 were reported after the cut-off date, one case of liver failure in a 40 year-old female and one case of liver injury in a 57 year-old male. One additional fatal case of liver disorder, related to crizotinib in study 1007 was reported after the data cut-off date for the Top line Summary (73 year old female). The applicant will submit a safety review of hepatic disorders in Q1 2013.

A total of 147 (98.7%) and 419 (95.4%) patients experienced 1972 and 3742 adverse events in studies 1001 and 1005, respectively.

Hepatic enzyme elevations collected as laboratory abnormality and AE were frequently reported (17.4% ALT increased, 14.1% AST increased, 7.4% blood phosphatase alkaline in pivotal study). Cases of drug-induced hepatotoxicity with fatal outcome have occurred during crizotinib treatment in less than 1% of patients in clinical trials. Concurrent elevations in ALT greater than 3 x ULN and total bilirubin greater than 2 x ULN without elevated alkaline phosphatase have been observed in less than 1% patients in clinical trials. Increases to Grade 3 or 4 ALT elevation were observed in 6% of patients in Study 1001 and 8% of patients in Study 1005. Grade 3 and 4 elevations were generally asymptomatic and reversible upon dosing interruption. Patients usually resumed treatment at a lower dose without recurrence; however, 1 patient from Study 1001 (<1%) and 3 patients from Study 1005 (1%) required permanent discontinuation from treatment. Transaminase elevations generally occurred within the first 2 months of treatment. Crizotinib should not be used in patients with severe hepatic impairment (see sections 4.2, 4.3, and 4.8 of the SmPC). Liver function tests should be monitored including ALT, AST, and total bilirubin twice a month during the first two months of treatment, then once a month and as clinically indicated, with more frequent repeat testing for Grades 2, 3 or 4 elevation. For patients who develop transaminase elevations, dose adjustment or discontinuation of treatment should be considered (see section 4.2 of the SmPC).

The risk of QT prolonged is expected regarding the risk with other tyrosine kinases and with regards to non-clinical data. In addition, PK/PD analysis suggested a relationship between crizotinib plasma concentration and QTc. QTcF intervals was ≥500 msec on at least 1 post baseline assessment in 4 of 308 patients (1.3%) who received crizotinib 250 mg BID in Studies 1001 and 1005. Maximum change in QTcF was ≥60 msec in 10 of 289 patients (3.5%) in these 2 studies. According to the updated data, in studies 1001 and 1005, 4 patients experienced an AE of ECG QT interval prolonged, 3 events were considered as drug related. In phase 3 study 1007, 2 deaths due to cardiac disorders (Arrhythmia, sudden death) were reported. In addition the following Grade 3/4 AES were reported in the crizotinib arm: 6 "Electrocardiogram QT prolonged" (4 crizotinib related) and 5 Syncope (2 crizotinib related).

QTc prolongation may lead to an increased risk for ventricular tachyarrhythmias (e.g. Torsade de Pointes) or sudden death. The risk of QTc prolongation may be increased in patients concomitantly taking antiarrhythmics and in patients with relevant pre-existing cardiac disease, bradycardia, or electrolyte disturbances (e.g., secondary to diarrhoea or vomiting). crizotinib be administered with caution to patients who have a history of or predisposition for QTc prolongation, or who are taking medicinal products that are known to prolong the QT interval. When using crizotinib in these patients, periodic monitoring with electrocardiograms and electrolytes should be considered.

One PAS study was proposed by the applicant to collect long-term safety data on crizotinib, to characterise the safety of crizotinib in subgroups of patients (e.g., elderly, patients with brain metastasis, renal and hepatic impairment), and further identify risk factors associated with QTc prolongation events (e.g., Torsade de pointes) in real world conditions. The Applicant committed to amend study A8081014 to include additional ECG time points and central blinded manual review. Furthermore, events such as sudden death, cardiac disorders, arrhythmias, syncope, dizziness, bradycardia, electrocardiogram QT prolonged, should be further presented and discussed together with the assessment potential QT prolongation (and the risk of electrolyte unbalances linked to important frequency of diarrhea and vomiting).

Crizotinib has been associated with severe, life-threatening, or fatal treatment-related pneumonitis in clinical trials with a frequency of 4 in 386 (1%) patients across Studies 1001 and 1005. All of these cases occurred within 2 months after the initiation of treatment. Monitor patients for pulmonary symptoms indicative of pneumonitis. Treatment with crizotinib should be withheld if pneumonitis is

suspected. Other causes of pneumonitis should be excluded, and the treatment should be permanently discontinued in patients diagnosed with treatment-related pneumonitis.

Physiopathological crizotinib data are compatible with ophthalmological toxicity of the drug. Vision disorder occurred in patients treated with crizotinib. This event was reported as mild (96%), moderate (3%), and severe (<1%) with median times to onset of 15 and 6 days in studies 1001 and 1005, respectively. None of the patients required dose reduction, or permanent discontinuation from crizotinib treatment for vision disorder; however 1 patient in study 1001 and 3 patients in study 1005 had temporary treatment discontinuation. Ophthalmological evaluation should be considered if vision disorder persists or worsens in severity.

Nausea, diarrhoea, vomiting, and constipation were the most commonly reported gastrointestinal events, and were primarily Grade 1 in severity. Supportive care for gastrointestinal events may include standard antiemetic and/or antidiarrhoeal or laxative medicinal products.

In case of non haematologic toxicities the following dose modifications are recommended:

CTCAE[a] Grade	Crizotinib treatment
Grade 3 or 4 alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevation with Grade ≤1 total bilirubin	To withhold treatment until recovery to Grade ≤1 or baseline, then resume at 200 mg twice daily[b]
Grade 2, 3 or 4 ALT or AST elevation with concurrent Grade 2, 3 or 4 total bilirubin elevation (in the absence of cholestasis or hemolysis)	To permanently discontinue
Any Grade pneumonitis[c]	Permanently discontinue
Grade 3 QTc prolongation	To withhold treatment until recovery to Grade ≤1, then resume at 200 mg twice daily[b]
Grade 4 QTc prolongation	Permanently discontinue

[a]NCI Common Terminology Criteria for Adverse Events
[b]In case of recurrence, withhold until recovery to Grade ≤1, then resume at 250 mg once daily. Permanently discontinue in case of further Grade 3 or 4 recurrence.
[c]Not attributable to NSCLC progression, other pulmonary disease, infection, or radiation effect. Withhold treatment if pneumonitis is suspected, and permanently discontinue if treatment-related pneumonitis is diagnosed.

In study 1001, decreases to Grade 3 or 4 leukocytes and platelets were each observed in patients at frequencies of <3%, and decreases to Grade 3 or 4 neutrophils and lymphocytes were observed at a frequency of 10% and 14%, respectively. In study 1005, decreases to Grade 3 or 4 leukocytes were observed in patients at a frequency of 3%, decreases to Grade 3 or 4 neutrophils were observed at a frequency of 9%, decreases to Grade 3 or 4 lymphocytes were observed at a frequency of 14%, and decreases to Grade 3 or 4 platelets were observed at a frequency of <1%. Complete blood counts including differential white blood cell counts should therefore be monitored, with more frequent repeat testing if Grade 3 or 4 abnormalities are observed, or if fever or infection occurs.

In case of haematologic toxicities, the following dose modifications are recommended:

CTCAE[b] Grade	Crizotinib treatment
Grade 3	To withhold treatment until recovery to Grade ≤2, then resume at the same dose schedule
Grade 4	To withhold treatment until recovery to Grade ≤2, then resume at 200 mg twice daily[c]

Two cases of photosensitivity grade 1 have occurred. Photosensitivity is therefore included as a potential risk in the RMP (see section 2.7).

Comparative safety data: Study A8081007 Top line summary

No new safety signal emerged from Study 1007 regarding crizotinib safety profile. However, the safety profile of crizotinib does not seem similar, in terms of AEs frequency/grading and in terms of AEs nature, compared to the safety profile of Chemotherapy.

All causality Grade 3-4 AEs or Treatment related Grade 3-4 AEs preferred term or clustered term with a frequency at least 2-fold greater in the crizotinib arm group compared with "chemotherapy" group were Hepatic disorders (elevated transaminase, hepatotoxicity), Respiratory disorders (Pulmonary embolism, Interstitial lung disease) and Cardiac Disorders (Electrocardiogram QT Prolonged, syncope).

All causality/Treatment related Grade 3-4 AEs PT reported with a frequency 2-fold greater in the chemotherapy arm compared with crizotinib were related to haematological toxicity, fatigue, stomatitis.

More hepatic events were reported in the crizotinib arm compared to the chemotherapy arm. No Grade 4 hepatic events were reported in chemotherapy arm. It has to be noted that an additional fatal case of hepatic failure (Hy's Law case) considered as related to crizotinib has been reported to the French Agency after the date of data cut-off of this Top Line Summary report. It concerns a patient enrolled in the 1007 study.

Only 33 % of the deaths reported are discussed in the top line summary. These data are insufficient to conclude on any difference between crizotinib and chemotherapy arms.

Additional safety data needed in the context of a conditional MA

In order to further characterise the safety profile of crizotinib, the applicant should submit updated safety (SAEs and deaths) data for both studies 1001 and 1005. The applicant should also submit the CSR of study 1007 which will provide comparative safety data against chemotherapy. Finally, in view of the hepatic events observed with crizotinib, the applicant should submit the safety review of main (severe) hepatic disorders from all available main studies of crizotinib (1001, 1005 and 1007) at the same time as the full CSR of Study 1007 by Q1 2013.

2.6.2. Conclusions on the clinical safety

The most common any grade adverse reactions (>20%) across studies 1001 and 1005 were vision disorder, nausea, diarrhoea, vomiting, oedema, constipation, and fatigue. The most common Grade 3 or 4 adverse reactions (≥ 3%) across both studies were increased ALT and neutropenia.

Crizotinib has been associated with severe, life-threatening, or fatal treatment-related pneumonitis and cases of QTc interval prolongation which may lead to an increased risk for ventricular tachyarrhythmias (e.g., Torsade de Pointes) or sudden death have been observed.

Drug-induced hepatotoxicity with fatal outcome has also occurred. This event is of particular concern and the applicant has been requested to submit safety review of hepatic disorders by Q1 2013.

Based on preliminary data from study 1007, Crizotinib seems more toxic than standard chemotherapy with greater hepatotoxicity, pneumotoxicity and cardiotoxicity, potentially life threatening and fatal as well as more GI disorders that may impact treatment adherence. The main toxicity observed with chemotherapy was haematological toxicity. However no difference is observed in global deaths reporting between crizotinib and chemotherapy arms.

However, these preliminary data are not complete and validated. Therefore, the applicant has committed to provide final safety data of studies 1001, 1005 and 1007, once available, and to update the SmPC accordingly..

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

The Applicant should submit the safety review of main (severe) hepatic disorders from all available main studies of crizotinib (1001, 1005 and 1007) at the same time as the full CSR of Study 1007 by Q1 2013.

The CHMP considers the following measures necessary to address issues related to safety:

- The Applicant should submit the CSR of Study A8081012 "A Phase 1 Study to Evaluate the Effect of Hepatic Impairment on the Pharmacokinetics of Crizotinib in Advanced Cancer Patients." By Q1 2014 and the Post-Authorisation Safety Study (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) by Q2 2018.

- The Applicant should present the results of a step-wise investigation in patients with severe and end-stage renal impairment is agreed. Single dose finding should be provided and the need of repeated dose investigation, depending upon single dose findings will be further discussed when single dose data are assessed by Q2 2013 .

- The Applicant should submit a definite assessment of the effect of age for the main studies A8081001, A8081005, A8081007 according to Population Modelling Analysis Plan at the time of submission of the study report for the pivotal study A8081007 by Q1 2013.

- The applicant should submit DDI studies with ketoconazole or rifampin at steady-state in order to allow defining dosing adjustments in case of co-administration by Q3 2015.

- The Applicant should amend study A8081014 to include additional ECG time points and central blinded manual review. Furthermore, events such as sudden death, cardiac disorders, arrhythmias, syncope, dizziness, bradycardia, electrocardiogram QT prolonged, should be further presented and discussed together with the assessment potential QT prolongation (and the risk of electrolyte unbalances linked to important frequency of diarrhea and vomiting) by Q1 2013.

- The Applicant should submit the results of the PASS study A8081038 (to estimate the incidence rate and incidence proportion over a 3-year period of observation for hepatotoxicity, pneumonitis/ILD, QTc prolongation related events, bradycardia, and visual disorder among lung cancer patients receiving crizotinib prescriptions) by Q2 2018.

- The Applicant should submit the results of the visual effect substudy as part of Study A8081001 by Q2 2014.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

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

Risk Management Plan

The applicant submitted a risk management plan

Table 21 Summary of the risk management plan

Safety Concern	Proposed Pharmacovigilance Activities (PV)	Proposed Risk Minimisation Activities (routine and additional)
Important Identified Risk		
Hepatotoxicity	Routine pharmacovigilance that includes a targeted questionnaire. A multi-national post-approval database surveillance study (A8081038) is planned.	Alanine aminotransferase increased is listed in the SPC as a very common ADR, and Aspartate aminotransferase increased is listed as a common ADR, see SPC Section 4.8. Dosing recommendations specify for Grade 3-4 ALT or AST elevation (with total bilirubin Grade ≤1): Withhold until recovery to Grade ≤1 or baseline, then resume at 200 mg twice daily; and to permanently discontinue crizotinib for Grade 2-4 ALT or AST elevation with concurrent Grade 2-4 Total bilirubin elevation (in the absence of cholestasis or hemolysis). SPC Section 4.3, Contraindications: Severe hepatic impairment (see SPC sections 4.2, 4.4, and 4.8). SPC Section 4.4. Crizotinib "should not be used in patients with severe hepatic impairment. Liver function tests including ALT, AST, and total bilirubin should be monitored twice a month during the first two months of treatment then once a month and as clinically indicated, with more frequent repeat testing for Grades 2, 3 or 4 elevation. For patients who develop transaminase elevations, see SPC Section 4.2."
Pneumonitis	Routine pharmacovigilance A multi-national post-approval database surveillance study (A8081038) is planned.	SPC Section 4.4. "Patients with pulmonary symptoms indicative of pneumonitis should be monitored. Crizotinib treatment should be withheld if pneumonitis is suspected. Other causes of pneumonitis should be excluded and crizotinib should be permanently discontinued in patients diagnosed with treatment-related pneumonitis." Pneumonitis is listed in the SPC as a common ADR, see SPC Section 4.8.

Safety Concern	Proposed Pharmacovigilance Activities (PV)	Proposed Risk Minimisation Activities (routine and additional)
QTc prolongation	Routine pharmacovigilance Additional pharmacovigilance Sub-study A8081007 with patients from A8081005. Study A8081014. A multi-national post-approval database surveillance study (A8081038) is planned.	SPC Section 4.4. "Crizotinib should be administered with caution to patients who have a history of or predisposition for QTc prolongation, or who are taking medicinal products that are known to prolong the QT interval. When using crizotinib in these patients, periodic monitoring with electrocardiograms and electrolytes should be considered. For patients who develop QTc prolongation, see SPC Section 4.2." SPC Section 4.2: "Dose reduction recommended as follows: Grade 3 QTc prolongation: Withhold until recovery to Grade ≤1 or baseline, then resume at 200 mg taken orally twice daily. Grade 4 QTc prolongation: Permanently discontinue." Electrocardiogram QT Prolonged is listed in the SPC as a common ADR, see SPC Section 4.8. Educational material.
Bradycardia	Routine Pharmacovigilance A multi-national post-approval database surveillance study (A8081038) is planned.	Bradycardia is listed in the SPC as a common ADR, see SPC Section 4.8.
Vision disorder	Routine pharmacovigilance Additional pharmacovigilance Study A8081001, Amendment #17 A multi-national post-approval database surveillance study (A8081038) is planned.	SPC Section 4.4 states "Ophthalmological evaluation should be considered if vision disorder persists or worsens in severity." SPC Section 4.7 states that caution should be exercised in relation to driving and operating machinery when experiencing vision disorder. Vision disorder is listed in the SPC as a very common ADR, see SPC Section 4.8. Educational material.
Important Potential Risks		
Renal cyst	Routine pharmacovigilance	Renal cyst is listed in the SPC as an uncommon ADR, see SPC Section 4.8.
Oedema	Routine pharmacovigilance	Oedema is listed in the SPC as a very common ADR, see SPC Section 4.8.
Leukopenia	Routine pharmacovigilance	Leukopenia is listed in the SPC as a common ADR, see SPC Section 4.8. See SPC Section 4.2. Per dose modification for hematologic toxicity, the following dose modification is recommended: Grade 3 Leukopenia: Withhold crizotinib until recovery to Grade ≤2, then resume at the same dose schedule. In case of recurrence, withhold until recovery to Grade ≤2, then resume at 250 mg once daily. Grade 4 Leukopenia: Withhold until recovery to Grade ≤2, then resume at 200 mg twice daily. In case of recurrence of G4 leukopenia, withhold until recovery to Grade ≤2, then resume at 250 mg once daily, and permanently discontinue in case of further Grade 4 recurrence.
Neuropathy	Routine pharmacovigilance	Neuropathy is listed in the SPC as a very common ADR, see SPC Section 4.8.

Safety Concern	Proposed Pharmacovigilance Activities (PV)	Proposed Risk Minimisation Activities (routine and additional)
Reproductive Toxicity	Routine pharmacovigilance	See SPC Section 4.6. Women of childbearing potential should be advised ot avoid becoming pregnant while receiving crizotinib. Adequate contraceptive methods should be used during therapy, and for at least 90 days after completing therapy. Crizotinib may cause fetal harm when administered to a pregnant woman. Studies in animals have shown reproductive toxicity. There are no data in pregnant women using crizotinib. If crizotinib is used during pregnancy, or if the patient or their partner becomes pregnant while receiving crizotinib, then the patient or their partner should be apprised of the potential hazard to the fetus. It is not known whether crizotinib and its metabolites are excreted in human milk. Because of the potential harm to the infant, mothers should be advised to avoid breast-feeding while receiving crizotinib (see Section 5.3). Based on non-clinical safety findings, male and female fertility may be compromised by treatment with crizotinib (see Section 5.3). Both men and women should seek advice for fertility preservation before treatment.
Photosensitvity	Routine pharmacovigilance	No specific risk minimization activity is considered necessary at this time.
Important Missing Information		
Patients with hepatic impairment	Routine pharmacovigilance Additional pharmacovigilance Study A8081012 A multi-national post-approval database surveillance study including hepatically impaired patients is planned (Study A8081038).	SPC Section 4.3, Contraindications: Severe hepatic impairment (see SPC sections 4.2, 4.4, and 4.8). SPC Section 4.4. Crizotinib "should not be used in patients with severe hepatic impairment. Liver function tests including ALT, AST, and total bilirubin should be monitored twice a month during the first two months of treatment then once a month and as clinically indicated, with more frequent repeat testing for Grades 2, 3 or 4 elevation. For patients who develop transaminase elevations, see SPC Section 4.2." In Section 4.2 of the SPC, information is provided about the lack of data in this subgroup of patients.
Patients with renal impairment	Routine pharmacovigilance Additional pharmacovigilance study in renally impaired patients (A8081020). A multi-national post-approval database surveillance study including renally impaired patients is planned (Study A8081038).	In Section 4.2 of the SPC, information is provided about the lack of data in this subgroup of patients.

Safety Concern	Proposed Pharmacovigilance Activities (PV)	Proposed Risk Minimisation Activities (routine and additional)
Elderly patients	Routine pharmacovigilance A multi-national post-approval database surveillance study including elderly patients is planned (Study A8081038).	It is noted in Section 4.2 of the SPC that clinical studies of crizotinib did not include sufficient numbers of patients aged 65 and older to determine whether they respond differently from younger patients.
Pediatric patients	Routine pharmacovigilance	As noted in Section 4.2 of the SPC, the safety and efficacy of crizotinib in pediatric patients have not been established. Crizotinib should not be used in pediatric population outside of clinical studies.
Pregnant and lactating women and women of childbearing potential	Routine pharmacovigilance	Section 4.6 in the SPC states that crizotinib may cause fetal harm. Women of childbearing potential should be advised to avoid becoming pregnant while receiving crizotinib. If crizotinib is used during pregnancy, or if the patient becomes pregnant while receiving crizotinib, then the patient should be apprised of the potential hazard to the fetus. Recommendation to use adequate contraceptive methods during therapy and for at least 90 days after completing therapy. Applicant-sponsored study protocols clearly state the requirement for screening pregnancy testing and adequate contraception during participation in studies.
Drug interaction with CYP3A inhibitors, inducers, substrates, proton pump inhibitors or H2 antagonists.	Routine pharmacovigilance Additional pharmacovigilance Study A8081001 Amendment #18 Additional pharmacovigilance Study A8081035	As stated in the SPC Section 4.4, the concomitant use of crizotinib with strong CYP3A4 inhibitors and inducers, or CYP3A4 substrates with a narrow therapeutic margin should be avoided.
Patients undergoing long-term treatment	Routine Pharmacovigilance A multi-national post-approval database surveillance study (A8081038) is planned.	The effects of crizotinib during and after long-term use have not been determined. No specific risk minimization activity is considered necessary at this time.

The CHMP, having considered the data submitted, was of the opinion that the below pharmacovigilance activities in addition to the use of routine pharmacovigilance are needed to investigate further some of the safety concerns:

Description	Due date
The Applicant should submit the safety review of main (severe) hepatic disorders from all available main studies of crizotinib (1001, 1005 and 1007) at the same time as the full CSR of Study 1007.	Q1 2013
The Applicant should submit the CSR of Study A8081012 "A Phase 1 Study to Evaluate the Effect of Hepatic Impairment on the Pharmacokinetics of Crizotinib in Advanced Cancer Patients." and the Post-Authorisation Safety Study (3-year post-approval multinational database study in Europe to further characterise the safety of crizotinib in patients, including those with hepatic impairment, in real-world settings).	Q1 2014 for Study A8081012 Q2 2018 for the 3-year PAS study
The Applicant should present the results of a step-wise investigation in patients with severe renal impairment. Single dose finding should be provided and the need	Q2 2013

Description	Due date
of repeated dose investigation, depending upon single dose findings will be further discussed when single dose data are assessed.	
The Applicant should submit a definite assessment of the effect of age for the main studies A8081001, A8081005, A8081007 according to Population Modelling Analysis Plan at the time of submission of the study report for the pivotal study A8081007.	Q1 2013
The applicant should submit DDI studies with ketoconazole or rifampin at steady-state in order to allow defining dosing adjustments in case of co-administration.	Q3 2015
The Applicant should amend study A8081014 to include additional ECG time points and central blinded manual review. Furthermore, events such as sudden death, cardiac disorders, arrhythmias, syncope, dizziness, bradycardia, electrocardiogram QT prolonged, should be further presented and discussed together with the assessment potential QT prolongation (and the risk of electrolyte unbalances linked to important frequency of diarrhea and vomiting).	Q1 2013
The Applicant should submit the results of the PASS study A8081038 (to estimate the incidence rate and incidence proportion over a 3-year period of observation for hepatotoxicity, pneumonitis/ILD, QTc prolongation related events, bradycardia, and visual disorder among lung cancer patients receiving crizotinib prescriptions). the protocol for PASS A8081038 will be submitted for approval prior to the start of the study.	Q2 2018
The Applicant should submit the results of the visual effect substudy as part of Study A8081001.	Q2 2014

The following additional risk minimisation activities were required.

The MAH should ensure that, at launch and thereafter, all Healthcare Professionals who are expected to use and/or prescribe XALKORI are provided with an educational pack.

The educational pack should contain the following:

1. Summary of Product Characteristics and Package Leaflet.
2. Educational material for Healthcare Professionals.
3. Patient brochure including a Patient Alert Card (text as agreed by the CHMP).

The educational material for Healthcare Professionals should contain the following key elements:

1. XALKORI prolongs the QTc interval which may lead to an increased risk for ventricular tachyarrhythmias (e.g. Torsade de Pointes) or sudden death.
2. The risk of QTc prolongation may be increased in patients concomitantly taking antiarrhythmics and in patients with relevant pre-existing cardiac disease, bradycardia, or electrolyte disturbances (e.g., secondary to diarrhoea or vomiting).
3. XALKORI should be administered with caution to patients:
    a. Who have a history of or predisposition for QTc prolongation.
    b. Who are taking medicinal products that are known to prolong the QT interval.
4. The need for a periodic monitoring with electrocardiograms and electrolytes should be considered when using XALKORI in these patients.

5. Patients who develop a grade 3 QTc prolongation should stop taking XALKORI until recovery to Grade ≤1, then resume at 200 mg twice daily.
6. Patients who develop a grade 4 QTc prolongation should stop taking XALKORI permanently.
7. That XALKORI may cause vision disorders, including diplopia, photopsia, blurred vision, visual impairment, and vitreous floaters.
8. Ophthalmological evaluation should be considered if vision disorder persists or worsens in severity.
9. The concomitant use of XALKORI with strong CYP3A4 inhibitors/inducers and CYP3A4 substrates with narrow therapeutic indices should be avoided.
10. The need to counsel patients about the risk of prolonged QTc and vision disorders and inform them of what symptoms and signs to be aware of and the actions to take.
11. The role and use of the Patient Alert Card.

2.8. User consultation

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

3. Benefit-Risk Balance

The initial Application/indication (treatment of previously treated ALK- positive advanced NSCLC) was supported by the results of two uncontrolled clinical trials evaluating ORR as the primary efficacy endpoint. No controlled study was available. Preliminary Top-line selected results of a controlled study (1007) have recently also been made available. These data are therefore considered supportive at this stage as the full clinical study report is not available.

Benefits

Beneficial effects

A high ORR and PFS has been observed with crizotinib in the 2 phase I/II uncontrolled studies, and are supported by the preliminary Top-line results of the phase III comparative study (1007).

ORR, DR and PFS are mature for both uncontrolled studies. Response rates and PFS seem important, are concordant between studies and durable, with an updated ORR of 60% and 53% for previously treated ALK-positive advanced NSCLC RE population in Study A8081001 and A8081005 respectively, and an updated median DRs of 48.1 weeks and 42.9 weeks respectively. Updated PFS were 9.2 months and 8.5 months respectively. These data allow to establish a relevant clinical benefit of crizotinib in ALK-positive NSCLC patients and seem to exceed second-line historical ORR controls from unselected advanced NSCLC patients and the ORRs from prior treatment of ALK-positive NSCLC patients.

Preliminary results of the comparative study 1007 and updated results from studies 1001 and 1005 therefore indicate that crizotinib has a positive clinically meaningful benefit (PFS, ORR, DR) as a single agent in previously pre-treated patients with ALK-positive advanced NSCLC (mainly adenocarcinomas)

Moreover, Applicant's selected top-line results of the randomized controlled phase III trial in pre-treated ALK-positive NSCLC (study 1007) have been provided. According to the data presented, crizotinib demonstrated a statistically significant and clinically relevant additional improvement in PFS of 4.7 months over second line chemotherapy pemetrexed-docetacel with 7.7 months (95% CI: 6.0, 8.8) with crizotinib compared to 3.0 (95% CI: 2.6, 4.3) months in the pemetrexed-docetaxel chemotherapy arm respectively, HR 0.487 (95% CI: 0.371, 0.638), p-value <0.0001).

Uncertainty in the knowledge about the beneficial effects

The evidence in favour of the use of crizotinib in pre-treated ALK-positive advanced NSCLC patients is based on results of a phase I-II study and supportive data from a phase II study. No full study report from randomized controlled studies is available at present. These results must be confirmed by more robust data (full study report) from the prospective comparative study (1007) and updated (full study report including updated OS) data from the 2 uncontrolled studies.

The pharmacokinetic characterisation of crizotinib has some deficiencies; effect of hepatic impairment and effect of severe renal impairment on crizotinib PK/PD and safety; reasons/impact for differences in exposure in Asian and drug-drug interactions; insufficient information in patients over 65 years of age. These deficiencies can be resolved post approval with the provision of additional data as reflected in section 2.7.

Additional data are needed in order to fully address the impact of crizotinib on QTc prolongation/heart rate reduction and should be correlated to AEs/SAES/deaths. The QTc assessment will be included in study A8081014.

Risks

Unfavourable effects

The most common adverse reactions observed in both studies (1001 and 1005) were vision disorders (visual impairment, vision blurred, vitreous floaters, and visual field defect) and GI disorders (nausea, diarrhea, vomiting, and constipation).

The most frequently reported Grade 3-4 adverse reactions included increased ALT. Hepatic enzyme elevations were frequently reported and led to permanent discontinuation of study drug. Additional cases of liver disorders have been reported from study 1005 and 1007 including Hy's law cases and death.

As expected with some Tyrosine kinase targeting drugs, crizotinib has been associated with study-drug related pneumonitis/ ILD (including pneumonitis with fatal outcome).

Cardiac disorders including QT prolongation, bradycardia, syncope, dizziness, sudden death have also been observed during the conducted studies.

Most of the decreased in neutrophil count was mild in severity. However, grade 3 and grade 4 neutropenia were common.

Uncertainty in the knowledge about the unfavourable effects

Results of study 1001 are based on a very limited population and limited follow-up and follow-up is even more limited for study 1005.

A longer follow-up and comparative data are necessary in order to better characterise the clinical impact, incidence and severity as well as risk factors for occurrence of QTc prolongation/bradycardia, liver toxicity and pneumonitis/ ILD. The applicant will therefore conduct a post-authorisation Safety Study (see section 2.7 RMP).

The Applicant will provide final results for the clinical studies included in the dossier. An analysis should be conducted separately for each clinical study. Pooled safety data in particular for events of interest, should also be presented (including analyses according to potential factors that could lead to over-exposure).

Hepatotoxicity was identified as an important risk, the Applicant will provide a specific safety review of main (severe) hepatic disorders, especially severe hepatic cases from all available studies (including 1001, 1005, 1007).

Balance

Importance of favourable and unfavourable effects

Crizotinib is intended as a new target therapy for pre-treated ALK-positive advanced NSCLC. No specific therapy for ALK-positive advanced NSCLC is available at present.

The effect size, measured in terms of ORR and PFS data of crizotinib from the 2 uncontrolled studies and preliminary data of the comparative phase III trial is large, consistent and potentially clinically significant when compared to results achieved after one or two lines of standard therapy in the general advanced NSCLC patient population. In addition, disease control seems to be maintained in a significant percentage of the treated patient population for which results are available at present.

Moreover, according to preliminary data of the comparative phase III trial, crizotinib allowed a statistically and clinically relevant additional improvement in PFS of 4.7 months over second line chemotherapy pemetrexed-docetacel.

However, only preliminary data have been submitted in order to allow direct comparison of efficacy and safety of criotinib versus chemotherapy (permetrexed/docetaxel) and full clinical study reports are expected.

Most adverse reactions were Grade 1 or 2 in severity. The most common any grade adverse reactions (>20%) across both studies were vision disorder, nausea, diarrhoea, vomiting, oedema, constipation, and fatigue. The most common Grade 3 or 4 adverse reactions (≥ 3%) across both studies were increased ALT and neutropenia.

The observed effect of crizotinib has been mainly obtained in patients with ALK+ NSCLC and with an histology of adenocarcinoma. Very limited data are available to date in patients with an histology other than adenocarcinoma, but benefit in terms of ORR and DR appeared to be smaller (PFS not provided). This has been mentioned in section 4.4 and 5.1 of the SmPC and additional data/analyses are required in patients with ALK+ NSCLC and an histology other than adenocarcinoma.

The effect of crizotinib on other than ALK mutations is not known, and additional data are expected, but the effect on one mutation may not preclude approval on an other mutations whose efficacy has been demonstrated.

Benefit-risk balance

The benefit/risk of crizotinib in the proposed indication is considered positive.

Additional data (including efficacy and safety) will be needed and should be provided Post-Approval (see Specific Obligation to complete post-authorisation measures) within defined timeframes.

Preliminary results of the comparative study 1007 and updated results from 2 open uncontrolled studies 1001 and 1005 indicate that crizotinib has a positive clinically meaningful benefit as a single agent in previously pre-treated patients with ALK-positive advanced NSCLC.

The benefit/risk of crizotinib in the proposed indication is considered positive based on the results of the uncontrolled studies and a statistically and clinical relevant additional improvement of median PFS of 4.7 months provided by crizotinib compared to second-line chemotherapy in ALK-positive NSCLC (based on Top-line preliminary results from study 1007).

Given that the comparative data (study 1007) are only selected top-line results and the study report has not been made available, only a conditional Approval can be granted and these interesting results must be confirmed by more robust data (full study report) of the direct prospective comparative study (1007) and updated (OS) data from the 2 uncontrolled studies.

Discussion on the benefit-risk balance

Crizotinib is intended as a new target therapy for pre-treated ALK-positive advanced NSCLC. No specific therapy for ALK-positive advanced NSCLC is available at present.

In general, it is considered that the identification of a biomarker that allows the selection of a patient population with a poor prognosis and responsive to the identified target treatment is a promising and valuable therapeutic approach to disease. However, no comparison between ALK-positive NSCLC natural history and treatment response and that of unselected NSCLC was performed. Thus no evidence of a more aggressive disease or unmet medical therapeutic need in ALK positive NSCLC compared to the general population of NSCLC is available.

Preliminary results of the comparative study 1007 and updated results from studies 1001 and 1005 indicate that crizotinib has a positive clinically meaningful benefit as a single agent in mostly previously pre-treated patients with ALK-positive advanced Non Small Cell adenocarcinomas.

The CHMP considered the granting of a conditional marketing authorisation. Xalkori aims at the treatment of seriously debilitating diseases or life-threatening diseases and falls within the scope of Commission Regulation 507/2006 on the conditional marketing authorisation. The Committee found that although comprehensive clinical data referring to the efficacy of the medicinal product had not been supplied, all of the following requirements were met:

- The risk-benefit balance of the medicinal product, as defined in Article 1(28a) of Directive 2001/83/EC, is positive.

Based on the data presented to date, crizotinib has shown important activity with an ORR of 60.3% (95% CI: 51.0%, 69.1%). The median PFS was 9.2 months (95% CI: 7.3 months, 12.7 months; N=125), with a 1-year survival probability of 72%. The crizotinib antitumor activity observed in Study A8081001 is supported by preliminary data from study A8081005, an ongoing, multicenter, multinational, open-label, single-arm, Phase 2 study in patients with previously treated ALK-positive advanced NSCLC and top line results from the ongoing comparative study A8081007. The clinical results obtained to date support the clinical benefit of single agent crizotinib in patients with ALK-positive advanced NSCLC.

- It is likely that the applicant will be in a position to provide comprehensive clinical data.

Randomized Phase 3 studies are ongoing in second-line NSCLC (Study A8081007) and in first-line non-squamous NSCLC (Study A8081014). As of June 2011, Study A8081007, which will confirm the clinical benefit of crizotinib in previously treated patients with ALK-positive advanced NSCLC, was 70% enrolled, and Study A8081007 was completed in June 2012.

- Unmet medical needs to be fulfilled.

Although there are treatments available for NSCLC, there is very limited information on the efficacy of anticancer therapies in ALK-positive NSCLC.

- The benefits to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required.

To date, there are no therapies specifically indicated for the treatment of patients with ALK-positive NSCLC. Molecularly targeted therapies such as crizotinib may offer patients an alternative therapeutic option.

The CHMP considered that the potential risks inherent in marketing Xalkori for the specific indication, while additional, more comprehensive data will be available in the future, would be offset by the potential benefit to the patients. The CHMP agreed that the RMP for Xalkori in the approved indication was adequate to address any identified and unknown risks.

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

4. Recommendations

Outcome

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

Conditions or restrictions regarding supply and use

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

Conditions and requirements of the Marketing Authorisation

Risk Management System

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 3.2 of the Risk Management Plan (RMP) presented in Module 1.8.2 of the marketing authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- at the request of the EMA

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

Prior to launch of the product in each Member State, the Marketing Authorisation Holder (MAH) shall agree the content and format of the educational material with the National Competent Authority.

The MAH should ensure that, at launch and thereafter, all Healthcare Professionals who are expected to use and/or prescribe XALCORI are provided with an educational pack.

The educational pack should contain the following:

1. Summary of Product Characteristics and Package Leaflet.
2. Educational material for Healthcare Professionals.
3. Patient brochure including a Patient Alert Card (text as agreed by the CHMP).

The educational material for Healthcare Professionals should contain the following key elements:

1. XALKORI prolongs the QTc interval which may lead to an increased risk for ventricular tachyarrhythmias (e.g. Torsade de Pointes) or sudden death.
2. The risk of QTc prolongation may be increased in patients concomitantly taking antiarrhythmics and in patients with relevant pre-existing cardiac disease, bradycardia, or electrolyte disturbances (e.g., secondary to diarrhoea or vomiting).
3. XALKORI should be administered with caution to patients:
    a. Who have a history of or predisposition for QTc prolongation.
    b. Who are taking medicinal products that are known to prolong the QT interval.
4. The need for a periodic monitoring with electrocardiograms and electrolytes should be considered when using XALKORI in these patients.
5. Patients who develop a grade 3 QTc prolongation should stop taking XALKORI until recovery to Grade ≤1, then resume at 200 mg twice daily.
6. Patients who develop a grade 4 QTc prolongation should stop taking XALKORI permanently.
7. That XALKORI may cause vision disorders, including diplopia, photopsia, blurred vision, visual impairment, and vitreous floaters.
8. Ophthalmological evaluation should be considered if vision disorder persists or worsens in severity.
9. The concomitant use of XALCORI with strong CYP3A4 inhibitors/inducers and CYP3A4 substrates with narrow therapeutic indices should be avoided.

10. The need to counsel patients about the risk of prolonged QTc and vision disorders and inform them of what symptoms and signs to be aware of and the actions to take.

11. The role and use of the Patient Alert Card.

Obligation to complete post-authorisation measures

The MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to address the question of comparative benefit/risk (crizotinib vs. chemotherapy) in patients with non adenocarcinoma histology ALK positive NSCLC, the MAH must provide additional data/analyses, including comparative data from the comparative study (A8081007) in order to address the benefit/risk of crizotinib (PFS/OS/ORR/safety) versus chemotherapy in ALK positive NSCLC patients according to histology (adenocarcinoma versus other).	Q1 2013

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

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

Description	Due date
The MAH should submit the CSR of study A8081007, expected in Q1 2013. The CSR should also include a detailed analysis of outcome on post-progression treatments in Study 1007 as well as efficacy and baseline data according to race (Caucasian/Asian) by treatment groups.	Q1 2013
The MAH should submit updated safety (SAEs and deaths) and efficacy (PFS, OS) data for both studies 1001 and 1005. The Applicant should compare and explain potential differences in OS for crizotinib in the 3 studies (1001, 1005 and 1007).	Q1 2013
The MAH should submit the safety review of main (severe) hepatic disorders from all available main studies of crizotinib (including 1001, 1005 and 1007).	Q1 2013

New Active Substance Status

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