CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202570Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	202570
Priority or Standard	Priority
Submit Date(s)	March 30th 2011
Received Date(s)	March 30th 2011
PDUFA Goal Date	September 30th 2011
Division / Office	DDOP/OODP/CDER
Reviewer Name(s)	Shakun Malik, MD
Review Completion Date	August 12th 2011
Established Name	Crizotinib
(Proposed) Trade Name	Xalkori
Therapeutic Class	NME
Applicant	Pfizer, Inc
Formulation(s)	Oral(PO)
Dosing Regimen	250mg orally twice daily
Indication(s)	Crizotinib is a kinase inhibitor indicated for the treatment of patients with locally advanced or metastatic anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer.
Intended Population(s)	Adult patients with advanced non-small cell lung cancer harboring a translocation or inversion event involving the Anaplastic Lymphoma Kinase (ALK) gene locus
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PDUFA Goal Date	September 30th 2011

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend approval of the drug crizotinib under accelerate approval regulation 21CFR 314 (Subpart H) for the treatment of patients with locally advanced or metastatic anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer.

My recommendation is based on evaluation of data from two Phase II single arm trials A8081005 (Study A) and A8081001 (Study B);

1. **Overall Response Rate** (ORR) noted in two trials below that is superior to any therapy approved for unselected advanced stage NSCLC and is likely to predict clinical benefit.
    - Study 1005 **(Study A)**: In 136 previously treated patients with advanced (locally advanced or metastatic) NSCLC based on the investigator assessments, there were 1 complete and 66 partial responses for an ORR of 50% (95% CI: 41%, 58%). The ORR by independent review was 42% (95% CI: 32%, 52%). Seventy-nine percent of objective tumor responses were achieved during the first 8 weeks of treatment. The median response duration was 41.9 weeks.

    - Study 1001 **(Study B)**: One hundred nineteen patients with ALK-positive advanced NSCLC were enrolled into Study B at the time of data cutoff. The median duration of treatment was 32 weeks. Based on the investigator assessments, there were 2 complete and 69 partial responses for an ORR of 61% (95% CI: 52%, 70%). The ORR by independent review was 52% (95% CI: 42%, 62%). Fifty-five percent of objective tumor responses were achieved during the first 8 weeks of treatment. The median response duration was 48.1 weeks.

Not all, but majority of these patients had received multiple prior therapies including platinum. The response rate seen in these single arm trials is much superior to any chemotherapeutic regimen even in the first line setting.

1.2 Risk Benefit Assessment

The trials supporting this application were both single arm and non-randomized, the magnitude of crizotinib benefits i.e. response rates of 50% in study A and 61.2 % in Study B was superior to all the drug regimens approved for the treatment of advanced metastatic NSCLC.

Safety however could not be adequately assessed due to the single arm trials. The adverse events noted seem favorable compared to the chemotherapeutic agents approved for NSCLC. The most common adverse reactions (≥25%) are vision disorder, nausea, diarrhea, vomiting, constipation, edema, fatigue, and decreased appetite.(Taken together, the data submitted in this application demonstrated a favorable benefit: risk profile for crizotinib treatment in patients with advanced NSCLC harboring a translocation or inversion event involving the ALK gene locus.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations for Postmarket Requirements and Commitments

To confirm the clinical benefits of crizotinib treatment and to fulfill the requirement for the recommended accelerated approval, the following post-marketed requirements are recommended:

1.4.1 Clinical PMR: Study report and datasets from ongoing Study A8081007, “Phase 3, Randomized, Open-Label Study of the Efficacy and Safety of PF-02341066 versus Standard of Care Chemotherapy (Pemetrexed or Docetaxel) in Patients with Advanced Non- Small Cell Lung Cancer Harboring a Translocation or Inversion Event Involving the Anaplastic Lymphoma Kinase Gene Locus. (Study is ongoing)

1.4.2 Clinical PMR Study report and datasets from A8081014: 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 lung harboring a translocation or Inversion Event Involving the Anaplastic Lymphoma Kinase Gene Locus. (Study is ongoing)

1.4.3 Clinical PMR**:** A clinical trial to explore response to and activity of crizotinib in ALK-negative patients based on current assay cut-off, in comparison to standard therapy and response in ALK-positive patients, additional biomarkers, and adequacy of current cut-off

1.4.4 Clinical PMR: Clinical trial (existing trial or new clinical trial) in which at least 30 patients are studied for the following examinations performed in these patients at baseline, 2 and 6 weeks after drug administration and 2-8 weeks after discontinuation of the therapy (single visit post therapy)

- Best corrected distance visual acuity
- Refractive error associated with best corrected distance visual acuity
- Pupil size under standardized lighting conditions
- Slit lamp biomicroscopy of the anterior segment
- Intraocular pressure
- Ocular coherence tomography of the macula
- Dilated fundus photography of the retina

1.4.5 Clinical Pharmacology PMRs

- Complete the ECG sub-study in trial A8081007 and submit the final study report, along with a thorough review of cardiac safety data to address any potential impact of crizotinib on QTc interval prolongation in patients.
- Conduct a multiple dose trial in humans to determine how to adjust the crizotinib dose when it is co-administered with a strong CYP3A inhibitor (e.g., ketoconazole).
- Conduct a multiple dose trial to determine the appropriate crizotinib dose in patients with various degrees of hepatic impairment.
- Conduct a multiple dose trial to determine the appropriate crizotinib dose in patients with severe renal impairment.
- Conduct a multiple dose trial in humans to determine how to dose crizotinib with regard to gastric pH elevating agents (i.e., a proton-pump inhibitor, an H2-receptor antagonist, and an antacid).
- Submit the study report on the ongoing in vitro evaluations induction potential of crizotinib on CYP2B and CYP2C enzymes
- **PMC:** To conduct exposure-response analysis for progression free survival, response rate, overall survival and safety endpoints utilizing data from confirmatory trials A8081007 and A8081014.

2 Introduction and Regulatory Background

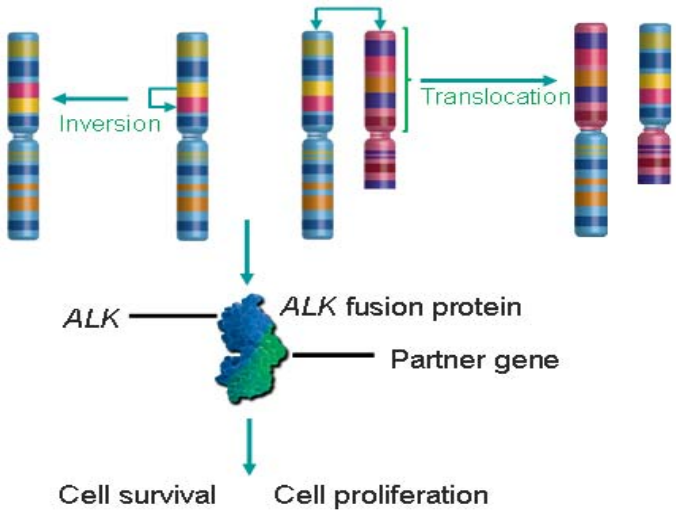
Lung Cancer remains the number one cause of cancer deaths in United States (1) and the World (2). The 5 year survival rate for patients with lung cancer remains dismal around 15% (3). Tobacco smoke exposure is a known cause of this cancer in most of the cases, however 10% -15 % of the patients are never/light smokers defined as less than 100 cigarettes in their lifetime. NSCLC histology comprises about 85% of the lung cancer cases and although surgery remains the only curative modality for this disease, most of these patients (70%) present at advanced stage and thus are not surgical candidates.

Despite multiple subtypes of NSCLC per WHO Criteria (4) until recently first-line treatment for advanced disease was platinum-based doublet chemotherapy. With the discovery of molecular targets and targeted therapies, new treatment options for these patients are evolving.

Bevacizumab a monoclonal antibody directed against vascular endothelial growth factor-A (VEGF-A) is approved, with carboplatin and paclitaxel, for first line treatment of unresectable, locally advanced, recurrent or metastatic non-squamous non-small cell lung cancer. Erlotinib, an Epidermal Growth Factor Receptor (EGFR) tyrosine kinase inhibitor, has been approved for treatment of locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen and for maintenance treatment of patients with locally advanced or metastatic NSCLC whose disease has not progressed after four cycles of platinum-based first-line chemotherapy. Although both these targeted agents approved for NSCLC do not require demonstration of specific molecular abnormalities in patient's tumor tissue, there is an increasing awareness of the importance of identifying specific NSCLC molecular drivers to appropriately direct targeted agents to patient populations. The literature review demonstrates that in clinical trials, when compared to chemotherapy, EGFR tyrosine kinase inhibitors are associated with a high response rate (70-80%) in NSCLC patients whose tumor harbor's EGFR favorable mutations (either del19 or exon 21 L858R) that is associated with improved PFS (5,6), however; no over all survival advantage has been demonstrated so far.

Soda et al recently discovered an inversion within chromosome 2p resulting in the formation of a fusion gene product associated protein-like 4 (EML4) gene and the ALK gene in NSCLC cell lines and archived clinical specimens (7). *EML4–ALK* fusion gene has been identified as a **key driver of oncogenesis** in a subset of NSCLC patients. *ALK* fusion gene results in formation of cytoplasmic chimeric proteins with constitutive kinase activity. Since then a number of variants of the EML4-ALK fusion gene have been discovered rarer fusion partners for *ALK* such as *KIF5B* and *TFG* have also been reported (8).

Figure 1 EML4-ALK fusion gene



In unselected population of patients with NSCLC the frequency of EML4-ALK has ranged from 1.5% to 6.7% (8-14), however in small series of selected population of never/light smokers the frequency noted has been significantly higher (15). The majority of ALK gene rearrangements have been observed in younger patients with adenocarcinoma histology with never or light smoking history (7, 12-16). ALK gene rearrangements have been rarely noted to be coincident with EGFR, human epidermal growth factor receptor 2 (HER2), or Kirsten rat sarcoma (KRAS) mutations (17).

During the Phase 1 study of crizotinib, 2 patients in the 50 mg cohort with ALK positive NSCLC were found to have stable disease at 1.5 and 7 months. This led to the inclusion of a Phase 2 extension cohort enrolling patients with ALK positive NSCLC.

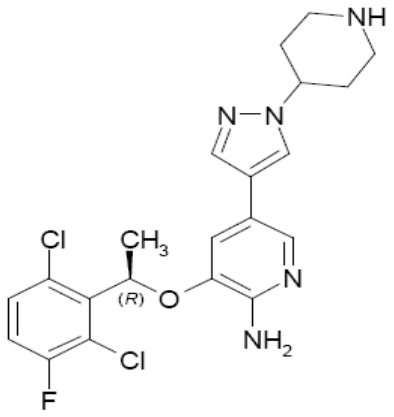
2.1 Product Information

Crizotinib is an oral receptor tyrosine kinase inhibitor. The molecular formula for crizotinib is $C_{21}H_{22}Cl_2FN_5O$. The molecular weight is 450.34 Daltons. Crizotinib is described chemically as (*R*)-3-[1-(2,6-Dichloro-3-fluorophenyl)ethoxy]-5-[1-(piperidin-4-yl)-1*H*-pyrazol-4-yl]pyridin-2-amine.

It is a selective adenosine triphosphatase (ATP)-competitive small-molecule inhibitor of ALK and c-Met/hepatocyte growth factor receptor (HGFR) tyrosine kinases and their oncogenic variants (i.e., ALK fusion proteins or c-Met/HGFR mutant variants). The drug demonstrated potent and selective growth inhibitory activity and induced apoptosis in tumor cell lines exhibiting ALK fusion events or exhibiting amplification of the ALK or MET gene locus and inhibited ALK and c-Met phosphorylation and anti-tumor efficacy in

models dependent on ALK and c-Met signaling. Antitumor efficacy was dose-dependent and correlated to inhibition of ALK fusion proteins (including EML4-ALK and NPM-ALK) in tumors in vivo.

Figure 2 Structural formula of Crizotinib



Molecular Formula	Molecular Weight
$C_{21}H_{22}Cl_2FN_5O$	450.34 Daltons

The commercial crizotinib drug product is a hard gelatin capsule formulation in two strengths (200 mg and 250 mg), with a [redacted] (b) (4) being used for capsule filling. The excipients (including the components in gelatin capsule shell and printing ink) used for manufacturing the drug product are all compendial grade. Crizotinib capsules 200 mg will be provided as white opaque/pink opaque hard gelatin capsules with “CRZ 200” printed on the body and “Pfizer” printed on the cap. The 250 mg strength will be provided as pink opaque/pink opaque hard gelatin capsules with “CRZ 250” and “Pfizer” printed on body and cap, respectively. The drug product will be packaged in HDPE bottles with child-resistant caps (60 counts/bottle).

Three formulations (powder in capsule (PIC), immediate release tablet, and intravenous solution) were used in clinical trials prior to the commercial capsule. The PIC formulation (10 mg, 50 mg, and 100 mg) was used for early stage Phase I studies. The immediate release tablet (50 mg and 100 mg) formulation, with [redacted] (b) (4) drug loading, was later developed to meet the increased demand for further clinical trials. However, due to the lower drug loading of the tablet, the commercial capsule formulation was developed

for administration convenience. The tablets and capsules use qualitatively similar excipients. The IV solution was developed for use in the absolute bioavailability study.

Device

Study A used the Vysis ALK Break Apart FISH Probe Kit to detect the presence of an ALK gene rearrangement and to thus, determine patient eligibility for study entry. The Vysis kit will be marketed as a qualitative test to detect rearrangements involving the ALK gene via fluorescence in situ hybridization (FISH) in formalin-fixed, paraffin-embedded NSCLC tissue specimens. Testing will be performed to aid in the identification of patients eligible for treatment with crizotinib. The kit uses formalin-fixed, paraffin-embedded tissue sections which have been mounted to glass slides. The tissue sections are deparaffinized and the DNA within the nuclei denatured to a single-stranded form. The DNA is then hybridized to 2 anti-sense ALK probes. During hybridization, the green probe binds to DNA within the ALK gene while the orange probe binds to DNA that is 3' to ALK gene. Following hybridization, the specimens are washed and the nuclei counterstained with 4,6 diamidino-2-phenylindole, a DNA-specific stain that fluoresces blue. Hybridization of the Vysis probes is viewed using a fluorescence microscope equipped with appropriate excitation and emission filters, allowing visualization of the orange and green fluorescent signals. When the ALK gene is rearranged, the green and orange probes are no longer next to each other and a split signal (green and orange signals separated by at least 2 signal diameters), single orange, or single green signal is seen. If $\geq$ 15 cells out of 100 contain a split signal, a single orange signal, or a single green signal the specimen contains an ALK gene rearrangement. Tests of the reproducibility of specimen interpretation between readers showed a kappa score of 0.72, suggesting substantial reproducibility. Tests of the reproducibility of specimen interpretation in the same reader showed an overall percent agreement of 100% (95% CI; 83.9,100). Reproducibility was also tested between laboratories. Here, the kappa score was 0.92, suggesting almost perfect reproducibility.

2.2 Tables of Currently Available Treatments for Proposed Indications

Currently there are no therapies that have been specifically approved for NSCLC patients with tumors harboring a translocation or inversion event involving the ALK gene locus. Discovery of this genetic alteration in the tumor of patients with NSCLC makes this a new subset for NSCLC patients. However, ALK positive patients have been traditionally treated with therapies for NSCLC.

All of the approved therapies for unresectable, locally advanced, recurrent or metastatic disease NSCLC have been based on improvement in overall survival compared to a comparator.

Table 1 Approved Therapies for advanced/metastatic NSCLC

Drug	Indication
Bevacizumab Non-squamous NSCLC	Initial treatment, in combination with carboplatin and paclitaxel
Docetaxel	After platinum therapy failure
	Initial treatment, in combination with cisplatin
Erlotinib	Maintenance treatment for patients whose disease has not progressed after four cycles of platinum based first-line chemotherapy
	After failure of at least 1 prior chemotherapy regimen
Gemcitabine	Initial treatment, in combination with cisplatin
Paclitaxel	Initial treatment, in combination with cisplatin
Pemetrexed Non-squamous NSCLC	Initial treatment in combination with cisplatin
	Maintenance treatment for patients whose disease has not progressed after four cycles of platinum based first-line chemotherapy
	After prior chemotherapy as a single agent
Vinorelbine	single agent or in combination with cisplatin for the first-line treatment of ambulatory patients

2.3 Availability of Proposed Active Ingredient in the United States

The commercial dosage formulation for crizotinib was developed as an immediate release hard gelatin capsule to deliver 200 mg and 250 mg crizotinib, using the (b) (4) (b) (4) approach at (b) (4) drug loading. A150 mg strength was also developed, but not proposed for commercialization. It was used during development and is now included in registration stability studies to bracket the 200 mg strength.

Please refer to CMC review

2.4 Important Safety Issues with Consideration to Related Drugs

Although several tyrosine kinase inhibitors have been approved, this is the first drug which inhibits the ALK gene.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

In October 2007, the applicant's Phase 1 trial was amended to include a Phase 2, ALK positive NSCLC cohort. The applicant, noting a partial response in 7/14 ALK positive patients, met with the Agency to discuss their registration strategy. The Agency expressed concern about the size of the database and recommended that the applicant conduct a randomized trial of crizotinib vs. conventional therapy. The Agency did suggest that if the applicant chose to pursue accelerated approval, "that you entertain a randomized study with an interim analysis of a surrogate end point in a larger population." In April 2010, the applicant again met with the Agency to discuss their registration strategy. They proposed the submission of 2 single arm studies of crizotinib in ALK positive NSCLC. The Agency stated that such a strategy may be acceptable for accelerated approval and noted that the overall registration strategy included the following studies.

- A8081007: Phase 3, Randomized, Open-label Study of the Efficacy and Safety of Crizotinib vs. Standard of Care (Pemetrexed or Docetaxel) in Patients with Advanced NSCLC Harboring a Translocation or Inversion Event Involving the Anaplastic Lymphoma Kinase Gene Locus
    - Patients will have received 1 prior platinum-based regimen. There is 1 interim analysis at 60% of events with α = 0.0038. At the final analysis, with 318 patients, the study will have 90% power to detect an improvement in PFS from 2.9 to 4.4 months with α = 0.025 and an 80% power to detect an improvement in OS from 8 to 11.5 months with α = 0.025.

- A8081014: Phase 3, Randomized, Open-label Study of the Efficacy and Safety of Crizotinib vs. Pemetrexed/Cisplatin or Pemetrexed/Carboplatin in Previously Untreated Patients with Non-Squamous Carcinoma of the Lung Harboring a Translocation or Inversion Event Involving the Anaplastic Lymphoma Kinase Gene Locus.
    - With 334 patients, the study will have 85% power to detect an improvement in PFS from 6 to 9 months with α = 0.025.

Key Meetings between the FDA and the Sponsor

23 April 2009: Type B meeting held to discuss the crizotinib registrational strategy and the study design for treatment of advanced NSCLC patients with tumors harboring an EML4-ALK fusion.

24 July 2009**:** A joint Pfizer and Abbott Molecular Diagnostic meeting with FDA's Office of In Vitro Diagnostics (OIVD) held to discuss the requirements for an investigational use only (IUO) assay.

14 April 2010: Type B meeting held to discuss sponsor's proposal for accelerated approval under Subpart H for crizotinib, based on studies A8081001 and A8081005. The registration strategy and the study design for previously untreated locally advanced or metastatic non-small cell lung cancer (NSCLC) positive for Anaplastic Lymphoma Kinase (ALK) fusion was also discussed.

11 May 2010: A joint Pfizer and Abbott Molecular Diagnostic meeting with FDA's OIVD held to respond to questions from the Agency regarding Pfizer's request for accelerated approval of crizotinib, discuss the potential for expedited review status and approval of the Vysis ALK BAP kit, and clarify the previously discussed concordance study in view of the proposed accelerated drug approval pathway.

29 July 2010: Type B Pre-NDA meeting to reach agreement between the sponsor and the Agency regarding the content and format of the NDA to be submitted for accelerated approval.

8 September 2010: Type B clinical pharmacology meeting scheduled to reach agreement on the content of the NDA related to clinical pharmacology. Pfizer agreed with FDA's feedback and cancelled the meeting. Pfizer's responses to FDA's internal meeting minutes were submitted to the crizotinib IND.

29 October 2010: Type B CMC meeting held to obtain agreement on several key development strategies that the Applicant is pursuing in preparation of the NDA.
15 February 2011: Type B follow-up CMC meeting scheduled to provide additional information and receive feedback on topics identified at the October 29, 2010 face to face meeting. Pfizer agreed with FDA's feedback and cancelled the meeting. Pfizer's responses to FDA's internal meeting minutes were submitted the crizotinib IND.

2.6 Other Relevant Background Information

07/14/2009 NO AGREEMENT SPECIAL PROTOCOL ASSESSMENT (SPA) On May 29, 2009, Pfizer submitted a clinical protocol titled "Phase 3, Randomized, Open-Label Study of the Efficacy and Safety of PF-02341066 Versus Standard of Care

Chemotherapy (Pemetrexed or Docetaxel) inpatients With Advanced Non-Small Cell Lung Cancer (NSCLC) Harboring a translocation or Inversion Event Involving the Anaplastic Lymphoma Kinase (ALK) Gene Locus." for special protocol assessment (SPA)

September 13, 2010: orphan status granted

March 31, 2011: PMA for Vysis ALK Break-Apart FISH Probe Kit Assay – submitted by Abbott Molecular

3 Ethics and Good Clinical Practices

The study was managed by Pfizer, Inc (the sponsor) and conducted by investigators contracted by and under the direction of the sponsor. The investigators were responsible for adhering to the study procedures described in the protocol, for keeping records of study drug, and for accurately completing and signing the CRFs/DCTs supplied by the sponsor.

The Sponsor relates that this study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. In addition, all local regulatory requirements were followed; in particular, those affording greater protection to the safety of study participants.
The final protocol, any amendments and informed consent documentation were reviewed and approved by the Institutional Review Board(s) (IRB) and/or Independent Ethics Committee(s) (IEC) at each of the investigational centers participating in the study.
Written informed consent was obtained prior to the patient entering the study (before initiation of protocol-specified procedures). The investigators explained the nature, purpose, and risks of the study to each patient. Each patient was informed that he/she could withdraw from the study at any time and for any reason. Each patient was given sufficient time to consider the implications of the study before deciding whether to participate. Patients who chose to participate signed an informed consent document.

Analysis of pharmacokinetic (PK) samples was performed by (b) (4) .

Anaplastic lymphoma kinase (ALK) testing by a Clinical Trial Assay (CTA) was performed by local laboratories. If a sample was not tested by the (b) (4) CTA, then samples were to be sent to (b) (4) for confirmation when possible.

ALK-positive status for eligibility in the ALK-positive non-small cell lung cancer (NSCLC) cohort was based on having a positive test by either the MGH fluorescence in situ hybridization (FISH-CTA or a local laboratory CTA.

ALK-negative status for inclusion into the ALK-negative non-small cell lung cancer (NSCLC) cohort was determined by the Investigational Use Only (IUO) assay (Abbott Molecular, Des Plaines, IL, US). Data management, data analysis, biostatistics, and medical writing were performed by the study

3.1 Submission Quality and Integrity

- Submission contains all components of e-CTD.
- Information in the datasets was compared to information contained in about 50% of the case report forms and was found to be acceptable. Electronic case report forms were used and all case report forms were submitted.
- Inspections of Massachusetts General Hospital (Drs. Jeffrey Clark and Alice Shaw), Seoul National University Hospital (Drs. Dong-Wan Kim and Yung-Jue Bang), and Pfizer by the Office of Scientific Investigation were classified as no action indicated or voluntary action indicated. Case report forms were compared to the source documents and were found to be reliable.

3.2 Compliance with Good Clinical Practices

The study was managed by Pfizer, Inc (the sponsor) and conducted by investigators contracted by and under the direction of the sponsor. The investigators were responsible for adhering to the study procedures described in the protocol, for keeping records of study drug, and for accurately completing and signing the CRF's supplied by the sponsor.

Submission contains the statement that these studies were conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. In addition, all local regulatory requirements were followed; in particular, those affording greater protection to the safety of study participants.

Written informed consent was obtained prior to the patient entering the study. The investigators explained the nature, purpose, and risks of the study to each patient. Each patient was informed that he/she could withdraw from the study at any time and for any reason. Each patient was given sufficient time to consider the implications of the study before deciding whether to participate. Patients who chose to participate signed an informed consent document.

The sponsor adds the following additional steps taken to minimize potential bias:

- Independent expert opinion sought for input into study design
- Study conducted at multiple sites
- The facilities performing the safety and efficacy evaluations were determined to be acceptable based on appropriate certification or historical performance and/or qualifications and credentials.
- Frequent monitoring of investigator trial sites
- The validity of the data collected during the study was confirmed by standard monitoring procedures.
- Selected individual sites were audited.
- During the course of processing data for this clinical trial, and as defined in the Data Management Plan, cleaning checks (e.g., querying data through electronic edit checks) were utilized to ensure that errors were identified and corrected.
- Subjects remained in the dose group they were enrolled in.
- The preliminary study report was appropriately reviewed by members of the project team and underwent review by Quality Control and Quality Assurance.
- Appropriate statistical methods were employed by I\I>e of an approved statistical analysis plan. Any changes to planned analyses were documented in the clinical study report.
- Assessments were performed at the time points for all subjects as specified in the protocol, except for discontinued subjects. Subjects who discontinued from study treatment early were asked to perform all end of treatment assessments provided subject safety was not compromised.
- All available scans were sent retrospectively to a third party radiology laboratory for confirmation of investigator derived tumor measurements.
- All available tumor samples were sent to an independent laboratory for confirmatory ALK testing.

OSI (Office of Scientific Investigations) at the FDA clinical branch audited four clinical investigators – Clark, Shaw, Kim, Bang and found that the clinical and toxicity data reported in the NDA appear reliable.

3.3 Financial Disclosures

The sponsor disclosed financial arrangements with investigators on Studies A and B as recommended in FDA guidance on *Financial Disclosure by Clinical Investigators*.

Per US FDA Form 3454, certification was provided for 1162 of the 1190 investigators listed in the study reports indicating:

- Certified investigators. A total of 1162 of the investigators were certified as having no Financial Arrangement as defined in 21 CFR 54.2.
- Due Diligence investigators. There were no Due Diligence investigators for these

studies.

Per US FDA Form 3455, 28/1190 investigators listed in the study report had financial information to disclose.

- 25 of the 28 investigators listed on the US FDA Form 3455 had significant payments of other sorts to disclose.
- 3 of the 28 investigators listed on the US FDA Form 3455 had equity in the sponsor to disclose.

The sponsor stated that all Investigator Initiated Research Grants associated with our investigators are paid directly to the Institution rather than to the individual investigator.

After review of the financial disclosure of the application following IR (information request was sent to the sponsor on May 16th 2011 as follows:

The payment for patient participation expenses are usually paid to the participating institution. Please explain the reason for the personal payments to the following PI's and sub-PI's.

(b) (6)		$155,200.00
		$56,913.00
		$52,000.00
		$57,500.00
		$42,750.00

The sponsor responded on May 24th, 2011 with the following:
The payments under Pfizer Expense Code 2140 (P/S Administrative & Commercial) (b) (6) incorrectly associated with (b) (6) Thus the total payments made to (b) (6) (b) (6) drop from $56,913.00 to $11,913.00. Therefore, (b) (6) should not be part of Form 3455 as his total payment was under $25,000.00.
Additionally, it should be noted that two Financial Disclosure Forms 3455 were provided for (b) (6) one for Study A8081005 and one for Study A8081007. Payments totaling $27,500.00 were recorded on Form 3455 for Study A8081005 as well as on Form 3455 from Study A8081007. Thus, this investigator received total payments from Pfizer of $30,000 as noted in the Financial Disclosure Form 3455 for Study A8081007.

Individual	Total Payments	Pfizer Expense Codes - Description
(b) (6)	$155,200.00	2164 – Scientific Consultantships 219H – TASAP – HCP 21M7 – Ad Board Mtgs - Honoraria
	~~$56,913.00~~ $11,913.00 Note explanation above.	2124 – DSMB Mtg – HCP Pmt (Honoraria) 2140 – P/S Administrative & Commercial 2164 – Scientific Consultantships 216H – Clinical Inv. Mtgs – Honoraria
	$52,000.00	219H – TASAP - HCP
	~~$57,500.00~~ $30,000.00 Note explanation above.	451H – Advisory Board – HCP Honoraria 4543 – Symposia Speakers 454H – Mkt Speaker Programs / HCP Honoraria 457H – HCP Consulting Honoraria
	$42,750.00	4543 – Symposium Speakers

TASAP: Therapeutic Area Scientific Advisory Panel
HCP: Health Care Professional
DSMB: Data Safety Monitoring Board
P/S: Professional Services

Reviewer's Comments: The number of subjects enrolled from these investigators is small and thus the financial disclosures do not raise questions about data integrity in Study A and B.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

4.2 Clinical Microbiology

NDA 202-570 is recommended for approval from the standpoint of product quality microbiology.

Refer to full Micro review

4.3 Preclinical Pharmacology/Toxicology

ALK is in normally expressed in neural cells, pericytes, and the endothelial cells of the adult brain. However, in repeat dose toxicology studies in the dog and rat, abnormalities were noted in the liver, gastrointestinal tract, heart, lymph nodes, and bone marrow. In animal studies, it was also noted that crizotinib concentrated in the eye with a half-life of 576 hours. Electroretinogram in the rat showed reduced dark adaption, but there were no treatment related ophthalmic findings in the repeat dose toxicology studies. An increase in QTc was seen in dog studies and crizotinib inhibits hERG at a concentration of 1.1 μM.

Crizotinib, based on the in vitro chromosome aberration assay and the in vivo micronucleus assay, is genotoxic, but it is not mutagenic (Ames assay). In reproductive toxicology studies, there was maternal mortality, post-implantation fetal loss, and decreased fetal weight. Teratogenicity was not seen. Crizotinib has been assigned Pregnancy Category D.

This application was recommended for approval by Pharmacology/Toxicology. The team states that the non-clinical studies submitted to this NDA provide sufficient information to support the use of crizotinib in the treatment of anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer.

Refer to full Pharmacology/Toxicology review

4.4 Clinical Pharmacology

Crizotinib is absorbed orally (more soluble in acid pH) and can be taken with or without food. Peak concentration is reached 4-6 hours after dosing and the terminal half-life is 42 hours. In patients taking crizotinib 250 mg twice a day, steady state is reached in 15 days. Crizotinib is metabolized in the liver by CYP3A4/5. Following oral administration, 63% of crizotinib is recovered in the feces and 22% in the urine. Crizotinib acts as a moderate CYP3A inducer and inhibitor and drug-drug interaction occurs with strong CYP3A inhibitors or inducers.

Crizotinib is highly protein bound and at steady state, the crizotinib mean AUC_{trough} is 3,880 ng·hr/mL while the median C_{trough} ranged from 242 to 319 ng/mL over cycles 1-4. The applicant estimates that these concentrations are capable of inhibiting kinases in which the IC_{50} < 114 nM. Despite this, in Study B an exposure-response relationship was seen between steady state trough concentration and patient response. The exposure-response relationship was less clear in Study A. No exposure-adverse event relationship was seen for crizotinib concentration and respiratory and liver related adverse events. Since it may be possible to increase the dose of crizotinib (dose limiting

toxicity in the Phase 1 study was fatigue in 2 patients), the clinical pharmacology group plans to examine this further in Studies 1007 and 1014.

This application was recommended for approval by clinical pharmacology

Refer to full clinical Pharmacology review

4.4.1 Mechanism of Action

Crizotinib is an inhibitor of receptor tyrosine kinases including ALK, Hepatocyte Growth Factor Receptor (HGFR, c-Met), and Recepteur d' Origine Nantais (RON). Crizotinib demonstrated concentration-dependent inhibition of ALK and c-Met phosphorylation in cell-based assays using tumor cell lines and demonstrated antitumor activity in mice bearing tumor xenografts that expressed EML4- or NPM-ALK fusion proteins or c-Met.

Refer to full clinical Pharmacology review

4.4.2 Pharmacodynamics

Metabolism

In vitro studies demonstrated that CYP3A4/5 were the major enzymes involved in the metabolic clearance of crizotinib. 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. *In vitro* studies in human liver microsomes demonstrated that crizotinib is a time-dependent inhibitor of CYP3A

Elimination

Following single doses of crizotinib, the apparent plasma terminal half-life of crizotinb was 42 hours in patients. Following the administration of a single 250 mg radiolabeled crizotinib dose to healthy subjects, 63% and 22% of the administered dose was recovered in feces and urine, respectively. Unchanged crizotinib represented approximately 53% and 1.3% of the administered dose in feces and urine, respectively.

Refer to full clinical Pharmacology review

4.4.3 Pharmacokinetics

Following oral administration of crizotinib, C_{max} was reached at 4 to 6 hours, with a terminal half-life of 42 hours in patients. The absolute oral bioavailability is 43%.

Crizotinib can be dosed without regard to food, as a standard high-fat meal reduces AUC_{inf} and C_{max} by only 15%.
Crizotinib demonstrated non-linear PK in humans in terms of dose proportionality and time-dependence. The steady state systemic exposure of crizotinib appears to increase with doses in a greater-than-proportional manner in the dose range of 200-300 mg BID. Following 250 mg crizotinib BID, steady state is reached within 15 days with an accumulation ratio of 4.5, and the exposure stayed stable over the treatment period of 112 days. However, apparent clearance (CL/F) at steady state (64 L/hr) was lower than that after a single dose (100 L/hr), likely due to auto-inhibition of CYP3A by crizotinib. In the mass balance trial with a single 250-mg dose of [^{14}C] crizotinib, the mean recovery of administered dose was 85%, with 63% (53% unchanged) in feces and 22% (1.3% unchanged) in urine. No dose adjustment is needed for mild or moderate renal impairment, as mean $C_{trough,ss}$ in these two groups are similar to that in normal renal function group. The effects of severe renal impairment and hepatic impairment are unknown.

Crizotinib is predominantly metabolized by CYP3A4/5 *in vitro*. At the same time, crizotinib is also a reversible inhibitor and a time-dependent inhibitor of CYP3A. Furthermore, crizotinib is possibly a CYP3A inducer, as crizotinib increases CYP3A4 mRNA levels by up to 29 fold, with no increase in CYP3A enzyme activity. *In vivo*, crizotinib at steady-state increases the AUC of midazolam by 3.7 fold, compared to midazolam alone. For a single dose of crizotinib, coadminstration of ketoconazole (a strong CYP3A inhibitor) increases the crizotinib AUC by 3.2 fold, while rifampin (a strong CYP3A inducer) decreases the crizotinib AUC by 82%. However, due to time-dependent inhibition on CYP3A by crizotinib, the effects of strong CYP3A inducers and inhibitors on the steady-state PK of crizotinib are unclear.

Crizotinib is not an inducer of CYP1A2. The potential of crizotinib to induce CYP2B or CYP2C *in vitro* is currently being evaluated by the sponsor. *In vitro,* crizotinib is a substrate and an inhibitor of P-glycoprotein (P-gp). It is not a substrate of breast cancer resistance protein (BCRP) or hepatic uptake transporters.

As the aqueous solubility of crizotinib is pH dependent, with higher pH resulting in lower solubility. Drugs that elevate the gastric pH may decrease the solubility of crizotinib and subsequently reduce its bioavailability. No formal drug interaction study has been conducted yet.

An exposure-response analysis was conducted for PFS in trials A8081005 and A8081001. According to the Kaplan-Meir plots based on concentration quartiles, there is a trend for increase in PFS with increasing exposure in A8081001 but this trend was not seen in A8081005. The analysis for trial A8081005 is considered preliminary because data are not fully mature at the time of cut-off.

Refer to full clinical Pharmacology review

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 2 Clinical Trials

Study Reports of Clinical Studies Pertinent to Clinical Efficacy and Safety							
A8081001 (Australia, Republic of Korea, United States)	Open-label, multicenter, multinational, dose-escalation, safety, PK, PD, and efficacy study of crizotinib in patients with advanced cancer	**Dose Escalation Cohort** Crizotinib Route: Oral Dose Regimen: 50-mg QD, 100-mg QD, 200 mg QD 200-mg BID 250-mg BID 300-mg BID **Recommended Phase 2 Dose (RP2D) Cohort** Crizotinib Route: Oral; Dose Regimen: 250-mg BID ALK-positive NSCLC ALK-negative NSCLC	Planned: 40 Enrolled: 38 Treated*: 36 Ongoing: 1 Planned ≥25 Enrolled: 119 Treated*: 119 Ongoing: 77 Enrolled: 5 Treated*: 5 Ongoing: 3 Enrolled: 50	Sex: 21M/15F Mean Age (min/max): 48.6 years (19-69) Race: 32W/1B/1A/2O Sex: 59M/60F Mean Age (min/max): 50.9 years (21-79) Race: 74W/3B/ 34A/8O Sex: 2M/3F Mean Age (min/max): 52.2 years (46-63) Race: 5W/0B/	Median treatment duration (min/max): 8.0 weeks (1.0-131.0) Median treatment duration (min/max): 31.9 weeks (0.7-101.7) Median treatment duration (min/max): 4 weeks (0.1-9.0)	19 April 2006/ Ongoing, data cutoff date 15 September 2010, database snapshot date 1 November 2010	A8081001

A8081005 (Australia, Canada, France, Germany, Hong Kong, Italy, Japan, Republic of Korea, Poland, Russian Federation, Spain, United States)	Open-label, single-arm, multicenter, multinational, Phase 2 study of efficacy and safety of crizotinib in patients with advanced ALK-positive NSCLC	Crizotinib Route: Oral; Dose Regimen: 250-mg BID	Planned: 250 Enrolled: 148 Treated*: 136 Ongoing: 119	Sex: 64M/72F Median Age (min/max): 52 years (29-82) Race: 87W/5B/43A/O1	Median treatment duration (min/max) 9 weeks (0.1- 36.1)	07 January 2010/ Ongoing, data cutoff date 15 September 2010, database snapshot date 29 October 2010	A8081005
A8081007 (Australia, France, Germany, Hungary, Italy, Japan, Republic of Korea, Russian Federation, Spain, United Kingdom, United States)	Open-label, randomized, multicenter, multinational, two-arm, Phase 3, study of the efficacy and safety of crizotinib versus standard of care chemotherapy (pemetrexed or docetaxel) in patients with advanced ALK-positive NSCLC	Crizotinib Route: Oral; Dose Regimen: 250-mg BID Standard of care Route: IV Dose Regimen: Pemetrexed 500 mg/m^2 or Docetaxel 75 mg/m^2 Day 1, every 21 days	Planned: 318 Treated with crizotinib*: 36	NA	NA	18 September 2009/Ongoing, database snapshot date 27 October 2010	A8081007

Study Reports of Pharmacokinetic Studies in Healthy Volunteers							
A8081008 (United States)	Open-label, 2-treatment, crossover, Phase 1 study of the relative bioavailability and safety of crizotinib powder-in-capsule (PIC) and immediate release tablet (IRT) formulations in healthy volunteers	Crizotinib Route: Oral Dose Regimen: 250-mg single dose	Planned : 20 Enrolled: 24 Treated: 24 Completed: 24	Sex: 24 M/0 F Mean Age (min/max): 32.1 years (19-53) Race: 5 W/14 B/1 A/4O	2 single doses (PIC, IRT) separated by ≥14 day washout	16 July 2009/ 31 August 2009	A8081008
A8081009 (United States)	Open-label, Phase 1, single-radiolabeled dose study of absorption, metabolism and excretion of [^{14}C]crizotinib in healthy male volunteers	[^{14}C]crizotinib Route: Oral Dose Regimen: 250-mg single dose	Planned: 6 Treated: 6 Completed: 6	Sex: 6 M/0F Mean Age (min/max): 43.2 years (41-45) Race: 2W/3B/1O	Single dose	15 March 2010/ 21 April 2010	A8081009
A8081010 (Belgium)	Open-label, 2-treatment, crossover, Phase 1 study of the absolute bioavailability and safety of crizotinib administered orally and IV in healthy volunteers	Crizotinib Route: Oral, IV Dose Regimen: 250-mg (oral), 50-mg (IV)	Planned: 14 Enrolled: 14 Treated: 14 Completed: 14	Sex: 14M/ 0F Mean Age (min/max): 35.7 years (19-55) Race: 13W/1O	Single oral dose and single IV (2 hr) dose separated by a 14 day washout	24 August 2010/ 29 September 2010	A8081010
A8081011 (Belgium)	Open-label, 4-treatment, crossover, Phase 1, bioequivalence and food effect study in healthy volunteers comparing 3 crizotinib formulations (the commercial image capsules [CIC] to the IRT and PIC) and the CIC in the fasted to fed state.	Crizotinib Route: Oral; Dose Regimen: 250-mg single dose	Planned: 36 Enrolled: 36 Treated: 36 Completed: 34 for IRT, 35 for PIC and CIC (fasted and fed)	Sex: 36 M/0 F Mean Age (min/max): 38.9 years (22-55) Race: 32W/3B/1O	4 single doses, each separated by 14-day washout	August 2010/ November 2010	A8081011

Protocol No. (Country)	Study Design and Objective	Treatment Groups	No. of Subjects	Demographics	Duration of Treatment	Study Start/Status	Study Report Location
A8081015 (United States)	Open-label, 2-treatment, crossover, Phase 1 study to estimate the effect of multiple doses of ketoconazole on the single dose pharmacokinetics of crizotinib in healthy volunteers	Route: Oral Dose Regimen: Crizotinib 150-mg single dose Ketoconazole 200-mg BID for 16 days	Planned : 15 Enrolled: 15 Treated: 15 Completed: 15	Sex: 15 M/0 F Mean Age (min/max): 36.5 years (22-49) Race: 13W/2B	2 single doses of crizotinib with or without ketoconazole separated by a 14-day washout.	22 July 2010/ 03 September 2010	A8081015
A8081016 (United States)	Open-label, 2-treatment, crossover, Phase 1 study to estimate the effect of multiple dose rifampin on the single dose pharmacokinetics of crizotinib in healthy volunteers	Route: Oral Dose Regimen: Crizotinib 250-mg single dose Rifampin 600-mg QD for 14 days	Planned : 15 Enrolled: 15 Treated: 15 Completed: 14	Sex: 14 M/1 F Mean Age (min/max): 38.9 years (30-55) Race: 15W/0B/0O	2 single doses of crizotinib with or without rifampin separated by a 14-day washout	26 July 2010/ 08 October 2010	A8081016

*Number of patients treated with crizotinib starting on Cycle 1, Day 1
Abbreviations: A = Asian, ALK = Anaplastic Lymphoma Kinase, B = Black, BID = Twice daily, CIC = commercial image capsule, F = Female, IRT = immediate release tablet, IV = Intravenous, M = Male, NA = Not available, No = Number, O = Other, PD = pharmacodynamics, PIC = powder-in-capsule, PK = pharmacokinetics, QD = once daily, RP2D = recommended phase 2 dose, W = White

KEY ONGOING TRIALS

A8081007: Phase 3, Randomized, Open-label Study of the Efficacy and Safety of Crizotinib vs. Standard of Care (Pemetrexed or Docetaxel) in Patients with Advanced NSCLC Harboring a Translocation or Inversion Event Involving the Anaplastic Lymphoma Kinase Gene Locus; and

- Patients entering A8081007 will have received 1 prior platinum-based regimen. There is 1 interim analysis at 60% of events with $\alpha = 0.0038$. At the final analysis, with 318 patients, it will have 90% power to detect an improvement in PFS from 2.9 to 4.4 months with $\alpha = 0.025$. A8081007 will also have 80% power to detect an improvement in OS from 8 to 11.5 months with $\alpha = 0.025$.

A8081014: Phase 3, Randomized, Open-label Study of the Efficacy and Safety of Crizotinib vs. Pemetrexed/Cisplatin or Pemetrexed/Carboplatin in Previously Untreated Patients with Non-Squamous Carcinoma of the Lung Harboring a Translocation or Inversion Event Involving the Anaplastic Lymphoma Kinase Gene Locus.

- A8081014 with 334 patients will have 85% power to detect an improvement in PFS from 6 to 9 months with $\alpha = 0.025$.

5.2 Review Strategy

Clinical review is was based on efficacy and toxicity data sets submitted by the sponsor for Study A and B, CSR's, CRF's, sponsor's presentation slides and literature review of

NSCLC harboring a translocation or inversion event involving the Anaplastic Lymphoma Kinase (ALK) gene locus.

5.3 Discussion of Individual Studies/Clinical Trials

STUDY A (A8081005): Phase 2, Open-Label Single Arm Study of the Efficacy and Safety of PF-02341066 in Patients with Advanced Non-Small Cell Lung Cancer (NSCLC) Harboring a Translocation or Inversion Involving the Anaplastic Lymphoma Kinase (ALK) Gene Locus

Anaplastic lymphoma kinase (ALK) testing by this Clinical Trial
The diagnostic test used to detect ALK fusion events is an ALK break-apart fluorescence in situ hybridization (FISH) assay performed by a central laboratory (Abbott Molecular, Des Plaines, IL, US).

Study Objectives:
Primary Objectives:
- To assess the antitumor efficacy of oral single-agent crizotinib administered to patients with advanced non-small cell lung cancer (NSCLC) after failure of at least 1 line of chemotherapy and harbor a translocation or inversion event involving the anaplastic lymphoma kinase (ALK) gene locus as measured by objective response rate (ORR); and
- To assess the safety and tolerability of oral crizotinib.

Secondary Objectives:
- To assess secondary measures of clinical efficacy including overall survival (OS), duration of response (DR), disease control rate (DCR) at 6 and 12 weeks, and progression-free survival (PFS);
- To determine pharmacokinetics (PK) in this patient population using population PK (POPPK) methods and explore correlations between PK, response, and/or safety findings;
- To explore the relationship of ALK gene fusion to the presence of ALK protein and fusion transcript;
- To correlate changes from baseline in expression of biomarkers in signaling pathways (including Janus kinase [JAK]/signal transducers and activators of transcription [STAT], mitogen-activated protein kinase [MEK]/extracellular signal-regulated kinases [ERK], and phosphatidyl inositol-3-kinase [PI3K]/AKT pathways) to PK and outcome measures;and
- To assess patient-reported outcomes (PRO) of health-related quality of life (HRQoL), disease/treatment-related symptoms of lung cancer, and general health status.

Study Design: Multicenter, multinational, open-label, single-arm, Phase 2 study of crizotinib in patients with advanced (locally advanced or metastatic) NSCLC harboring a translocation or inversion event involving the ALK gene locus.

First Subject Visit: 07 January 2010
Data Cutoff Date: 15 September 2010,

Patients enrolling in this study were either
(1) Randomized into the chemotherapy arm of the ongoing Phase 3 Study A8081007 and progressed, or
(2) Received prior chemotherapy and were ineligible for Study A8081007.

The sample size of 250 patients was determined based on the expected number of patients who would roll over from Study A8081007 and additional patients who would be enrolled based on other eligibility criteria. The sample size was also considered adequate to estimate ORR and detect adverse events (AEs) of low frequency.

Crizotinib 250 mg twice daily was administered orally continuously in 21-day cycles.

Efficacy analyses are based on the investigator's evaluation of disease assessments. Study treatment was to be continued until the occurrence of disease progression or clinical deterioration, unacceptable toxicity, patient's withdrawal of consent, or protocol non-compliance. Crizotinib treatment could be continued after disease progression if the patient was considered to be deriving clinical benefit as judged by the investigator.

Radiographic disease assessments for objective disease response and progression were to be performed at 6-week intervals (12-week intervals for bone scans) following the first dose of crizotinib. All available tumor assessments were to be reviewed by an independent radiology laboratory and are reported under separate cover.

Routine safety evaluations have included monitoring for AEs and periodic physical examinations, hematology and chemistry evaluations, and electrocardiograms (ECGs).

Protocol Amendments
The original protocol (dated 24 June 2009) was amended 9 times during the study.
Following are the Key Amendments:

- **Amendment 1** (dated 12 August 2009), patients who were ineligible to enroll in Study A8081007 because they were treated with docetaxel as part of their platinum-based prior chemotherapy, yet had NSCLC that was predominantly squamous-cell carcinoma and, thus, were not eligible to be dosed with pemetrexed, were allowed to enroll in this study.

- **Amendment 2** (dated 27 August 2009), the RECIST version was modified to Version 1.1, and patients with spinal cord compression, carcinomatous meningitis, or leptomeningeal disease were no longer excluded.

- **Amendment 3** (dated 21 December 2009), the NCI CTCAE version was modified to version 4.0, the primary endpoint was modified to add safety as a co-primary endpoint, timing of tumor measurements was modified from a per cycle basis to a calendar basis, and crizotinib was allowed to be administered without regards to meals.

- **Amendment 7** (dated 22 June 2010), the patient-reported VSAQ-ALK was included, additional ECG monitoring was added for patients with QTc ≥500 msec, modifications of the eligibility criteria (which included cutoffs for hemoglobin and platelet counts) were included, washout period for cardiovascular (CV) or cerebrovascular events was decreased, hypertension exclusion criteria was deleted, all available scans were required to be reviewed by a third-party radiology laboratory, a treatment delay to up to 42 days without requiring discontinuation was now allowed; and metabolites of crizotinib were to be evaluated, if possible.

- **Amendment 8** (dated 05 August 2010), additional safety monitoring for the potential AEs of pneumonitis was added and an exclusion criterion to exclude patients with known interstitial fibrosis or interstitial lung disease was added.

KEY Inclusion Criteria

1. Histologically or cytologically proven diagnosis of NSCLC that was locally advanced or metastatic.
2. Positive for translocation or inversion events involving the ALK gene locus (e.g., resulting in EML4-ALK fusion) as determined by an ALK break-apart FISH assay and defined by an increase in the distance of 5' and 3' ALK probes or the loss of the 5' probe.
3. Met 1 of the following criteria:
    - Randomized to Arm B (pemetrexed or docetaxel) of Study A8081007 and was discontinued from treatment due to RECIST-defined progression of disease as determined by independent radiology review.
    - Ineligibility for Study A8081007 due to (1) prior treatment for advanced disease with more than 1 chemotherapy regimen, (2) prior treatment with only 1 chemotherapy regimen for advanced disease and that regimen was not platinum-based, (3) prior treatment with pemetrexed as part of their platinum-based chemotherapy and did not meet the docetaxel eligibility requirements from Study A8081007, or (4) treated with docetaxel as part of their platinum-based prior chemotherapy, but had NSCLC that was predominantly squamous-cell carcinoma and thus, not eligible to be dosed with pemetrexed.
4. Eastern Cooperative Oncology Group (ECOG) performance status 0 to 3
5. adequate organ function

KEY Exclusion Criteria

1. Eligibility for Study A8081007.
2. No prior chemotherapy for advanced NSCLC, or erlotinib or gefitinib as the only prior treatment for advanced NSCLC.
3. Ongoing cardiac dys-arrhythmias or corrected QT (QTc) interval >470 msec.
4. Use of drugs or foods that are known potent cytochrome P450 3A4 (CYP3A4) inhibitors.
5. Use of drugs that are known potent CYP3A4 inducers
6. Use of drugs that were CYP3A4 substrates with narrow therapeutic indices
7. For Japan only: patients who have the following complications or symptoms:
    - Serious wound such as chronic wound, or Grade ≥3 gastrointestinal ulcer,
    - Serious gastrointestinal symptoms such as Grade ≥3 diarrhea.

Study Treatment

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

Safety Evaluation

Physical Examination was performed at baseline and on Day 1 of each cycle.
Laboratory studies included Hematology, Blood Chemistry and Coagulation at baseline, Days 1 and 15 on cycle 1 and then day 1 of each cycle unless ALT ≥Grade 3 or ALT ≥Grade 2 and total bilirubin ≥Grade 2, then liver function tests needed to be repeated every 48 to 72 hours until ALT ≤Grade 2.
The ECG on Day 1 of Cycles 1 and 2 were obtained at 0 hour (predose) and 2 to 6 hours following morning crizotinib dosing. If the QTc was prolonged (>500 msec), then the ECG was read by a cardiologist at the site for confirmation.

Schedule of Activities

Protocol Activities	Screening [a]	Study Treatment [b]			End of Treatment	
		Cycle 1		Cycles ≥2		
	≤ 28 Days Prior to Dosing	Day 1 (±2) [c]	Day 15 (± 2)	Day 1 (± 2; except as noted below)	End of Txt / Withdrawal [d]	Post Txt Follow-up
Baseline Documentation						
Informed consent [e]	X					
Medical/Oncological history [f]	X					
Baseline signs/symptoms		X				
Mandatory tumor tissue for molecular profiling [g]	X					
Physical examination [h]	X	(X)		X	X	
ECOG performance status	X	X		X	X	
Ophthalmologic examination [i]	X			Cycle 5, then every 4 cycles (France only)		
Laboratory Studies						
Hematology [j]	X	(X)	X	X	X	
Blood chemistry [k]	X	(X)	X	X	X	
Coagulation [l]	X					
12-lead electrocardiogram [m]	X	X		Cycle 2		
Pregnancy test (as appropriate) [n]	X				X	
Disease Assessments						
Tumor assessments (including scans) [o]	X			every 6 weeks (±1 week)	X	
Other Clinical Assessments						
Adverse events [p]	X	X	X	X	X	X
Concomitant medications/treatments [q]	X	X	X	X	X	X
EORTC QLQ-C30, QLQ-LC13, EQ-5D, and VSAQ-ALK [r]		X		X	X	
Multiple gated acquisition scan or echocardiogram (France and Ireland only)	X			Cycle 3, then every 4 cycles		
Survival follow-up [s]						X
Study Treatment						
Crizotinib		Twice Daily				
Special Laboratory Studies						
Optional tumor tissue for molecular profiling [t]	X			Cycle 2	X	
Pharmacokinetics [u]		X		Cycles 2, 3, 5		
Optional blood sample for pharmacogenomics [v]		X				

Efficacy Evaluations

Tumor assessments were to be performed as scheduled according to the calendar days regardless of treatment delays. Post baseline tumor assessments were to be performed every 6 weeks from the date of the first dose of crizotinib (with the exception of bone scans that were performed, if required, every 12 weeks) until radiographic progressive disease (PD) had been documented. A computed tomography (CT) or magnetic resonance imaging (MRI) scan was to be performed whenever disease progression was suspected (e.g., symptomatic deterioration). The determination of antitumor efficacy was based on objective tumor assessments made according to RECIST (Version 1.1).

Crizotinib Dose Modifications for Treatment-Related Toxicity

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Nonhematologic general (except as noted below)	Continued at the same dose level.	Continued at the same dose level.	Withheld dose until toxicity was Grade ≤1 or had returned to baseline, then resumed treatment at the same dose level or reduced the dose by 1 level at the discretion of the investigator.[a]	Withheld dose until toxicity was Grade ≤1, or had returned to baseline, then reduced the dose by 1 level and resumed treatment, or discontinued at the discretion of the investigator.[a]
ALT elevation with total bilirubin Grade <2	Continued at the same dose level.	Continued at the same dose level.	Withheld dose until toxicity was Grade ≤1 or had returned to baseline, then resumed treatment by reducing the dose to 150 mg BID. If Grade 3 ALT elevation recurred, discontinued permanently. If Grade 3 ALT elevation did not recur after at least 4 weeks, the dose may have been escalated to 200 mg BID.	See Grade 3

[a] Patients who developed Grade 4 hyperuricemia or Grade 3 hypophosphatemia without clinical symptoms may have continued study treatment without interruption at the discretion of the investigator. Nausea, vomiting, or diarrhea must have persisted at Grade 3 or 4 despite maximal medical therapy to require dose modification.

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
ALT elevation concurrent with total bilirubin elevation Grade ≥2	Continued at the same dose level.	Withheld dose until toxicity was Grade ≤1 or had returned to baseline, then resumed treatment by reducing the dose to 150 mg BID. If these laboratory changes recurred, discontinued permanently. If Grade 2 ALT and total bilirubin elevations did not recur after at least 4 weeks, the dose may have been escalated to 200 mg BID.	Discontinued treatment and did not retreat.	Discontinued treatment and did not retreat.
Left ventricular systolic dysfunction	Continued at the same dose level.	Continued at the same dose level.	Discontinued treatment and did not retreat.	Discontinued treatment and did not retreat.
Prolonged QTc interval	Continued at the same dose level.	Assessed electrolytes and concomitant medications. Corrected any electrolyte or magnesium abnormalities.	Interrupted crizotinib until recovery to baseline. Assessed and corrected electrolytes and concomitant medications. Resumed treatment by reducing the dose to 150 mg BID and, if no recurrence after at least 4 weeks, dose may have been escalated to 200 mg BID.	Discontinued treatment and did not retreat.

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Pneumonitis (in absence of disease progression, pulmonary embolism, positive cultures, or radiation effect)	Withheld dose until toxicity was Grade 0, ie, had returned to baseline, and then resumed treatment at the same dose. Discontinued permanently if pneumonitis recurred.	Withheld dose until toxicity was Grade 0, ie, had returned to baseline, and then resumed treatment at the same dose. Discontinued permanently if pneumonitis recurred.	Discontinued treatment and did not retreat.	Discontinued treatment and did not retreat.
Visual disturbance	Continued at the same dose level. Repeated ophthalmologic examination.[b]	Continued at the same dose level. Repeated ophthalmologic examination.[b]	Interrupted crizotinib until recovery. Repeated ophthalmologic examination.[b] Resumed treatment by reducing the dose to 200 mg BID.	Discontinued treatment and did not retreat. Repeated ophthalmologic examination.[b]
Hematologic (excluding lymphopenia)[c]	Continued at the same dose level.	Continued at the same dose level.	Withheld dose until toxicity was Grade ≤2, or had returned to baseline, then resumed treatment at the same dose level.[c]	Withheld dose until toxicity was Grade ≤2, or had returned to baseline, then reduced the dose by 1 level and resumed treatment.[c]

[b] Ophthalmologic examination included visual acuity and slit lamp and should have been performed by an ophthalmologist.
[c] Patients who developed Grade 3 or 4 lymphopenia without other dose-limiting events (eg, opportunistic infection) may have continued study treatment without interruption

Protocol deviations recorded on this study, including patients who entered the study even though they did not strictly meet inclusion/exclusion criteria, patients who deviated from the conduct of the study after the start of study treatment, and those patients who did not undergo study evaluations as required by the protocol. None of the observed protocol deviations appeared to impact the conclusions of this report.

Protocol Deviations Study A
N=136

Total	16
Eligibility Criteria	2
Missing screening safety labs	3
Wrong dosage	1
Study drug not held for toxicity	1
SAE not submitted	1
Dose reduction	1
Consent related	7

Key Reasons for study treatment discontinuation included:

1. Patients request;
2. Discretion of the investigator or Sponsor for safety;
3. Disease progression by RECIST unless the patient was considered to be deriving clinical benefit by the investigator; and
4. Unacceptable toxicity or Death.

STUDY B (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

The study was conducted at 8 study centers in Australia (1), Republic of Korea (1) and United States (6)

Anaplastic lymphoma kinase (ALK) testing by a Clinical Trial
Assay (CTA) was performed by local laboratories. If a sample was not tested by the Massachusetts General Hospital (MGH) CTA, then samples were to be sent to MGH for confirmation when possible. ALK-positive status for eligibility in the ALK-positive NSCLC cohort was based on having a positive test by either the MGH fluorescence in situ hybridization (FISH-CTA) or a local laboratory CTA. ALK-negative status for inclusion into the ALK-negative NSCLC cohort was determined by the Investigational Use Only (IUO) assay (Abbott Molecular, Des Plaines, IL, US).

Study Objectives:

1. To determine the MTD and potential Phase 2 dose(s) of crizotinib.
2. To characterize the plasma PK profile following oral administration of crizotinib, including a MDZ study to evaluate the potential for time-dependent inhibition (TDI) of CYP3A4 at different crizotinib dose levels.
3. To determine the safety, tolerability and the DLT of crizotinib.
4. To determine the pharmacodynamic effects of crizotinib on levels of soluble plasma biomarkers (HGF/Scatter factor, soluble c-Met/HGFR, VEGF, and IL-8) and on the phosphorylation status of target receptor (c-Met/HGFR) in tumor samples from surgery or biopsy when available.
5. To document evidence of antitumor activity, including tumor response rate (by RECIST for solid tumors and response criteria for lymphomas and multiple myelomas), duration of response (DR), time to tumor response (TTR), PFS, overall survival (OS) at 6 and 12 months, and others as appropriate.

Study Design:

This was a multicenter, multinational, open-label, dose-escalation, safety, PK, PD, and antitumor activity study of crizotinib administered as a single oral agent to patients with advanced malignancies.

Inclusion Criteria

KEY inclusion criteria

1. Tumor eligibility:
    - All cohorts except RP2D enriched population cohort: Histologically confirmed advanced malignancies (except for leukemias) refractory to standard of care therapy, or for whom no standard of care therapy is available.
    - RP2D enriched population cohort: Histologically confirmed advanced malignancies that meet one of the following criteria:
        i. Positive for c-Met amplification by FISH (excluding polysomy)
        ii. Positive for ALK chromosomal translocations or gene amplification including but not limited to NPM-ALK positive anaplastic large cell lymphoma, inflammatory myofibroblastic tumors or echinoderm microtubule-associated protein-like 4 (EML4)-ALK positive non-small cell lung cancer.
        iii. Positive for known c-Met kinase domain activating mutations including but not limited to V1110L, H1112L, H1112Y, H1124D, M1149T, T1191I, V1206L, L1213V, V1238I, M1268T, P1009S, T1010I, R988C, V941L but excluding Y1248C, Y1248H, Y1248D, Y1253D
        iv. Chromosomal translocations/fusions that lead to altered transcriptional regulation of c-Met and/or HGF including metastatic alveolar soft part sarcoma, clear cell sarcoma, rhabdomyosarcoma, or translocation associated renal cell carcinoma. Patients with these tumors may enter the study prior confirmation of c-Met and/or HGF alterations.
        v. Positive for chromosomal translocations at ROS gene including, but not limited to CD74-ROS and SLC34A2-ROS fusion events in NSCLC and FIG-ROS in glioblastoma

    - **ALK marker negative NSCLC cohort:** Histologically or cytologically proven diagnosis of NSCLC that is locally advanced or metastatic and of the adenocarcinoma subtype (including mixed adeno-squamous histology). Patients must have had received only one prior chemotherapy and this regimen must have been platinum-based. Patients who have also been treated with an EGFR tyrosine kinase inhibitor may have entered the

trial. All patients had to either be non-smokers, ex-smokers or light smokers (≤ 10 pack-years).

2. Solid tumors must have measurable disease as per Response Evaluation Criteria in Solid Tumors (RECIST v. 1.0). Target lesions that have been previously irradiated were not be considered measurable (lesion) unless an increase in size was observed following completion of radiation therapy. RECIST v 1.1 was used to evaluate tumors for patients in the ALK marker negative NSCLC cohort.
3. Able, in the investigator's opinion, to receive at least 2 cycles of treatment.
4. Adequate organ function as defined by the following criteria:

KEY Exclusion Criteria

1. Concurrent use of drugs that are CYP3A4 substrates with narrow therapeutic indices,
2. Patients with known interstitial fibrosis or interstitial lung disease.
3. For c-Met dependent tumors, prior therapy specifically directed against c-Met or HGF; for ALK dependent tumors, prior therapy specifically directed against ALK.
4. Ongoing cardiac dysarhythmias

This study was originally designed as a Phase 1 dose-escalation study in patients with any tumor type (except leukemia) followed by a RP2D expansion cohort to include at least 8, but no more than 15 patients, to further evaluate the safety and PK of the MTD of crizotinib. During this phase 1 study, 2 patients in the 50 mg cohort with ALK positive NSCLC were found to have stable disease at 1.5 and 7 months. This led to amendment 4 which provided a Phase 2 extension cohort enrolling patients with ALK positive NSCLC.

The study drug was administered orally once or twice a day in continuous 28-day cycles except 21-day cycles for patients in the ALK marker negative NSCLC cohort

There was be a lead-in period in which single-dose pharmacokinetics of crizotinib or MDZ (for patients participating in the MDZ sub-study).

Each dose cohort initially included a minimum of 3 evaluable patients for assessment of toxicity within the first cycle. Dose escalation occurred in 100% increments until either of the following occurrences: (1) drug related toxicity of Grade 2 severity occurs in 2 or more patients within a dose level; or (2) mean unbound AUC0-24 exceeds 2.4 μg·h/mL (the highest unbound AUC tested in the one-month toxicology studies). Escalation increments then became 40%. In any cohort, if 1 patient experienced a DLT, 3 additional patients were enrolled to that dose level. If 2/3 or 2/6 patients experience a DLT, no further dose escalation occurred.

Protocol Amendments

The original protocol dated 05 December 2005 was amended 15 times. Key amendments noted are:

Amendment 4: 29 October 2007: EML4-ALK-positive NSCLC patients were allowed to enter,

Amendment 7: 23 June 2008: patients with ECOG of 2 were allowed and c-Met translocation/fusions as an option for the RP2D-enriched cohort was added.

Amendment 12: 9 November 2009: cohort consisting of NSCLC patients who were negative for the ALK translocation was added (25-40) and a screening ophthalmology examination was added, with any follow-up as clinically indicated.

Amendment 15, 5 August 2010: safety monitoring for potential AEs of Pneumonitis was added, exclusion criteria were updated to exclude patients with interstitial fibrosis or interstitial lung disease, and treatment guidelines for selected crizotinib-related AEs were added.

Efficacy Evaluations - Tumor Imaging

Screening/baseline imaging assessments were to include computed tomography (CT) or magnetic resonance imaging (MRI) scans of the chest, abdomen, and pelvis. Brain scans and bone scans were to be performed at baseline if disease was suspected. Scans were to be repeated every other cycle and were to assess only areas of known disease unless other sites of disease were suspected. For patients in the ALK-negative NSCLC cohort, tumor assessments were to be performed every 6 weeks (based on a calendar schedule) starting after the first dose of crizotinib.

Safety Evaluations

Investigators were supposed to obtain and record on the CRF/DCT all observed or volunteered AEs, the severity (mild, moderate, or severe) of the events, and the investigator's opinion of the relationship to the study treatment. Adverse events included adverse drug reactions, illnesses with onset during the study, and exacerbation of pre-existing illnesses.

Schedule of Activities

Protocol Activity	Screening*	Lead-in PK Period[20]	Cycle 1= 28 days**		Cycle 2 = 28 days**		Every 4 weeks**(after Cycle 2-Cycle 5)	Every 8 Weeks****	End of Treatment
	Day –14 to Day 0	Day -7	Day 1 (pre-dose)	Day 15	Day 1	Day 15	Day 1		
Informed consent[1]	X								
Medical history[2]	X								
Physical examination[3]	X		X		X		X		X
Weight, height, temperature, BP, pulse[4]	X		X		X		X		X
ECOG performance status[5]	X		X		X		X		X
12-Lead electrocardiogram (ECG)[6]	X		X	X	X				
Registration/Hematology[7]	X		(X)	X	X		X		X
Chemistry[8]	X		(X)	X	X		X		X
Coagulation tests[9]	X		(X)	X	X				
Urinalysis[10]	X		(X)		X		X		
Ophthalmology Examination[21]	X								
Safety assessment (adverse events)[11]	X		X	X	X	X	X		X
Tumor assessment * [12]	X							X	X
Survival[13]	Until at least 1 year after the final dose								
Concomitant medications[14]	X		X	X	X	X	X		
Pregnancy test[15]	X								X
Special Laboratory Studies									
Plasma sampling for full PF-02341066 PK in patients not participating in the MDZ study[16]		X	X	X	X				
Plasma sampling for full PF-02341066 PK in patients participating in the MDZ study[17]			X	X	X				
Two plasma sampling points for PF-02341066 PK[18]						X	X (up to Cycle 5)		
Plasma sampling for full MDZ PK[19]		X			X				
Blood sample for PF-02341066 metabolite profiling[20]				X					
Blood sample for pharmacogenomics[21]	X								
24-hour urine collection for PF-02341066[22]				X					
Urine Sample for 6 beta-hydroxycortisol/cortisol (6B-OHC/C) ratio[23]			X	X	X				

6 Review of Efficacy

Efficacy Summary

This new drug application is supported by 2 single arm studies (Study A and Study B). Response rate of 50% in Study A and 61% in study B that is higher than any approved single and or combined chemotherapeutic agent for the treatment of NSCLC along with favorable safety profile compared to these chemotherapeutic agents is the basis for approval for this application.

6.1 Indication

Crizotinib is a kinase inhibitor indicated for the treatment of patients with locally advanced or metastatic anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer. ALK positivity will be assessed through the use of the Vysis ALK Break Apart FISH Probe Kit.

6.1.1 Demographics

Median age was 52 years on Study A and 51 years on Study B. The female/male ratio and racial distribution was similar on both studies with 63.1% of patients characterized as Caucasian, 30.2% Asian, 3.1% Black, and 3.5% Other. The majority of the patients were non-smokers or former smokers and the majority of patients on both trials had a diagnosis of adenocarcinoma.

Given the fact that the 5 year survival rate for patients with lung cancer is around 15%, the median time from diagnosis on both studies was surprisingly long in some patients. This finding raises the question whether ALK positivity is also a better prognostic indicator or if some of the patients at the edge of this range (e.g., patients diagnosed with NSCLC 13.7 years prior to study entry), in fact, had a second primary tumor.

Table 3 Demographic and Disease Characteristics in Studies A and B

Baseline and Disease Characteristics		
	Study A (1005) N = 136	Study B (1001) N = 119
Sex		
Male	47%	50%
Female	53%	50%
Age (years),		
Median (range)	52 (29-82)	51 (21-79)
Race		
White	64%	62%
Black	4%	3%
Asian	32%	29%
Other	1%	7%
ECOG Performance Status		
0	27%	35%
1	54%	53%
2	18%	12%
3	0	1%
Smoking Status		
Non-smoker	68%	72.%
Former Smoker	29%	27%
Smoker	4%	1%
Stages		
Locally Advanced	6%	4%
Metastatic	94%	96%
Histological Subtype		
Adenocarcinoma	97%[1]	98%[2]
Squamous Cell Carcinoma	0	1%
Adenosquamous Carcinoma	2%	0
Non-small Cell Lung Cancer NOS	1%	1%
Prior Therapy		
Surgery	98%	98%
Radiation Therapy	57%	57%
Chemotherapy	99%	93%

The table below provides information on prior chemotherapy, both in terms of the number of prior regimens and the percentage of patients who received FDA-approved agents for NSCLC. While every patient has not received all prior chemotherapy, substantial numbers of patients have received each of the approved agents. Since data was available, we also examined patient response to each of these agents. In general, the response rate of ALK + patients is consistent with that of NSCLC patients in the literature. Response to erlotinib (regardless of the extent of prior therapy) was 4.7% in the two studies.

Table 4 Prior chemotherapy

Number of Prior Chemotherapy Regimens for Metastatic Disease		
	Study A N = 136	Study B N = 119
0 Prior Regimens	0	6.7%
1 Prior Regimen	9.6%	26.9%
2 Prior Regimens	27.2%	13.4%
3 Prior Regimens	27.2%	19.3%
4-12 Prior Regimens	36.0%	27.7%
Prior Adjuvant/Metastatic Chemotherapy		
	N = 136	N = 111
Bevacizumab	40.4%	34.2%
Erlotinib	47.8%	43.2%
Gemcitabine	44.9%	35.1%
Pemetrexed	88.2%	54.1%
Platinum Compounds	95.6%	95.5%
Taxanes (docetaxel, paclitaxel)	74.3%	64.0%
Vinorelbine	20.6%	22.5%

The table below provides information on the baseline tumor characteristics of patients on Studies A and B. Disease burden is assessed by the sum of the longest diameter (SLD) of the target lesions. The SLD in both trials is small and subset analyses of the primary endpoint will be conducted in patients with various degrees of tumor burden. The metastatic pattern in patients with ALK positive NSCLC appears typical of patients with NSCLC as a whole.

Table 5 Baseline Tumor Characteristics

	Study A	Study B
IRC Sum of the Longest Diameter	N = 93	N = 103
Median (range)	5.2 cm (1.0-19.6)	5.3 cm (1.0-43.7)
INV Sum of the Longest Diameter	N = 135	N = 114
Median (range)	6.7 cm (1.1-62.5)	8.7 cm (1.0-42.5)
INV Sites of Target Lesions	N = 135	N = 114
Lung	70.4%	72.8%
Lymph Node	38.5%	63.2%
Liver	35.6%	27.2%
Adrenal	7.4%	8.8%
Chest/Chest Wall	3.7%	2.6%
Brain	2.2%	0.9%

6.1.2 Subject Disposition

Both studies are ongoing and contain several populations with a variety of cutoff dates. The table below outlines these populations and provides information on the disposition for Safety Population.
Among the 5 patients in which discontinuation was listed as due to Patient Decision/Lost to Follow Up, 1 died due to an adverse event 5 days after discontinuation and 1 reported a grade 3 adverse event the day prior to discontinuation.

Table 6 patient disposition

	Study A (1005)	Study B (1001)
Efficacy Population	136 (Data cutoff 2-1-11)	119 (Data cutoff 9-15-10)
Safety Population 1 (Deaths, Discontinuations, SAEs)	261	136
Safety Population 2 (Grade 1-4 AEs)	136	119
	Study A (Data cutoff 2-1-11)	Study B (Data cutoff 2-1-11)
Patients Treated	261	136
Ongoing	205	79
Discontinued	56	57
Adverse Events	9	4
Progressive Disease	31	30
Death	13	16
Lost to Follow Up/Patient Decision	1/2	1/1
Other	0	5[1]

[1]Clinical progression in 5 pts

6.1.3 Analysis of Primary Endpoint(s)

The primary endpoint was response rate as assessed by the investigators. The response-evaluable population had received crizotinib, had an adequate baseline scan, and had a follow up scan > 6 weeks after starting crizotinib. The number of patients available for IRC review is smaller than the number of patients undergoing INV review. This is due to problems with the transmission of the scans to the independent reviewers and due to the lack of target lesions on IRC review on some of these scans. The findings of the IRC show a slightly lower response rate but support the findings of the investigators.

One hundred thirty-six patients with ALK-positive advanced NSCLC from Study A were analyzed at the time of data cutoff. The median duration of treatment was 22 weeks. Based on the investigator assessments, there were 1 complete and 67 partial responses for an ORR of 50% (95% CI: 42%, 59%). The ORR by independent review was 42% (95% CI: 32%, 52%). Seventy-nine percent of objective tumor responses were achieved during the first 8 weeks of treatment. The median response duration was 41.9 weeks.

One hundred nineteen patients with ALK-positive advanced NSCLC were enrolled into Study B at the time of data cutoff. The median duration of treatment was 32 weeks. Based on the investigator assessments, there were 2 complete and 69 partial responses for an ORR of 61% (95% CI: 52%, 70%). The ORR by independent review was 52% (95% CI: 42%, 62%). Fifty-five percent of objective tumor responses were achieved during the first 8 weeks of treatment. The median response duration was 48.1 weeks.
The number of patients with brain metastases in both studies was small. However, responses within the brain were not noted in these patients.

Table 7 Efficacy data from Studies A and B

Primary Endpoint				
	Study A		Study B	
	INV N = 135	IRC N = 105	INV N = 116	IRC N = 105
Response Rate [95% CI]	67 (50%) [42%, 59%]	44 (41.9%) [32%, 52%]	71 (61.2%) [52%, 70%]	55 (52.4%) [42%, 62%]
Complete Response	1	1	2	0
Partial Response	67	43	69	55
Duration of Response				
Median (range)[1]	41.9 weeks (6.1, 42.1)	33.1 weeks (18.7, NR)	48.1 weeks (4.1, 76.6)	58.1 weeks (36.3, NR)

[1]Kaplan-Meier method with censored values

While INV-determined response rate was the primary endpoint, discrepancies between INV and IRC review were examined. In Study A, among the 67 patients assessed as CR or PR by INV, the IRC assessed the scan as a CR or PR in 44 patients. In Study B, among the 71 patients assessed as CR or PR by INV, the IRC did not note any CR and but PR in 55patients.
I
On subset analysis, there was no clear difference in response by performance status, sex, age, number of prior chemotherapeutic regimens, or in the percentage of cells found to have a rearrangement in the ALK gene by FISH. There was, however, a difference in response by race showing Asian patients with a higher response rate. An exposure-response analysis was conducted for ORR in trials by Pharmacometrics division of the FDA for both Study A and B. Asian patients had higher drug exposures and thus there was a higher proportion of Asians in the highest quartile compared to the lowest quartile. The increased response in Asian patients was thought to be due to a lower average body weight and thus, to a higher dose of crizotinib on a mg/kg basis.

In some patients in Studies A and B, a prolonged period between diagnosis and study entry was recorded. It is unclear if these patients, in fact, had a 2nd primary lesion. Among the 19 patients in whom the time between diagnosis and study entry was reported to be > 5 years, 6 (31.6%) were responders. Of more concern are the 48 patients on Study A who were reported to have metastatic or recurrent disease > 18 months prior to entry. In these patients, 24 (50.0%) were responders. This is consistent with the patient population as a whole.

Table 8 Sub group analysis

Subgroup Analyses		
	Study A N = 135	Study B N = 116
Response by Performance Status		
0	54.1%	53.8%
1	52.1%	62.9%
≥ 2	36.0%	73.3%
Response by Race		
Asian	60.5%	82.4%
Non-Asian	44.6%	52.4%
Response by Region		
US	44.3%	46.9%
Non-US	55.4%	94.3%
Response by Number of Prior Chemotherapy Regimens		
0 Prior Regimens	NA	85.7%
1 Prior Regimen	50.0%	54.6%
2 Prior Regimens	54.1%	60.0%
3 Prior Regimens	42.5%	76.5%
≥ 4 Prior Regimens	51.0%	50.0%
Response by Disease Burden		
Baseline SLD ≤ Median	42.7%	52.2%
Baseline SLD > Median	56.7%	53.7%

6.1.4 Subpopulations

ALK translocation Negative NSCLC patients:
At the FDA's recommendation a cohort consisting of ALK negative patients was added (25-40) to Study B with amendment #12. The prelim data was submitted on June 10th, 2011 for 23 such patients. Some of these patients were found to be ALK positive on pre-screening by other diagnostic test methods however; they were negative by the Vysis ALK Break Apart FISH assay.

Twenty-three (23) patients with locally advanced or metastatic ALK negative NSCLC in this cohort received crizotinib. Their patient demographics were similar to the ALK positive patients described above.

Table 9 Demographics ALK -ive NSCLC

Sex	
Male Female	13 (57%) 10 (43%)
Age	
	Median 57 Range 34 – 80
Race	
White Black Asian	16 (70%) 1 (4%) 4 (17%)
Smoking History	
Never Smoked Ex-Smoker Smoker	13 (57%) 9 (39%) 1 (4%)
Prior Therapies	
Prior Radiation Prior Systemic Therapies	13 (57%) 22 (96%)

The results for efficacy noted in this small sub-set of ALK negative patients were surprising. This high response rate was not consistent with the thought that crizotinib only worked on patients with ALK mutation positive NSCLC. Five of 19 response evaluable patients responded for an investigator response rate of 26.3% (95% CI 9.1%, 51.2%). Two additional patients have a single assessment of PR. If confirmed, the response rate in this population would be 7/20 (35.0%). This is similar to the RR in patients with ALK positive NSCLC in Study A. 49.6%.

It is unclear if this finding is related to the assay or to the ability of crizotinib to target other genetic abnormalities associated with NSCLC such as c-Met or ROS. It may be that a substantial number of patients with NSCLC (or with other tumors) could benefit from crizotinib. The study of patients with ALK negative NSCLC will be a post-marketing requirement.

Table 10 Efficacy Results for ALK Negative cohort

Complete response	**0**
Partial response	**5 (26.3%)**
Stable disease	**2 (10.5%)**
Objective progression	**3 (15.8%)**
Early death	**2 (10.5%)**
Indeterminate	**7 (36.8%)**
Objective Response Rate (CR+PR)	**5 (26.3%)** [95% CI 9.1, 51.2]

Issues identified with these Results:

- Do we have a defined population for which this drug works? Are the responses related to ALK and other somatic aberrations?

- What does this mean for Validated Diagnostic test?
  - Is the 15 % cut off for FISH not right?

Based on pre-clinical data patient whose tumor carries activated ROS or overexpressed or amplified c-MET could potentially respond to crizotinib based on inhibition of one of these other targets.

The sponsor is retrospectively testing tumor samples from this cohort of ALK-negative NSCLC patients for other characteristics.

A PMR as a clinical study has been generated in which additional patients without prescreening for ALK mutation will be enrolled.

7 Review of Safety

Safety Summary

- Overall, 450 subjects had received crizotinib at the time of NDA submission and are included in the safety analysis. One hundred ten of the 450 subjects were healthy volunteers enrolled in clinical pharmacology studies with no for whom no safety data was submitted. The cohorts whose data was submitted were: 255 patients with ALK positive NSCLC;
- 85 patients on Study B without ALK positive NSCLC;
- An additional 142 patients on Studies A and B with ALK positive NSCLC;
- An additional 32 patients on Studies A and B without ALK positive NSCLC; and
- 71 patients with ALK positive NSCLC on Study 1007.

The Safety Update, using a later cutoff of February 1, 2011, provided only information on patient deaths and SAEs. Of these subjects, 255 had ALK-positive locally advanced or metastatic NSCLC and received crizotinib 250 mg orally twice daily in Studies A and B. Since they comprised the target population and the recommended dosing regimen for crizotinib treatment, they were the focus of the crizotinib safety review for which grade 1-5 adverse events are available.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The primary population for evaluating safety in the clinical studies was all patients on Studies A and B who received at least 1 dose of crizotinib starting on Cycle 1 Day 1. All AEs reported after the start of treatment on Cycle 1 Day 1, as well as pre-existing conditions that worsened during the treatment period, were considered to be treatment emergent AEs. Treatment-related AEs were those judged by the investigator to be at least possibly related to crizotinib, or for which drug relatedness was recorded as unknown by the investigator. All AEs experienced during the safety evaluation period (from first dose through at least 28 days after the last dose of crizotinib) were to be reported to the Sponsor, whether or not the AE was considered by the investigator to be treatment-related. All treatment-related AEs occurring at any time after initiation of treatment were to be reported to the Sponsor and were to be followed until they resolved, until the investigator assessed them as chronic or stable, or until the patient was lost to follow-up.

Abnormal laboratory test results were to be considered **adverse events** if they were associated with symptoms, required additional diagnostic testing, led to a change in trial dosing, and/or were otherwise considered to be an adverse event by the Investigator. Laboratory results assigned adverse events status was graded in accordance with NCI CTCAE. In the AE data presentations, each Preferred Term (PT) was counted only once for each subject, regardless of the number of times the subject experienced the same AE. If the severity of the AE changed over time, then the maximum severity grade was reported.

Laboratory Safety Assessments: Blood and urine samples were evaluated as specified in individual study protocols. Investigators may have requested additional tests to be performed for the purposes of planning treatment administration, modifying doses, or following up on AEs. Laboratory test abnormalities were graded in accordance with NCI CTCAE Version 3.0 for both studies. The number and percent of patients with abnormal laboratory test results were summarized by maximum NCI CTCAE grade. Summaries of shifts in laboratory test results between baseline (prior to morning dosing on Cycle 1 Day 1) and post-baseline times of testing were produced.

These 2 studies used different common toxicity criteria versions (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] Version 3.0 in Study 1001 and Version 4.0 in Study 1005). The pooled analysis combined the data without adjustment for any differences in grading between Versions 3.0 and 4.0 of the NCI CTCAE.

7.1.2 Categorization of Adverse Events

Serious Adverse Events: An SAE is any untoward medical occurrence at any dose that:

- Resulted in death
- Was life-threatening (immediate risk of death);
- Required inpatient hospitalization or prolongation of existing hospitalization;
- Resulted in persistent or significant disability/incapacity; or
- Resulted in congenital anomaly/birth defect.

Other important medical events were considered SAEs if they jeopardized the patient or required medical or surgical intervention to prevent one of the outcomes listed in this definition. Progression of the malignancy under study (including signs and symptoms of disease progression) was not to be reported as an SAE unless the outcome was fatal during the study or within the safety reporting period. Hospitalization due to signs and symptoms of disease progression was not to be reported as an SAE. If the malignancy had a fatal outcome during the study or within the safety reporting period, (from first dose through 28 days after administration of the last dose of crizotinib), then the event

leading to death was to be recorded as an AE and as an SAE with NCI CTCAE Grade 5. For all SAEs, the Investigator was obligated to pursue and provide information on the appropriate data collection tool and to provide additional information as requested by the sponsor. Generally, this included a detailed description of the SAE, including available autopsy findings as appropriate, which allowed a complete assessment of the case and determination of the possible causality by the sponsor. The Investigator's assessment of causality also was provided. If causality was unknown, then the event was attributed to crizotinib.

Deaths: Assessment of deaths "on study" included all deaths that occurred during the safety evaluation period from first dose of crizotinib through 28 days after administration of the last dose of crizotinib. Patients continue (d) to be followed for long-term survival for at least 12 months after the individual patient's last dose of crizotinib in Study A and B. Cause of death was summarized, and individual listings of patients who died were provided.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Adverse events were collected in Study A using CTC v 4 and in Study B using CTC v 3. Despite this, the percentage of patients experiencing various adverse events is similar in the two trials and data from patients with ALK positive NSCLC in these two trials is presented together. Formal pooling of data was not done.

7.2 Adequacy of Safety Assessments

In general, safety assessments on Studies A and B were adequate. However, the applicant will be asked, as a post-marketing requirement, to further characterize the ophthalmic findings in patients reporting vision disorders.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

While the number of patients in the safety database is adequate, the number of patients with ALK positive NSCLC is small. Further, the Safety Update did not provide information on grade 1-4 adverse events in these patients, but only provided information on serious adverse events and patient deaths. Data from patients who received crizotinib, but did not have ALK positive NSCLC is helpful in establishing the safety profile. However, many of these patients, including those on the dose escalation study and those with tumors not responding to crizotinib, were exposed to crizotinib for a short period. Information from these patients may not, therefore, adequately reflect the

adverse events associated with crizotinib. Finally, the absence of randomized controlled trials in this submission makes it difficult to distinguish adverse events due to disease progression and those due to crizotinib. The safety profile of crizotinib will be further refined by the submission of data from Studies 1007 and 1014. This will be a post-marketing requirement.

7.2.2 Duration of Exposure

The table below provides information on patient exposure to crizotinib on Studies A and B. A substantial number of patients on both studies required treatment interruption. The median duration of interruption was 7 days on Study A and 6.5 days on Study B. Despite this, 32 patients remained on Study B for more than 1 year. While only 1 patient has been treated on Study A for more than 1 year, Study A began approximately 4 years after initiation of Study B.

Duration of Exposure in Studies A and B		
	Study A N = 136	Study B N = 119
Duration of Exposure		
Median (range)	5.1 months (0.2-12.2)	7.8 months (0.4-23.5)
Dose Interruption	36.0%	45.4%
Dose Reduction	44.1%	29.4%

7.2.3 Explorations for Dose Response

Based on the data collected in Studies A and B, the proposed dose of 250 mg BID seems reasonable. Further dose response exploration has been requested as PMR study.

7.3 Major Safety Results

7.3.1 Deaths

In the ALK positive NSCLC cohorts of Studies A and B, 45 patients died within 28 days of study drug. Among the 45 patients, 32 deaths were due to progressive disease and 13 due to an adverse event. Adverse events that occurred within 28 days of study drug

and that led to death are included in the table below. Two deaths in Study A (1 death of unknown cause, 1 death attributed to pneumonitis by the investigator) and 1 death in Study B (DIC) were considered treatment related. Six (6) crizotinib-treated patients in Study 1007 had SAEs with a fatal outcome. Five (5) occurred within 28 days of the last dose of study treatment, and 2 were considered treatment-related (Cardiac arrest and respiratory failure, Interstitial lung disease)

	Study A and B N = 255	Study A and Study B N = 397	1007	Study B-Other than ALK Positive NSCLC Cohort
Adverse Event	10 (3.9%)	13 (3.3%)		
Pneumonia	2	2	1	2
Pneumonitis	1	1	2	
Respiratory Failure			1[1]	2
Septic Shock/DIC	2	2		1
ARDS	1	1	1	
Hypoxia	1	2		
Cardiac Arrest				1
Cardiovascular Event		1		
Death NOS	1	1		
Dyspnea		1		
Empyema	1	1		
Myocardial Infarction				1
Pleural Effusion				1
Pulmonary Hemorrhage	1	1		

In a single arm study in NSCLC, it is difficult to discern whether respiratory events, particularly those that occurred in patients with a performance status of 0-2 within 28 days of study entry, are related to crizotinib or to the underlying disease.

Pneumonitis has been identified as an adverse event associated with crizotinib and will be discussed below. Septic shock or DIC has been reported in 4 patients (1 patient had pneumonia resulting in septic shock and is listed as pneumonia in the table). In 2 patients, this appeared to be associated with pneumonia. Two additional patients developed DIC. In the first, yeast was found in the blood and DIC was associated with acute renal failure. Little information has been provided about the 2nd patient, but atrial fibrillation and SOB were followed by acute renal failure, hypotension and DIC. Infectious events and DIC will be monitored in ongoing trials.

In addition to a large number of missing death narratives, cause of death was not clear on some of the patients. Information requesting hospital records, scan reports and additional death narratives was requested by the FDA.

A number of patients who died were note to have deteriorating pulmonary status (dyspnea, pneumonia, respiratory failure etc.). It is difficult to analyze pulmonary

symptom deterioration in lung cancer patients with underlying pulmonary symptoms without a comparator arm. The investigators attributed death in most of these patients to the underlying disease.

7.3.2 Nonfatal Serious Adverse Events

Serious adverse events occurred in 23.7% of the 397 patients and in 24.3% of the 255 patients with ALK positive NSCLC on Studies A and B. Events that occurred in > 2% of the 397 patients included pneumonia (4.0%) and dyspnea (3.0%). Serious adverse events in the remainder of the safety database were similar. However, elevation of ALT/AST was reported as a SAE in 2 patients in 1007.

Grade 3-4 adverse events occurred in 40.8% of the 255 patients in Studies A and B. Events in > 5% of patients included elevated ALT/AST, dyspnea, pneumonia and neutropenia. ALT elevation is discussed further below.

7.3.3 Dropouts and/or Discontinuations

Among the 136 patients in Study A, 7 (5.1%) patients discontinued due to an adverse event while among the 119 patients in Study B, 3 (2.5%) patients discontinued due to an adverse event. The most common treatment-related AEs associated with permanent discontinuation was ALT increased (3 patients; 2.2%) and pneumonitis (2 patients; 1.5%). In addition, 1 patient in Study B discontinued due to autoimmune thyroiditis. This event occurred in a 26 yrs old female with clear cell sarcoma and was associated with the development of thyroid microsomal antibodies and thyroid peroxidase antibody and with a decrease in TSH. Reports of thyroid disease will continue to be followed in patients on crizotinib.

7.3.4 Significant Adverse Events

The table below provides information on treatment emergent and treatment related adverse events in at least 25% of patients on Studies A and B. Adverse events were collected in Study A using CTC v 4 and in Study B using CTC v 3. Despite this, the percentage of patients experiencing various adverse events is similar in the two trials.

Esophageal disorder includes a variety of preferred terms ranging from dyspepsia to esophageal obstruction and ulcer. One patient developed hematemesis due to a pill ulcer. These adverse events should be studied more closely in a randomized trial. Dizziness and related disorders were also reported in a substantial number of patients and should be examined more closely in a randomized trial. None of the reports of dizziness were grade 3-4. **Visual disorders** are discussed further below.

Table 11 Grade 1-4 Adverse Events in > 25% of Patients

Table : Grade 1-4 Adverse Events in ≥ 25% of Patients				
	Study A		Study B	
	Treatment Emergent N = 136	Treatment Related N = 136	Treatment Emergent N = 119	Treatment Related N = 119
All	136 (100%)	131 (96.3%)	117 (98.3%)	114 (95.8%)
Eye Disorders				
Visual Disorder[1]	83 (61.0%)	80 (58.8%)	76 (63.9%)	75 (63.0%)
Gastrointestinal Disorders				
Nausea	86 (63.2%)	78 (57.4%)	59 (49.6%)	58 (48.7%)
Vomiting	68 (50.0%)	59 (43.4%)	48 (40.3%)	42 (35.3%)
Diarrhea	67 (49.3%)	58 (42.6%)	57 (47.9%)	51 (42.9%)
Constipation	53 (39.0%)	37 (27.2%)	45 (37.8%)	32 (26.9%)
Esophageal Disorder[2]	21 (15.4%)	9 (6.6%)	30 (25.2%)	20 (16.8%)
General Disorders				
Edema/Peripheral Edema	54 (39.7%)	39 (28.7%)	43 (36.1%)	33 (27.7%)
Fatigue	50 (36.8%)	34 (25.0%)	30 (25.2%)	17 (14.3%)
Metabolism and Nutrition				
Decreased Appetite	42 (30.9%)	30 (22.1%)	29 (24.4%)	20 (16.8%)
Nervous System Disorder				
Dizziness[3]	26 (19.1%)	19 (14.0%)	35 (29.4%)	25 (21.0%)
Respiratory Disorders				
Cough/Productive Cough	38 (27.9%)	7 (5.1%)	16 (13.4%)	2 (1.7%)
Dyspnea/Exertional Dyspnea	35 (25.7%)	5 (3.7%)	22 (18.5%)	0

[1]Includes diplopia, photopsia, vision blurred, visual field defect, visual impairment, vitreous floaters, and visual brightness.
[2]Includes dyspepsia, dysphagia, epigastric discomfort/burning, esophagitis, esophageal obstruction, pain, spasm, and ulcer, gastroesophageal reflux, odynophagia, and reflux esophagitis.
[3]Includes balance disorder, dizziness postural, and presyncope

Since the ALK receptor is known to occur on neural cells, reports of dizziness, dysgeusia, and neuropathy were carefully examined. Dizziness was reported in 61 patients (23.9%), 44 treatment-related, in Studies A and B. Grade 2 events were reported in 3 patients with the remainder of the events grade 1. Among the treatment-related events, 30/60 had resolved at the time of data cutoff. Dysgeusia was less commonly reported than dizziness and was still reported in > 10% of patients (12.9%) on Studies A and B. Finally, treatment-related neuropathy was reported in 33 patients. The majority of these patients had received prior neurotoxic chemotherapy. It is difficult to determine whether these events represent a worsening of pre-existing disease or

were due to an interaction between crizotinib and a pre-existing neuropathy. Data from a randomized study will be needed to fully evaluate these events.

7.3.5 Submission Specific Primary Safety Concerns

Fatal Pneumonitis: Pneumonitis was reported in 5 patients (on days 6, 12, 18, 41 and 53) in Studies A and B and in 1 patient (day 10) in Study 1007. Two of these events resulted in death. Three of the 6 patients had a prior history of pulmonary embolism. Steroids and antibiotics were used in the majority of the patients with pneumonitis. It appears that none of these patients underwent prior radiation therapy to the chest, but radiation pneumonitis was reported in 3 additional patients.

Visual disorders: Visual disorders were reported in the majority of patients (163 out of 255) and preferred terms reported in more than 1 patient include visual impairment, photopsia, blurred vision, vitreous floaters, diplopia, photophobia, and visual field defect. Most of these are grade 1 events with grade 2 events reported in 3 patients. Most patients did not require the dose discontinuation or reduction and most events occurred while the patient was receiving crizotinib 250 mg bid. However, 1 event was reported in a patient receiving 150 mg/d. The median day of onset for the first event was day 9 (range; day 1-173). Only 80 of the 181 reported events had resolved at data cutoff. Among these 80 events, the median duration was 55.5 days. Ophthalmic examinations were performed in a limited number of patients and abnormalities were reported as a change from normal to abnormal in 6 patients. The Sponsor will be asked to more carefully examine a cohort of patients for changes in their slit lamp and fundcoscopic examinations in a **PMR** study.

Liver Function test abnormalities: No patient has experienced liver failure. However, grade 3-4 elevation in ALT has been seen in 10 patients. One patient had a grade 3 elevation in ALT accompanied by grade 2 elevations in bilirubin. This patient's laboratory abnormalities improved on discontinuation of crizotinib. A hepatology consult was obtained by the FDA with Dr John Senior.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Visual acuity, slit lamp examination, and fundoscopy were done in a limited number of pts and results were described as normal/abnormal. An ophthalmology consult was

conducted at the FDA by Dr Wiley Chambers and based on his assessment a **PMR** to further characterize these events has been added.

Table : Grade 1-4 Adverse Events in ≥ 25% of Patients				
	Study A		Study B	
	Treatment Emergent N = 136	Treatment Related N = 136	Treatment Emergent N = 119	Treatment Related N = 119
All	136 (100%)	131 (96.3%)	117 (98.3%)	114 (95.8%)
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Dyspnea/Exertional Dyspnea	35 (25.7%)	5 (3.7%)	22 (18.5%)	0

Visual acuity, slit lamp examination, and fundoscopy were done in a limited number of pts and results were described as normal/abnormal. An ophthalmology consult was conducted at the FDA by Dr Wiley Chambers and based on his assessment a **PMR** to further characterize these events has been added.

7.4.2 Laboratory Findings

In Study A and B grade 3 or 4 neutropenia, thrombocytopenia, and lymphopenia were seen in 5.2%, 0.4%, and 11.4% of patients, respectively. Grade 3 or 4 ALT laboratory elevations were observed in 6.3% of patients in Studies A and Study B. Grade 3 and 4 elevations were generally asymptomatic and reversible upon dosing interruption. Patients usually resumed treatment at a lower dose without recurrence; however, 3 patients from Study A (2%) and 1 patient from Study B (less than 1%) required permanent discontinuation from treatment. Concurrent elevations in ALT greater than 3

x ULN and total bilirubin greater than 2 x ULN without elevated alkaline phosphatase were detected in 1/255 (less than 0.5%) o of patients with available laboratory data across both studies.

Study A Labs Baseline and on study grade 1-4

	Baseline				On Study			
Laboratory	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Neutrophils	1/136	1/126			26/134	18/134	7/134	2/134
Hemoglobin	57/136	12/136	1/136		71/134	15/134	1/134	
Platelets	7/136	1/136			19/134			
Lymphocytes	18/122	15/122	11/122		18/134	30/134	20/134	5/134
ALT	16/135	2/135			66/135	20/135	7/135	2/135
Bilirubin	2/135				3/135	1/135	1/135	
Creatinine	5/135				37/135	4/135		
Hyperglycemia	29/135	5/135	1/135		62/135	21/135	4/135	
Hypoglycemia	3/135				24/135	5/135		
Hypophosphatemia	1/128	3/128	1/128		1/135	21/135	7/135	
Hypoalbuminemia	20/135	13/135			39/135	46/135	7/135	

Study B Labs Baseline and on study grade 1-4

	Baseline				On Study			
Laboratory	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Neutrophils	2/115	1/115			16/117	22/117	3/117	1/117
Hemoglobin	47/116	12/116			70/117	15/117	1/117	
Platelets	2/116				12/117		1/117	
Lymphocytes	8/84	16/84	2/84	1/84	15/117	24/117	13/117	1/117
ALT	17/115	1/115			69/117	9/117	6/117	1/117
Bilirubin	1/105				3/116	1/116		
Creatinine	5/116	1/116			21/117	6/117		
Hyperglycemia	26/116	5/116			44/117	18/117	5/117	
Hypoglycemia	3/116				24/117	3/117		
Hypophosphatemia		4/116	1/116		7/117	42/117	6/117	
Hypoalbuminemia	13/114	17/114			39/117	40/117	2/117	

7.4.4 Electrocardiograms (ECGs)

A definitive QT study has not been performed with crizotinib and the EKGs included in this submission were of insufficient quality to determine the mean increase in QTcF. Three of 306 patients developed a QTcF $\geq$ 500 ms and 3% of patients had an increase in QTcF $\geq$ 60 ms. In the safety database, extrasystoles were reported in 3 patients and tachycardia in 1 patient.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

No meaningful exposure response relationship for respiratory and liver related adverse events was observed in trials A and B. Overall, the incidence of these adverse events for hematological toxicities, ALT and AST elevations and respiratory infections were too low to conduct a meaningful exposure-response analysis.

7.5.2 Drug-Drug Interactions

The effects of co-administration of ketoconazole (a strong CYP3A inhibitor) and rifampin (a strong CYP3A inducer) on the PK and safety of a single dose crizotinib in healthy subjects have been evaluated in trials 1015 and 1016, respectively. Compared to crizotinib alone, the co-administration with ketoconazole increases AUC_{inf} and C_{max} of crizotinib by 216% and 44%, while the co-administration with rifampin decreases AUC_{inf} and C_{max} of crizotinib by 82% and 69%. However, dose adjustments for the co-administration of CYP3A inhibitors or inducers can not be recommended based on the above available results due to the time-dependent pharmacokinetics of crizotinib.

PMR will be requested to conduct multiple dose trials in humans to determine how to adjust the crizotinib dose when it is co-administered with a strong CYP3A inhibitor (e.g., ketoconazole) or a strong CYP3A inducer (e.g.,rifampin).

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Carcinogenicity studies have not been conducted.

7.6.2 Human Reproduction and Pregnancy Data

No fertility and early embryonic development studies were submitted in humans.
The embryo-fetal development effects of crizotinib were studied in the rat and rabbit. Maternal toxicity including decreased body weight and food consumption was observed in the animal studies. Increased post-implantation loss consisting of early resorptions

and a decrease in fetal body weight was observed compared to controls. In addition a skeletal variation of unossifed metatarsals was observed, however, the incidence was minimal. No teratogenicity was observed in this study.

Dedicated fertility and pre- and post-natal studies were not required and were not conducted with crizotinib, though findings from the general toxicology studies suggest that crizotinib can negatively impact fertility. Pregnancy category D is recommended.

7.6.3 Pediatrics and Assessment of Effects on Growth

Pediatric patients were not included in these clinical studies with crizotinib. Studies required that patients be more than 18 years of age to meet eligibility criteria. Therefore, the safety of crizotinib in pediatric patients has not been established. Request for Waiver of Pediatric Studies for this indication was submitted with the original submission. It is exempted under Orphan Product designation.

The sponsor plans to pursue pediatric trials in anaplastic large cell lymphoma and neuroblastoma.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

N/A

8 Postmarket Experience

N/A

9 Appendices

9.1 Literature Review/References

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

9.2 Labeling Recommendations

See final labeling.

9.3 Advisory Committee Meeting

An advisory committee meeting was not held. However, the FDA findings will be discussed with two Special Government Employees and their comments will be included in an update to this report.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHAKUNTALA M MALIK
08/13/2011

VIRGINIA E MAHER
08/13/2011

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 202570 **Applicant: Pfizer** **Stamp Date: March 30th, 2011**

Drug Name: Crizotinib **NDA Type: NME**

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			electronic
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			Additional Data submission planned May 30th 2011.
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			Additional Data submission planned May 30th 2011.
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	505 (b)1			
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: A8081001 Study Title: Phase 1 Safety, Pharmacokinetic and	X			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pharmacodynamic Study of PF-02341066, a c-Met/HGFR Selective Tyrosine Kinase Inhibitor, Administered Orally to Patients with Advanced Cancer. Sample Size: For the dose-escalation cohort, a total of 38 patients were assigned to study treatment, Arms: Single arm dose escalation study. Location in submission: CSR				
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? **Pivotal Study # A8081001** RP2D expansion cohort of patients with NSCLC who were ALK positive. **Pivotal Study #2 A8081005** Single arm Phase II study of patients with NSCLC who were ALK positive.			X	This is an NME (ALK inhibitor) for patients with ALK-Positive NSCLC with greater than expected RR in a single arm Expansion cohort of a phase I trial.
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			The applicant is seeking Accelerated Approval in accordance with 21 CFR 314 Subpart H.
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			Additional Data submission planned May 30th 2011.
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?		X		The applicant is submitting a phase I trial single arm and a phase II trial as supportive trial for as basis for AA. Additional data of safety and efficacy will be submitted 60 days after the submission.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?		X		This single arm trial has been submitted for AA consideration due to high response rate noted in this subset of NSCLC. Additional data will be submitted on day 60th from the submission date.
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming			X	

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	the applicability of foreign data in the submission to the U.S. population?				
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?		X		No raw datasets have been submitted by the applicant. The FDA may request this if deemed necessary
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	The FDA may request additional data this if deemed necessary
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Shakun Malik, MD	May 5, 2011
Reviewing Medical Officer	Date
Virginia E Maher, MD	
Clinical Team Leader	Date

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/s/

SHAKUNTALA M MALIK
05/09/2011

VIRGINIA E MAHER
05/10/2011