

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202570Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	July 12, 2011
From	V. Ellen Maher, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	202570/S0
Applicant	Pfizer, Inc.
Date of Submission	March 30, 2011
PDUFA Goal Date	September 30, 2011
Proprietary Name / Established (USAN) names	Xalkori/crizotinib
Dosage forms / Strength	200 mg, 250 mg capsules
Proposed Indication(s)	Anaplastic lymphoma kinase-positive advanced non-small cell lung cancer
Recommended:	Approval

1. Introduction

On March 30, 2011, Pfizer submitted a new drug application for the use of crizotinib in the treatment of anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC). This application is supported by 2 single arm studies (Study A and Study B) evaluating the response rate of crizotinib. Issues in the review of this application include:

- An incomplete understanding of the safety signals associated with crizotinib;
- The atypical disease characteristics of the patients with NSCLC entered on these trials;
- The use of response rate as a surrogate endpoint; and
- The availability of approved drugs and biologics in NSCLC.

2. Background

Crizotinib is a receptor tyrosine kinase inhibitor with activity against c-MET, RON, ROS, and the constitutively active kinase formed by ALK gene rearrangement. The half-maximal effective concentration (EC₅₀) of crizotinib against each of these targets is shown below.

Target	In Vitro EC ₅₀
EML4-ALK	0.5 nM (24 nM)IC
WT c-MET	0.62 nM (11 nM)IC
RON RTK	9.1 nM (80 nM)EC
ROS RTK	60 nM

ALK inhibition by crizotinib results in reduced downstream signaling in ERK, Akt, STAT3, and PLCγ1, pathways known to contribute to cellular growth and development. In animal models, expression of the ALK fusion protein in lung alveolar cells, without other genetic alterations, leads directly to the development of lung cancer. ALK rearrangements are

estimated to occur in 1-7% of NSCLCs (Clin Cancer Res 2009 15:5216). During the Phase 1 study of crizotinib, 2 patients in the 50 mg cohort with ALK positive NSCLC had 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. This application includes 2 single arm trials, one from this Phase 2 extension (Study B) and the other a single arm, Phase 2 trial (Study A). Both have shown a response rate and duration of response that is markedly higher than that expected with approved therapy.

Approved agents for NSCLC are shown in the table below. The majority have received regular approval based on an improvement in overall survival. To grant accelerated approval of any drug, the drug must treat a serious or life-threatening illness and must provide “meaningful therapeutic benefit to patients over existing treatments” (21 CFR 314.500). While not every patient on these 2 single arm studies has received all approved therapy, the majority of patients have received standard first and second line therapy for NSCLC. Further, given the presence of a specific genetic rearrangement, patients with ALK positive NSCLC represent a unique patient population. Finally, accelerated approval can be granted on a “surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit” (21 CFR 314.510). Here, the applicant has chosen to submit 2 trials in which the primary endpoint is response rate rather than overall survival (an endpoint thought to directly measure clinical benefit). Given the marked improvement, over existing NSCLC therapies, in response rate and duration of response of crizotinib, it is likely that these responses will translate into clinical benefit for patients harboring the ALK translocation.

Drug	Indication	Basis of Approval
Bevacizumab Non-squamous	Initial treatment, in combination with carboplatin and paclitaxel	Overall Survival
Docetaxel	After platinum therapy	Overall Survival
	Initial treatment, in combination	Overall Survival
Erlotinib	Maintenance treatment	Progression-free Survival ¹
	After failure of at least 1 prior regimen	Overall Survival
Gemcitabine	Initial treatment, in combination with cisplatin	Overall Survival
Paclitaxel	Initial treatment, in combination with cisplatin	Overall Survival ²
Pemetrexed Non-squamous	Initial treatment in combination with cisplatin	Overall Survival
	Maintenance treatment	Overall Survival
	After prior chemotherapy	Overall Survival
Vinorelbine	Initial treatment, single agent or in combination	Overall Survival

¹The primary endpoint was PFS. The study also demonstrated a statistically significant improvement in OS.

²The difference in OS was not statistically significant.

Regulatory History

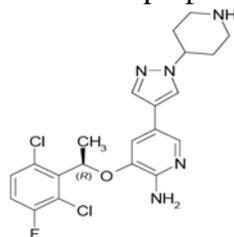
In October 2007, the applicant's Phase 1 trial was amended to include a Phase 2, ALK positive NSCLC cohort. The applicant, noting a partial response in 7/14 ALK positive patients, met with the Agency to discuss their registration strategy. The Agency expressed concern about the size of the database and 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 $\alpha = 0.0038$. 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 $\alpha = 0.025$ and an 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.
 - With 334 patients, the study will have 85% power to detect an improvement in PFS from 6 to 9 months with $\alpha = 0.025$.

3. CMC/Device

Chemistry, Manufacturing, and Control

The applicant has pursued a quality-by-design approach to the manufacture of crizotinib (shown below). The R enantiomer of Form A is proposed to be the active form of crizotinib.



Crizotinib is synthesized in (b) (4) steps, (b) (4) and (b) (4)
(b) (4) All excipients are compendial. Crizotinib is provided in 200 and 250

mg capsules and will have a 15 month expiry when stored in the commercial package at 25°C. While the commercial drug product is supplied in capsule form, crizotinib tablets and crizotinib powder in capsules (PIC are different from the commercial product) were used in Studies A and B. The applicant does not have information on the patients treated solely with crizotinib tablets, solely with PIC or with a combination of the two. During the review period, CMC conveyed a substantial number of comments to the applicant concerning their quality-by-design approach. These were ultimately addressed and the CMC reviewers recommend approval. Establishment inspections were acceptable.

Device

The Vysis ALK Break Apart FISH Probe 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. The Vysis test was used to select patients for entry into Study A. This kit uses formalin-fixed, paraffin-embedded tissue sections 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. During hybridization, the green probe binds to complementary DNA that is centromeric to the breakpoint while the orange probe binds to complementary DNA that is telomeric to the breakpoint. 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. 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 ≥ 15 of 100 cells contains a split signal, a single orange signal, or a single green signal, the tissue contains an ALK gene rearrangement. Tests of the reproducibility of specimen interpretation between readers showed a kappa score of 0.72, when equivocal results are included, suggesting substantial reproducibility. When the equivocal results were resolved, the kappa statistic was 1.00, suggesting almost perfect 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. There was no relationship between the site of analysis and FISH classification.

4. Nonclinical Pharmacology/Toxicology

ALK is 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. Electroretinograms in the rat showed reduced dark adaptation, but there were no treatment related ophthalmic findings in the repeat dose toxicology studies. At 1.1 μM , crizotinib inhibits hERG and an increase in QTc was seen in dog studies.

Crizotinib is genotoxic, but not mutagenic. In reproductive toxicology studies, maternal mortality, post-implantation fetal loss, and decreased fetal weight were seen. Teratogenicity was not seen. Crizotinib has been assigned Pregnancy Category D.

5. Clinical Pharmacology/Biopharmaceutics

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. No dose adjustment is needed for mild or moderate renal impairment. The effects of severe renal impairment and hepatic impairment are unknown. 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 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. Since it may be possible to increase the dose of crizotinib (dose limiting toxicity Phase 1 was fatigue), the clinical pharmacology group plans to examine the exposure-response relationship further in Studies 1007 and 1014.

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical- Efficacy

Table 3 provides criteria for Study A and for the ALK positive NSCLC cohort in Study B. Study B also included a dose escalation cohort, an ALK negative NSCLC cohort, and a cohort of patients treated at crizotinib 250 mg bid with a variety of malignancies. The applicant has termed this cohort “Other”. It included patients with lesions in the c-MET/hepatocyte growth factor pathway, ROS, or ALK (e.g., anaplastic large cell lymphoma).

Table 3: Study Design		
	Study A (1005)	Study B (1001: ALK+ NSCLC Cohort)
Eligibility Criteria	<ol style="list-style-type: none"> 1. Locally advanced or metastatic NSCLC containing an ALK translocation or inversion event by the Vysis ALK Break Apart Assay 2. Progressive disease on the control arm of a randomized study of crizotinib OR ineligible for a randomized study 3. Measurable disease 4. Prior chemotherapy for NSCLC; erlotinib, gefitinib not considered prior therapy 5. Performance status 0-3 6. No grade 1-2 cardiac arrhythmia, uncontrolled atrial fibrillation, QTc > 470 msec 	<ol style="list-style-type: none"> 1. Locally advanced or metastatic NSCLC containing an ALK translocation or gene amplification by a local laboratory developed test 2. Measurable disease 3. Performance status 0-2 4. No gr 1-2 cardiac arrhythmia, uncontrolled atrial fibrillation, QTc > 470 msec
Treatment	Crizotinib 250 mg po BID; tablets <ul style="list-style-type: none"> • Cycles defined as 21 d. 	Crizotinib 250 mg po BID; powder in capsules or tablets <ul style="list-style-type: none"> • Cycles defined as 28 d.
Safety Monitoring	NCI CTCAE v 4.0 CBC, Chemistries: baseline, C1D15, q cycle EKG: baseline, then C1D1, C2D1 prior to dose and at 2 h, 6 h post dose Ophthalmology evaluation: baseline, w/ visual disorder; visual symptom assessment questionnaire	NCI CTCAE v 3.0 CBC, Chemistries: baseline, C1D15, q cycle EKG: baseline, then C1D1, C1D15, C2D1 prior to dose and 4-6 h post dose; then C1D2 and q cycle prior to dose Ophthalmology evaluation: baseline, w/ visual disorder
Endpoint Evaluation	Imaging: baseline, q 8 wks until INV-determined progression or start of a new cancer therapy	Imaging: baseline, q 6 wks until INV-determined progression or start of a new cancer therapy
Primary Endpoint	Response rate by Investigator using RECIST v 1.0 95% confidence intervals	Response rate by Investigator using RECIST v1.1 95% confidence intervals
Secondary Endpoints	Duration of response Time to response Disease control rate at 8 and 16 wks Progression free survival; 6 mo PFS Overall Survival; 6 and 12 mo OS	Overall survival; 6 and 12 mo OS Duration of response Disease control rate at 6 and 12 wks Progression free survival Time to response
Statistical Plan	<p>The primary analysis population includes patients who: 1) received crizotinib, 2) had an adequate baseline tumor assessment, and 3) had ≥ 1 adequate post-baseline tumor assessment. Patients who died or withdraw due to disease progression are included in this population. The post-baseline assessment must be ≥ 6 wks from the 1st dose.</p> <p>The primary endpoint will be confirmed by an assessment of response by an Independent Radiology Committee. The primary analysis population is the same.</p>	

Changes in Study Conduct

Study A (1005) was amended 9 times. Amendment 7 added the Independent Review Committee (IRC) and allowed for a treatment delay ≤ 42 days. It also added a visual assessment questionnaire. Dose modification and criteria for pneumonitis and for a QTc > 500 were added in Amendments 7 and 8.

Study B (1001) was amended 15 times. It includes several substudies in which patients received a single dose of crizotinib on day -7 and then began daily crizotinib on day 1. Amendment 4 provided for an ALK positive NSCLC cohort and Amendment 12 for an ALK negative NSCLC cohort. Amendment 12 also substituted crizotinib capsules for tablets and provided for a baseline ophthalmology examination in all patients. Amendment 15 provided dose modification and monitoring criteria for pneumonitis. The independent radiology review committee (IRC) was added as an amendment to the statistical analysis plan.

Patient Disposition

Study A was conducted at 57 sites while Study B, which began as a Phase 1 trial, was conducted at 8 sites. Fifty-six percent of patients were from the US in Study A and 71% in Study B. To be eligible for Study A an ALK translocation must have been documented using the Vysis ALK Break Apart FISH Assay. A variety of laboratory developed assays were used to document the ALK translocation in Study B.

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 of Safety Population 1. Note that 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. Information on all patient deaths and discontinuations in Safety Population 1 is included in the Safety section.

	Study A (1005)	Study B (1001)
Efficacy Population	135 (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

¹Clinical progression in 5 pts

Patient Demographics and Baseline Characteristics

Median age was 52 years on Study A and 51 years on Study B. Both studies, unlike most studies of NSCLC, contained a nearly equal proportion of males and females. 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 patients were non-smokers or former smokers. Among former smokers, the median time since discontinuation was 15 years and 10 years on Studies A and B, respectively.

The median time from diagnosis on both studies was surprisingly long. It is unclear if 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. The sample date for ALK testing was examined in patients diagnosed more than 5 years prior to study entry and the sample collection dates in all

patients were within the year prior to study entry. Finally, the majority of patients on both trials had an adenocarcinoma. Additional information on tumor histology is provided in the footnote below the table. Thirteen patients entered Study A after disease progression on the control arm of randomized trials of crizotinib.

Table 5: Baseline and Disease Characteristics		
	Study A (1005) N = 136	Study B (1001) N = 119
Performance Status		
0	27.2%	35.1%
1	54.4%	52.6%
2	18.4%	11.8%
3	0	0.8%
Smoking Status		
Non-smoker	67.6%	72.3%
Former Smoker	28.7%	26.9%
Smoker	3.7%	0.8%
Median Time Since Diagnosis	2 years (0.15-13.7)	1.22 years (0.04-20.7)
Median Time Since Metastatic/Recurrent Disease	0.9 years (0.005-11.3)	Not Collected
Stage		
Locally Advanced	6.6%	4.2%
Metastatic	93.4%	95.8%
Histological Subtype		
Adenocarcinoma	97.1% ¹	98.3% ²
Squamous Cell Carcinoma	0	0.8%
Adenosquamous Carcinoma	2.2%	0
Non-small Cell Lung Cancer NOS	0.7%	0.8%
Prior Therapy		
Surgery	99.3%	98.3%
Radiation Therapy	56.6%	57.1%
Chemotherapy for Metastatic Disease	100.0%	86.6%

¹Includes adenocarcinoma NOS (93), signet ring (11), acinar (7), bronchoalveolar (7), solid (6), papillary (5), mixed acinar and papillary (2), and large cell (1).

²Includes adenocarcinoma NOS (115), bronchoalveolar (1), and large cell (1).

The following table provides information on the number of prior chemotherapy regimens and the percentage of patients receiving FDA-approved agents for NSCLC. While every patient has not received all approved chemotherapy, substantial numbers of patients have received each of the approved agents. Since data was available, patient response was examined to each agent. In general, the response rate of ALK positive patients is consistent with that of NSCLC as a whole. Response to erlotinib was 4.7% in the two studies.

Table 6: Prior Chemotherapy		
Number of Prior Chemotherapy Regimens for Metastatic Disease		
	Study A N = 136	Study B N = 119
0 Prior Regimens	0	12.6%
1 Prior Regimen	9.6%	31.1%
2 Prior Regimens	27.2%	20.2%
3 Prior Regimens	27.2%	14.3%
4-12 Prior Regimens	36.0%	21.8%
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 baseline tumor characteristics of patients on Studies A and B is outlined below. 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 were conducted in patients with varying degrees of tumor burden. The metastatic pattern in patients with ALK positive NSCLC appears typical of NSCLC as a whole.

Table 7: 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%

Primary Endpoint

The table below provides information on the primary endpoint for Studies A and B. The primary endpoint was investigator (INV)-determined response rate on the response-evaluable population (see Study Design). Despite the ability of ALK gene rearrangements to induce an oncogenic phenotype in the absence of other mutations/amplifications, crizotinib induced primarily partial rather than complete response. Although the number of patients with brain metastases was small, it appears that these lesions do not respond to crizotinib.

The IRC-determined response rate was slightly lower than the INV-determined response rate, but does support the findings of the investigators. Note that the number of patients available for IRC review is smaller than the number available for INV review. This is due to problems

with the transmission of the scans to the IRC and to the lack of target lesions on IRC review of some scans. In Study A, 34 of the 67 patients with INV-determined response (CR or PR) were found to have a response by the IRC. In Study B, 52 of the 71 patients with INV-determined response had a response IRC assessment.

Table 8: Primary Endpoint				
	Study A		Study B	
	INV N = 135	IRC N = 105	INV N = 116	IRC N = 105
Response Rate [95% CI]	67 (49.6%) [40.9%, 58.4%]	44 (41.9%) [32.3%, 51.9%]	71 (61.2%) [51.7%, 70.1%]	55 (52.4%) [42.4%, 62.2%]
Complete Response	1	1	2	0
Partial Response	66	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)

¹Kaplan-Meier method with censored values

In addition to INV-IRC discrepancies, patient progression was also examined. Among the patients who did not achieve a response on Study A, a new lesion was the basis of progression in slightly more than half the patients. Likewise, among the patients who responded and later progressed, slightly more than half the patients progressed with new lesions. Among patients on Study B who responded and later progressed, approximately 1/3 progressed due to the presence of a new lesion.

Subset Analyses

To further understand the response to crizotinib, a number of subset analyses were carried out and selected analyses are shown in the table below. There was no clear difference in response by performance status, sex, age, and number of prior chemotherapeutic regimens.

Further, there was also no difference in response by tumor burden. This was of particular concern since the median SLD in both studies is very small. Finally, the percentage of cells found to have a rearrangement in the ALK gene was not related to response. In both studies, there was a marked difference in response by race. The clinical pharmacology group has examined this and found that this difference appears to be related to body size. That is, the higher response rate in Asians (who also had a smaller body size) may be explained by their higher dose of crizotinib (on a mg/kg basis).

Table 9: 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	46.2%	54.6%
2 Prior Regimens	62.2%	60.0%
3 Prior Regimens	43.2%	76.5%
≥ 4 Prior Regimens	45.8%	50.0%
Response by Disease Burden		
Baseline SLD ≤ Median	42.7%	52.2%
Baseline SLD > Median	56.7%	53.7%

Some patients in Studies A and B were reported to have a prolonged period between diagnosis and study entry. Among the 19 patients in whom the time between diagnosis and study entry was reported to be > 5 years, 6 (31.6%) were responders. That is, the high response rates in these studies are not driven by these “atypical” patients. 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 and, again, did not drive the high response rates in these studies.

ALK Negative Non-Small Cell Lung Cancer

Twenty-three (23) patients with locally advanced or metastatic ALK negative NSCLC have received crizotinib. ALK status was determined using the Vysis kit. Eight of the 23 (34.8%) had not received prior chemotherapy for metastatic disease. Five of 19 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 would be 7/20 (35.0%). This is similar to the response rate in patients with ALK positive NSCLC in Study A. 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. The applicant is retrospectively testing tumor samples for the presence of these genetic abnormalities. The study of additional patients with ALK negative NSCLC will be a post-marketing requirement.

Other Malignancies

Two patients with NSCLC with unknown ALK status in the “Other” Cohort on Study B had a partial response.

8. Safety

The focus of the safety review will be on the adverse event information from 255 patients with ALK positive NSCLC from Studies A and B. The original NDA submission provided this data with a cutoff of September 15, 2010. The original NDA submission also provided adverse event information for 85 patients on Study B who did not have ALK positive NSCLC. The Safety Update, using a later cutoff of February 1, 2011, provided only information on patient deaths and SAEs. This was provided for:

- 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.

This review does not provide information on adverse events which occurred between day -7 (single dose) and day 1 (continuous dosing). These adverse events were supplied in Listing 6.3.1 and were primarily gastrointestinal events with 1 report of a grade 2 ALT elevation.

Exposure

The table below provides information on patient exposure to crizotinib on Studies A and B. Thirty-two patients on Study B have remained on crizotinib for > 1 year. While only 1 patient has been treated on Study A for > 1 year, Study A began approximately 4 years after initiation of Study B.

A substantial number of patients on both studies required treatment interruption or dose reduction. The median duration of interruption was similar on both studies, 7 days on Study A and 6.5 days on Study B. It is, however, unclear why the percentage of patients who underwent dose reduction is higher on Study A. .

	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%

Deaths and Discontinuations

In the ALK positive NSCLC cohorts of Studies A and B, 45 patients died within 28 days of study drug. This includes 10 patients who died during their first 28 days on study. 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 led to death are included in the table below. The table includes information on all patients with ALK positive NSCLC who received crizotinib (N = 397) and on the 255 patients in the efficacy population in which all

adverse event data is available. The table also include information on 5 patients in Study 1007 (ALK positive NSCLC) who died within 28 days of crizotinib.

In reviewing this table, respiratory events and septic shock stand out as areas of concern. In a single arm study in NSCLC, it is difficult to discern whether respiratory events are related to crizotinib or to the underlying disease. Pneumonitis has been identified as an adverse event associated with crizotinib and is discussed below. Septic shock or DIC were reported in 4 patients (1 patient listed as pneumonia had pneumonia resulting in septic shock). In 2 patients, septic shock was associated with possible pneumonia. In 2 additional patients, the cause of death was listed as DIC. In the first patient, yeast was found in the blood and DIC was associated with acute renal failure. In the second, atrial fibrillation and dyspnea were followed, 6 days later, by reports of DIC, acute renal failure, and hematuria. Infectious events and DIC will continue to be monitored during crizotinib development.

Table 11: Deaths Due to an Adverse Event Within 28 Days of Crizotinib

	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		

¹With cardiac arrest

Among the 255 patients with ALK positive NSCLC in which all safety data is available, 7 (5.1%) patients on Study A and 3 (2.5%) patients on Study B discontinued due to an adverse event. Of note, 1 patient in Study B discontinued due to autoimmune thyroiditis. This event occurred in a 26 year 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.

Serious Adverse Events and Grade 3-4 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 occurring in $\geq 2\%$ 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, elevated ALT/AST was reported as a SAE in 2 patients on Study 1007. Grade 3-4 adverse events occurred in 40.8% of the 255 patients in Studies A and B. Events in $\geq 5\%$ of patients included elevated ALT/AST, dyspnea, pneumonia and neutropenia.

Grade 1-4 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 each of the adverse events is similar in the two trials.

	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	87 (64.0%)	84 (61.8%)	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

¹Includes diplopia, photopsia, vision blurred, visual field defect, visual impairment, vitreous floaters, visual acuity reduced, and visual brightness.

²Includes dyspepsia, dysphagia, epigastric discomfort/burning, esophagitis, esophageal obstruction, pain, spasm, and ulcer, gastroesophageal reflux, odynophagia, and reflux esophagitis.

³Includes balance disorder, dizziness postural, and presyncope

Visual disorders were reported in 163 patients in Studies A and B. Preferred terms in more than 1 patient include visual impairment, photopsia, blurred vision, vitreous floaters, diplopia, photophobia, and visual field defect. Grade 2 events were reported in 3 patients. The remainder are grade 1 events. Most events occurred while the patient was receiving crizotinib 250 mg bid. However, 1 event was at 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 applicant will be asked, as a post-marketing requirement, to more carefully examine a cohort of patients for changes in their slit lamp and fundoscopic examinations.

Esophageal disorder included a variety of preferred terms ranging from dyspepsia to esophageal obstruction and ulcer. One patient developed hematemesis due to a pill ulcer. At present, it is unclear whether these events are related to crizotinib or to waxing and waning of an underlying disease such as GERD. These adverse events will be studied more closely in a randomized trial.

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 occurred in 3 patients with the remainder grade 1 events. Among the treatment-related events, 30/60 had resolved at the time of data cutoff. Dysgeusia was less common 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.

Finally, angioedema (treated with dexamethasone) was reported in 1 patient narrative. It is unclear whether this event was related to study drug and it is not included in the datasets or case report forms. Examination of the datasets, identified no other hypersensitivity reactions.

Significant Adverse Events

Pneumonitis was reported in 5 patients in Studies A and B and in 1 patient in Study 1007. All events occurred within 2 months of entry and 2 of these events resulted in death. Three of the 6 patients had a prior history of pulmonary embolism. Steroids and antibiotics were used in 5 of the 6 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.

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 (<1%) developed a QTcF \geq 500 ms and 3% had an increase in QTcF \geq 60 ms. In the safety database, extrasystoles were reported in 3 patients and tachycardia in 1 patient.

Laboratories

Minimal hematologic toxicity has been reported with crizotinib. Grade 3-4 neutropenia was seen in 13/255 (5.1%) patients with ALK positive NSCLC on Studies A and B. Temporary suspension or dose reduction resulted in improvements in the ANC. Grade 3 thrombocytopenia was reported in 1 patient (may be related to XRT to the spine).

Abnormal liver function tests have been seen with crizotinib and 1 patient had a concomitant elevation in ALT > 3xULN and total bilirubin to > 2xULN. This patient was noted to have upper abdominal pain, an elevated lipase, and a moderately distended gall bladder by US. However, nuclear medicine imaging was negative for cholecystitis and alkaline phosphatase was not elevated. ALT did improve with discontinuation of crizotinib. While the cause of this

patient's elevated liver function tests is unclear, it should be noted that an additional patient had a repeat elevation in ALT on re-exposure to crizotinib. Overall, 16/255 (6.3%) of patients with ALK positive NSCLC on Studies A and B had a grade 3-4 elevation in ALT while 3 (1.2%) had a grade 2-3 elevation in bilirubin. Liver function tests will be closely examined in Studies 1007 and 1014.

9. 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.

10. Pediatrics

Crizotinib has been granted orphan drug status for this indication. The sponsor plans to pursue pediatric trials in anaplastic large cell lymphoma and neuroblastoma.

11. Other Relevant Regulatory Issues

Audits of two clinical sites and of the applicant by the Division of Scientific Investigation were acceptable. Twenty-five investigators received significant payments from the applicant and three had equity in Pfizer. The number of patient enrolled by these investigators was small and did not affect the study outcome.

12. Labeling

Please see final labeling. Since prior treatment did not have an effect on patient response, the indication statement will not specify a requirement for prior therapy.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action: Approval
- Risk Benefit Assessment
 - Risk
Further follow up and examination the adverse event profile of crizotinib in a randomized trial will be necessary to fully define the safety signals associated with crizotinib. Note, however, that crizotinib appears to be less toxic than conventional chemotherapy.
 - Benefit
Compared to conventional chemotherapy, a marked elevation in response rate and duration of response has been seen with crizotinib. It is thought that

this will translate into an improvement in overall survival in this patient population. The application will be asked to present the comparative findings from randomized trials of crizotinib vs. conventional chemotherapy.

- Recommendation for Postmarketing Risk Management Activities

None

- Recommendation for other Postmarketing Study Commitments

Subpart H Accelerated Approval

1. Clinical study report and datasets from A8081007
2. Clinical study report and datasets from A8081014

Section 505(o)

1. Submit the study report on the ongoing *in vitro* evaluations of induction potential of crizotinib on CYP2B and CYP2C enzymes.
2. Clinical trial in which careful ophthalmologic observations are conducted in at least 30 patients.
3. A clinical trial to explore response to and activity of crizotinib in ALK-negative patients based on the current Vysis assay cutoff.
4. Complete the ECG sub-study in trial A8081007 and submit the final study report, along with a thorough review of cardiac safety data.
5. Conduct a multiple dose trial in patients to determine how to adjust the crizotinib dose when it is coadministered with a strong CYP3A inhibitor (e.g., ketoconazole).
6. Conduct a multiple dose trial in patients to determine how to adjust the crizotinib dose when it is coadministered with a strong CYP3A inducer (e.g., rifampin).
7. Conduct a multiple dose trial to determine the appropriate crizotinib dose in patients with various degrees of hepatic impairment.
8. Conduct a single dose trial to determine the appropriate crizotinib dose in patients with severe renal impairment.
9. Conduct a multiple dose trial in patients to determine how to dose crizotinib with regard to gastric pH elevating agents.

Post-Marketing Commitments

1. To conduct an exposure-response analysis for progression free survival, response rate, overall survival and safety endpoints utilizing data from confirmatory trial A8081007.
2. To conduct exposure-response analysis for progression free survival, response rate, overall survival and safety endpoints utilizing data from confirmatory trial A8081014.

- Recommended Comments to Applicant

None

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

/s/

VIRGINIA E MAHER
08/11/2011