CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202570Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	August 26, 2011
From	Robert L. Justice, M.D., M.S.
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	202570
Applicant Name	Pfizer Inc
Date of Submission	3/30/11
PDUFA Goal Date	9/30/11
Proprietary Name / **Established (USAN) Name**	XALKORI/ crizotinib
Dosage Forms / Strength	Capsules, 200 mg and 250 mg
Proposed Indication(s)	treatment of anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC)
Action/Recommended Action for NME:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Shakuntala Malik
Statistical Review	Lijun Zhang, Shenghui Tang, Meiyu Shen
Pharmacology Toxicology Review	Brenda Gehrke, Whitney Helms, John Leighton
CMC Review/OBP Review	Zedong Dong, Debasis Gosh, Donghao Lu, Richard Lostritto, Karen Riviere
Microbiology Review	Stephen Langille
Clinical Pharmacology Review	Pengfei Song, Anshu Marathe
DDMAC	Marybeth Toscano, Richard Lyght
OSI	Robert Young
CDTL Review	Ellen Maher
OSE/DMEPA	Kimberly DeFronzo, Denise Baugh, Kevin Wright
OSE/DDRE	
OSE/DRISK	Latonia Ford, Amarilys Vega
Other: Consults	Wiley Chambers, John Senior, Rosane Charlab Orbach

OND = Office of New Drugs
DDMAC = Division of Drug Marketing, Advertising and Communication
OSE = Office of Surveillance and Epidemiology
DMEPA = Division of Medication Error Prevention and Analysis
OSI = Office of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DRISK = Division of Risk Management
CDTL = Cross-Discipline Team Leader

Division Director Summary Review

1. Introduction

This new drug application for XALKORI (crizotinib) Capsules was submitted on 3/30/11 for the indication of treatment of patients with anaplastic lymphoma kinase-positive (ALK-positive) advanced non-small cell lung cancer (NSCLC). Because of the high objective response rates in two single-arm trials in patients with ALK-positive NSCLC, the application was given a priority review. This review will briefly discuss the clinical trial efficacy and safety results and the recommendations of each review discipline.

2. Background

The following summary of crizotinib's mechanism of action is from the Acting Pharmacology Team Leader's Review.

> The pharmacology studies submitted to this NDA demonstrate that crizotinib is a kinase inhibitor. Like other approved kinase inhibitors crizotinib targets a several proteins at clinically relevant concentrations including c-Met/hepatocyte growth factor receptor (HGFR), anaplastic lymphoma kinase (ALK), and Recepteur d'Origine Nantais (RON). Though the drug has its strongest potency against c-Met, the clinical development of crizotinib has focused on patients with tumors expressing ALK gene translocation products. ALK has an important role during development, particularly in neural development, but has limited expression in normal cells. Translocations with the *ALK* gene have led to the expression of oncogenic fusion proteins resulting in dysregulated expression of, and increased signaling through this kinase. Crizotinib was able to inhibit the growth of tumors derived from various cell types expressing c-Met/HGFR, and either EML-ALK4 or NPM-ALK4 translocations both *in vitro* and in a series of xenograft experiments conducted in athymic mice. Treatment of these mice with the drug also led to decreased phosphorylation of a number of downstream targets in the tumors, decreases in proliferation markers, and increases in apoptotic markers, further demonstrating the pharmacologic activity of crizotinib.

ALK rearrangements are estimated to occur in 1-7% of patients with NSCLC (Clin Cancer Res 2009 15:5216). In October 2007, the sponsor's phase 1 trial was amended to include a phase 2 ALK-positive cohort based on partial responses in 7/14 previously treated patients with ALK-positive NSCLC.

An End-of-Phase 2 meeting was held on 4/23/09. The sponsor asked about accelerated approval based on a single-arm study. The FDA expressed concern about the size of the database and recommended a randomized trial vs. conventional therapy (docetaxel or pemetrexed). Accelerated approval could be considered based on an interim analysis of a

surrogate endpoint in the randomized trial. The sponsor was advised to discuss their proposed companion diagnostic with CDRH.

At a meeting on 4/14/10, the sponsor asked whether it would be acceptable to submit an NDA for accelerated approval based on two single-arm trials in patients with ALK-positive NSCLC, if the safety profile remained acceptable and the observed ORR results were maintained. The FDA stated that it would be acceptable to submit the data but whether the response rate would support accelerated approval would be a review issue and would depend on the final response rate, the durations of response, and the risk:benefit ratio. The sponsor also asked whether one phase 3 study (A8081014) would be sufficient for full approval. The FDA cautioned about relying on a single trial, recommended overall survival as the primary endpoint, and stated that whether PFS would support full approval would be a review issue and would likely require an ODAC discussion. There was additional discussion about the companion diagnostic.

A general pre-NDA meeting was held on 7/29/10 to discuss technical aspects of the submission and a CMC pre-NDA meeting was held on 9/24/10.

3. CMC/Device

I concur with the conclusions reached by the chemistry reviewers regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of fifteen months.

The companion diagnostic, the Vysis ALK Break-Apart FISH Probe Kit (Abbott Molecular, Inc.), will be approved concurrently with crizotinib. The test is designed to detect rearrangements of the anaplastic lymphoma kinase (ALK) gene in NSCLC.

There are no outstanding CMC or device issues.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewers that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewers that there are no outstanding clinical pharmacology issues that preclude approval. I also concur with the recommended PMR's and PMC's. See section 13.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

This accelerated approval is based on the results of two single-arm studies. The following excerpt from the agreed-upon package insert summarizes the trials and their results.

> The use of single-agent XALKORI in the treatment of locally advanced or metastatic ALK-positive NSCLC was investigated in 2 multi-center, single-arm studies (Studies A and B). Patients enrolled into these studies had received prior systemic therapy, with the exception of 15 patients in Study B who had no prior systemic treatment for locally advanced or metastatic disease. In Study A, ALK-positive NSCLC was identified using the Vysis ALK Break-Apart FISH Probe Kit. In Study B, ALK-positive NSCLC was identified using a number of local clinical trial assays. The primary efficacy endpoint in both studies was Objective Response Rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST). Response was evaluated by the investigator and by an independent radiology review panel. Duration of Response (DR) was also evaluated. Patients received 250 mg of XALKORI orally twice daily. Demographic and disease characteristics for Studies A and B are provided in Table 4.

Table 4: Demographic and Disease Characteristics in Studies A and B

Characteristics	Study A N=136	Study B N=119
Sex, n (%)		
Male	64 (47)	59 (50)
Female	72 (53)	60 (50)
Age (years)		
Median (range)	52 (29-82)	51 (21-79)
Race, n (%)		
White	87 (64)	74 (62)
Black	5 (4)	3 (3)
Asian	43 (32)	34 (29)
Other	1 (1)	8 (7)
ECOG PS at baseline, n (%)		
0	37 (27)	41 (35)
1	74 (54)	63 (53)
2 – 3[a]	25 (18)	15 (13)
Smoking status, n (%)		
Never smoked	92 (68)	86 (72)
Former smoker	39 (29)	32 (27)
Current smoker	5 (4)	1 (1)
Disease stage, n (%)		
Locally advanced	9 (7)	5 (4)
Metastatic	127 (93)	114 (96)
Histological classification, n (%)		
Adenocarcinoma	130 (96)	116 (98)
Large cell carcinoma	1 (1)	1 (1)
Squamous cell carcinoma	0	1 (1)
Adenosquamous carcinoma	3 (2)	0
Other	2 (2)	1 (1)
Prior systemic therapy for locally advanced or metastatic disease -- number of regimens, n (%)		
0	0	15 (13)
1	13 (10)	34 (29)
2	37 (27)	20 (17)
3	37 (27)	17 (14)
≥4	49 (36)	33 (28)

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

One hundred thirty-six patients with locally advanced or metastatic ALK-positive NSCLC from Study A were analyzed at the time of data cutoff. The median duration of treatment was 22 weeks. Based on investigator assessments, there was 1 complete and 67 partial responses for an ORR of 50% (95% CI: 42%, 59%). 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 locally advanced or metastatic ALK-positive NSCLC were enrolled into Study B at the time of data cutoff. The median duration of treatment was 32 weeks. Based on investigator assessments, there were 2 complete and 69 partial responses for an ORR of 61% (95% CI: 52%, 70%). Fifty-five percent of objective tumor responses were achieved during the first 8 weeks of treatment. The median response duration was 48.1 weeks.

Efficacy data from Studies A and B are provided in Table 5.

Table 5: Locally Advanced or Metastatic ALK-Positive NSCLC Efficacy Results from Studies A and B [a]

Efficacy Parameter	**Study A N=136**	**Study B N=119**
ORR (CR+PR)[b] [% (95% CI)]	50% (42%, 59%)	61% (52%, 70%)
Number of Responders	68	71
Duration of Response[c] [Median (range) weeks]	41.9 (6.1+, 42.1+)	48.1 (4.1+, 76.6+)

[a]Response as assessed by the Investigator.
[b]One patient was not evaluable for response in Study A; 3 patients were not evaluable for response in Study B.
[c]Preliminary estimate using Kaplan-Meier method.
+Censored values

Since the investigator's determination of response was the primary endpoint, the results of the independent radiology review (IRR) panel's assessment are not shown above. The following excerpt from the Statistical Review and Evaluation summarizes the initial IRR response rates and the updated IRR response rates that were submitted on 8/17/11. Study A is Study 1005 and Study B is Study 1001.

In Study 1005, IRR response rate was 41.9% (95% CI: 32.3%, 51.9%) in IRR response evaluable patient population (n=105), and was 32.3% (95% CI: 24.6%, 40.9%) in safety-analysis population (n=136).

In Study 1001, IRR response rate was 52.4% (95% CI: 42.4%, 62.2%) in IRR response evaluable patient population (n=105), and was 46.2% (95% CI: 37.0%, 55.6%) in safety-analysis population (n=119).

On 17 August 2011, the applicant submitted updated objective response data per IRR assessments for both studies. Study 1005 had 1 complete response and 62 partial responses, with an IRR response rate of 46.3% (95% CI: 37.7%, 55.1%) in safety-analysis population (n=136). Study 1001 had 63 partial responses, with an IRR response rate of 52.9% (95% CI: 43.6%, 62.2%) in safety-analysis population (n=119).

The initial IRR response rates were somewhat lower than the investigator response rates, particularly in the safety-analysis population. However, not all scans were available for the

initial review. The updated IRR response rates were higher for both studies and closer to the investigator assessed response rates.

The following summary of the available data on the activity of crizotinib in patients with locally advanced or metastatic NSCLC that is ALK-negative is from the CDTL Review.

> 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.

Since the activity of crizotinib in patients with ALK-negative NSCLC is not a safety issue, it will be a postmarketing commitment.

8. Safety

The following summary of safety is from the adverse reactions section of the agreed-upon package insert.

> In Studies A and B, patients with locally advanced or metastatic ALK-positive NSCLC received crizotinib 250 mg orally twice daily continuously. Among the 255 patients for whom data on Grade 1-4 adverse reactions are available, median exposure to study drug was 5.1 months in Study A and 7.8 months in Study B. Dosing interruptions occurred in 36% and 45% of patients in Studies A and B, and lasted greater than 2 weeks in 13% and 19% of patients in Studies A and B, respectively. Dose reductions occurred in 44% and 29% of patients in Studies A and B, respectively. The rates of treatment-related adverse events resulting in permanent discontinuation were 6% in Study A and 3% in Study B. The most common adverse reactions (≥25%) across both studies were vision disorder, nausea, diarrhea, vomiting, edema, and constipation. Grade 3-4 adverse reactions in at least 4% of patients in both studies included ALT increased and neutropenia.
>
> Among the 397 patients for whom information on deaths and serious adverse reactions are available, deaths within 28 days of the last dose of study drug occurred in 45 patients. Ten (2.5%) patients died within 28 days of their first dose of study drug. Causes of death included disease progression (32 patients), respiratory events (9), and other (4). Respiratory causes of death included pneumonia (2), hypoxia (2), ARDS (1), dyspnea (1), pneumonitis (1), empyema (1), and pulmonary hemorrhage (1). Other

causes of deaths included septic shock, DIC, cardiovascular event, and death due to unknown cause (1 each). Serious adverse events in greater than or equal to 2% of patients included pneumonia, dyspnea, and pulmonary embolism. Table 3 lists the common adverse reactions on Studies A and B in patients receiving XALKORI.

Table 3: Adverse Reactions in ≥10% of Patients with Locally Advanced or Metastatic ALK-Positive NSCLC on Studies A and B[1]

Adverse Event	Treatment Emergent N=255		Treatment Related N=255	
	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)
Eye Disorders				
Vision Disorder[2]	163 (64%)	0	159 (62%)	0
Gastrointestinal Disorders				
Nausea	145 (57%)	2 (<1%)	136 (53%)	0
Diarrhea	124 (49%)	1 (<1%)	109 (43%)	0
Vomiting	116 (45%)	3 (1%)	101 (40%)	0
Constipation	98 (38%)	2 (<1%)	69 (27%)	1 (<1%)
Esophageal Disorder[3]	51 (20%)	3 (1%)	29 (11%)	0
Abdominal Pain[4]	40 (16%)	1 (<1%)	20 (8%)	0
Stomatitis[5]	27 (11%)	1 (<1%)	15 (6%)	1 (<1%)
General Disorders				
Edema[6]	97 (38%)	2 (<1%)	72 (28%)	0
Fatigue	80 (31%)	6 (2%)	51 (20%)	4 (2%)
Chest Pain/Discomfort[7]	30 (12%)	1 (<1%)	3 (1%)	0
Fever	30 (12%)	1 (<1%)	2 (<1%)	0
Infections and Infestations				
Upper Respiratory Infection[8]	50 (20%)	1 (<1%)	4 (2%)	0
Investigations				
Alanine Aminotransferase Increased	38 (15%)	17 (7%)	34 (13%)	14 (5%)
Aspartate Aminotransferase Increased	29 (11%)	7 (3%)	24 (9%)	5 (2%)
Metabolism and Nutrition				
Decreased Appetite	69 (27%)	3 (1%)	49 (19%)	0
Musculoskeletal				
Arthralgia	29 (11%)	3 (1%)	4 (2%)	0
Back Pain	28 (11%)	0	2 (<1%)	0
Nervous System Disorders				
Dizziness[9]	60 (24%)	0	42 (16%)	0
Neuropathy[10]	58 (23%)	1 (<1%)	34 (13%)	1 (<1%)
Headache	34 (13%)	1 (<1%)	10 (4%)	0
Dysgeusia	33 (13%)	0	30 (12%)	0
Psychiatric Disorders				
Insomnia	30 (12%)	0	8 (3%)	0
Respiratory Disorders				
Dyspnea	57 (22%)	16 (6%)	5 (2%)	3 (1%)
Cough	54 (21%)	3 (1%)	9 (4%)	0
Skin Disorders				
Rash	41 (16%)	0	25 (10%)	0

[1]Study A used CTCAE v4.0, and Study B used CTCAE v3.0.

[2]Includes diplopia, photopsia, photophobia, vision blurred, visual field defect, visual impairment, vitreous floaters, visual brightness, and visual acuity reduced.
[3]Includes dyspepsia, dysphagia, epigastric discomfort/pain/burning, esophagitis, esophageal obstruction/pain/spasm/ulcer, gastroesophageal reflux, odynophagia, and reflux esophagitis.
[4]Includes abdominal discomfort, abdominal pain, abdominal pain upper, and abdominal tenderness.
[5]Includes mouth ulceration, glossodynia, glossitis, cheilitis, mucosal inflammation, oropharyngeal pain/discomfort, oral pain, and stomatitis.
[6]Includes edema, edema localized, and peripheral edema.
[7]Includes chest pain, chest discomfort, and musculoskeletal chest pain.
[8]Includes nasopharyngitis, rhinitis, pharyngitis, and upper respiratory tract infection.
[9]Includes balance disorder, dizziness, and presyncope.
[10]Includes burning sensation, dysesthesia, hyperesthesia, hypoesthesia, neuralgia, paresthesia, peripheral neuropathy, peripheral motor neuropathy, and peripheral sensory neuropathy.

Vision disorders including visual impairment, photopsia, vision blurred, vitreous floaters, photophobia, and diplopia were reported in 159 (62%) patients in clinical trials. These events generally started within two weeks of drug administration. Ophthalmological evaluation should be considered, particularly if patients experience photopsia or experience new or increased vitreous floaters. Severe or worsening vitreous floaters and/or photopsia could also be signs of a retinal hole or pending retinal detachment. Caution should be exercised when driving or operating machinery by patients who experience vision disorder…

Neuropathy as defined in Table 3 and attributed to study drug by the investigator was reported in 34 (13%) patients. While most events were Grade 1, Grade 2 motor neuropathy and Grade 3 peripheral neuropathy were reported in 1 patient each. Dizziness and dysgeusia were also very commonly reported in these studies, but were all Grade 1 or 2 in severity.

Bradycardia has been reported in 12 (5%) patients treated with XALKORI. All of these cases were Grade 1 or 2 in severity.

Complex renal cysts have been reported in 2 (1%) patients treated with XALKORI. There were no reports of abnormal urinalyses or renal impairment in these cases.

Laboratory Abnormalities

Grade 3 or 4 neutropenia, thrombocytopenia, and lymphopenia were seen in 5.2%, 0.4%, and 11.4% of patients, respectively.

Three reported adverse reactions warrant inclusion in the Warnings and Precautions section. Crizotinib has been associated with severe, life-threatening, or fatal treatment-related pneumonitis in clinical trials with a frequency of 4 in 255 (1.6%) patients across Studies A and B. All of these cases occurred within 2 months after the initiation of treatment. Therefore, patients should be monitored for pulmonary symptoms indicative of pneumonitis and should

be evaluated for the cause of pneumonitis. In patients diagnosed with treatment-related pneumonitis, crizotinib should be permanently discontinued.

Grade 3 or 4 ALT elevation was observed in 7% of patients in Study A and in 4% of patients in Study B. They were generally asymptomatic and reversible upon dosing interruption. Although patients usually resumed treatment at a lower dose without recurrence, 3 patients from Study A (2%) and 1 patient from Study B (less than 1%) required permanent drug discontinuation. 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%) of patients with available laboratory data across both studies. Criteria are provided for monitoring liver function tests and for treatment interruption, dose reduction and drug discontinuation.

QTc prolongation has been observed and crizotinb should be avoided in patients with congenital long QT syndrome. In patients with congestive heart failure, bradyarrhythmias, electrolyte abnormalities, or who are taking medications that are known to prolong the QT interval, periodic monitoring with electrocardiograms (ECGs) and electrolytes should be considered. Criteria are provided for drug discontinuation, treatment interruption, and dose reduction.

9. Advisory Committee Meeting

The application was not referred to an FDA advisory committee because it did not raise significant safety or efficacy issues in the intended population. However, the application was discussed independently with two SGE's. Both recommended approval.

10. Pediatrics

PREA does not apply because of orphan drug exclusivity.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

- Proprietary name: XALKORI was found to be acceptable by DMEPA.
- Physician labeling: Agreement has been reached on the physician labeling.
- Immediate container labels: Minor problems in the immediate container label were identified by DMEPA and CMC. The FDA agreed that the applicant could launch with the originally submitted container labels so that the drug could get to patients quicker. However, the applicant is required to make the revisions with the next printing in September.

- Patient labeling: Agreement has been reached on patient labeling.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

  Accelerated approval

  The following two postmarketing trials are required to confirm clinical benefit.

  1789-1

  Clinical trial report and datasets from A8081007: Phase 3, Randomized, Open-label Study of the Efficacy and Safety of PF-02341066 vs. Standard of Care (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

Final Protocol Submission:	09/2009 (submitted)
Trial Completion:	12/2013
Final Report Submission:	06/2014

  1789-2

  Clinical trial report and datasets from 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

Final Protocol Submission:	06/2010 (submitted)
Trial Completion:	12/2015
Final Report Submission:	06/2016

- Risk Benefit Assessment

  As noted in Table 4 above, these two studies enrolled patients who had received multiple prior systemic therapies. Twenty-eight to 36% of patients had received four or more treatment regimens. Despite this, the objective response rates in these studies (50% and 61%) were higher than would be expected with standard chemotherapy. In addition, the median durations of response were 41.9 and 48.1 weeks, respectively. It is likely that these responses will translate into an improvement in progression-free survival and overall survival in the ongoing confirmatory trials.

The most common adverse reactions were vision disorder, nausea, diarrhea, vomiting, edema, and constipation. The incidence of Grade 3-4 adverse reactions was low compared to other chemotherapy agents. The most common Grade 3-4 adverse reactions were ALT increased (5%) and neutropenia (5.2%). The major safety concerns are vision disorders and severe, life-threatening, or fatal treatment-related pneumonitis which occurred in 1.6% of patients. Almost all of the vision disorders were Grade 1 and there is a PMR that will require better characterization of this toxicity. Pneumonitis has been seen with other kinase inhibitors and is difficult to evaluate in a single arm trial in patients with NSCLC who often have pneumonitis due to disease or other treatments. Again, the confirmatory trials will further characterize this safety signal.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

  None

- Recommendation for other Postmarketing Requirements and Commitments

  Postmarketing Requirements (PMR)

  The following PMR recommended by Clinical Pharmacology is intended to identify an unexpected serious risk of drug interactions caused by the induction of human CYP2B and CYP2C enzymes by crizotinib.

  1789-3

  Submit the final report on the ongoing *in vitro* evaluations of induction potential of crizotinib on CYP2B and CYP2C enzymes.

Final Protocol Submission:	12/2011
Study Completion:	12/2011
Final Report Submission:	12/2011

  The following PMR recommended by the ophthalmologic consultant is intended to assess a known serious risk of visual disorders with crizotinib.

  1789-4

  Clinical trial (existing trial or new clinical trial) in which at least 30 patients are studied. The following examinations should be 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).

  1. Best corrected distance visual acuity
  2. Refractive error associated with best corrected distance visual acuity

3. Pupil size under standardized lighting conditions
4. Slit lamp biomicroscopy of the anterior segment
5. Intraocular pressure
6. Ocular coherence tomography of the macula
7. Dilated fundus photography of the retina

Final Protocol Submission:	10/2011
Trial Completion:	12/2013
Final Report Submission:	06/2014

The following PMRs recommended by Clinical Pharmacology are intended to assess signals of a serious risk of QT prolongation, drug-drug interactions with CYP3A inhibitors and inducers and gastric pH elevating drugs, and increased concentrations of crizotinib in patients with hepatic impairment or severe renal impairment.

1789-5

Complete the ECG sub-study in trial A8081007 and submit the final report, along with a thorough review of cardiac safety data to address any potential impact of crizotinib on QTc interval prolongation in patients.

Final Protocol Submission:	09/2009 (submitted)
Trial Completion:	12/2013
Final Report Submission:	06/2014

1789-6

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).

Final Protocol Submission:	03/2012
Trial Completion:	01/2015
Final Report Submission:	07/2015

1789-7

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).

Final Protocol Submission:	03/2012
Trial Completion:	01/2015
Final Report Submission:	07/2015

1789-8

Conduct a multiple dose trial to determine the appropriate crizotinib dose in patients with various degrees of hepatic impairment.

Final Protocol Submission:	09/2011
Trial Completion:	07/2013
Final Report Submission:	01/2014

1789-9

Conduct a trial in humans to determine the appropriate crizotinib dose in patients with severe renal impairment.

Final Protocol Submission:	09/2011
Trial Completion:	04/2012
Final Report Submission:	10/2012

1789-10

Conduct a 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).

Final Protocol Submission:	01/2012
Trial Completion:	03/2013
Final Report Submission:	09/2013

Postmarketing Commitments

The following PMC recommended by CDRH is intended to further explore the observed responses in patients with ALK-negative NSCLC.

1789-11

To assess the adequacy of the current cut-off, conduct a clinical trial to explore response to crizotinib in ALK-negative patients based on current assay cut-off. This should be compared to historic controls and to the response in ALK-positive patients. Additional biomarkers should be assessed in ALK-negative patients.

Final Protocol Submission:	10/2011
Trial Completion:	05/2013
Final Report Submission:	11/2013

The following PMCs recommended by Clinical Pharmacology are intended to provide exposure-response analyses based on the two confirmatory trials.

1789-12

To conduct exposure-response analysis for progression-free survival, response rate, overall survival and safety endpoints utilizing data from confirmatory trial A8081007 and to submit the analysis plan for review.

Final Protocol Submission:	09/2009 (submitted)
Analysis Plan Submission:	05/2012
Trial Completion:	12/2013
Final Report Submission:	06/2014

1789-13

To conduct exposure-response analysis for progression free survival, response rate, overall survival and safety endpoints utilizing data from confirmatory trial A8081014 and to submit the analysis plan for review.

Final Protocol Submission:	06/2010 (submitted)
Analysis Plan Submission:	05/2012
Trial Completion:	12/2015
Final Report Submission:	06/2016

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/s/

ROBERT L JUSTICE
08/26/2011