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RESEARCH**

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES - STATISTICAL REVIEWER'S ADDENDUM

NDA/BLA Serial Number: NDA 202570

Drug Name: CRIZOTINIB

Indication(s): Anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC)

Applicant: Pfizer, Inc.

Date(s): Submission Date: 30 March 2011
PDUFA Due Date: 30 September 2011

Review Priority: Priority

Biometrics Division: Division of Biometrics 5 (HFD-711)

Statistical Reviewer: Lijun Zhang, Ph.D.

Concurring Reviewers: Shenghui Tang, Ph.D., Team Leader
Rajeshwari Sridhara, Ph.D., Division Director

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Project Manager: Diane Hanner

Keywords:

Anaplastic Lymphoma Kinase, Non-Small Cell Lung Cancer, Single-Arm, Objective Response Rate, Response Duration

This is an addendum to Dr. Lijun Zhang's statistical review (dated August 5, 2011).

ORR Analysis per Investigator Assessments (Primary Efficacy Analysis)

FDA and the applicant reached a consensus that patient 10391003 in Study 1005 was a partial responder. Therefore, the total number of responders should be 68 out of 135 patients evaluable for response. The objective response rate and its corresponding 95% confidence interval was calculated as 50% (95% CI: 42%, 59%) for Study 1005.

ORR Analysis per Independent Radiology Reviews

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).

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/s/

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08/23/2011

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES-TEAM LEADER'S MEMO

NDA/BLA Serial Number: NDA 202570

Drug Name: CRIZOTINIB

Indication(s): Anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC)

Applicant: Pfizer, Inc.

Date(s): Submission Date: 30 March 2011
PDUFA Due Date: 30 September 2011
Review Completion Date: 05 August 2011

Review Priority: Priority

Biometrics Division: Division of Biometrics 5 (HFD-711)

Primary Reviewer: Lijun Zhang, Ph.D.

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Keywords:
Anaplastic Lymphoma Kinase, Non-Small Cell Lung Cancer, Single-Arm, Objective Response Rate, Response Duration

This is an original New Drug Application (NDA) submission seeking an accelerated approval of crizotinib for the treatment of anaplastic lymphoma kinase (ALK) positive advanced non-small cell lung cancer (NSCLC). The applicant has submitted results from two single-arm studies: A8081005 (phase 2, second-line therapy) as a pivotal study and A8081001 (phase 1 expansion cohort) as a supportive study. The primary efficacy endpoint was the objective response rate (ORR) in both studies. Per FDA analyses, the ORR was 49.6% (95% CI: 40.9%, 58.4%) in Study A8081005 and 61.2% (95% CI: 51.7%, 70.1%) in Study A8081001, based on the investigator tumor assessments. The medians of response duration were 41.9 and 48.1 weeks in studies A8081005 and A8081001, respectively.

For further details regarding the designs, data analyses, and results of both Study A8081005 and Study A8081001, please refer to the statistical review by Dr. Lijun Zhang, (August 5, 2011).

This team leader concurs with the recommendations and conclusions of the statistical reviewer (Dr. Lijun Zhang) of this application. The efficacy conclusions should rely on clinical judgment, since there were no comparators in these two single-arm studies. Whether the endpoint and the size of the effect on this endpoint are adequate for accelerated approval is a clinical decision.

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/s/

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08/05/2011

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08/05/2011



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA Serial Number: NDA 202570

Drug Name: CRIZOTINIB

Indication(s): Anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC)

Applicant: Pfizer, Inc.

Date(s): Submission Date: 30 March 2011
PDUFA Due Date: 30 September 2011
Review Completion Date: 04 August 2011

Review Priority: Priority

Biometrics Division: Division of Biometrics 5 (HFD-711)

Statistical Reviewer: Lijun Zhang, Ph.D.

Concurring Reviewers: Shenghui Tang, Ph.D., Team Leader
Rajeshwari Sridhara, Ph.D., Division Director

Medical Division: Oncology Drug Products (HFD-150)

Clinical Team: Shakun Malik, M.D.
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1. EXECUTIVE SUMMARY

Crizotinib, a new molecular entity (NME), is a small-molecule inhibitor of anaplastic lymphoma kinase (ALK) receptor tyrosine kinase. In the current original New Drug Application (NDA) submission, the applicant seeks an accelerated approval of crizotinib for the treatment of ALK positive advanced non-small cell lung cancer (NSCLC). It is based primarily on two single-arm studies: A8081005 (phase 2, second-line therapy) as a pivotal study and A8081001 (phase 1 expansion cohort) as a supportive study. The primary efficacy endpoint was the objective response rate (ORR) in both studies. Per FDA analyses, the ORR was 49.6% (95% CI: 40.9%, 58.4%) in Study A8081005 and 61.2% (95% CI: 51.7%, 70.1%) in Study A8081001, based on the investigator tumor assessments. The medians of response duration were 41.9 and 48.1 weeks in studies A8081005 and A8081001, respectively. The efficacy conclusions should rely on clinical judgment, since there were no comparators in these two single-arm studies. Whether the endpoint and the size of the effect on this endpoint are adequate for accelerated approval is a clinical decision.

2. INTRODUCTION

2.1 Overview

Non-small cell lung cancer (NSCLC) is the most common fatal malignancy in the United States, with an ORR of 15% to 32% by first-line treatment and less than 10% by second-line treatment in patients with advanced NSCLC. ALK-positive NSCLC accounts for 3% to 5% of all NSCLC.

The proposed indication is for the treatment of ALK-positive advanced NSCLC. There are four ongoing clinical studies of crizotinib in ALK-positive advanced NSCLC under IND 73,544: A8081001 (phase 1 expansion cohort), A8081005 (phase 2, second-line therapy), A8081007 (phase 3, second-line therapy), and A8081014 (phase 3, first-line therapy). This NDA is based primarily on two single-arm studies: A8081005 as a pivotal study and A8081001 as a supportive study. For simplicity, the last 4 characters of each study ID will be used to represent each study hereafter.

Study 1005 was entitled “Phase 2, Open-Label, Single Arm study of the Efficacy and Safety of PF-02341066 in Patients with Advanced Non-Small Cell Lung Cancer Harboring a Translocation or Inversion Involving the Anaplastic Lymphoma Kinase (ALK) Gene Locus”. The original protocol of Study 1005 was dated 24 June 2009 and amended 9 times thereafter. Following implementation of Amendment 1 (dated 12 August 2009), patients who were ineligible to enroll in Study 1007 could enroll in this study. In Amendment 2 (dated 27 August 2009), the RECIST version was modified to Version 1.1.

Enrollment of Study 1005 was ongoing as of the study cutoff date (15 September 2010) in the original NDA submission, and 148 patients have been enrolled from 66 study sites in North America, Europe, Asia, and Australia. A total of 136 patients have received at least one dose of study treatment. The 60-day clinical data update (cutoff date: 01 February 2011) provided further efficacy data for these 136 patients, though 265 patients have been enrolled at this time.

Study 1001 was entitled “A 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 original protocol of Study 1001 was dated 05 December 2005 and amended 15 times thereafter. The study was initially designed as a phase 1 dose-escalation study followed by a recommended phase 2 dose (RP2D) expansion cohort to further evaluate the safety and PK of the MTS of crizotinib. In Amendment 4, EML4-ALK-positive NSCLC patients were allowed to enter. In Amendment 12, a cohort consisting of ALK FISH negative NSCLC patients was added (n=25-40) to assist in validating the companion FISH diagnostic. In Amendment 14, retrospective evaluation of all tumor scans from ALK-positive and ALK-negative NSCLC patients by independent radiology group (IRR) was added.

As of the clinical data cutoff date (15 September 2010), Study 1001 enrolled 38 patients in the dose-escalation cohort, 119 patients in the RP2D ALK-positive NSCLC cohort, 5 patients in the RP2D ALK-negative NSCLC cohort, and 50 in the RP2D other cohort, from 8 sites in the United States, Korea, and Australia. The study accrual is ongoing. On June 10, 2011, the applicant submitted an updated report for the ALK-negative NSCLC cohort per the Agency’s request. A total of 23 ALK-negative NSCLC patients were enrolled and treated as of 27 May 2011.

The primary efficacy endpoint in both studies was objective response rate (CR + PR) based on the investigator tumor assessments.. No statistical inference on comparison was conducted in both single-arm, open-label studies. Two retrospective analyses, i.e., a covariate-matched analysis and a covariate-adjusted modeling analysis, were performed to support the primary findings from the single-arm study, 1001.

In Study 1005, ALK-positive NSCLC was identified using the Vysis ALK Break-Apart FISH Probe Kit assay which is under FDA review for marketing. In Study 1001, ALK-positive NSCLC was identified using a number of local clinical trial assays.

The randomized studies 1007 and 1014 are both open-label studies with PFS as the primary endpoint, and Study 1007 is powered for overall survival as well. The accrual for both studies is ongoing.

Table 1: Overview of Studies Included in the Submission

Study No.	Population, Phase, and Study Design	Treatment Period	Follow-Up Period	Number of Enrolled Patients^a	Efficacy Endpoints
1005 (pivotal)	Phase 2, Open-Label, Single Arm study for Efficacy and Safety in Patients with ALK-positive Advanced NSCLC	Treated until PD, unacceptable toxicity, consent withdrawal, or protocol noncompliance	Follow-up for survival every 2 months until death, or until the last patient discontinued crizotinib treatment, whichever came first	ALK-positive: 148	Primary: ORR Secondary: DR, DCR, OS, PFS

1001 (supportive)	Phase 1 Safety, Pharmacokinetic and Pharmacodynamic Study, in Patients with Advanced Cancer	Treated until PD, unacceptable toxicity, consent withdrawal, non-protocol anti-cancer therapy, or investigator's decision	Follow-up for survival every 3 months for a minimum of 1 year after last dose of crizotinib	Dose escalation cohort: 38 ALK-positive cohort: 119 ALK-negative cohort: 5 ^b Other: 50	Primary: ORR Secondary: DR, DCR, OS, PFS
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^a Enrollment number is based on the data from the original NDA submission.

^b Study 1001 ALK-negative cohort has enrolled 25 patients in the 10 June 2011 update, and 23 patients were confirmed as ALK-negative.

2.2 Data Sources

Electronic submission including protocols, SAPs, study reports, and analysis datasets for the original NDA submission is located on network with network path:

<\\CDSESUB1\EVSPROD\NDA202570\0002>. The 60-day clinical data update for studies 1005 and 1001 is located at: <\\CDSESUB1\EVSPROD\NDA202570\0009>. On June 13, 2011, the applicant submitted an update on ALK-negative cohort of Study 1001, and the network path is <\\CDSESUB1\EVSPROD\NDA202570\0016>

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

There are no major issues identified on data quality from the statistical perspective, except for some minor issues, such as inadequate comments in the data define file which was then revised according to the FDA's request.

3.2 Evaluation of Efficacy

The efficacy of this application was based on two single-arm studies, study 1005 and study 1001, for the indication of ALK-positive advanced NSCLC treatment. For Study 1005, this efficacy review is based on the 60-day update data; for Study 1001, this review focuses on ALK-positive NSCLC cohort.

3.2.1 Overall Study Design

Study 1005

Study 1005 is an ongoing, open-label, single-arm phase 2 study of oral crizotinib in patients with ALK-positive advanced NSCLC who have been treated with at least one prior chemotherapy

regimen. Patients were treated with 250 mg BID oral crizotinib continuously in 3-week cycles until the occurrence of PD or clinical deterioration, unacceptable toxicity, patient's withdrawal of consent, or protocol noncompliance. However, crizotinib treatment could be continued beyond RECIST-defined PD, if, in the judgment of the investigator, there was evidence of clinical benefit. Disease assessment was to have included a CT or MRI scan at baseline, and every 6 weeks from the date of first dose of crizotinib. The evaluation of antitumor efficacy for ALK-positive NSCLC was based on investigator-assessed ORR by RECIST (version 1.1).

Study 1001

Study 1001 is an ongoing phase 1 study of oral crizotinib to identify the MTD in patients with advanced cancers and evaluate the efficacy in RP2D enriched cohorts.

The study includes 3 parts:

1. Dose escalation for determination of MTD for twice daily (BID) dosing.
2. RP2D cohorts
 - a. ALK-positive NSCLC
 - b. ALK-negative NSCLC, and
 - c. Other – ALK-dependent tumors other than NSCLC and c-Met-dependent tumors
3. Dose escalation for determination of MTD for once daily (QD) dosing. This cohort was initiated shortly before the database cut-off date for this NDA submission and was not included in the clinical study report.

In the ALK-positive NSCLC cohort, patients were treated with 250 mg BID oral crizotinib continuously in 4-week cycles, until the occurrence of progressive disease (PD) or clinical deterioration, unacceptable toxicity that did not improve with dosing interruption, dose reduction, and/or standard medical therapy, patient's withdrawal of consent, investigator's determination that it was in the patient's best interest to discontinue therapy, or initiation of treatment with another anticancer therapy. Crizotinib treatment could be interrupted to allow surgery and/or palliative radiation therapy to localized sites of disease progression. Crizotinib treatment could have been continued beyond RECIST-defined PD if, in the opinion of the investigator, the benefit/risk assessment justified continuation of treatment.

Disease assessment at baseline (screening) was to include a CT or MRI scan of the chest, abdomen, and pelvis; brain and bone scans were to be performed if disease at these sites was suspected. Scans were to be repeated at all sites of known disease every 2 cycles (i.e., every 8 weeks unless treatment delayed). The antitumor efficacy evaluation was based on investigator-assessed ORR according to RECIST (version 1.0).

3.2.1.2 Efficacy Endpoints

For both Study 1005 and Study 1001, the primary efficacy endpoint was overall confirmed ORR, defined as the proportion of patients with confirmed complete response (CR) or confirmed partial response (PR) according to RECIST (RECIST v1.1 and RECIST v1.0 in 1005 and 1001,

respectively), relative to the response-evaluable population (defined in Section 3.2.1.4). Confirmed responses were those that persist on repeat imaging study ≥ 4 weeks after initial documentation of response. In both studies, the primary analyses of ORR used the investigator's recorded measurements and assessments for target, non-target, and new lesions to programmatically evaluate response using rules based on RECIST. In addition, all available scans were retrospectively reviewed by IRR.

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

Time to Response was defined as the time in weeks from the date of the first dose of crizotinib to first documentation of objective tumor response (CR or PR) that was subsequently confirmed. TTR was only calculated for patients in the response-evaluable population who had a confirmed objective tumor response.

Duration of Response was defined as the time in weeks from the first documentation of objective tumor response (CR or PR) that was subsequently confirmed to the first documentation of objective disease progression or death on study due to any cause, whichever occurred first. DR was only calculated for patients in the response-evaluable population who had a confirmed objective tumor response.

Disease Control Rate at 6 weeks, 8 weeks, and 16 weeks were defined as the percent of patients in the response-evaluable population with a confirmed CR, confirmed PR, or SD according to RECIST-defined tumor response assessments at 6 and 12 weeks (Study 1005), or 8 and 16 weeks (Study 1001), respectively, after the first dose of crizotinib.

Progression-Free Survival was defined in months as the time from the date of the first dose of crizotinib to the date of first documentation of objective tumor progression or death due to any cause, whichever occurred first, in the safety-analysis population. Only deaths that occurred within 2 assessment intervals (~ 16 weeks) after the last dose of crizotinib were included in the PFS analysis.

Overall Survival was defined in months as the time from the date of the first dose of crizotinib to the date of death due to any cause in the safety-analysis population. All deaths were included in the analysis.

3.2.1.4 Efficacy Analysis Population

The safety-analysis (SA) population included all enrolled patients who received at least one dose of crizotinib starting on Cycle 1 Day 1. The safety-analysis population was the primary population for evaluating patient characteristics, treatment administration, and safety endpoints.

The response-evaluable (RE) population was defined as all patients in the safety-analysis population who had an adequate baseline disease assessment. The response-evaluable population was used in the primary efficacy analyses.

In addition, for any preliminary (interim) reporting of the data, patients also needed to meet 1 of the following 2 criteria:

- Had at least one post-baseline disease assessment performed at least 6 weeks after treatment start
- Withdrew from the study or experienced progression/death at any time on study

The independent review response-evaluable (IRR RE) population was defined identically to the response-evaluable population, however, the assessments were based on IRR rather than the investigator, with the following exceptions: patients were included in the IRR response-evaluable population without having baseline tumor evaluation by IRR if the investigator evaluation was recorded as an early death (within 42 days from first dose) or withdrawn from the study without a tumor assessment.

3.2.1.4 Sample Size Determination

The target sample size of Study 1005 was 250. The sample size was determined based on the expected number (n=100) of patients who would cross-over from the chemotherapy comparator arm of Study 1007, an ongoing, randomized, phase 3 study of crizotinib in patients with previously treated ALK-positive NSCLC, and additional patients (n=150) who would be enrolled based on other eligibility criteria. This sample size was also considered adequate to detect adverse events of low frequency ($\geq 1\%$).

The number of patients enrolled in the dose escalation phase of Study 1001 was dependent upon the observed safety profile and study objectives, which would determine the number of patients per dose level, the number of dose escalations and the number of cohorts. It was anticipated that a total of approximately 40 patients would be enrolled in the dose escalation phase.

The RP2D ALK-positive NSCLC cohort in Study 1001 was originally designed to enroll at least 25 patients. During the study, enrollment was expanded to further explore the safety and efficacy of this cohort. There was no specified sample size.

The main objective of the RP2D ALK- negative NSCLC cohort in Study 1001 was to evaluate the objective response in this group of patients and to compare with the objective response observed from ALK-positive NSCLC patients enrolled in Study 1007 and/or 1005. Response to crizotinib among ALK-negative patients was expected to be low, therefore, the ALK-negative NSCLC cohort in Study 1001 was first limited to a total of 25 patients. If ≤ 3 objective responses (CR or PR) have been observed in the first 25 ALK marker negative patients, no additional ALK marker negative NSCLC patients would have been enrolled into this trial. If > 3 objective responses have been observed among the 25 ALK marker negative patients, additional patients would have been enrolled in this trial as noted in Table 2.

Table 2. Power Calculation for ALK-Negative NSCLC Cohort

Responses in First 25 ALK - Patients	Additional ALK -Patients to be Enrolled	Total ALK - Patients in this Trial	Exact 90% CI * Around ORR (column 1/ column 3 x 100)	Exact 90% CI Around 40% ORR Assumed for 160 ALK + Patients (Protocol 1007/1005)
4	5	30	(5%, 28%)	(34%, 47%)
5	10	35	(6%, 28%)	(34%, 47%)
6	15	40	(7%, 27%)	(34%, 47%)

Note: if ≥ 7 responses have been observed among the first 25 ALK marker negative subjects then no additional patients would have been enrolled beyond 40 until read out of study 1007 and/or 1005 study results.

[Source: Study 1001 SAP V3 Table 4]

Reviewer's Comments:

In Study 1007, patients randomized to the comparator arm (standard chemotherapy with docetaxel or pemetrexed) who experienced disease progression, confirmed by the independent radiology laboratory used for the study, were permitted to crossover to crizotinib treatment by enrolling in Study 1005.

3.2.1.5 Efficacy Analysis Methods

The primary efficacy endpoint was the objective response rate (ORR = CR+ PR) and the primary efficacy analysis was based on the response-evaluable population. Exact 2-sided 95% confidence intervals based on the F distribution were calculated for all proportion estimates.

Estimates of time-to-event endpoints were obtained using the Kaplan-Meier method. DR and TTR were also summarized using descriptive statistics for confirmed objective responders.

3.2.2. Efficacy Results from the Applicant

3.2.2.1 Patient Disposition, Demographic and Baseline Characteristics

Patients Enrollment and Treatment Discontinuation

As of the cutoff date for the original NDA submission, Study 1005 enrolled 148 patients, of whom, 136 patients received study treatment (including 13 patients who crossed over from the comparator arm of Study 1007) and had documentation of initiating crizotinib treatment. Three patients were enrolled in error and did not receive study treatment, and 9 patients did not yet have documentation of study treatment administration. Update on these 136 treated patients was submitted in the 60-day clinical update, in which, 43 (29.1%) patients discontinued treatment, and 93 (62.8%) patients were ongoing with treatment, as shown in Table 3.

Study 1001 enrolled a total of 174 patients to the RP2D cohorts, including 119 patients in the ALK-positive NSCLC cohort, 5 patients in the ALK-negative NSCLC cohort, and 50 in the RP2D other cohort from 8 sites in the United States, Korea, and Australia. Six patients in the RP2D other cohort did not receive study treatment. At the time of study cut-off, the proportions

of patients who discontinued treatment were 35.3% in the ALK-positive NSCLC cohort, 40.0% in the ALK-negative NSCLC cohort, and 84.1% in the RP2D other cohort. The most common reason for discontinuation was disease progression (Table 3).

Table 3. Patient Disposition, Safety-Analysis Population

Number (%) of Patients	Study 1005	Study 1001 RP2D Cohorts		
	ALK-Positive NSCLC 250 mg BID	ALK-Positive NSCLC 250 mg BID	ALK-Negative NSCLC 250 mg BID	Other 250 mg BID
Treated	136	119	5	44
Ongoing at data cut-off date	93 (68.4)	77 (64.7)	3 (60.0)	7 (15.9)
Discontinued	43 (31.6)	42 (35.3)	2 (40.0)	37 (84.1)
Adverse event	6 (4.4)	3 (2.5)	0	3 (6.8)
Progressive disease	26 (19.1)	25 (21.0)	1 (20.0)	24 (54.5)
Patient died	6 (4.4)	8 (6.7)	1 (20.0)	1 (2.3)
Patient no longer willing to participate in study	2 (1.5)	1 (0.8)	0	2 (4.5)
Global deterioration of health status	2 (1.5)	0	0	0
Lost to Follow-Up	1 (0.7)	0	0	0
Other	0	5 (4.2)	0	7 (15.9)

[Source: Study 1005 60-day clinical updates Table 13.1.3.1.1 and Study 1001 CSR Table 13.1.3.1b]

Treatment Exposure

As of the study cut-off date, the median duration of treatment was 22.3 weeks and 31.8 weeks in Studies 1005 and 1001 for all treated patients, respectively.

Table 4. Treatment Duration, Safety-Analysis population

	Study 1005 (n=136)	Study 1001 (n=119)
Duration of treatment (weeks)		
Mean (SD)	23.1 (11.1)	35.3 (22.7)
Median	22.3	31.8
Range	0.9, 53.1	0.9, 101.7
Category of treatment duration, n (%)		
≤4 wks	8 (5.9)	8 (6.7)
>4 and ≤12 wks	16 (11.8)	12 (10.1)
>12 and ≤24 wks	61 (44.9)	20 (16.8)
>24 and ≤52 wks	50 (36.8)	49 (41.2)
>52 and ≤ 104 wks	1 (0.7)	30 (25.2)

[Source: Study 1005 60-day clinical updates Table 13.3.1.1 and Study 1001 CSR Table 13.3.3.1b]

Reviewer's Comment

The median treatment duration of Study 1005 is shorter than that of Study 1001.

Demographic and Baseline Characteristics

The demographic and baseline characteristics for treated patients in Study 1005 and RP2D ALK-positive cohort of Study 1001 are presented in Tables 5 and 6.

Table 5. Demographics Characteristics, Safety-Analysis Population

	Study 1005 (n=136)	Study 1001 (n=119)
Sex, n (%)		
Male	64 (47.1)	59 (49.6)
Female	72 (52.9)	60 (50.4)
Age (years)		
Mean (SD)	52.7 (11.3)	50.9 (13.0)
Median	52.0	51.0
Range	29, 82	21, 79
Age in category, n (%)		
<65 years	117 (86.0)	103 (86.6)
≥65 years	19 (14.0)	16 (13.4)
Race, n (%)		
White	87 (64.0)	74 (62.2)
Black	5 (3.7)	3 (2.5)
Asian	43 (31.6)	34 (28.6)
Other	1 (0.7)	8 (6.7)
Smoking classification, n (%)		
Never smoked	92 (67.6)	86 (72.3)
Ex-smoker	39 (28.7)	32 (26.9)
Smoker	5 (3.7)	1 (0.8)
Body weight (kg)*		
Mean (SD)	70.2 (17.7)	71.0 (16.2)
Median	67.0	68.8
Range	41.0, 151.0	35.5, 116.9

*Body weight information was not available in one patient enrolled in Study 1001

[Source: Study 1005 60-day clinical updates Tables 13.2.1.1, 13.2.1.2 and Study 1001 CSR Tables 13.2.1.1b, 13.2.1.2b]

Table 6. Baseline Disease Characteristics and Prior Tumor Treatment, Safety-Analysis population

	Study 1005 (n=136)	Study 1001 (n=119)
Disease Characteristics		
Histological Classification		
Adenocarcinoma	130 (95.6)	116 (97.5)
Large cell carcinoma	1 (0.7)	1 (0.8)
Squamous cell carcinoma	0	1 (0.8)
Adenosquamous carcinoma	3 (2.2)	0
Other	2 (1.5)	1 (0.8)
ECOG PS at baseline		
0	37 (27.2)	41 (34.5)
1	74 (54.4)	63 (52.9)
2	25 (18.4)	14 (11.8)
3	0	1 (0.8)
Disease Stage		
Locally advanced	9 (6.6)	5 (4.2)
Metastatic	127 (93.4)	114 (95.8)
Sum of the Longest Diameter (centimeters)		
Median (range)	6.7 (1.1 – 62.5)	8.7 (1.0, 42.5)
Prior Tumor Treatments		
Prior Surgery, n (%)		
No	1 (0.7)	2 (1.7)
Yes	135 (99.3)	117 (98.3)
Prior Radiation Therapy, n (%)		
No	59 (43.4)	51 (42.9)
Yes	77 (56.6)	68 (57.1)
Types of prior systemic treatment regimens, n (%)		
Adjuvant/neoadjuvant	26 (19.1)	19 (16.0)
Advanced/metastatic	136 (100.0)	103 (86.6)
# of Advanced/Metastatic Regimen, n (%)		
0	0	15 (12.6)
1	16 (11.8)	37 (31.1)
2	41 (30.1)	24 (20.2)
3	39 (28.7)	17 (14.3)
≥4	40 (29.4)	26 (21.8)
Type of Prior Systemic Therapy		
Prior platinum-based therapies	129 (94.9)	105 (88.2)
Prior EGFR TKI therapies	74 (54.4)	57 (47.9)

[Source: Study 1005 60-day clinical updates Tables 13.2.2.2, 13.2.6, 13.3.2.2.2.X and Study 1001 CSR Tables 13.2.2.2, 13.2.6b, 13.3.2.2.2bx]

Reviewer's Comments:

There were no apparent differences between Study 1005 and Study 1001 in respect to demographic, baseline characteristics, and prior tumor treatment, except the number of prior advanced/metastatic regimens, in the safety-analysis population.

3.2.2.3 Results and Conclusions

Primary Endpoint Results

Primary Efficacy Analyses

The primary efficacy endpoint was ORR in the response-evaluable population for both studies. The primary analyses of tumor response used the investigator's recorded measurements and assessments for target, non-target, and new lesions to programmatically evaluate response using rules based on RECIST (RECIST v1.1 in Study 1005 and RECIST v1.0 in Study 1001).

In Study 1005, 136 patients were treated as of the cutoff date for the original NDA submission, and 76 patients were response evaluable. In the 60-day update, 133 out of these 136 patients were evaluable and included in the updated response-evaluable population, with 3 patients excluded due to either no adequate baseline assessment (n=2) or no adequate post-baseline tumor measurement 6 weeks after treatment started (n=1). The applicant reported that based on the 60-day update data, the ORR was 51.1% with a 95% CI of (42.3% - 59.9%) in the response-evaluable population.

In Study 1001, 3 patients without post-baseline disease assessments were not included in the response-evaluable population of ALK-positive NSCLC PR2D cohort. In the response-evaluable population (n=116), the ORR was 61.2% with a 95% CI of (51.7% -70.1%).

The efficacy results from both studies are summarized in Table 7.

Table 7. Summary of Best Overall Response based on Investigator Assessments, Response-Evaluable Population

	Study 1005 (n=133)	Study 1001 (n=116)
Best Response, n (%)		
Complete Response (CR)	1 (0.8)	2 (1.7)
Partial Response (PR)	67 (50.4)	69 (59.5)
Stable Disease (SD)	45 (33.8)	31 (26.7)
Objective Progression (PD)	10 (7.52)	6 (5.2)
Early Death ^a	5 (3.8)	3 (2.6)
Indeterminate ^b	5 (3.8)	5 (4.3)
Objective Response Rate, n (%) (ORR = CR + PR)	68 (51.1)	71 (61.2)
95% Exact CI ^c	(42.3, 59.9)	(51.7, 70.1)

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

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

^c Using exact method based on F distribution

[Source: Study 1005 60-day clinical updates Table 13.4.1.1 and Study 1001 CSR Table 13.4.1.1]

Reviewer's comments

- Both Study 1005 and Study 1001 are ongoing single-arm, open-label studies. No statistical inference on comparison was conducted within both studies.
- FDA's analyses on ORR are summarized in Section 3.2.3.

Retrospective Analyses on ORR

To give perspective to the efficacy results from the single arm Study 1001, the applicant performed two retrospective analyses: (1) to simulate outcomes of randomized controlled studies of crizotinib versus standard advanced NSCLC treatment, a covariate-matched analysis was conducted which the efficacy outcomes of ALK-positive, advanced NSCLC patients in Study 1001 were compared with those from matched ALK unselected patients drawn from the control arms of 3 other advanced NSCLC studies (Paclitaxel/Carboplatin, Gemcitabine/Cisplatin, erlotinib) ; and (2) a covariate-adjusted modeling analysis was performed to retrospectively predict the ORR of 116 ALK-positive advanced NSCLC patients in Study 1001 as if they were treated with one of the agents from the control arms of the 3 randomized studies.

From the covariate-matched analysis, the applicant reported that the ORRs in the covariate-matched historical controls ranged from 10% to 24%. Similar results were reported using the covariate-adjusted modeling approach with estimated ORRs for the standard regimens ranging from 15% to 21%, after simultaneous adjustment for baseline characteristics. Overall, the estimated magnitude of the ORRs generated for controls using both approaches were lower than the ORR of 61% observed with crizotinib in Study 1001.

Reviewer's Comments

These retrospective analyses are viewed as exploratory.

ORR Analysis per Independent Radiology Reviews

In both studies, all available scans were retrospectively reviewed by an independent radiology laboratory.

In Study 1005, 105 patients were included in the IRR response-evaluable population. Among the 31 patients treated but not included in the IRR response-evaluable population, 12 patients were excluded due to inadequate baseline assessment per IRR criteria, and 19 patients had no post-baseline assessment 6 weeks after treatment started. The IRR-assessed ORR in Study 1005 was 41.9% (95% CI: 32.3% -51.9%).

Of the 116 patients in the response-evaluable population of Study 1001, 11 patients did not have adequate scans for inclusion in the IRR response-evaluable population. Three of the 11 patients had investigator-assessed PRs. Among the 105 patients included in IRR response-evaluable population, 84 patients had complete scans with acceptable quality, while 21 patients had incomplete scans but were adequate for inclusion in the IRR response-evaluable population

because of having the minimum required scans needed, early death, or withdrawal before first tumor assessment. The IRR-assessed ORR was 52.4% (95% CI: 42.4% -62.2%).

Table 8. Summary of Best Overall Response per Independent Reviewers, IRR Response-Evaluable Population

	Study 1005 (n=105)	Study 1001 (n=105)
Best Response, n(%)		
Complete Response (CR)	1	0
Partial Response (PR)	43 (41.0)	55 (52.4)
Stable Disease (SD)	40 (38.1)	31 (29.5)
Objective Progression (PD)	11 (10.5)	10 (9.5)
Early Death	5 (4.8)	3 (2.9)
Indeterminate	5 (4.8)	6 (5.7)
Objective Response Rate, n (%) (ORR = CR + PR)	44 (41.9)	55 (52.4)
95% Exact CI	(32.3, 51.9)	(42.4, 62.2)

[Source: Study 1005 60-day clinical updates Table 13.4.6.1 and Study 1001 CSR Table 13.4.6.1]

Reviewer's Comment

The ORRs per IRR appear 10% lower compared to the rates by investigator assessments in both studies.

Tumor Assessment Agreement Rate

In Study 1005, among the 102 patients included in both of the investigator response-evaluable and IRR response-evaluable populations, the investigator and the IRR had agreement on 75 patients (33 responders and 42 non-responders), for a total event agreement rate of 73.5%.

In Study 1001, among the 105 patients included in both of the investigator response-evaluable and IRR response-evaluable populations, the investigator and the IRR had agreement on 86 patients (52 responders and 34 non-responders), for a total event agreement rate of 81.9%.

Table 9. Response Status by Assessment Types

	Investigator Assessment, n			Total
	Objective Responder	Non-Objective Responder	Not Included in INV RE	
Study 1005				
IRR Assessment, n				
Objective Responder	33	9	2	44
Non-Objective Responder	18	42	1	61
Not Included in IRR RE	17	14	--	31
Total	68	65	3	136
Study 1001				
IRR Assessment, n				
Objective Responder	52	3	0	55
Non-Objective Responder	16	34	0	50
Not Included in IRR RE	3	8	--	11
Total	71	45	0	116

[Source: Study 1005 60-day clinical updates Table 13.4.6.2 and Study 1001 CSR Table 13.4.6.2]

Efficacy Results in ALK-negative NSCLC cohort of Study 1001

Efficacy data for ALK-negative cohort was updated with a cutoff date of 27 May 2011. Of the 25 patients enrolled, 2 patients were determined as not belonging to ALK-negative cohort. The preliminary efficacy data included 19 patients who were considered response evaluable. Four patients were excluded from response-evaluable population due to either lack of adequate baseline tumor assessment (n=3) or no post-baseline tumor assessment at least 6 weeks after the first crizotinib dose (n=1). Based on investigator assessment, a total of 0 CRs and 5 PRs were reported for an ORR of 26.3% (95% CI: 9.1%, 51.2%).

Reviewer's Comment

The estimate of response rate from such a small cohort (n=19 in response-evaluable population) is not reliable to make any conclusion and a larger study is necessary for further exploration. However, this suggests that crizotinib has activity in ALK-negative patients. The applicant noted that crizotinib is known to inhibit other targets that may be relevant in lung cancer including ROS and c-MET. As a result, an ALK-negative NSCLC patient whose tumor carries activated ROS or over expressed or amplified c-MET could potentially respond to crizotinib based on inhibition of one of these other targets. The applicant is investigating these characteristics from this cohort.

Secondary Endpoint Results

The secondary efficacy endpoints in the two studies included time to response, duration of response, disease control rate, progression-free survival, and overall survival.

Response Duration

In Study 1005, of the 68 patients who had a confirmed CR/PR at the study cut-off time, 14 patients had experienced subsequent disease progression or death. The median of response duration was 41.9 weeks by Kaplan-Meier method. Among the 14 responders who subsequently had an event (progression or death), the median DR was 12.8 weeks (range: 7.1-41.9 weeks), based on descriptive statistics.

At the time of data cut-off, using the Kaplan-Meier method, the median DR estimate per investigator assessment in Study 1001 was 48.1 weeks. Based on descriptive statistics, the median DR among the subset of patients with an event was 26.2 weeks (range: 8.1 – 72.9 weeks).

Table 10. Duration of Response

	Study 1005 (n=133)	Study 1001 (n=116)
Number of Patients with Response, n (%)	68	71
With subsequent disease progression or death	14 (20.6)	26 (36.6)
Without subsequent disease progression or death	44 (79.4)	45 (63.4)
Duration of Response		
Median, weeks (range) ^a	41.9 (6.1 ⁺ , 42.1 ⁺)	48.1 (4.1 ⁺ , 76.6 ⁺)
Median among patients with events, weeks (range) ^b	12.8 (7.1, 41.9)	26.2 (8.1, 72.9)

^a Calculation based on Kaplan-Meier analysis

^b Calculation based on descriptive statistics

⁺ Censored data

[Source: Study 1005 60-day clinical updates Table 13.4.1 and Study 1001 CSR Table 13.4.4.1]

Reviewer's Comment

The estimates of DR median using Kaplan-Meier method are not robust, due to the small percentage of responders with subsequent disease progression or death.

Time to Response

In Study 1005, among the 68 responders, the median time to response was 6.1 weeks (range: 0.1-24.3 weeks); for the 71 responders in Study 1001, the median time to response was 7.7 weeks with a range from 4.3 to 39.6 weeks. During the first 8 weeks of treatment, 79% and 55% objective tumor responses were achieved in Study 1005 and in Study 1001, respectively.

Disease Control Rate

Study 1005 had 83% patients in the response-evaluable population maintained evidence of disease control (CR, PR or SD) at 6 weeks, and 72% at 12 weeks after the first dose of crizotinib. The disease control rate in Study 1001 was 79% at week 8 and 67% at week 16.

Progression-Free Survival and Overall Survival

The median of PFS in the ALK-positive NSCLC cohort of Study 1001 was 10 months (95% CI: 8.2, 14.7 months), in the safety-analysis population. The median of OS has not been reached and the median follow-up time was 11 months (95% CI: 9.2 – 12.8 months).

The applicant submitted an updated overall survival analysis for 136 patients enrolled in the ALK-positive RP2D cohort in the 60-day clinical data update. The updated median follow-up time was 14.8 months (95% CI: 12.7 – 16.4 months).

The summary of PFS, OS, and the updated OS of Study 1001 is presented in Table 11.

Table 11. Progression-Free Survival and Overall Survival, Study 1001 Safety-Analysis population

	Study 1001
Progression-Free Survival	
Total number of patients, n	119
Number of events on study, n (%)	50 (42.0)
Median PFS, months (95% CI)	10.0 (8.2, 14.7)
Overall Survival	
Total number of patients, n	119
Number of deaths, n (%)	23 (19.3)
Median OS, months (95% CI)	NR
6-month Survival Probability, % (95% CI)	90.0 (82.7, 94.4)
12-month Survival Probability, % (95% CI)	80.5 (70.9, 87.2)
Overall Survival (60-day clinical data update)	
Total number of patients, n	136
Number of deaths, n (%)	40 (29.4)
Median OS, months (95% CI)	NR
6-month Survival Probability, % (95% CI)	87.5 (80.4, 92.2)
12-month Survival Probability, % (95% CI)	75.7 (66.8, 82.5)

[Source: Study 1001 CSR Tables 13.4.3.1, 13.4.5.1 and 60-day clinical update Table 13.4.3.1]

Reviewer's Comments:

- The PFS and OS results from a nonrandomized single-arm study without comparators are not interpretable.
- Please note that deaths occurred after 2 assessment intervals (~16 weeks) since the last dose of crizotinib were not included in the PFS analysis, while all deaths were included in the OS analysis.

- In Study 1001, 13 of the 23 deaths occurred within 28 days of last dose of crizotinib. At the 60-day update, 40 deaths were observed in Study 1001, of whom, 19 occurred within 28 days of last dose. Study 1005 had 21 deaths out of the 136 treated patients at the 60-day update, and 16 deaths occurred within 28 days of last dose of crizotinib.

3.2.3. Efficacy Analyses by the FDA

Number of Prior Systemic Regimens

The FDA has analyzed the number of prior advanced/metastatic systemic regimens, as summarized in Table 12. In both studies, percentage of patients who received 4 or more prior regimens was higher per FDA analyses compared to the applicant analyses.

Table 12. Number of Prior Advanced/Metastatic Regimens (FDA analyses)

	Study 1005 (n=136)	Study 1001 (n=119)
# of prior advanced /metastatic regimens, n (%)		
0	0	15 (12.6)
1	13 (9.6)	34 (28.6)
2	37 (27.2)	20 (16.8)
3	37 (27.2)	17 (14.3)
≥4	49 (36.0)	33 (27.7)

Objective Response Rate

Per FDA review, for Study 1005, the response-evaluable population had 135 patients and IRR response-evaluable population had 105 patients. The number of patients in the response-evaluable population is different with the one used by the applicant. In Study 1005, the investigator-based ORR was 49.6% (95% CI: 40.9% - 58.4%) and IRR-based ORR was 41.9% (95% CI: 32.3% - 51.9%). The response results for Study 1005 per FDA analyses are summarized in Table 13.

FDA analyses confirmed the analysis population size and response rate for Study 1001 reported by the applicant, as shown in Section 3.2.2.3 Table 7.

Table 13. Summary of Best Overall Response and Response Duration of Study 1005 (FDA Analyses)

	INV (N=135)	IRR (N=105)
Best Response, n (%)		
Complete Response (CR)	1 (0.7)	1
Partial Response (PR)	66 (48.9)	43
Stable Disease (SD)	46 (34.1)	39
Objective Progression (PD)	12 (8.9)	11
Early Death ^a	5 (3.7)	5
Indeterminate ^b	5 (3.7)	6
Objective Response Rate, n (%) (ORR = CR + PR)	67 (49.6)	44 (41.9)
95% Exact CI ^c	40.9, 58.4	32.3, 51.9
# of Patients with Response, n(%)	67	44
With subsequent disease progression or death	14 (20.9)	13 (30.0)
Without subsequent disease progression or death	53 (79.1)	31 (70.0)
Duration of response		
Median (range) ^d , weeks	41.9 (6.1+, 42.1+)	33.1 (6.1+, 42.1+)
Median among patients with events (range) ^e , weeks	12.8 (7.1, 41.9)	17.3 (12.0, 36.1)

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

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

^c Using exact method based on F distribution

^d Calculation based on Kaplan-Meier analysis

^e Calculation based on descriptive statistics

Conclusions for Efficacy

The ORR was 49.6% with a 95% CI of (40.9%, 58.4%) in the single-arm phase 2 study (N=135, response-evaluable population), and 61.2% with a 95% CI of (51.7%, 70.1%) in the phase 1 study ALK-positive NSCLC enrichment cohort (N=116, response-evaluable population).

3.3 Evaluation of Safety

Please refer to Clinical Evaluations of this application for safety results and conclusions for safety.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Table 14 summarized Studies 1005 and 1001 ORR subgroup analyses by gender, age, race and geographic region.

Table 14. ORR by Gender, Age, Race, and Region, FDA-Response-Evaluable Population

Baseline Characteristic	Study 1005	Study 1001
	ORR, % (n) [95% CI] (N = 135)	ORR, % (n/N) [95% CI] (N = 116)
Overall ORR	49.6% (67/135) [40.9, 58.4]	61.2% (71/116) [51.7, 70.1]
Sex		
Male	42.2% (27/64) [29.9, 55.2]	61.0% (36/59) [47.4, 73.5]
Female	56.3% (40/71) [44.1, 68.1]	61.4% (35/57) [47.6, 74.0]
Age		
<65 years	49.1% (57/116) [39.7, 58.6]	60.0% (60/100) [49.7, 69.7]
≥65 years	52.6% (10/19) [28.9, 75.6]	68.8% (11/16) [41.3, 89.0]
Race		
White	44.7% (38/85) [33.9, 55.9]	50.7% (36/71) [38.6, 62.8]
Asian	60.5% (26/43) [44.4, 75.0]	82.4% (28/34) [65.5, 93.2]
Black	40.0% (2/5) [5.3, 85.3]	66.7% (2/3) [9.4, 99.2]
Other	50.0% (1/2) [1.3, 98.7]	62.5% (5/8) [24.5, 91.5]
Race group		
Asian	60.5% (26/43) [44.4, 75.0]	82.4% (28/34) [65.5, 93.2]
Non-Asian	44.6% (41/92) [34.2, 55.3]	52.4% (43/82) [41.1, 63.6]
Region group		
U.S.	44.3% (31/70) [32.4, 56.7]	46.9% (38/81) [35.7, 58.3]
Non U.S.	55.4% (36/65) [42.5, 67.7]	94.3% (33/35) [80.8, 99.3]

Reviewer's comments:

- ORR was higher in Asian and non U.S. region in both studies, which might be due to different drug exposure (see Clinical Pharmacology review). Note that patients enrolled in non U.S. region had higher percentage of Asians (57.1% and 82.9% in Study 1005 and Study 1001, respectively).
- In Study 1005, females had higher ORR than males (56% vs. 42%). However, it was not observed in Study 1001.
- In both studies, ORR was slightly higher in older patients (≥65 years old) than ORR in younger patients (<65 years old).

4.2 Other Special/Subgroup Populations

The reviewer performed subgroup analyses for objective response rate by ECOG performance status, number of prior advanced/metastatic regimen for NSCLC, and smoking status. The objective response rates ranged from 36% to 62% in Study 1005 and 50% to 86% in Study 1001 (Table 15).

Table 15. Additional ORR Subgroup Analyses, FDA-Response-Evaluable Population

Baseline Characteristic	Study 1005	Study 1001
	ORR, % (n) [95% CI] (N = 135)	ORR, % (n) [95% CI] (N = 116)
Overall ORR	49.6% (67/135) [40.9, 58.4]	61.2% (71/116) [51.7, 70.1]
ECOG performance status		
0	54.1% (20/37) [36.9, 70.5]	53.8% (21/39) [37.2, 69.9]
1	52.1% (38/73) [40.0, 63.9]	62.9% (39/62) [49.7, 74.8]
2	36.0% (9/25) [18.0, 57.5]	78.6% (11/14) [49.2, 95.3]
3	N/A	0 (0/1)
Number of prior advanced/metastatic regimens		
0	N/A	85.7% (12/14) [57.2, 98.2]
1	46.2% (6/13) [19.2, 74.9]	54.6% (18/33) [36.4, 71.9]
2	62.2% (23/37) [44.8, 77.5]	60.0% (12/20) [36.1, 80.9]
3	43.2% (16/37) [27.1, 60.5]	76.5% (13/17) [51.1, 93.2]
≥4	45.8% (22/48) [31.4, 60.8]	50.0% (16/32) [31.9, 68.1]
Smoking Classification		
Never Smoker	51.7% (47/91) [40.9, 62.3]	63.1% (53/84) [51.9, 73.4]
Ever or Current Smoker	45.5% (20/44) [30.4, 61.2]	56.3% (18/32) [37.7, 73.6]

5. SUMMARY AND CONCLUSIONS

This application was for accelerated approval of single-agent crizotinib for the treatment of ALK-positive advanced NSCLC. The primary efficacy endpoint was the objective response rate in two ongoing single-arm studies: Study 1005 (phase 2) and Study 1001 (phase 1 expansion cohort). By the study cutoff dates, a total of 136 patients were treated in the phase 2 study 1005 and 119 patients treated in the ALK-positive enrichment cohort of Study 1001.

5.1 Statistical Issues and Collective Evidence

Both studies 1005 and 1001 are open-label, single-arm, non-randomized trials to evaluate the efficacy and safety of single agent crizotinib. The primary efficacy endpoint was the objective response rate (CR + PR). No statistical inference on comparison was conducted. The PFS and OS results from a nonrandomized single-arm study without comparators are not interpretable. There are no major statistical issues identified in this application.

5.2 Conclusions and Recommendations

Study 1005 and Study 1001 expansion cohort were designed to determine the antitumor efficacy of single-agent crizotinib in ALK-positive NSCLC patients. Per FDA analyses, ORR was of 49.6% (95% CI: 40.9%, 58.4%) in Study 1005, and 61.2% (95% CI: 51.7%, 70.1%) in Study 1001, based on investigator assessment data. The median of response duration was 41.9 and 48.1 weeks for studies 1005 and 1001, respectively. Whether the endpoint and the size of the effect on this endpoint in these single-arm studies are adequate for accelerated approval is a clinical decision.

SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer: Lijun Zhang, Ph.D.
Date: 04 August 2011

Concurring Reviewer(s)

Statistical Team Leader: Shenghui Tang, Ph.D.

Biometrics Division Director: Rajeshwari Sridhara, Ph.D.

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Project Manager:

Medical Officer: Shakun Malik, M.D.

Medical Team Leader: Virginia E. Maher, M.D.

Primary Statistical Reviewer: Lijun Zhang, Ph.D.

Statistical Team Leader: Shenghui Tang, Ph.D.

Biometrics Division Director: Rajeshwari Sridhara, Ph.D.

Lillian Patrician

CHECK LIST

Number of Pivotal Studies: 1

Trial Specification

Specify for each trial:

Protocol Number (s): A8081005

Protocol Title (optional): Phase 2, Open-Label, Single Arm study of the Efficacy and Safety of PF-02341066 in Patients with ALK-positive Advanced NSCLC

Phase: 2

Control: single-arm

Blinding: open-label

Number of Centers: 135

Region(s): North America, Europe, Asia, and Australia

Treatment Arms: crizotinib

Treatment Schedule: 250 mg orally bid

Randomization: No

Primary Endpoint: objective response rate

Primary Efficacy Analysis Population: response-evaluable population

Statistical Design: single arm descriptive

Adaptive Design: No

Primary Statistical Methodology: descriptive

Interim Analysis: No

Sample Size: 250

Sample Size Determination: considering the probability detecting AE with small frequency

Was there an **Alternative Analysis** in case of violation of assumption? No.

- Were there any major changes, such as changing the statistical analysis methodology or changing the primary endpoint variable? No.
- Were the **Covariates** pre-specified in the protocol? No.
- Did the Applicant perform **Sensitivity Analyses**? No
- How were the **Missing Data** handled? Patients with incomplete response data in the RE population were considered as non-responders
- Was there a **Multiplicity** involved? No.
- **Multiple Secondary Endpoints:** Yes. Not included in the label

Were Subgroup Analyses Performed? Yes

- Were there any **Discrepancies** between the protocol/statistical analysis plan vs. the study report? No.
- Overall, was the study positive (Yes/No)? Yes

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/s/

LIJUN ZHANG
08/05/2011

SHENGHUI TANG
08/05/2011

RAJESHWARI SRIDHARA
08/05/2011



STATISTICAL REVIEW AND EVALUATION

Biometrics Division: VI (HFD-705)

NDA No.:	202-570
SERIAL NO.:	S-000
DATE RECEIVED BY THE CENTER:	March 30, 2011
DRUG NAME:	crizotinib
DOSAGE FORM:	Capsules
INDICATION:	Oncology
SPONSOR:	Pfizer, Inc.
DOCUMENTS REVIEWED:	Submission dated March 30, 2011 and subsequent responses
NAME OF STATISTICAL REVIEWER:	Meiyu Shen, Ph.D. (HFD-705)
PROJECT MANAGER:	Don Henry

Meiyu Shen, Ph.D., Mathematical Statistician

Concur:

Yi Tsong, Ph.D.
Deputy Director, DBVI

Distribution: NDA 202-570
HFD-705/Y. Tsong, Ph.D.
ONDQA/Don Henry

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EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

1.1 Purpose of this statistical consultation

Pfizer submitted manufacturing process development and analytical procedures development and validation in NDA 202-570. In this submission, the sponsor requested the (b) (4) of the method operable design region (MODR) for high performance liquid chromatography in Validation of Analytical Procedure Drug substance (3.2.S.4.3) and drug product in Validation of Analytical Procedures (3.2.P.5.3). (b) (4)

On March 30, 2011, Division of Biometrics VI received the official request for the following consult: “perform statistical evaluations of the proposed design space for the manufacturing process.” In this review document, the statistical reviewer reviewed the original submission and the sponsor’s responses to 06-July-2011 FDA Query and 08-July-2011 FDA Query.

(b) (4)

11 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

MEIYU SHEN
07/27/2011

YI TSONG
07/27/2011

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 202570

Applicant: Pfizer Inc.

Stamp Date: 3/30/2011

Drug Name: Crizotinib

NDA/BLA Type: NME

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	Y			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	Y			Changes made in each amendment was included
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	Y			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	Y			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the statistical 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.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

Lijun Zhang

05/02/2011

Reviewing Statistician

Date

Shenghui Tang

05/02/2011

Supervisor/Team Leader

Date

File name: 5_Statistics Filing Checklist for a New NDA_BLA110207

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/s/

LIJUN ZHANG
05/03/2011

SHENGHUI TANG
05/03/2011