CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202570Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY
GENOMICS GROUP REVIEW

NDA/BLA Number	202570
Submission Date	March 30, 2011
Applicant Name	Pfizer, Inc
Generic Name	Crizotinib
Proposed Indication	ALK-positive advanced NSCLC
Primary Reviewer	Rosane Charlab Orbach, Ph.D.
Secondary Reviewer	Issam Zineh, Pharm.D., M.P.H.

1 Background

The EML4-ALK fusion gene has been identified as an oncogenic driver in a small subset of non-small cell lung cancer (NSCLC). Crizotinib is an oral, ATP-competitive small molecule receptor tyrosine kinase (RTK) inhibitor of ALK (including ALK oncogenic fusion variants) and of the c-Met/Hepatocyte growth factor receptor (c-Met/HGFR). Pre-clinical studies suggest activity against other targets such as RON. As part of it's development program, the sponsor used an enrichment strategy in early phase clinical studies leading up to a restricted entry (ALK+) phase 2 study to support accelerated approval. The key purpose of this memo is to assess whether data support targeted use of crizotinib solely in ALK+ patients and outline outstanding issues from a pharmacogenomics perspective.

2 Submission Contents Related to Genomics

In addition to a phase 1 study of all-comers (A8081001) that initially identified a small subset of NSCLC patients with ALK+ to have achieved stable disease, the sponsor conducted an ALK+ restricted-entry expansion cohort and a single-arm trial in ALK+ patients (A8081005). Data from these trials were submitted in the NDA.

3 Key Issues and Summary of Findings

3.1 Overview of Patient Selection Issue

Although initially developed against c-Met, crizotinib showed pre-clinical and clinical activity against ALK. Due to ALK emergence as a potentially relevant oncogenic target at the time, crizotinb development was shifted to target ALK+ NSCLC. The test used in the registration trial to select ALK+ patients is a FISH with break-apart probes, which identifies ALK rearrangement events. The FISH assay cannot distinguish between the different fusion partners or rearranged variants of ALK. There are limited data in ALK- NSCLC patients in this NDA.

3.2 Outstanding Issues

3.2.1 Crizotinib Effect in ALK- patients

Preliminary data on 23 ALK- patients were submitted to FDA on June 10th, 2011. Some patients who tested ALK- by the Vysis ALK Break Apart FISH assay tested ALK+ by other

diagnostic tests. Seven of 19 ALK- patients with response data experienced either an investigator response or a single assessment of partial response. This 35% response rate, if confirmed, suggests crizotinib may be effective in patients without diagnostically-defined ALK+ status. It is not clear if responders are false negatives (e.g., due to an inappropriate assay cut-off) or if crizotinib is inhibiting other oncogenic targets relevant to ALK negative NSCLC (see clinical review for details).

3.2.2 Resistance

As with other TKI inhibitors, resistance to crizotinib due to secondary mutations has been described (PMID: 21791641; 21502504). Tumor sample acquisition at progression is planned (A8081005). These, perhaps, can be used to identify molecular resistance mechanisms. Key review questions regarding acquired resistance as a determinant of overall crizotinib efficacy will be addressed contingent on the additional data obtained from two phase 3 trials intended to support crizotinib's full approval (i.e., A8081007 and A8081014) in which OS and PFS will be key endpoints.

3.2.3 Safety

A potential for drug-induced liver injury was noted. TKI-induced liver injury has been observed to have a genetic component (PMID: 21245432). From the current submission, it is unknown whether germline DNA was collected and is available for patients that experienced crizotinib-associated ALT elevations. Germline DNA collection from all future crizotinib studies for safety assessment will be requested through IND.

4 Summary and Conclusions

Crizotinib exhibited significant activity in the population studied (see clinical review for details). This activity will be confirmed with meaningful clinical endpoints in two efficacy studies as part of crizotinib's full registration program. Outstanding issues include whether (1) crizotinib is also effective in ALK- patients, (2) resistance mechanisms will limit crizotinib efficacy in the definitive efficacy trials, and (3) genetic determinants of crizotinib-associated liver dysfunction can be identified in order to enhance risk/benefit balance.

5 Recommendations

The data support accelerated approval of crizotinib for ALK+ NSCLC from the Genomics perspective. A comment to the IND regarding DNA collection for safety pharmacogenetics and a post-marketing commitment to generate additional data in the ALK- patients are warranted.

5.1 Post-marketing studies

Given the potential activity of crizotinib in the ALK- population based on the sponsor's preliminary data, a definitive study of crizotinib efficacy in this population is warranted. PMC to test crizotinib in ALK- NSCLC has been discussed with the team. No further recommendations from the Genomics Group for PMC/PMRs.

5.2 Label Recommendations

None.

Rosane Charlab Orbach, Ph.D. Reviewer, Genomics Group, OCP	Issam Zineh, Pharm.D., M.P.H. Associate Director, Genomics Group, OCP

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

/s/

ROSANE CHARLAB ORBACH
08/26/2011

ISSAM ZINEH
08/26/2011
Concu

Clinical Pharmacology Review	
NDA	202570
Submission Date	March 30, 2011
Brand Name	Xalkori®
Generic Name	Crizotinib; PF-02341066
Dosage Form / Strength	Oral Capsules/ 200 mg, 250 mg
Related IND	73544
Applicant	Pfizer Inc.
OCP Reviewer	Pengfei Song, Ph.D.
Pharmacometrics Reviewer	Anshu Marathe, Ph.D.
OCP Team Leader	Qi Liu, Ph.D.
Pharmacometrics Team Leader	Christine Garnett, Pharm.D.
OCP Division	Division of Clinical Pharmacology 5
ORM Division	Division of Drug Oncology Products
Submission Type; Code	Original NDA; 505 (b)(1); New Molecular Entity
Dosing Regimen	250 mg Orally Twice Daily (BID)
Indication	Treatment of Anaplastic Lymphoma Kinase (ALK)-Positive Advanced Non-Small Cell Lung Cancer (NSCLC)

Table of contents

List of Tables

List of Figures

1 EXECUTIVE SUMMARY

Crizotinib, a new molecular entity, is a small-molecule kinase inhibitor. The applicant seeks an accelerated approval of crizotinib for the treatment of anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC). The proposed dosage of crizotinib is 250 mg administered orally twice daily (BID), continuously, with or without food. Results from two single-arm trials (A8081005 and A8081001) in patients with ALK-positive NSCLC are submitted to support the accelerated approval. Objective response rate (ORR), the primary efficacy endpoint, was 50% (N=136) and 61% (N=119) in trials A8081005 and A8081001, respectively.

Exposure-response (ER) analyses indicated a lower ORR in the lowest quartile of steady state trough concentrations ($C_{trough,ss}$) compared to other quartiles (24% vs > 70% in trial A8081001, and 47% vs > 60 in trial A8081005). The proposed dosage appears acceptable, as even the lowest quartile of $C_{trough,ss}$ in pivotal trial A8081005 showed an ORR of 47%, compared to 10-24% using historical controls. ER analyses utilizing data from confirmatory trials A8081007 and A8081014 may provide further information on the appropriateness of 250 mg BID dose.

Following oral administration of crizotinib, C_{max} is reached within 4 to 6 hours, with a mean $T_{1/2}$ of 42 hours. Absolute oral bioavailability is 43%. Crizotinib can be dosed without regard to food, as a standard high-fat meal reduces AUC_{inf} and C_{max} by only 15%.

Crizotinib demonstrated non-linear pharmacokinetics (PK) in terms of dose proportionality and time-dependence. The steady state systemic exposure of crizotinib appears to increase with doses in a greater-than-proportional manner in the dose range of 200-300 mg BID. Following crizotinib 250 mg BID, steady state is reached within 15 days and stayed stable, with a median accumulation ratio of 4.5. However, apparent clearance (CL/F) at steady state (64 L/hr) was lower than that after a single dose (100 L/hr), likely due to auto-inhibition of CYP3A by crizotinib.

Following the oral administration of a single 250 mg radiolabeled crizotinib dose to healthy subjects, 63% (53% unchanged) and 22% (1.3% unchanged) of the administered dose was recovered in feces and urine, respectively. No dose adjustment is needed for mild or moderate renal impairment, as mean $C_{trough,ss}$ in these two groups are similar to that in normal renal function group. The effects of severe renal impairment and hepatic impairment are unknown.

Crizotinib is predominantly metabolized by CYP3A4/5 *in vitro*, at the same time, it is also a reversible and time-dependent inhibitor of CYP3A. Furthermore, crizotinib is possibly a CYP3A inducer, as crizotinib increases CYP3A4 mRNA levels by up to 29 fold, with no increase in CYP3A enzyme activity. *In vivo*, crizotinib (at steady-state) increases AUC of midazolam by 3.7 fold compared to midazolam alone. Due to the time-dependent PK of crizotinib, the effects of strong inducers or inhibitors of CYP3A4 on the PK of crizotinib at steady-state can not be predicted, because the drug interaction studies that the sponsor has conducted only evaluated single dose PK of crizotinib.

The aqueous solubility of crizotinib is pH dependent. No drug interaction study has been conducted with gastric pH elevating agents.

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology has reviewed NDA 202570. This NDA is acceptable from a clinical pharmacology perspective, provided that the Applicant and the Agency come to a mutually satisfactory agreement regarding the labeling language, the post-marketing requirements and post-marketing commitments.

1.2 POST-MARKETING REQUIREMENTS (PMRS) AND COMMITMENTS (PMCS)

The following issues should be addressed as PMRs:

1. Conduct a multiple dose trial in humans to determine how to adjust the crizotinib dose when it is coadministered with a strong CYP3A inhibitor (e.g., ketoconazole).
2. Conduct a multiple dose trial in humans to determine how to adjust the crizotinib dose when it is coadministered with a strong CYP3A inducer (e.g., rifampin).
3. Conduct a multiple dose trial to determine the appropriate crizotinib dose in patients with various degrees of hepatic impairment.
4. Conduct a multiple dose trial to determine the appropriate crizotinib dose in patients with severe renal impairment.
5. 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/or an antacid).
6. Complete the ECG sub-study in trial A8081007 and submit the final study report, along with a thorough review of cardiac safety data to address any potential impact of crizotinib on QTc interval prolongation in patients.
7. Submit the study report on the ongoing *in vitro* evaluations of induction potential of crizotinib on CYP2B and CYP2C enzymes.

The following issue should be addressed as a PMC:

1. Conduct exposure-response analysis utilizing data from confirmatory trials A8081007 and A8081014 to further evaluate the appropriateness of 250 mg BID dose for all patients.

Signatures:

Pengfei Song, Ph.D. Reviewer Division of Clinical Pharmacology 5	Qi Liu, Ph.D. Team Leader Division of Clinical Pharmacology 5
Anshu Marathe, Ph.D. Pharmacometrics Reviewer Division of Pharmacometrics	Christine Garnett, Pharm.D. Pharmacometrics Team Leader Division of Pharmacometrics
Cc: DDOP: CSO - Diane Hanner; MTL - Virginia E. Maher; MO - Shakun Malik DCP-5: DDD - Brian Booth; DD – Nam Atiqur Rahman	

1.3 CLINICAL PHARMACOLOGY SUMMARY

Crizotinib, a new molecular entity, is a small-molecule kinase inhibitor. In this original NDA, single-arm trials A8081005 and A8081001 were submitted to support an accelerated approval of crizotinib for the treatment of ALK-positive advanced NSCLC. The proposed dosage of crizotinib is 250 mg administered BID, continuously, with or without food. Objective response rate (ORR) in trials A8081005 and A8081001 was 50% and 61%, respectively.

ER analyses indicated a lower ORR in the lowest quartile of $C_{trough,ss}$ compared to other quartiles (24% vs >70% in trial A8081001 and 47% vs > 60 in trial A8081005). The proposed dosage appears acceptable, as even the lowest quartile of in pivotal trial A8081005 showed an ORR of 47%, compared to 10-24% of historical controls. ER analyses in the ongoing Phase 3 trials A8081007 and A8081014 may provide further information on the appropriateness of 250 mg BID dose.

Crizotinib appears to be associated with concentration-dependent QT interval prolongation. Due to ECG acquisition and interpretation issues, large increase in QT interval (i.e., ~20 ms) can not be reliably excluded.

Following oral administration of crizotinib, C_{max} was reached at 4 to 6 hours, with a terminal half-life of 42 hours in patients. The absolute oral bioavailability is 43%. Crizotinib can be dosed without regard to food, as a standard high-fat meal reduces AUC_{inf} and C_{max} by only 15%.

Crizotinib demonstrated non-linear PK in humans in terms of dose proportionality and time-dependence. The steady state systemic exposure of crizotinib appears to increase with doses in a greater-than-proportional manner in the dose range of 200-300 mg BID. Following 250 mg crizotinib BID, steady state is reached within 15 days with an accumulation ratio of 4.5, and the exposure stayed stable over the treatment period of 112 days. However, apparent clearance (CL/F) at steady state (64 L/hr) was lower than that after a single dose (100 L/hr), likely due to auto-inhibition of CYP3A by crizotinib.

In the mass balance trial with a single 250-mg dose of [^{14}C] crizotinib, the mean recovery of administered dose was 85%, with 63% (53% unchanged) in feces and 22% (1.3% unchanged) in urine. No dose adjustment is needed for mild or moderate renal impairment, as mean $C_{trough,ss}$ in these two groups are similar to that in normal renal function group. The effects of severe renal impairment and hepatic impairment are unknown.

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

Crizotinib is not an inducer of CYP1A2. The potential of crizotinib to induce CYP2B or CYP2C *in vitro* is currently being evaluated by the sponsor. *In vitro,* crizotinib is a substrate and an

inhibitor of P-glycoprotein (P-gp). It is not a substrate of breast cancer resistance protein (BCRP) or hepatic uptake transporters.

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

2 QUESTION BASED REVIEW

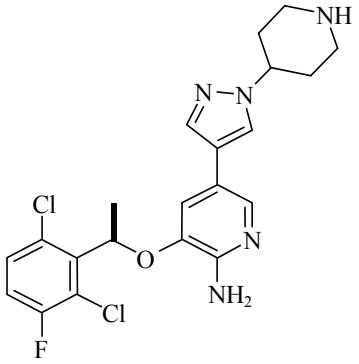
2.1 GENERAL ATTRIBUTES

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Crizotinib, the drug substance, is a white to pale yellow powder. The drug product Xalkori® is supplied as hard gelatin capsules containing 200 mg or 250 mg of crizotinib. The following is a brief summary of the physico-chemical properties of crizotinib:

Physico-chemical properties of crizotinib

- Structure:



- Established Name: Crizotinib, PF-02341066
- Molecular Weight: 450.34 Daltons
- Molecular Formula: $C_{21}H_{22}Cl_2FN_5O$
- LogP: 4.28
- LogD at pH 7.4: 1.65
- PKa: 9.4 (piperidinium cation) and 5.6 (pyridinium cation)
- Chemical Name (CAS): (R)-3-[1-(2,6-Dichloro-3-fluoro-phenyl)-ethoxy]-5-(1-piperidin-4-yl-1H-pyrazol-4-yl)-pyridin-2-ylamine
- Solubility: Crizotinib solubility in aqueous media decreases with increasing pH (Table 1).

Table 1. PH-dependent aqueous solubility of crizotinib

Aqueous Solution	Initial pH[a]	Final pH	Solubility (mg/mL)
			(b) (4)

[a] measured immediately following addition of crizotinib drug substance to media.

Source: Table 3.2.S.1.3-1 of Module 3 Quality

2.1.2 What are the proposed mechanisms of action and therapeutic indications?

Crizotinib is a small-molecule inhibitor of c-mesenchymal-epithelial transition factor/hepatocyte growth factor receptor (c-Met/HGFR) and ALK tyrosine kinases. The proposed indication of crizotinib is for the treatment of ALK-positive advanced NSCLC.

2.1.3 What are the proposed dosage and route of administration?

The proposed dosage of crizotinib is 250 mg oral capsules twice daily (BID), continuously, with or without food.

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

There are four ongoing clinical trials of crizotinib in patients with ALK-positive NSCLC: 1001 (A8081001, Phase 1 trial including a dose-escalation phase and extension phase at MTD), 1005 (A8081005, Phase 2 as a second line treatment), 1007 (A8081007, Phase 3 as second-line treatment) and 1014 (A808101, Phase 3 as first-line treatment). The dosage of 250 mg BID that is being tested in all trials was the maximal tolerated dose (MTD) determined in the dose escalation phase of trial 1001. Per protocol, rich or sparse PK samples are collected from all patients in all ongoing trials. For simplicity, the last 4 characters of trial ID will be used to represent trial hereafter.

Results from the single-arm trials 1005 and 1001 are submitted to support the efficacy and safety of crizotinib for an accelerated approval. In the pivotal trial 1005, an ORR of 50% was observed in 136 evaluable patients with ALK-positive advanced NSCLC that had previously received at least one chemotherapy. In the supportive trial 1001, an ORR of 61% was observed in the expansion cohort of 119 patients with ALK-positive NSCLC.

Six biopharmaceutical or clinical pharmacology trials conducted in healthy subjects are included in the current NDA submission (Table 2): 1008 (relative bioavailability), 1010 (absolute bioavailability), 1011 (bioequivalence and food effect), 1009 (mass balance), 1015 (drug interaction with ketoconazole), and 1016 (drug interaction with rifampin). The applicant also submitted two population PK and PK-PD reports:

- PMAR-0192: Population PK analysis with pooled data from 250 patients in trials 1001 and 1005) to assess the effects of intrinsic and extrinsic factors.
- PMAR-00224: PK/PD analysis for QTc prolongation evaluation, using data from 326 patients in trials 1001 and 1005.

Furthermore, per FDA's request during the review process, the applicant submitted exposure-response analyses reports (PMAR-0243 for trial 1005 and PMAR-0242 for trial 1001).

Table 2. Crizotinib studies for pharmacokinetic analysis

Protocol Number	Study Type	Treatment (Dose/ Formulation)	N	Full PK Sampling	Sparse Sampling	NCA	PopPK
Single Dose Studies in Healthy Subjects							
A8081008*	Relative BA of PIC vs IR tablet	Criz 250 mg PIC Criz 250 mg IR tablet	24	X		X	
A8081009	^{14}C Radiolabeled ADME	Criz 250 mg Extemporaneously prepared oral suspension	6	X		X	
A8081010*	Absolute BA	Criz 50 mg IV Criz 250 mg IR tablet	14	X		X	
A8081011*	BE of FC vs IR tablet and PIC, food effect with FC	Criz 250 mg IR tablet Criz 250 mg PIC Criz 250 mg FC (fed and fasted)	36	X		X	
A8081015	DDI (Ketoconazole)	Criz 150 mg IR tablet; Ketoconazole: 200 mg BID (16 days)	15	X		X	
A8081016	DDI (Rifampin)	Criz 250 mg IR tablet; Rifampin: 600 mg QD (14 days)	15	X		X	
Multiple dose Study in Cancer Patients							
A8081001	Dose-Escalation Cohorts	Criz all doses PIC 50 mg QD 100 mg QD 200 mg QD 200 mg BID 250 mg BID 300 mg BID	37 3 4 8 7 9 6	X	X	X	X
	RP2D Cohorts ALK-positive NSCLC ALK-negative NSCLC Other Midazolam substudy† Food effect substudy†	Criz 250 mg BID PIC or IR table)	171 119 5 47 14 13	X	X	X	X
A8081005	Phase 2,efficacy and safety study	Criz 250 mg BID IR tablet	136		X		X

Source: Table 2 of Summary of Clinical Pharmacology

2.2.2 What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical studies?

The primary efficacy endpoint for trials 1005 and 1001 is objective response rate (ORR). ORR is defined as the percent of patients in the efficacy evaluation population achieving a confirmed complete response (CR) or confirmed partial response (PR) according to Response Evaluation Criteria in Solid Tumors (RECIST, version 1.0). Confirmed responses (CR or PR) were those that persisted on repeat imaging at least four weeks after initial documentation of response.

The safety profiles are coded by system organ class (SOC) and Preferred Term according to Medical Dictionary for Regulatory Activities (MedDRA) terminology (Version 13.0). AE severity are graded according to NCI CTCAE (Version 3.0).

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes. Crizotinib, the primary active moiety, and the major active metabolite PF-06260182 are appropriately identified and measured in all clinical trials.

Crizotinib is the major circulating moiety that accounts for 33% of the radioactivity in pooled plasma over 96 hours post-dose. As crizotinib is equally distributed between plasma and blood cells (with a blood to plasma ratio of 1.01 at 1 μM), the plasma is an appropriate matrix for monitoring crizotinib PK.

PF-06260182 (with two constituent diastereomers PF-06270079 and PF-06270080), is the only identified metabolite accounting for > 10% of circulating radioactivity. Compared to crizotinib, PF-06270079 and PF-06270080 are approximately 3- to 8-fold less potent against ALK and 2.5- to 4-fold less potent against c-Met/HGFR *in vitro*.

To evaluate the contribution of active metabolites, a pharmacological activity index (PAI) was proposed by the applicant as follows:

$$PAI = \frac{\text{metabolite } AUC_u}{\text{parent } AUC_u} \times \frac{\text{pharmacological activity of parent}}{\text{pharmacological activity of metabolite}}$$

where AUC_u represents the unbound AUC.

The PAI was 2~4% for each diastereomer after a 250 mg single dose.

2.2.4 Exposure-response

2.2.4.1 Is there an exposure-response relationship for objective response rate (ORR), the primary efficacy endpoint?

Yes, there is evidence of exposure-response relationship for ORR in trials 1005 and 1001.

An exposure-response analysis was conducted for ORR in trials 1005 and 1001. Patients with PK samples (N=120 in trial 1005, N=114 in trial 1001) were divided into quartiles based on their steady state trough concentrations and the proportion of patients with response were determined for each quartile (Figure 1). The exposure-response relationship is less steep in trial 1005 compared to trial 1001. Higher ORR of approximately 60% is observed in the patients with higher drug exposure in the upper quartiles compared to a lower response rate of 47% in the lower quartiles (Table 1 in PM review) in trial 1005. In trial 1001, the ORR was 24% in the lowest quartile, while the response rate was 75% or greater in the upper three quartiles (Table 2 in PM review). Similar results were obtained when the population predicted average steady state concentration ($C_{avg,ss}$) was used as the exposure measure (see Section 4.3 in PM review).

However, the difference in ORR is not only due to crizotinib concentrations but is also likely due to other confounding factors that are not balanced between the quartiles (for details see PM review). To account for these confounding factors, a logistic regression analysis was conducted that included all these factors. A step-wise logistic regression analysis identified log-transformed $C_{trough,ss}$ as significant predictor of response in trial 1001. In trial 1005, log-transformed $C_{avg,ss}$ was identified as a significant predictor of response (see Table 5 in PM review). Sponsor's analysis also identified these as significant predictors.

Trial 1005 Trial 1001

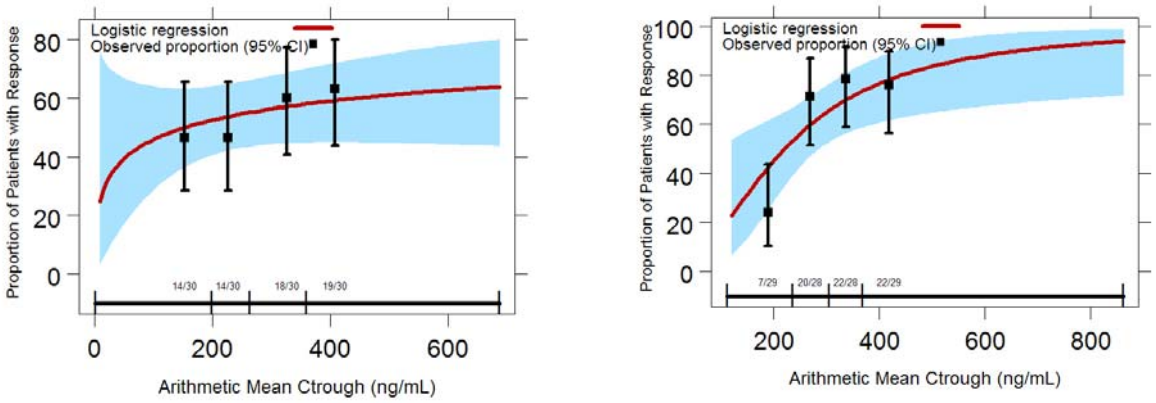


Figure 1: The proportion of patients with ORR versus mean steady state trough concentrations of crizotinib in trials 1005 and 1001. Solid black symbols represent the observed percentage of patients responding to treatment in each $C_{trough,ss}$ quartile. The vertical black bars represent the 95% confidence interval. The exposure range in each $C_{trough,ss}$ quartile is denoted by the horizontal black line. Mean $C_{trough,ss}$ represents the arithmetic mean of the observed $C_{trough,ss}$ in various cycles after steady state was reached.

Please see Pharmacometrics review by Dr. Anshu Marathe for more information.

2.2.4.2 Is there an exposure-response relationship for progression free survival (PFS), the secondary efficacy endpoint?

An exposure-response analysis was conducted for PFS in trials 1005 and 1001 (Figure 2). There is trend for increase in PFS with increasing exposure in trial 1001 but this trend was not seen in trial 1005. The analysis for trial 1005 is considered preliminary because data are not fully mature at the time of cut-off. Thus this analysis will primarily focus on PFS data from trial 1001.

In trial 1001, a clear separation is observed between PFS of the lowest quartile and the upper three quartiles in Figure 2. The upper three quartiles overlap and show no clear separation, possibly suggesting saturation of response at those exposures. This is consistent with objective response rate where similar response rate of ~70% was observed for the upper three quartiles (Figure 1). The median PFS in the lowest quartile in trial 1001 is 7.1 months while the median PFS in the upper three quartiles is greater than 10 months. As mentioned previously the difference in PFS is not only due to exposure but also due to other confounding risk factors that might not be balanced between the lowest and upper quartiles. To account for these confounding risk factors, a Cox proportional model was developed. While numerically, it was observed that increasing exposure decreased hazard, this relation was not statistically significant. A likely reason for not seeing a statistically significant relationship is that while the lowest quartile was separated from others, there was overlap in the upper three quartiles which possibly suggests saturation. Thus, a stepwise Cox proportional analysis was done that included all likely demographic factors and concentration as a categorical covariate, *i.e.*, lowest quartile versus the combined upper three quartiles. The model suggested higher hazard in the lowest quartile compared to the upper three quartiles with a hazard ratio of 3.2 (90%CI: 1.62–6.36) (Table 8 in

Pharmacometrics review by Dr. Marathe).

Trial 1005 Trial 1001

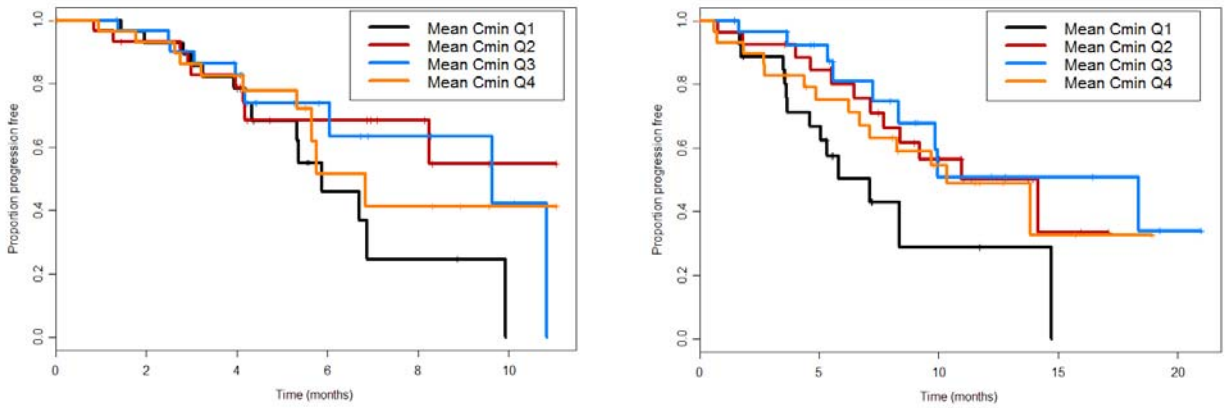


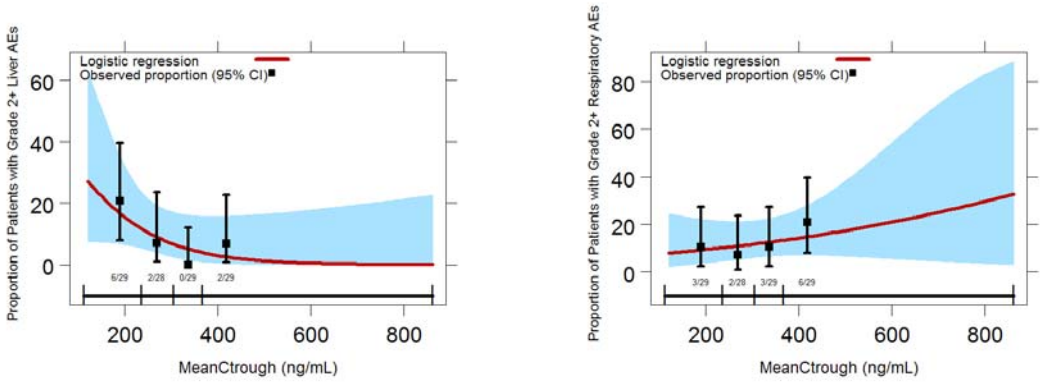
Figure 2: Kaplan-Meier plots for PFS for patients in various quartiles (Q1, Q2, Q3 and Q4) based on the mean steady state trough concentrations. $C_{trough,ss}$ represents the arithmetic mean of the observed C_{trough} in various cycles after steady state was reached.

Please see Pharmacometrics review by Dr. Anshu Marathe for more information.

2.2.4.3 Is there evidence of exposure-response for safety?

No meaningful exposure response relationship for respiratory and liver related adverse events was observed in trials 1001 and 1005 (Figure 3). Overall, the incidence of these adverse events for hematological toxicities, ALT and AST elevations and respiratory infections were low in trials 1001 and 1005 to conduct meaningful exposure-response analysis.

Trial 1001



Trial 1005

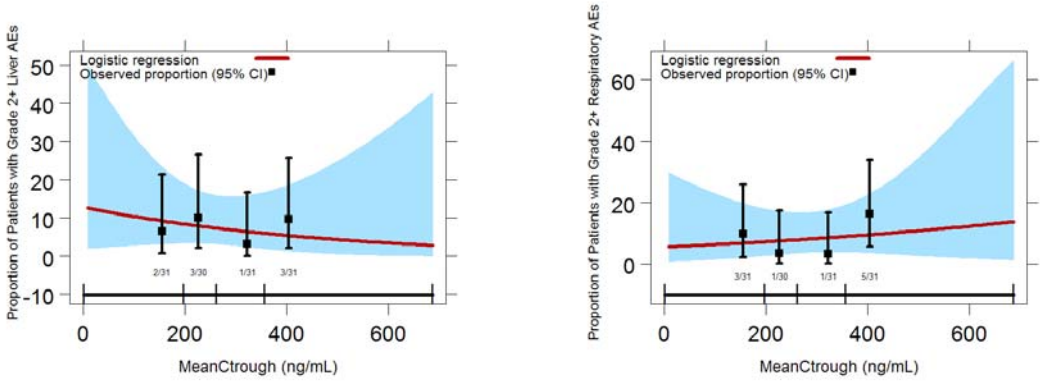


Figure 3: The probability of patients with A) Grade 2+ liver related AEs (left panel) and B) Grade 2+ respiratory related AEs (right panel)–steady state C_{trough} of crizotinib in trials 1001 and 1005. Solid black symbols represent the observed percentage of patients experiencing AEs in each C_{trough} quartile. The black bars represent the 95% confidence interval. The solid red line represents the mean logistic regression prediction. The shaded area represents the 95% confidence interval. The exposure range in each C_{trough} quartile is denoted by the horizontal black line.

Please see Pharmacometrics review by Dr. Anshu Marathe for more information.

2.2.4.4 Does crizotinib prolong the QT or QTc interval?

Crizotinib appears to be associated with concentration-dependent QT interval prolongation (P<0.001). Because of ECG acquisition and interpretation issues, large increases in QT interval (i.e., ~20 ms) can not be reliably excluded. The IRT-QTc review recommends a PMR to complete and submit an ongoing QTc assessment at 250 mg BID in the ECG sub-study in trial 1007 to gain reliable estimation of QT effect size.

Please see IRT-QTc review by Dr. Hao Zhu for more information.

2.2.4.5 Is the dose and dosing regimen selected by the applicant consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

Yes. The selected dosage appears acceptable with the known relationships between dose-concentration-response. There are various unresolved dosing related issues regarding the drug interactions, and organ dysfunctions.

The selected dosage regimen of 250 mg BID appears acceptable at this time, with the following rationales:

1. The dosage of 250 mg BID was the MTD determined in the dose escalation phase of trial 1001. There were a total of 3 DLTs observed in 3 of 34 patients in the dose-escalation cohort. The first DLT was Grade 3 ALT increase at the 200 mg QD dose level. At 300 mg BID, 2 out of 6 patients experienced Grade 3 Fatigue. As per protocol, dose escalation was halted, and the next cohort of 3 patients was enrolled and treated at the 250 mg BID dose level without further DLTs. This cohort was further expanded to have 6 evaluable patients (2 patients were not evaluable) with no DLTs encountered. Therefore, the dose level of 250 mg BID was considered as MTD for further evaluation in all ongoing trials (1001, 1005, 1007, and 1014).
2. Based on the exposure-response analysis of trial 1005, the proposed dose of 250 mg BID seems reasonable. In contrast to trial 1001, subjects in the lowest quartile had a response rate of 47% in trial 1005, which is higher than the response rate (10-24%) of historical controls, *i.e.,* patients on standard of care. While subjects in the lowest quartile (112-235 ng/mL) in trial 1001 have 24% response rate, this was not consistent with the results from trial 1005. With the data submitted, it is not clear what factors are responsible for low exposures or low response rate in the lowest quartile in trial 1001. Since trials 1001 and 1005 are small trials, exposure-response analysis is limited to address the discrepancies observed between the two trials and to conclusively determine if the dose is appropriate for all patients. Additionally, the PFS data from the pivotal trial 1005 was not fully mature at the time of submission of this application to conduct a meaningful exposure-response relationship. Further exposure-response relationship evaluations on more clinically meaningful endpoints such as PFS and OS in trials 1007 and 1014 (where PK samples will be collected from all patients over multiple cycles according to the current protocols) may provide more information on the appropriateness of the dosage of 250 mg BID.

Unresolved dosing and administration issues of crizotinib to be addressed as PMRs include:

- dose adjustment in patients with various degrees of hepatic impairment
- dose adjustment in patients with severe renal impairment
- dose adjustment in patients receiving strong CYP3A inhibitors
- dose adjustment in patients receiving strong CYP3A inducers
- dose adjustment in patients receiving gastric pH-elevating agents

Unresolved dosing and administration issues of crizotinib to be addressed as PMC include:

- low response of 24% in patients with crizotinib concentration less than 235 ng/mL in trial 1001 and discrepancies in the exposure-response analysis between trials 1001 and 1005.

2.2.5 Pharmacokinetic characteristics of the drug and its major metabolites

Crizotinib demonstrated non-linear pharmacokinetics in humans in terms of dose proportionality and time dependence. The systemic exposure of crizotinib appears to increase with dose in a less-than-proportional manner following single dose, but in a more-than-proportional manner at steady state. Furthermore, apparent clearance (CL/F) at steady state (64.5 L/hr) was lower than that after a single dose (100 L/hr), likely due to the auto-inhibition of CYP3A by crizotinib. However, no significant changes in $C_{trough,ss}$ following 250 mg BID were observed over a treatment period of 112 days.

2.2.5.1 What are the single-dose Pharmacokinetic parameters of Crizotinib and PF-06260182?

Single-dose pharmacokinetics of crizotinib

The single-dose pharmacokinetics of crizotinib have been evaluated in six clinical pharmacology or biopharmaceutical trials (1008, 1009, 1010, 1011, 1015, and 1016) in healthy subjects and in patients with advanced tumors in trial 1001. The single-dose pharmacokinetics of crizotinib in humans have the following features:

- Peak plasma crizotinib concentration occurs at a T_{max} of 4 to 6 hours. Mean C_{max} and AUC_{inf} of crizotinib ranges from 100 to 135 ng/mL and from 2,192 to 2,946 ng·hr/mL, respectively. Following C_{max}, plasma crizotinib concentrations declined in a multi-exponential manner. The terminal half-life is 42 hours in patients with advanced tumors.
- A standard high-fat meal reduces AUC_{inf} and C_{max} by 15% in healthy subjects (trial 1011) and in patients with advanced solid tumors (trial 1001), but with no changes in T_{max} , $T_{1/2}$, or variability in AUC and C_{max}.
- The absolute oral bioavailability of crizotinib was 43% after a single dose of 250 mg in healthy subjects, when referring to a single dose of 50 mg via constant intravenous infusion over a 2-hour period.
- The mean volume of distribution (Vss) of crizotinib following a single intravenous dose of 50 mg is 1,772 liters. Binding of crizotinib to plasma proteins is 91% in humans.
- The mean apparent clearance of crizotinib is 100 L/hr after a single oral dose of 250 mg.

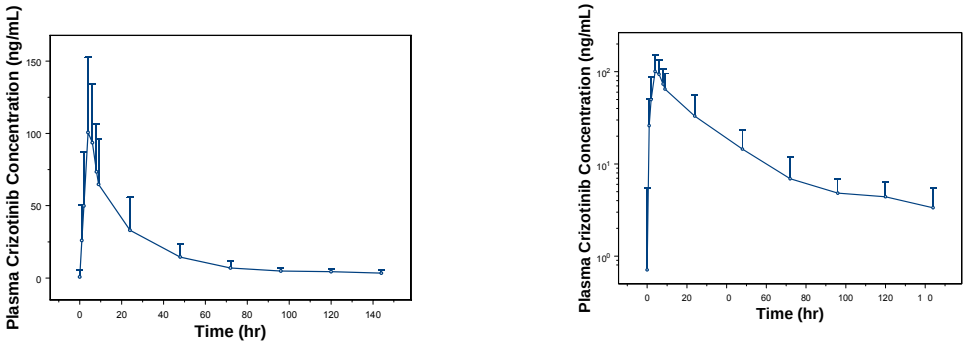


Figure 4: The time-concentration profiles of crizotinib in patients (N=46) with advanced tumors following single 250 mg oral dose under fasting conditions on Day-7, on a normal scale (left) and on a semi-log scale (right)

Table 3. Summary of Crizotinib PK parameters in studies with a single 250 mg oral dose of crizotinib

Study/ Treatment Group	Formulation	N	AUC_{inf} (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$t_{1/2}$ (hr)	CL/F (L/hr)	V_z/F (L)
Healthy Subjects ((Fasting)								
A8081009	Suspension†	6	2777 (38)	109 (46)	3.0 (2.0-6.0)	94.0 (15)	90.1 (26)	12110 (35)
A8081016	IR tablet	15	2192 (27)	102 (33)	5.0 (4.0-6.0)	33.1 (21)	119 (31)§	5940 (55)§
A8081008	PIC	24	2946 (31)	113 (29)	6.0 (2.0-8.0)	29.5 (16)	84.9 (35)	3567 (47)
	IR tablet	24	2723 (33)	112 (30)	6.0 (2.0-8.0)	29.1 (16)	91.8 (37)	3809 (43)
A8081011	PIC	35	2665 (41)	119 (39)	5.0 (2.0-6.0)	35.3 (18)	93.8 (48)	4703 (53)
	IR tablet	35	2890 (34)	126 (28)	5.0 (1.0-8.0)	34.6 (12)	86.5 (33)	4290 (37)
	FC	35	2887 (36)	135 (33)	5.0 (2.0-6.0)	34.9 (14)	86.6 (56)	4313 (77)
A8081010	IR tablet	14	2321 (34)	100 (28)	5.0 (4.0-6.0)	29.0 (10)	108 (32)	4478 (35)
Patients with Advanced Solid Tumors								
A8081001*								
Dose escalation	PIC	9	1817 (33)[a]	87.0 (34)	4.0 (1.0-9.0)	47.1 (16)	138 (32)[a]	9230 (30)[a]
RP2D all	PIC or IR tablet‡	46	2489 (51)[b]	108 (38)	4.0 (2.0-9.3)	42.4 (21)[c]	100 (50)[b]	5946 (63)[b]
ALK-positive NSCLC		39	2510 (50)[f]	109 (37)	4.0 (2.0-9.3)	43.7 (20)[d]	99.6 (46)[f]	6101 (64)[f]
ALK-negative NSCLC		4	ND	96.8 (40)	5.1 (2.2-8.8)	ND	ND	ND
Other		7	2366 (61)[e]	104 (48)	6.0 (4.0-6.1)	33.5 (14)[e]	106 (70)[e]	5060 (65)[e]

PIC = powder in capsule, IR = immediate release, FC = formulated capsule, ND = not determined
Geometric mean (%CV) for AUC_{inf}, AUC_{last}, C_{max}, CL/F, and V_z/F; arithmetic mean (%CV) for $t_{1/2}$; median (range) for T_{max}
*Day -7 values presented for A8081001 except Cycle 1 Day 1 data presented for ALK negative NSCLC.
‡PIC and IR tablet are bioequivalent (Module 2, Section 2.7.1.2.3).
†Extemporaneously prepared oral suspension
§Arithmetic mean
[a]N=8; [b]N=29; [c]N=31; [d]N=27; [e]N=4; [f]N=25

Source: Table 21 of Summary of Clinical Pharmacology (NDA 202570)

Single-dose pharmacokinetics of PF-06260182

Following a single oral dose of crizotinib, PF-06260182 formation was rapid with a median T_{max} of 5.0 - 6.0 hours, and a mean terminal half-life of 22 hours. Mean AUC_{inf} ratio of PF-06260182 to crizotinib ranged from 0.14 to 0.17 across studies (Table 4). Based on limited data from trial 1001, mean AUC_{inf} ratio of PF-06260182 was 0.16 to crizotinib following single-dose of crizotinib.

Table 4. Summary of PF-06260182 PK parameters in studies following a single 250 mg oral dose of crizotinib

	Formulation	N	AUC_{inf} (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$t_{1/2}$ (hr)	AUC_{inf} M/P Ratio
Healthy Subjects (Fasting)							
A8081016	IR tablet	15	379 (30)	29.9 (32)	5.0 (4.0-8.0)	22.2 (14)	0.168 (16)
A8081011		35				NC	NC
	PIC		402 (55)	29.7 (46)	6.0 (4.0-8.0)		
	IR tablet		442 (46)	32.2 (36)	6.0 (4.0-8.0)		
	FC		447 (49)	33.0 (34)	5.0 (4.0-10.0)		
A8081010	IR tablet	14	360 (31)	26.5 (24)	5.0 (5.0-6.0)	NC	0.144 (13)
Patients with Advanced Solid Tumors							
A8081001*	PIC or IR tablet†	1	419	27.5	6.0	24.1	0.16

PIC = powder in capsule, IR = immediate release, FC = formulated capsule, NC = not calculated, M/P = metabolite/parent, i.e PF-06260182/crizotinib
Geometric mean (% CV) for AUCs, C_{max}, and AUC M/P ratio; median (range) for T_{max}; arithmetic means (%CV) for $t_{1/2}$.
*RP2D on Day -7 only.
†PIC and IR table are bioequivalent (Module 2, Section 2.7.1.2.3)

Source: Table 22 of Summary of Clinical Pharmacology (NDA 202570)

2.2.5.2 What are the multiple-dose pharmacokinetic parameters of crizotinib and PF-06260182?

Multiple-dose pharmacokinetics of crizotinib and PF-06260182 were evaluated in patients with advanced solid tumors in trials 1001 and 1005.

Multiple-dose pharmacokinetics of Crizotinib

Multiple-dose pharmacokinetics of crizotinib in patients have the following features:

- Steady state is reached within 15 days after multiple 250 mg BID in patients with cancers, with a mean AUC_{τ} (CV%) of 3,880 ng·hr/mL (36%) and a mean C_{max} of 411 ng/mL (44%) on Day 15 of Cycle 1. No significant changes in $C_{trough,ss}$ following 250 mg BID were observed up to four treatment cycles, with median $C_{trough,ss}$ ranging from 242 to 319 ng/mL over Days 15-112 (Table 5).
- Crizotinib AUC_{τ} increased with median accumulation ratios ranging from 1.6-3.8 and 3.9-5.3 after QD and BID dosage, respectively(Table 10).
- A lower CL/F was observed on Day 15 (64.5 L/hr) and Day 29 (60.1 L/hr) after the first crizotinib dose of 250 mg BID compared to the CL/F seen after a single dose (100 L/hr). This decrease indicates non-linear pharmacokinetics of crizotinib, which is likely due to auto-inhibition of CYP3A by crizotinib.

Table 5. Summary of crizotinib pharmacokinetic parameters in trial 1001 with multiple 250 mg oral doses of crizotinib in patients with advanced solid tumors

Cohort	Visit	N	C_{max} (ng/mL)	AUC_{τ} (ng•hr/mL)	T_{max}* (hr)	CL/F (L/hr)
Dose escalation	CID15	5	327 (25)	3084 (32)	4.0 (1.0-6.1)	81.0 (28)
	C2D1	5	328 (25)	3054 (32)	4.0 (4.0-6.0)	81.8 (25)
RP2D all	C1D15	24	411 (44)	3880 (36)[a]	4.0 (0.0-9.0)	64.5 (56)[a]
	C2D1	18	478 (38)	4164 (38)[b]	4.0 (0.0-9.0)	60.1 (44)[b]
ALK-positive NSCLC	C1D15	10	493 (16)	4717 (9)[c]	5.1 (0.0-9.0)	53.0 (9)[c]
	C2D1	10	559 (25)	4490 (23)[d]	5.0 (2.0-9.0)	55.7 (21)[d]
Other	C1D15	14	361 (60)	3461 (46)[e]	2.1 (1.0-8.6)	72.2 (59)[e]
	C2D1	8	393 (54)	3861 (51)	4.0 (0.0-6.0)	64.8 (53)

Source: CSR A8081001, Tables 13.5.2.1, and 13.5.2.2a.
C = Cycle; D = Day; N = number of subjects
Presented in geometric mean (CV%) unless otherwise indicated; τ = 12 hours
* T_{max} presented in median (range)
[a]N=19; [b]N=16; [c]N=7; [d]N=8; [e]N=12

Source: Table 23 of Summary of Clinical Pharmacology (NDA 202570)

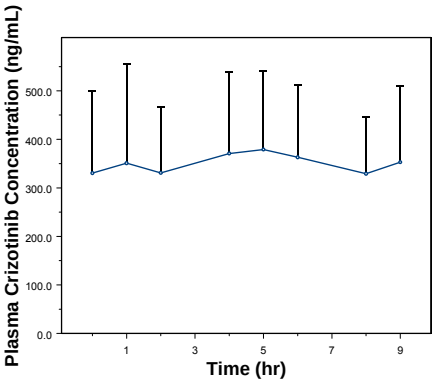


Figure 5: The time-concentration profiles of crizotinib on Day 15 of Cycle 1 in patients (N=156) with advanced solid tumors following 250 mg twice daily oral dose in trial 1001

Multiple-dose pharmacokinetics of PF-06260182

Following 250 mg crizotinib BID, the mean AUC_{τ} and C_{trough} ratios of PF-06260182 to crizotinib were 0.32 and 0.20 - 0.23 in trial 1001 (Table 6), respectively.

Table 6. Summary of crizotinib lactam (PF-06260182) pharmacokinetics parameters in trial 1001 following a multiple 250 mg twice daily oral dose of crizotinib

Cohort	Visit	N	C_{max} (ng/mL)	AUC_{τ} (ng•hr/mL)	T_{max} (hr)	AUC_{τ} M/P ratio
RP2D	C1D15	2*	96; 154	946; 1670	6.0; 8.0	ND
	C2D1	2*	124; 147	1320; 1330	4.0; 4.0	0.31; 0.32

M/P = metabolite/parent; ND = not determined; N = number of subjects
*Both were Asian patients with ALK-positive NSCLC
Note: individual values presented
τ = 12 hours

Source: Table 24 of Summary of Clinical Pharmacology (NDA 202570)

2.2.5.3 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

Similar single-dose PK of crizotinib and PF-06260182 were observed between healthy subjects and patients with advanced tumors.

See Section 2.2.5.1 for more information.

2.2.5.4 What are the characteristics of drug absorption?

After oral dosing, crizotinib is absorbed with peak plasma concentration occurring between 4-6 hours under fasting conditions. The mean absolute bioavailability of a single dose of 250 mg oral crizotinib is 43% (range: 31.8% - 66.3%). A single 50 mg dose of crizotinib administered via intravenous infusion over 2 hours (Trial 1010) was used as the reference.

Compared to fasting conditions, a standard high-fat meal decreases the systemic exposure by an average of 15% following a single dose of 250 mg crizotinib in patients with advanced solid

tumors (Trial 1001) and in healthy subjects (Trial 1011). Therefore, crizotinib may be taken with or without food.

The aqueous solubility of crizotinib is pH dependent, with decreased solubility at higher pH (Table 1). Drugs that elevate the gastric pH (such as proton pump inhibitors, H2 blockers, or antacids) may decrease the solubility of crizotinib and subsequently reduce its bioavailability. In fact, population PK analysis (PMAR00192) indicated concomitant proton pump inhibitor (esomeprazole, omeprazole, and lansoprazole) decreased the absorption rate constant (Ka) of crizotinib (See Pharmacometrics review by Dr. Marathe for more information). Since no formal studies have been conducted yet, a PMR will therefore be requested to conduct a multiple dose trial in humans to determine how to dose crizotinib with regard to gastric pH elevating agents (i.e., a proton-pump inhibitor, an H2-receptor antagonist, and an antacid).

See Sections 2.1.1, 2.5.4, 2.5.6 for more information.

2.2.5.5 What are the characteristics of drug distribution?

Plasma protein binding

The average binding of crizotinib to proteins in human plasma was 90.7%, in a concentration-independent manner from 0.5 μM (225 ng/mL) to 20 μM (9,000 ng/mL) (Study PDM-014). Crizotinib (1 μM, 450 ng/mL) is highly bound to human serum albumin (HSA) with a mean unbound fraction of 0.062 and moderately bound to α-1 acid-glycoprotein (AAG) with a mean unbound fraction of 0.263 (Study 144558) at physiological concentrations of these two human plasma proteins.

The average binding in human plasma for PF-06270079 and PF-06270080, the constituent diastereomers of the circulating lactam metabolite PF-06260182 (M10), was 94.5% and 94.1%, respectively, independent of the concentrations from 0.5 to 5 μM (232 and 2320 ng/mL).

Blood to plasma ratio

Crizotinib was relatively equally distributed between plasma and blood cells (Study PDM-015). The blood-to-plasma ratios of crizotinib in vitro in humans were 1.14, 1.01, 1.16 at concentrations of 45, 450 and 4500 ng/mL respectively.

P-Glycoprotein

Crizotinib is a substrate for P-glycoprotein *in vitro*. See Section 2.4.2.4.

Volume of distribution

The mean volume of distribution (V_{ss}) of crizotinib was 1,772 liters following 50 mg intravenous dose (Trial 1010). See Section 2.5.4.

2.2.5.6 Does the mass balance trial suggest renal or hepatic as the major route of elimination?

The mass balance study suggested that fecal excretion was the predominant route of elimination. Crizotinib undergoes extensive hepatic metabolism, primarily by CYP3A4/5. Non-metabolic elimination such as biliary excretion can not be excluded. Renal excretion plays an important role in the elimination of metabolites.

Trial 1009 evaluated the absorption, distribution, metabolism, and excretion (ADME) of crizotinib in six healthy male subjects after a single 250-mg dose of [^{14}C]crizotinib administered as an oral suspension. The mean recovery of the administered radioactivity was 85.3% within 480 hours, with individual values ranging from 68.6% to 91.3% (Figure 6). The mean recovery of radioactivity in feces was 63.1% of the dose, with individual values ranging from 53.5% to 68.7%. The mean recovery of radioactivity in urine was 22.2% of dose, with individual values ranging from 15.1% to 28.8%.

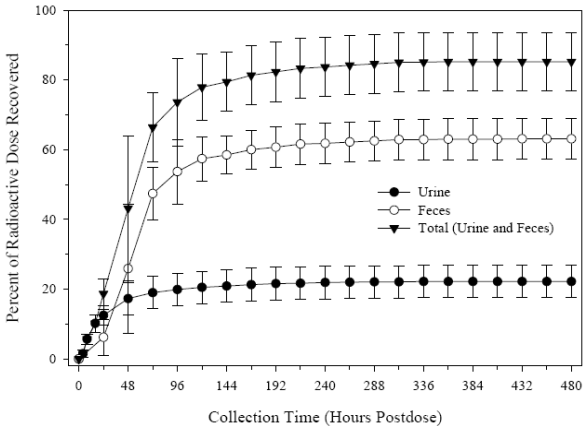


Figure 6: Mean radioactive dose recovered in urine and feces after a single 250-mg (100-µCi) oral dose of [^{14}C]-crizotinib to six healthy male subjects

Source: Figure 2 of Trial 1009 final study report.

The presence of circulating metabolic product(s) in plasma is indicated in Figure 7. The plasma crizotinib radioactivity AUC_{last} ratio was approximately 0.12. When plasma samples 96 hrs post-dose were pooled, the unchanged crizotinib was the major circulating component accounting for 33% of the circulating radioactivity. A lactam metabolite (M10, PF-06260182), formed via oxidation of the piperidine ring of crizotinib, accounts for 10% of circulating radioactivity. Other minor metabolites including glucuronide (M1) and sulfate (M3) conjugates of O-desalkyl crizotinib (M4, PF-03255243), O-desalkyl crizotinib lactam (M2, PF-06268935), and a sulfate conjugate of M2 (M8), accounts for < 10% of circulating radioactivity individually.

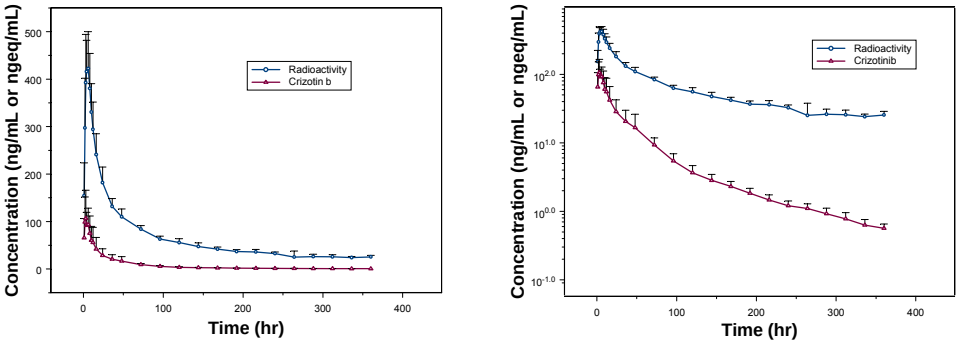


Figure 7: Mean (±SD) concentration-time profiles of crizotinib and total radioactivity in plasma in healthy subjects (N=6)

Unchanged crizotinib was the major excreted component in feces, accounting for an average of 53% of total administered dose. In urine, the percent of total administered dose excreted as unchanged crizotinib was 1.3% (Table 7). The major excreted component in urine, accounting for 4.5% of the administered dose, was a sulfate conjugate of O-desalkyl crizotinib lactam (M8). No other metabolites accounted for > 1% of total administered dose in excreta.

Table 7. Pharmacokinetics of crizotinib (PF-02341066) in 6 healthy male subjects receiving a single oral 250-mg dose of crizotinib containing approximately 100 μCi of [^{14}C]crizotinib

Parameter (units)	Plasma PF-02341066	Plasma Radioactivity
Plasma		
N, n	6, 6	6, 2
AUC_{inf} (ng.hr/mL)[b]	2777 (38)	29000, 29600 [c]
AUC_{last} (ng.hr/mL)[b]	2686 (40)	22830 (11)
C_{max} (ng/mL)[b]	109 (46)	436 (19)
T_{max} (hr)	2.99 (1.98-6.00)	5.00 (2.98-6.00)
$t_{1/2}$ (hr)	94.0 (15)	134, 178 [c]
CL/F (L/hr)	90.1 (26)	8.61, 8.44 [c]
Urine	**PF-02341066**	
N, n	6, 6	
Ae (ng)	3250000 (59)	
Ae (%)	1.30 (59)	
CLr (L/hr)	2.51 (14)	

N = number of subjects; n = number of subjects contributing to the mean for AUC_{inf}, $t_{½}$, and CL/F; NC = not calculated; CV = coefficient of variation.
[a] Geometric mean (% CV) for AUC_{inf}, AUC_{last}, C_{max}, CL/F, Ae, Ae% and CLr; arithmetic mean (% CV) for $t_{1/2}$; median (range) for T_{max}; individual values for AUC_{inf}, $t_{1/2}$, and CL/F of plasma radioactivity due to the limited number of subjects.
[b] Units for radioactivity parameters are ng-eq/mL (C_{max}) or ng-eq·hr/mL (AUC).
[c] Individual values for the 2 evaluable subjects.

Source: Table 11 of Trial 1009 final study report

Also see Section 2.2.5.7.

2.2.5.7 What are the characteristics of drug metabolism?

The metabolism of crizotinib was studied *in vivo* and *in vitro*, as summarized below:

***In vitro* evaluation**

Crizotinib is predominantly metabolized by CYP3A4/5 i*n vitro*. Using human liver microsomes, CYP3A4/5 enzymes were the major enzymes contributing to the metabolism of crizotinib (84% inhibition by troleandomycin, a CYP3A inhibitor). The 17% inhibition of crizotinib metabolism by quinidine (CYP2D6 inhibitor) (Table 8) was not confirmed with the recombinant CYP2D6 enzyme.

Table 8. Inhibition of crizotinib (PF-02341066) metabolism at 10 μM in human liver microsomes by selective Cytochrome P450 inhibitors

CYP Inhibitor	% Contribution
Furafyline (30 μM) (CYP1A2)	NC
Quercetin (10 μM) (CYP2C8)	NC
Sulfaphenazole (5 μM) (CYP2C9)	NC
(+)N-3-Benzylnirvanol (5 μM) (CYP2C19)	NC
Quinidine (10 μM) (CYP2D6)	17
Trolenadomycin (100 μM) (CYP 3A4)	84

Note: Percent remaining of PF-02341066 in human liver microsomes without chemical inhibitors was 51% at the end of incubation (60 min).
NC, no contribution observed

Source: Table 1 of Study PDM-019 report

Furthermore, the relative contributions of 7 recombinantly expressed CYP isoforms to the metabolism of PF-02341066 were evaluated. The prediction indicated that CYP-mediated metabolism of crizotinib is mediated primarily by CYP3A4 (99.4%), with minor contribution by CYP2C19 (0.5%) and CYP2D6 (0.1%).

In vivo evaluations

Mass balance trial suggested that crizotinib is extensively metabolized to crizotinib lactam, glucuronide (M1), *O*-desalkyl crizotinib (M4, PF-03255243) and its sulfate conjugate (M3), *O*-desalkyl crizotinib lactam (M2, PF-06268935), and the sulfate conjugate of M2 (M8). In the pooled plasma samples collected within 96 hours post-dose of a 250 mg single dose of [^{14}C]crizotinib, crizotinib and crizotinib lactam accounted for 33% and 10% of circulating radioactivity, respectively. No other single circulating component accounted for > 10% of radioactivity.

It was proposed that CYP enzymes (b) (4) Upon oxidation of crizotinib to crizotinib lactam (M10, PF-06260182), a new chiral center is introduced, resulting in the formation of 2 constituent diastereomers of M10 (PF-06270079 and PF-06270080). Following IV administration in trial 1010, the plasma PF-06260182 to crizotinib ratio was lower (0.034) compared to the ratio observed after oral dosing (0.15), suggesting potential pre-systemic formation of PF-06260182 (Table 24).

The proposed metabolites of crizotinib in plasma are presented in Figure 8.

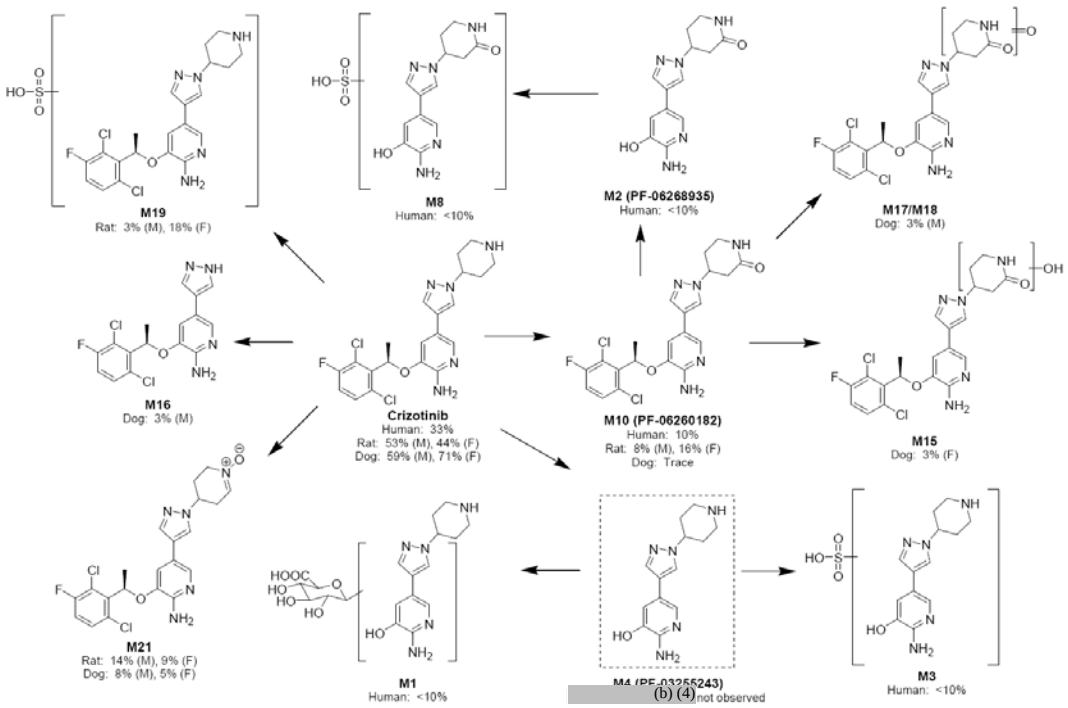


Figure 8: Proposed metabolic pathways of crizotinib in rat, dog, and human

Source: Figure 14 of Summary of Clinical Pharmacology (NDA 202570)

Also see Sections 2.2.5.2, 2.2.5.6 and 2.5.4.

2.2.5.8 What are the characteristics of drug elimination and excretion?

Elimination

Following a single oral administration of 250 mg [^{14}C]crizotinib, a mean of 63% and 22% of the drug-related radioactivity was recovered in the feces and urine, respectively. Excretion of unchanged crizotinib in the urine was negligible (1.3%). Hepatic, and potentially gastrointestinal, metabolism plays a significant role in crizotinib elimination; however, non-metabolic pathways such as biliary excretion can not be excluded. The kidney appears to play an important role in the elimination of metabolites.

Clearance

The mean oral clearance of crizotinib is 100 L/hr after a single crizotinib dose of 250 mg. Lower CL/F on Day 15 of Cycle 1 (64.5 L/hr) and Day 1 of Cycle 2 (60.1 L/hr) indicated nonlinear PK characteristics, likely due to auto-inhibition of CYP3A. Crizotinib pharmacokinetics at steady state can not be predicted by the single dose PK data.

Half-Life ($T_{1/2}$)

Following a single 250 mg doses of crizotinib, the mean apparent terminal half life of crizotinib was 42 hours in patients and ranged from 29-35 hours in healthy subjects. It is noted that the apparent terminal $T_{1/2}$ was 94 hours in mass balance trial 1009, where PK samples were collected over a prolonged time.

Also see Sections 2.2.5.1 and 2.2.5.2.

2.2.5.9 Based on PK parameters, what is the degree of linearity or non-linearity based in the dose-concentration relationship?

Crizotinib demonstrated non-linear pharmacokinetics in humans. The systemic exposure of crizotinib increases with dose in a less-than-proportional manner after single dose over the range 50-300 mg (Table 9, Figure 9), but in a more-than-proportional manner at steady state after multiple doses (50-200 mg QD and 200-300 mg BID) (Table 9, Figure 10).

Multiple-dose pharmacokinetics of crizotinib can not be predicted by single-dose pharmacokinetics, possibly due to the time-dependent inhibition of crizotinib on CYP3A enzyme. However, no significant changes in steady state trough concentrations following 250 mg BID have been observed for up to four treatment cycles (Table 11, Figure 11).

Table 9. AUC and C_{max} after single and multiple doses of crizotinib during the dose escalation phase of trial 1001

	Dose (mg)	N	Study Day	C_{max} (ng/mL)	AUC_{inf} or AUC_{τ} (ng•hr/mL)
Single Dose	50	3	Day -7	24.2 (36)	274 (21)
	100	4	C1D1	54.9 (56)	NA
	200	15	Day -7 or C1D1	63.0 (55)	1268 (72)[a]
	250	9	Day -7 or C1D1	87.0 (34)	1817 (33)
	300	6	Day -7 or C1D1	117 (32)	2320[b]
Multiple Dose (QD)	50	3	C1D15	24.4 (52)	206 (64)
	100	4	C1D15	85.7 (69)	1087 (37)
	200	8	C1D15	149 (27)	2047 (48)
Multiple Dose (BID)	200	4	C1D15	189 (48)	1780 (61)
	250	5	C1D15	327 (25)	3084 (32)
	300	4	C1D15	420 (48)	4067 (55)

Source: Appendix A, Table 4.
Geometric mean (%CV) reported.
C = Cycle, D = Day, N = number of patients
AUC_{inf} for Single Dose; AUC_{τ} for Multiple Dose; τ = 24 hours for QD; τ = 12 hours for BID
[a]N=9; [b]N=1;

Source: Table 26 of Summary of Clinical Pharmacology (NDA 202570)

Dose proportionality following single dose of crizotinib

Using C_{max} and AUC obtained either on Day -7 or Day 1 of Cycle 1 from 36 patients in trial 1001, a power model was applied to test dose proportionality. The slope for the power model on logarithmic scale is 0.74 for C_{max} with a 90% confidence interval of (0.438, 1.034) and 0.72 for AUC with a 90% confidence interval of (0.37, 1.08). Therefore, the systemic exposure of crizotinib appears to increase with dose in a less than proportional manner over a range from 50 mg to 300 mg single dose of crizotinib.

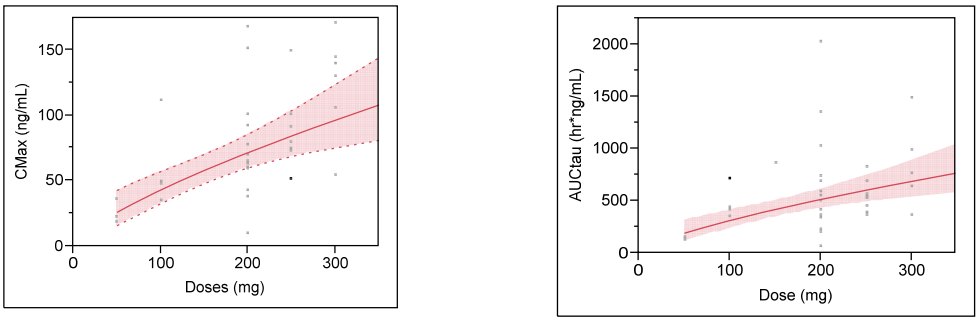


Figure 9: Crizotinib C_{max} (left) and AUC (right) in the lead-in period (Day -7) or Day 1 increased with dose with a slope of 0.74 (0.44, 1.03) for Cmax and 0.72 (0.37, 1.08) for AUC from 50 to 300 mg single dose of crizotinib. The shaded area is the 90% confidence interval of the slope.

Dose proportionality following multiple doses of crizotinib

Using C_{trough} and AUC_{tau} data (N=13) on Day 15 of Cycle 1 following BID doses in trial 1001, a power model was applied to test dose proportionality (Figure 10). The slope for the power model on logarithmic scale is 2.21 for C_{trough} with a 90% confidence interval of (0.50, 3.92) and 2.06 for AUC_{tau} with a 90% confidence interval of (0.64, 3.48). Therefore, the systemic exposure of crizotinib appears to increase with dose in a more-than-proportional manner over a dose range from 200 mg to 300 mg BID in patients. For QD dosing schedule, the slope (90% CI) of the power model is 1.54 (1.12, 1.97) for AUC_{tau} and 1.25 (0.81, 1.69) for C_{trough} in 15 patients. This non-linearity is possibly due to the time-dependent inhibition of crizotinib on CYP3A in patients.

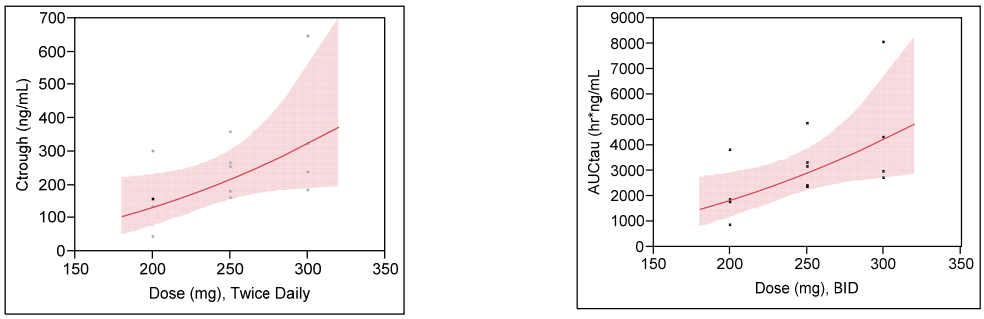


Figure 10: Crizotinib C_{trough} (left) and AUC_{tau} (right) on Day 15 of Cycle 1 following twice daily oral doses of crizotinib increased with doses, with a slope of 2.21 (0.50, 3.92) for Cmax and 2.06 (0.64, 3.48) for AUC_{tau} from 200 to 300 mg twice daily of crizotinib in 13 patients with advanced solid tumors

Accumulation following multiple doses

Crizotinib plasma concentrations appeared to reach steady state within 15 days after repeated oral administration of crizotinib (QD or BID) in trial 1001, with median accumulation ratios ranging from 1.6-3.8 and 3.9-5.3 after QD and BID dosing regimens, respectively (Table 10). An accumulation ratio of 4.5 (range: 4.4-8.7) was observed on day 15 following 250 mg crizotinib BID.

Table 10. Pharmacokinetic parameters of crizotinib during the dose escalation phase of trial 1001

Parameters, Units	Parameter Summary Statistics[a] by Crizotinib Treatment					
	50 mg QD	100 mg QD	200 mg QD	200 mg BID	250 mg BID	300 mg BID
Day -7 (single dose)						
N, n	3, 3		8, 7	5, 2	9, 8	1
T_{max}, hr	2.0 (1.8-4.1)	NA	4.1 (1.1-6.0)	4.0 (4.0-4.1)	4.0 (1.0-9.0)	2.02
C_{max}, ng/mL	24.2 (36)	NA	67.6 (60)	55.7 (46)	87.0 (34)	130
AUC_{τ}, ng*hr/mL	137 (8)	NA	659 (66)	338(46)	558 (33)	863
AUC_{inf}, ng*hr/mL	274 (21)	NA	1378 (69)	729; 1230	1817 (33)	2320
CL/F, L/hr	182 (21)	NA	145 (156)	163; 274	138 (32)	129
Vz/F, L	13144 (32)	NA	10010 (183)	12600; 20500	9230 (30)	8510
$t_{1/2}$, hr	50.2 (12)	NA	49.5 (28)	51.7; 53.5	47.1 (16)	45.7
Cycle 1 Day 1 (single dose)						
N		4		2		5
T_{max}, hr	NA	2.5 (1.0-4.0)	NA	4.0; 4.0	NA	4.0 (2.1-8.0)
C_{max}, ng/mL	NA	54.9 (56)	NA	63.3; 65.0	NA	114 (36)
AUC_{τ}, ng*hr/mL	NA	458 (34)	NA	357; 413	NA	764 (50)
Cycle 1 Day 15 (multiple doses)						
N	3	4	8	4	5	4
T_{max}, hr	2.0 (1.0-4.0)	2.5 (0.0-6.1)	4.1 (1.0-6.0)	5.0 (2.1-8.0)	4.0 (1.0-6.1)	5.0 (4.0-6.2)
C_{max}, ng/mL	24.4 (52)	85.7 (69)	149 (27)	189 (48)	327 (25)	420 (48)
C_{trough}, ng/mL	7.47 (4.81-10.8)	30.6 (23.5-52.4)	44.1 (30.8-160)	132; 183[b]	259 (159-356)[c]	279 (183-403)
AUC_{τ}, ng*hr/mL	206 (64)	1087 (37)	2047 (48)	1780 (61)	3084 (32)	4067 (55)
CL/F, L/hr	243 (63)	91.8 (27)	97.8 (44)	112 (61)	81.0 (28)	73.7 (42)
R_{ac}	1.61 (0.72-2.89)	2.36 (2.20-2.61)	2.80 (1.12-25.8)	4.85 (3.74-18.7)	4.53 (4.36-8.70)	4.87 (3.39-7.47)
Cycle 2 Day 1 (multiple doses)						
N	3	3	5	3	5	3
T_{max}, hr	1.0 (1.0-4.0)	4.0 (2.0-4.0)	4.0 (2.0-4.2)	4.0 (4.0-4.0)	4.0 (4.0-6.0)	4.1(4.0-9.0)
C_{max}, ng/mL	48.0 (21)	134 (49)	146 (34)	239 (12)	328 (25)	475 (43)
C_{trough}, ng/mL	8.75 (7.39-31.5)	29.7 (23.4-45.1)[c]	29.4 (0.631-38.1)	110; 178[b]	229 (228-378)[d]	255 (6.10-274)
AUC_{τ}, ng*hr/mL	426 (40)	1596 (31)	1719 (63)	2256 (13)	3054 (32)	3240; 4100[b]
CL/F, L/hr	117 (51)	62.6 (26)	116 (51)	88.5 (14)	81.8 (25)	73.3; 92.6[b]
R_{ac}	3.79 (1.98-3.97)	3.39 (3.14-3.83)	1.62 (1.46-3.13)	4.65 (4.18-4.88)	5.27 (3.73-8.77)	3.94 (3.75-4.13)

Source: CSR A8081001, Tables 13.5.1.6 and 13.5.2.1.

N=number of patients; n= number of patients where terminal $t_{1/2}$ was determined; NA=not applicable; CV=coefficient of variation; parameters defined in Table 4.

[a]Geometric mean (%CV) for all except: median (range) for T_{max}, C_{trough}, and R_{ac}, arithmetic mean (%CV) for $t_{1/2}$. [b]n=2; [c] n=4; [d] n=3. Note: individual values presented where N≤2

2.2.5.10 How do the PK parameters change with time following chronic dosing?

Cycle independence

No noticeable changes in $C_{trough, ss}$ of crizotinib and PF-06260182 were observed following 250 mg crizotinib BID over the treatment period of 112 days (Figure 11, Table 11).

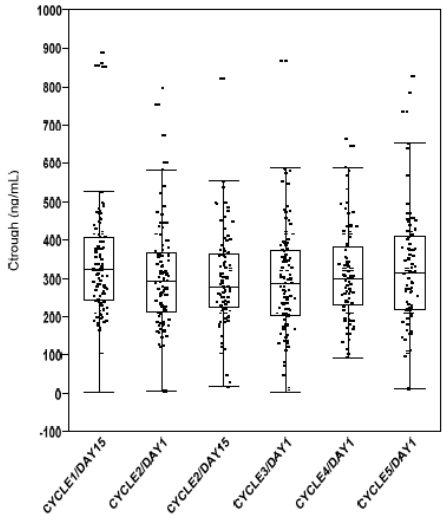


Figure 11: Cycle-independent steady state trough concentrations of crizotinib in patients with advanced solid tumors following 250 mg twice daily oral doses of crizotinib (Trial 1001)

Table 11. Median trough concentration (ng/mL) of crizotinib and active metabolite PF-06260182 following multiple 250 mg oral doses of crizotinib (trials 1001 and 1005)

Cohort	C1D15		C2D1		C2D15		C3D1		C4D1		C5D1	
	N	Ctrough	N	Ctrough	N	Ctrough	N	Ctrough	N	Ctrough	N	Ctrough
Crizotinib												
Trial A8081001												
Dose escalation	5	254 (159-356)	3	229 (228-378)	4	206 (107-326)	3	165 (156-295)	2	152;165		NA
RP2D all[b]	144	306 (1.48-1030)	137	279 (3.17-849)	107	278 (16.7-819)	116	271 (0.57-869)	99	298 (90.8-664)	91	310 (10.5-826)
ALK-positive NSCLC	102	321.5 (1.48-888)	104	292 (3.43-797)	90	278.5 (16.7-819)	101	286 (0.57-869)	92	298 (90.8-664)	85	314 (10.5-826)
ALK-negative NSCLC	3	333 (188- 346)	3	339 (263-569)		NA	1	218		NA		NA
Other	39	262 (31.2-1030)	30	249 (3.17-849)	17	288 (37.6-563)	14	238 (9.42-691)	7	236 (119-587)	6	179 (156-434)
Trial A8081005		NA	71	252 (1.38-622)		NA	66	276.5 (0.803-755)		NA	59	300 (1.77-857)
PF-06260182												
Trial A8081001												
RP2D all[c]	5	119 (47.5-186)	5	105 (71.0-111)	5	85.1 (71.0-142)	5	111 (77.6-142)	5	107 (86.3-174)	5	113 (105-131)
Trial A8081005		NA	71	58.3 (0.00-329)		NA	66	64.9 (0.00-229)		NA	59	65.1 (0-202)

N = number of observations; C_{trough} = trough (predose) concentration, C = Cycle, D = Day, NA = not applicable,
a: 28 days per cycle in Study A8081001 Dose escalation, RP2D ALK-positive NSCLC, and other; 21 days per cycles in Study A8081001 ALK negative NSCLC and Study A8081005
b: The overall summary for RP2D all includes the data from RP2D ALK-positive NSCLC and Other (28 days per cycle), and ALK-negative.NSCLC (21 days per cycle).
c All are ALK-positive patients

2.2.5.11 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

Moderate variability in crizotinib PK parameters has been observed in both healthy subjects and patients with advanced solid tumors. Following multiple oral crizotinib dosing of 250 mg BID, the coefficient of variation (%CV) is 36-38% and 38-44% for AUCτ and C_{max}, respectively. CV% values in AUC_{inf} and C_{max} range from 28% to 34% for oral administration compared to 18% to 19% following intravenous infusion (Trial 1010).

The variability may be attributable to the variation in extrinsic factors (concomitant medications, live styles, measurement errors in PK concentration) and intrinsic factors (e.g., bodyweight, race, gastro-intestinal pH variation, genetics, etc) in patients with cancers.

2.3 INTRINSIC FACTORS

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

No formal studies have been conducted to assess the effect of age, gender, race, body weight , height, BSA, renal or hepatic function on the pharmacokinetics and or response of crizotinib.

Body weight, race, and ECOG performance score were identified as significant covariates on the oral clearance (CL/F) of crizotinib in the population PK analysis. Body weight is positively correlated with CL/F of crizotinib with the flat dose of 250 mg BID, which at least in part explained the higher systemic exposure and response rate observed in Asians than that in Caucasians. The CL/F of crizotinib also differs between single dose and multiple doses of crizotinib, possibly due to auto-inhibition of CYP3A by crizotinib.

Of the 167 patients with evaluable PK data in RP2D cohort in trial 1001, 125 were non-Asian and 42 were Asian. Following a single 250 mg crizotinib dose, no overt differences in concentration-time profiles and PK parameters were observed between Asian and non-Asian patients. After 15 days of 250 mg BID dosing, crizotinib Cmax and AUCτ in Asian patients were, respectively, 1.57 (90% CI: 1.16-2.13) and 1.50 (90% CI: 1.10-2.04) fold those seen in non-Asian patients. Comparison of body weight- (BW-) and body surface area- (BSA-) adjusted crizotinib PK parameters suggests that body size may be a factor that influences the PK difference seen between Asian and non-Asian patients (Table 12).

Table 12. Pharmacokinetic parameters of crizotinib in Asian and non-Asian patients

Parameters, Units	PK Parameters		BSA Adjusted PK Parameters		BW Adjusted PK Parameters	
	Asian	Non-Asian	Asian	Non-Asian	Asian	Non-Asian
Day -7 (Single Dose)						
N	17	29	17	28	17	29
T_{max}, hr	6.00 (3.98-8.02)	4.00 (2.00-9.33)	NA	NA	NA	NA
C_{max}, ng/mL	108 (40)	109 (38)	97.1 (35)	113 (39)	88.5 (36)	114 (44)
AUC_{τ}, ng*hr/mL	724 (47)	752 (36)	652 (41)	781 (38)	594 (41)	786 (43)
AUC_{inf}, ng*hr/mL	2696 (46)[a]	2286 (57)[b]	2369 (42)[a]	2476 (51)[b]	2128 (43)[a]	2595 (50)[b]
CL/F, L/hr	92.7 (54)[a]	109 (46)[b]	105 (57)[a]	101 (46)[b]	117 (61)[a]	96.3 (50)[b]
V_z/F, L	5127 (58)[a]	6969 (62)[b]	5834 (65)[a]	6432 (61)[b]	6492 (70)[a]	6134 (63)[b]
$t_{1/2}$, hr	39.3 (19)[c]	45.7 (21)[a]	NA	NA	NA	NA
Cycle 1 Day 1 (Single Dose)						
N	24	74	24	73	24	74
T_{max}, hr	6.00 (2.00-9.00)	4.01 (1.00-9.08)	NA	NA	NA	NA
C_{max}, ng/mL	130 (34)	90.5 (47)	116 (40)	93.7 (45)	107 (48)	93.6 (47)
AUC_{τ}, ng*hr/mL	946 (34)[d]	598 (45)[e]	869 (34)[d]	619 (44)[f]	809 (39)[d]	621 (47)[e]
Cycle 1 Day 15 (Multiple Dose)						
N	13	11	13	11	13	11
T_{max}, hr	4.03 (0.00-9.03)	2.17 (1.00-8.62)	NA	NA	NA	NA
C_{max}, ng/mL	506 (23)	322 (67)	439 (22)	318 (58)	393 (23)	315 (52)
AUC_{τ}, ng*hr/mL	4696 (11)[g]	3137 (55)[h]	3974 (14)[g]	3067 (47)[h]	3460 (21)[g]	3039 (41)[h]
CL/F, L/hr	53.3 (12)[g]	79.7 (58)[h]	62.9 (17)[g]	81.5 (51)[h]	72.3 (25)[g]	82.2 (47)[h]
R_{ac}	4.92 (3.06-13.1)[h]	4.75 (3.30-8.00)[i]	NA	NA	NA	NA
Cycle 2 Day 1 (Multiple Dose)						
N	12	6	12	6	12	6
T_{max}, hr	6.00 (2.00-9.02)	3.98 (0.00-4.00)	NA	NA	NA	NA
C_{max}, ng/mL	535 (26)	381 (63)	469 (28)	378 (51)	426 (33)	376 (44)
AUC_{τ}, ng*hr/mL	4491 (23)[g]	3671 (60)	3875 (20)[g]	3645 (49)	3467 (23)[g]	3622 (42)
CL/F, L/hr	55.7 (22)[g]	68.1 (56)	64.5 (20)[g]	68.6 (50)	72.1 (25)[g]	69.0 (46)
R_{ac}	4.75 (2.75-15.4)[h]	4.80 (4.31-6.93)[j]	NA	NA	NA	NA

Source: CSR A8081001, Table 13.5.2.2c

N=number of patients; NA=not applicable; T_{max}=time to C_{max}; R_{ac}=accumulation ratio; BSA=body surface area; BW=body weight; CV=coefficient of variation; PK=pharmacokinetic; RP2D=recommended Phase 2 dose;

Geometric mean (%CV) for all except: median (range) for T_{max} and R_{ac}, arithmetic mean (%CV) for $t_{1/2}$

[a] n=15; [b] n=14; [c] n=16; [d] n=20; [e] n=68; [f] n=67; [g] n=10; [h] n=9; [i] n=7; [j] n=4

Source: Table 17 of Clinical Pharmacology Summary of NDA 202570

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

No dose adjustment is needed for patients with mild and moderate renal impairment. No dose adjustments can be recommended for the special populations including with hepatic impairment or severe renal impairment. PMRs will be required to conduct a multiple dose trial to determine the appropriate crizotinib dose in patients with various degrees of hepatic impairment, and in patients with severe renal impairment.

2.3.2.1 Pediatric patients

Safety and effectiveness of crizotinib have not been established in pediatric patients. A full pediatric waiver has been granted by FDA on May 11, 2011, as crizotinib has been designated as an orphan drug for the treatment of ALK-positive NSCLC.

2.3.2.2 Body size

Low body weight may be related with low plasma clearance and subsequent higher systemic exposure and possible higher ORR. See Sections 2.2.4, 2.3.1 for more information.

2.3.2.3 Sex

No significant difference in the $C_{trough, ss}$ was observed between males and females (Figure 12).

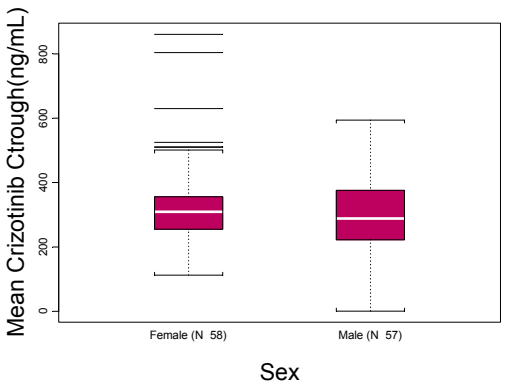


Figure 12: The effect of sex on the $C_{trough, ss}$ of crizotinib in patients with ALK-positive NSCLC following oral 250 mg of crizotinib twice daily.

2.3.2.4 Elderly

Age was not identified as a significant covariate in population pharmacokinetic analysis.

2.3.2.5 Hepatic impairment

No formal hepatic impairment trials have been conducted. Clinical trials 1001 and 1005 excluded patients with ALT or AST >2.5 x ULN, or if due to underlying malignancy, > 5.0 x ULN or with total bilirubin >1.5 x ULN. Population PK analysis did not select transaminases as significant covariates influencing crizotinib.

As crizotinib is extensively metabolized by CYP 3A in liver, liver dysfunction is expected to increase the plasma concentrations of crizotinib. A PMR will be required to conduct a multiple dose trial to determine the appropriate crizotinib dose in patients with various degrees of hepatic impairment. This trial should be conducted as a multiple dose trial due to the non-linear pharmacokinetics of crizotinib that was possibly caused by time-dependent inhibition of CYP3A.

2.3.2.6 Renal impairment

No formal trial has been conducted in patients with renal impairment. Clinical trials 1001 and 1005 excluded patients with serum creatinine > 2 x ULN.

The FDA conducted analysis using mean $C_{trough,\ ss}$ and baseline creatinine clearance obtained from the clinical trial 1001. Results indicated a trend of increasing $C_{trough,ss}$ with decreasing creatinine clearance (CLcr) (Figure 13, Figure 14). However, due to the small magnitude of the increase in either mild (60 mL/min ≤ creatinine clearance (CLcr) < 90 mL/min, N=47) renal impairment or moderate (30 mL/min ≤ CLcr < 60 mL/min, N=27) renal impairment groups compared to the normal renal function group (CLcr ≥ 90 mL/min, N=33), no dose adjustment is needed for such two groups. In addition, no recommendation can be made for the dose adjustment in patients with severe renal impairment, based on the limited data available (N=1).

A PMR will be requested to conduct a multiple dose trial to determine the appropriate crizotinib dose in patients with severe renal impairment. This trial should be conducted as a multiple dose trial due to the non-linear pharmacokinetics of crizotinib that was possibly caused by time-dependent inhibition of CYP3A.

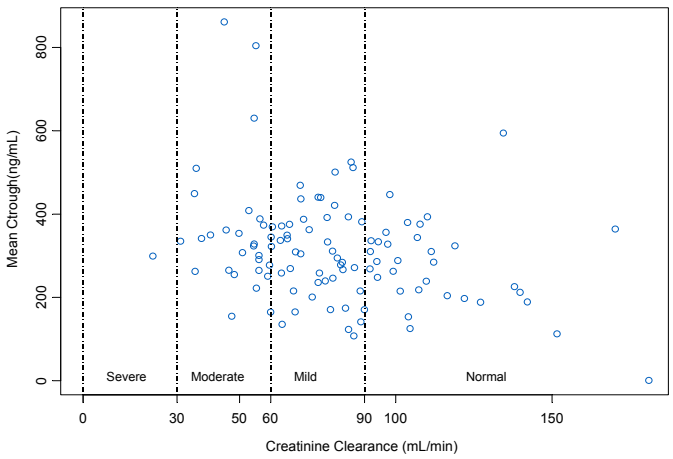


Figure 13: The effect of renal function on the $C_{trough,ss}$. Each dot represents one patient baseline creatinine clearance (CLcr), which was defined as normal renal function (CLcr ≥ 90 mL/min, N=33), mild (60 mL/min ≤ creatinine clearance (CLcr) < 90 mL/min, N=47), moderate (30 mL/min ≤ CLcr < 60 mL/min, N=27), and severe (CLcr < 30 mL/min, N=1) renal impairment.

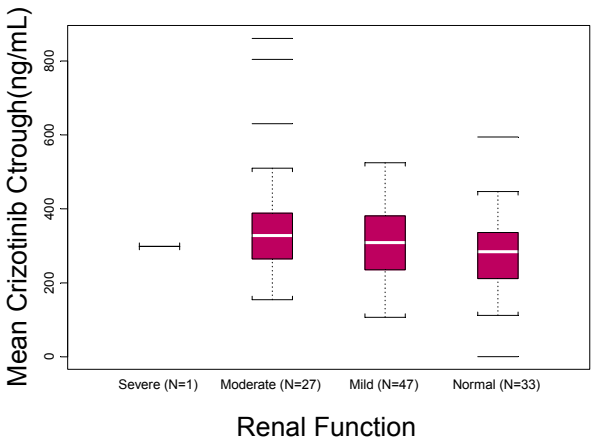


Figure 14: The box-plot of mean crizotinib trough concentration at steady-state versus renal function groups. Based on each patient's baseline creatinine clearance (CLcr), renal function groups are defined as normal renal function (CLcr ≥ 90 mL/min, N=33), mild (60 mL/min ≤ creatinine clearance (CLcr) < 90 mL/min, N=47), moderate (30 mL/min ≤ CLcr < 60 mL/min, N=27), and severe (CLcr < 30 mL/min, N=1) renal impairment.

2.3.2.7 Race/Ethnicity

After 250 mg twice daily dosing, steady-state crizotinib C_{max} and AUC_{τ} in Asian patients were 1.57- (90% CI: 1.16-2.13) and 1.50- (90% CI: 1.10-2.04) fold of those seen in non-Asian patients, respectively. Also see Section 2.3.1.

2.3.2.8 What pregnancy and lactation use information is there in the application?

Crizotinib is pregnancy category D drug. Crizotinib can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of crizotinib in pregnant women. In non-clinical studies in rats and rabbits crizotinib was embryotoxic and fetotoxic at exposures similar to and above those observed in humans at the recommended clinical dose of 250 mg BID.

2.4 EXTRINSIC FACTORS

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

Extrinsic factors that may affect the dose-exposure and/or dose–response relationship of crizotinib include CYP3A inhibitors, CYP3A inducers, and/or gastric pH elevating agents. High-fat meal decreases the systemic exposure of crizotinib by 15% in patients after a single dose of crizotinib in patients. Other extrinsic factors such as herbal products, smoking or alcohol use have not been evaluated in formal clinical studies.

2.4.2 Drug-drug interactions

2.4.2.1 Is there an *in vitro* basis to suspect *in-vivo* drug-drug interactions?

Yes. *In vitro* bases exist for potential *in vivo* drug-drug interactions between crizotinib with CYP3A inhibitors and inducers, CYP3A substrates, P-gp substrates, and gastric pH elevating agents.

CYP3A4/5 are identified as the major CYP isozymes responsible for the metabolism of crizotinib. Inhibitors and inducers of CYP3A are expected to affect the pharmacokinetics of crizotinib, which was confirmed by *in vivo* studies with ketoconazole and rifampin. See Sections 2.2.5.7, and 2.4.2.7.

Crizotinib was identified as an inhibitor of CYP3A (IC_{50} = 7.3 μM for testosterone) *in vitro*. Furthermore, crizotinib showed time-dependent inhibition on CYP3A isozymes in human liver microsomes with a k_{inact} of 0.11 min^{-1} and K_I of 3.0 μM. Therefore, crizotinib has a potential to increase plasma concentrations of co-administered drugs that are substrates of CYP3A. This was confirmed by the inhibitory effect of multiple doses of crizotinib on the metabolism of midazolam, and the decrease of oral clearance of crizotinib itself. See Sections 2.4.2.3, and 2.4.2.7.

Crizotinib was identified as an inhibitor of P-glycoprotein (P-gp) *in vitro*. Therefore, crizotinib has a potential to increase plasma concentrations of co-administered drugs that are substrates of P-gp. See Section 2.4.2.4.

As the aqueous solubility of crizotinib is pH dependent, with higher pH resulting in lower solubility. Drugs that elevate the gastric pH (e.g., a proton-pump inhibitor, an H2-receptor antagonist, or an antacid) may decrease the solubility of crizotinib and subsequently reduce its bioavailability. No formal drug interaction study has been conducted.

Also see Section 2.1.1.

2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

Yes. Crizotinib is a substrate of CYP3A4/5, and the polymorphisms of (b) (4) may affect the metabolism of crizotinib in humans.

Approximately 84% to 99% of the overall hepatic clearance is attributed to CYP3A4/5 and the remaining contribution could be attributed to CYP2C19 and CYP2D. Due to the minor contribution of CYP2C19 and CYP2D6 in the metabolism of crizotinib, the genetic polymorphisms of (b) (4) are not expected to significantly influence the

metabolism of crizotinib in humans.

Also see Section 2.2.5.7.

2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

Yes, crizotinib is an inhibitor of CYP3A *in vitro* and *in vivo*. Crizotinib also induces the mRNA expression of CYP3A, but no induction of CYP3A enzyme activity was observed *in vitro*. A PMR will be required to submit the on-going *in vitro* evaluation of induction potential of crizotinib on CYP2B and CYP2C enzymes.

In-vitro inhibition

Crizotinib is not an inhibitor for CYP1A2, CYP2C8, CYP2C19, or CYP2D6 *in vitro* (Table 13). However, crizotinib demonstrated inhibitory effect on CYP3A with IC_{50} values of 8.2 μM, and 7.3 μM, for felodipine oxidase and testosterone 6β-hydroxylase activities, respectively. Accordingly, the [I]/Ki ratios are estimated as > 0.1, given the observed mean C_{max} at steady state of 411 ng/mL (0.91 μM) on Day 15 of Cycle 1 following 250 mg BID (Table 5). Therefore, *in vivo* drug interactions with CYP3A substrates is likely.

Table 13. Inhibitory effect of crizotinib on CYP isozymes in human liver microsomes

CYP Isozyme	Substrate Activity	IC_{50} (μM) (Mean ±SE)	[I]/IC_{50}
CYP1A2	Phenacetin *O*-	>30	NA
CYP2B6	Bupropion hyd	22 ± 2	0.04
CYP2C8	Amodiaquine *N*	>30	NA
CYP2C9	Diclofenac 4'-h	23 ± 2	0.04
CYP2C19	S-Mephenytoin	>30	NA
CYP2D6	Dextromethorp	>30	NA
CYP3A	Felodipine oxic	8.2 ± 1.3	0.11
CYP3A	Midazolam 1'-h	>30	NA
CYP3A	Testosterone 6	7.3 ± 0.7	0.13

Note: [I] is 411 ng/nL (0.91 μM), the observed mean $C_{max,ss}$ in patients with advanced solid tumors (N=24) at Day 15 of Cycle 1 following 250 mg twice daily.

Source: Modified from Table 1 of Study 153034 Report

In-vitro time-dependent inhibition

Time-dependent inactivation of CYP3A by crizotinib was characterized by preincubating crizotinib for up to 40 minutes at various concentrations in human liver microsomes (0.5 mg/mL protein). The formation of l'-hydroxy-midazolam from midazolam was used as a marker for CYP3A activity. The maximum rate of inactivation (k_{inact}) and inhibitor concentration associated with the 50% maximal inactivation rate (K_I) for CYP3A were estimated to be was 0.11 min^{-1} and 3.0 μM, respectively (Figure 15).

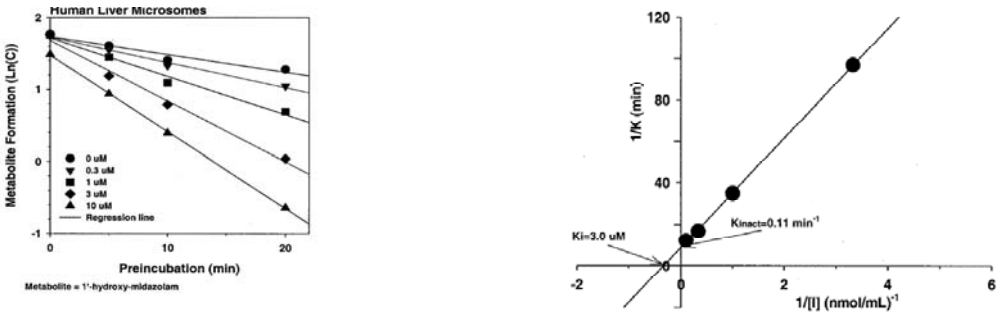


Figure 15: Effect of pre-incubation with crizotinib on CYP3A activity (left) and Kitz-Wilson plot (right) for CYP3A inactivation in human liver microsomes.

Source: Figures of Study PDM-017 report

***In vivo* inhibition:**

The potential of crizotinib to inhibit CYP3A in humans was confirmed in a clinical drug interaction assessment in patients with advanced solid tumors. Co-administration of crizotinib (250 mg BID for 28 days) with midazolam (2 mg, single oral dose), a sensitive probe CYP3A substrate, increased midazolam plasma AUC by 3.7 fold, indicating that crizotinib inhibits CYP3A *in vivo*.

See Section 2.4.2.7.

***In vitro* induction**

The potential of crizotinib to reduce plasma concentrations of co-administered CYP3A or CYP1A2 substrates *in vivo* is low. Crizotinib induces CYP3A mRNA expression but no changes were observed in the enzymatic activity *in vitro*. Assessment of induction potential of crizotinib on CYP2B or CYP2C enzymes is on-going. A PMR will be required to submit this study report.

In vitro study 153446 investigated the potential of crizotinib to induce CYP3A4 (probe testosterone) and CYP1A2 (probe resorufin) in three lots of cryopreserved human hepatocytes. Crizotinib did not induce either CYP3A or CYP1A2 enzyme activity. However, crizotinib caused marked induction of CYP3A4 based on mRNA levels in human cryopreserved hepatocytes at concentrations up to 7 µM (3150 ng/mL) (Table 14). This lack of CYP3A4 activity induction is likely due to the crizotinib-mediated time-dependent inhibition of CYP3A4.

In vivo, co-administration of crizotinib increased midazolam plasma AUC, indicated crizotinib-mediated CYP3A inhibition rather than induction.

Table 14. Summary of CYP3A induction potential of crizotinib three lots of cryoperserved human hepatocytes

	Activity data		mRNA	
Human Hepatocytes	**EC_{50} (uM)**	**E_{max}**	**EC_{50} (uM)**	**E_{max}**
Lot HIE	N/A	N/A	0.47	6.4
Lot Hu8020	N/A	N/A	0.79	23
Lot Hu4026	N/A	N/A	3.1	29

N/A Not applicable

Source: Study 153446 report

2.4.2.4 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

P-glycoprotein Substrate

Yes. Crizotinib is a substrate of P-glycoprotein (P-gp).

Table 15. Permeability and bi-directional transport of crizotinib (PF-02341066) using wild-type, human MDR1 or BCRP-transfected Madin-Darby canine kidney (MDCK) cells

PF-02341066 Conc. (μM)	MDCK			MDR1-MDCK			BCRP-MDCK		
	Mean AB Papp[a]	Mean BA Papp[a]	BA/AB Ratio[b]	Mean AB Papp[a]	Mean BA Papp[a]	BA/AB Ratio[b]	Mean AB Papp[c]	Mean BA Papp[c]	BA/AB Ratio[b]
0.1	4.07	17.1	4.20	1.26	28.4	22.5	1.38	1.02	0.74
0.5	2.75	17.4	6.33	0.93	31.2	33.6	0.96	1.03	1.07
2	3.56	17.5	4.92	1.22	24.2	19.8	1.66	2.13	1.28
5	4.67	15.7	3.36	2.37	25.2	10.6	2.70	2.90	1.07
10	4.63	13.2	2.85	2.76	19.8	7.17	3.87	4.15	1.07
15	5.05	12.6	2.50	3.34	21.5	6.44	5.70	5.68	1.00
20	8.70	10.7	1.23	4.85	19.0	3.92	7.32	6.51	0.89
50	18.6	15.5	0.83	14.8	19.2	1.30	17.2	11.1	0.65
Control[d]	16.4	18.6	1.13	7.07	22.3	3.15	1.41	7.70	5.46

Additional Information:
[a]Apparent Permeability or Papp values are $\times 10^{-6}$ cm/sec.
[b]BA/AB Ratios of >2.5 are considered conclusive for active efflux (positive for substrate).
[c]BCRP-transfected cells are produced from a cell background of lower efflux-expressing MDCK cells.
[d]Data for quinidine is included to demonstrate functional MDR1 efflux and topotecan for BCRP.

Source: Table 1 of Study 174737 report

P-glycoprotein Inhibitor

In vitro, crizotinib is an inhibitor of P-gp mediated transport, with an estimated IC_{50} of 5.79 μM on digoxin efflux.

2.4.2.5 Are there other metabolic/transporter pathways that may be important?

The uptake of crizotinib into human hepatocytes *in vitro* was passive at concentrations of 1 to 25 μM (450 and 11,250 ng/mL) compared to complete inhibition of rosuvastatin uptake (positive control) by rifamycin, which indicated that crizotinib was not a substrate for hepatic uptake transporters (Study 194244).

Crizotinib-mediated inhibition of hepatic transporters OATP1B1 and OATP1B3 was evaluated *in vitro* in studies using cell lines expressing these human transporters and specific OATP probe substrates (Study 181858, Study 095303). Crizotinib demonstrated a weak, concentration-dependent inhibitory effect on pravastatin (OATP1B1 substrate) and rosuvastatin (OATP1B3 substrate) uptake, with IC_{50} values of 48 and 44 μM, respectively.

Crizotinib demonstrated weak inhibition of BCRP-mediated efflux of topotecan *in vitro*, with less than 42% inhibition observed at the highest concentration of 30 μM (13,500 ng/mL) (Study 182103).

Crizotinib has not been evaluated as a substrate for renal secretory transporters (organic cation transporter [OCT2], and organic anion transporters [OAT] 1 and 2).

2.4.2.6 Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?

No co-administration of other drugs are specified in the label, as crizotinib is indicated for the treatment ALK-positive NSCLC as a single agent treatment.

2.4.2.7 Are there any *in-vivo* drug-drug interaction study that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

Yes. The effects of coadministration of ketoconazole (a strong CYP3A inhibitor) and rifampin (a strong CYP3A inducer) on the PK and safety of a single dose crizotinib in healthy subjects have been evaluated in trials 1015 and 1016, respectively. Compared to crizotinib alone, the co-administration with ketoconazole increases AUC_{inf} and C_{max} of crizotinib by 216% and 44%, while the co-administration with rifampin decreases AUC_{inf} and C_{max} of crizotinib by 82% and 69%.

However, dose adjustments for the coadministration of CYP3A inhibitors or inducers can not be recommended based on the above available results due to the time-dependent pharmacokinetics of crizotinib. Therefore, PMRs will be requested to conduct multiple dose trials in humans to determine how to adjust the crizotinib dose when it is coadministered with a strong CYP3A inhibitor (e.g., ketoconazole) or a strong CYP3A inducer (e.g., rifampin).

Drug interaction with strong CYP3A inhibitor

Trial 1015 was an open-label, 2-period, 2-treatment, 1-sequence, crossover, single-dose study of crizotinib alone or with ketoconazole in the fasted state to healthy adult volunteers. Each subject receive treatments A (150 mg crizotinib on Day 1) followed by B (200 mg ketoconazole twice daily orally on an empty stomach from Day 1 to Day 16 for 16 days, 150 mg crizotinib on Day 4), with a washout period of at least 14 days.

Results suggested that compared to crizotinib administration alone, the co-administration of ketoconazole increases the AUC_{inf} and C_{max} of crizotinib by a mean of 216% and 44%, respectively (Figure 16,Table 16). AUC_{inf} and C_{max} of metabolite PF-06260182 was also increased by a mean of 417% and 61%, respectively(Table 16). The pharmacokinetic parameters of crizotinib and PF-06260182 were summarized in Table 17.

Table 16. Effect of multiple doses of ketoconazole on the pharmacokinetics of single dose of crizotinib and active metabolite PF-06260182

Parameter (units)	Test	Reference	Ratio (%, Test/Reference) of Adjusted Means	90% CI	
Crizotinib					
AUC_{inf} (ng·hr/mL)	3986	1260	316.36	286.17	349.73
AUC_{last} (ng·hr/mL)	3929	1197	328.31	296.42	363.63
C_{max} (ng/mL)	94.47	65.54	144.13	126.42	164.33
PF-06260182					
AUC_{inf} (ng·hr/mL)	920.6	178.1	516.98	457.88	583.72
AUC_{last} (ng·hr/mL)	897.4	172.7	519.65	460.42	586.50
C_{max} (ng/mL)	26.94	16.69	161.42	143.09	182.09

Note: Test = crizotinib 150 mg + ketoconazole 200 mg BID; reference = crizotinib 150 mg

Source: Adapted From Tables 13 and 15 in Trial 1015 report.

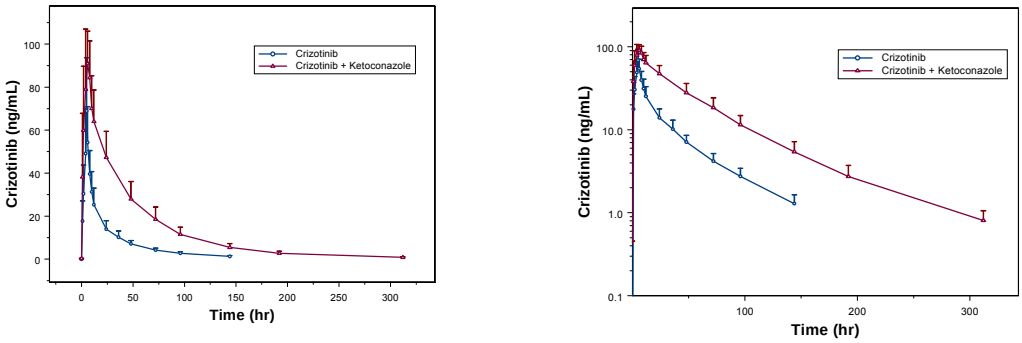


Figure 16: The time-concentration profiles of crizotinib in healthy subjects (N=15) on a normal scale (left) and on a semi-log scale (right), following a single 150 mg oral crizotinib dose alone or coadministered with 200 mg ketoconazole twice daily in a two-treatment, two period, one-sequence crossover design

Table 17. Pharmacokinetic parameters of crizotinib and active metabolite with and without multiple doses of ketoconazole

Pharmacokinetic Parameter (units)	Crizotinib 150 mg	Crizotinib 150 mg + Ketoconazole 200 mg BID
Crizotinib		
N	15	15
AUC_{inf} (ng·hr/mL)	1260 (25)	3986 (25)
AUC_{last} (ng·hr/mL)	1197 (25)	3929 (25)
CL/F (L/hr)	122.6 (26)	38.85 (27)
C_{max} (ng/mL)	65.54 (35)	94.47 (20)
T_{max} (hr)	5.0 (2.0-5.0)	6.0 (1.0-8.0)
VZ/F (L)	6580 (29)	3122 (36)
$t_{1/2}$ (hr)	37.13 (12)	54.87 (11)
PF-06260182		
N	15	15
AUC_{inf} (ng·hr/mL)	178.1 (31)	920.6 (35)
AUC_{last} (ng·hr/mL)	172.7 (31)	897.4 (35)
C_{max} (ng/mL)	16.69 (28)	26.94 (20)
T_{max} (hr)	5.0 (4.0-6.0)	8.0 (6.0-10.0)
$t_{1/2}$ (hr)	14.22 (47)	41.79 (22)
$MRAUC_{inf}$	0.1371 (14)	0.2239 (18)
$MRAUC_{last}$	0.1399 (14)	0.2217 (18)
MRC_{max}	0.2469 (25)	0.2766 (18)

Note: Geometric mean (%CV) for all except: median (range) for Tmax; arithmetic mean (%CV) for t½. MRCmax: Metabolite ratio Cmax; MRAUC: Metabolite ratio AUC.

Source: Adapted from Tables 12 and 14 in trial 1015 report.

Drug interaction with strong CYP3A inducer

Trial 1016 was an open-label, 2-period, 2-treatment, 1-sequence, crossover, single-dose study of crizotinib alone or with strong CYP 3A inducer rifampin in the fasted state to healthy adult volunteers. Each subject receive treatments A (250 mg crizotinib on Day 1), followed by B (600 mg rifampin once daily after overnight fasting from Day 1 to Day 14, and 250 mg crizotinib on Day 9), with a washout period of at least 14 days.

Compared to crizotinib alone, the co-administration of rifampin decreases the AUC_{inf} and C_{max} of crizotinib by an average 82% and 69%, respectively (Figure 17, Table 18). The AUC_{inf} and C_{max} of metabolite PF-06260182 was also decreased by a mean of 94% and 89%, respectively (Table 18). The ratios of metabolite (PF-06260182) to parent (crizotinib) in C_{max} and AUC were decreased by 65%-68% (Table 19).

Table 18. Effect of multiple doses of rifampin (600 mg once daily) on the single-dose pharmacokinetic parameters of crizotinib and active metabolite PF-06260182

Parameter (units)	Test	Reference	Ratio (%, Test/Reference)	90% CI
Crizotinib				
AUC_{inf} (ng·hr/mL)	399.2	2192	18.21	(16.14, 20.54)
AUC_{last} (ng·hr/mL)	370.3	2103	17.60	(15.48, 20.02)
C_{max} (ng/mL)	32.14	102.1	31.49	(26.43, 37.51)
PF-06260182				
AUC_{inf} (ng·hr/mL)	21.79	378.6	5.75	(4.86, 6.81)
AUC_{last} (ng·hr/mL)	20.28	369.5	5.49	(4.64, 6.49)
C_{max} (ng/mL)	3.291	29.88	11.01	(9.02, 13.45)

Note: Test = crizotinib 250 mg + Rifampin 600 mg QD; reference = crizotinib 250 mg

Source: Adapted from Tables 10 and 12 of trial 1016 report.

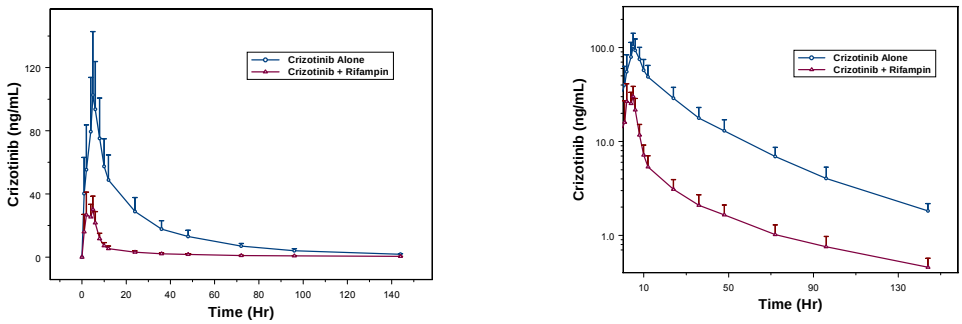


Figure 17: The time-concentration profiles of crizotinib in healthy subjects (N=15) on a normal scale (left) and on a semi-log scale (right), following a single 150 mg oral crizotinib dose alone or coadministered with 600 mg rifampin once daily in a two-treatment, two-period, one-sequence crossover design

Table 19. Single-dose pharmacokinetic parameters of crizotinib and active metabolite PF-06260182 with and without rifampin (600 mg once daily)

Pharmacokinetic Parameter (units)	Crizotinib 250 mg	Crizotinib 250 mg + Rifampin 600 mg QD
Crizotinib		
N	15	14
AUC_{inf} (ng*hr/mL)	2192 (27)	397.2 (26)
AUC_{last} (ng*hr/mL)	2103 (28)	368.6 (27)
C_{max} (ng/mL)	102.1 (33)	32.06 (33)
T_{max} (hr)	5.00 (4.00-6.00	3.00 (2.00-5.00)
t½ (hr)	33.07 (21)	48.23 (12)
CL/F (L/hr)	118.8 (31)	648.6 (25)
Vz/F (L)	5940 (55)	45720 (34)
PF-06260182		
N	15	14
AUC_{inf} (ng*hr/mL)	378.6 (30)	21.78 (39)
AUC_{last} (ng*hr/mL)	369.5 (31)	20.28 (38)
C_{max} (ng/mL)	29.88 (32)	3.291 (35)
T_{max} (hr)	5.00 (4.00-8.00	5.00 (2.00-6.00)
t½ (hr)	22.20 (14)	2.318 (16)
$MRAUC_{inf}$	0.1676 (16)	0.05319 (21)
$MRAUC_{last}$	0.1703 (15)	0.05332 (21)
MRC_{max}	0.2839 (24)	0.09958 (37)

Note: Geometric mean (%CV) for all except: median (range) for Tmax; arithmetic mean (%CV) for t½. MRCmax: Metabolite ratio Cmax; MRAUC: Metabolite ratio AUC.

Source: Adapted From Tables 9 and 11 in trial 1016 report.

Drug interaction with sensitive CYP3A substrate

The effect of multiple doses of crizotinib on a sensitive CYP3A substrate was evaluated in a sub-study of Trial 1001, where patients with advanced solid tumors received a single 2-mg oral dose of midazolam (MDZ, a sensitive CYP3A substrate) on Day -7 and again concurrently with crizotinib on Cycle 2 Day 1, at dose levels of 100 mg QD, 250 mg BID and 300 mg BID.

Compared to midazolam alone, the co-administration of crizotinib increases AUC_{inf} and C_{max} of crizotinib by an average of 116% and 32% , 265% and 102%, 250% and 139%, at dose levels of 100 mg QD, 250 mg BID, and 300 mg BID, respectively (Figure 18,Table 20).

Table 20. Pharmacokinetic parameters of plasma midazolam for pre- and post-crizotinib co-administration

Parameters, Units	N	Pretreatment Adjusted Geometric Mean	N	Posttreatment Adjusted Geometric Mean	Ratio (Post/Pre)	90% CI
100 mg QD of Crizotinib						
AUC_{inf}, ng*hr/mL	4	41.8	3	90.3	2.16	(1.61, 2.90)
C_{max}, ng/mL	4	15.0	3	19.7	1.32	(0.97, 1.80)
T_{max}, hr	4	0.53 (0.52-1.03)	3	1.00 (0.52-1.02)		
$t_{1/2}$, hr	4	5.19 (45)	3	7.22 (5)		
300 mg BID of Crizotinib						
AUC_{inf}, ng*hr/mL	5	37.7	2	132	3.50	(1.41-8.68)
C_{max}, ng/mL	5	13.7	2	32.6	2.39	(1.72, 3.32)
T_{max}, hr	5	0.50 (0.42-1.03)	2	0.77 (0.53-1.00)		
$t_{1/2}$, hr	5	5.36 (45)	2	5.69; 8.22		
250 mg BID of Crizotinib						
AUC_{inf}, ng*hr/mL	14	32.1	8	117	3.65	(2.63-5.07)
C_{max}, ng/mL	14	12.8	8	25.8	2.02	(1.39-2.92)
T_{max}, hr	14	0.50 (0.42-2.00)	8	0.50 (0.50-1.05)		
$t_{1/2}$, hr	14	4.38 (36)	8	7.80 (26)		

Source: Adapted from Tables 102-105 in trial 1001 study report.

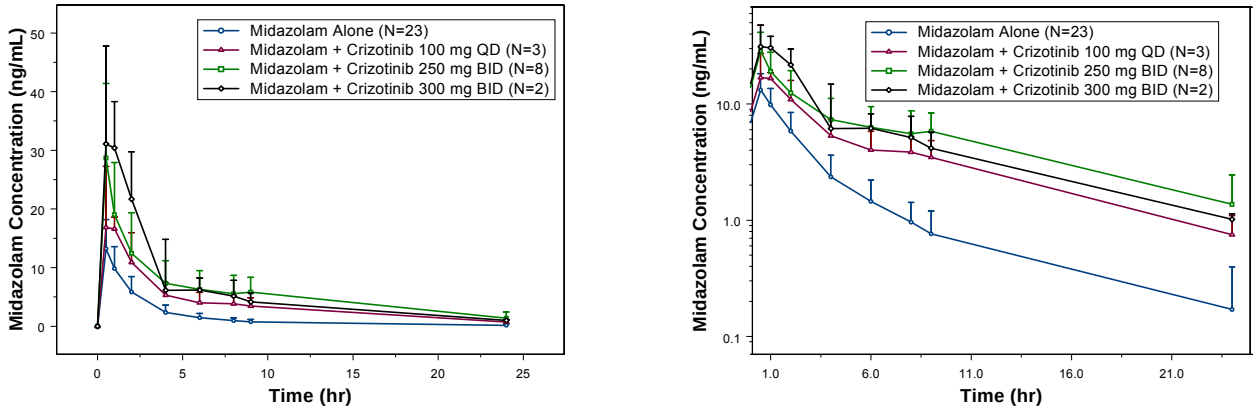


Figure 18: The time-concentration profiles of midazolam in patients with advanced solid tumor on a normal scale (left) and on a semi-log scale (right), following a single midazolam oral dose of 2 mg administered alone on Day -7 or concurrently with crizotinib on Day 29 at dose levels of 100 mg once daily, 250 mg twice daily, and 300 mg twice daily

2.5 GENERAL BIOPHARMACEUTICS

2.5.1 Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

Crizotinib is designated as a Biopharmaceutics Classification System (BCS) class 4 drug (low solubility and low permeability). However, it has not received official BCS classification/designation from the FDA.

Crizotinib was classified as a BCS class 4 compound because the maximum dose of 250 mg does not fully dissolve in 250 mL of buffers over the range of pH 1 to pH 6.8 (Table 1). Categorization of crizotinib as a low permeability drug is based on the observations of low permeability and the efflux transport across Caco-2 cell monolayer (Table 21). The efflux transport is partly sturable between 10 and 100 μM of crizotinib, likely due to saturable P-gp efflux transport (Table 15).

Table 21. Summary of Caco-2 cell permeability data for crizotinib

Assay	Permeability ($x10^{-6}$ cm/sec)		
	A->B	B->A	
Concentration Dependency			BA/AB
crizotinib (1 μM)	<LOQ	20.1 ± 7.0	nd
crizotinib (10 μM)	<LOQ	15.9 ± 2.3	nd
crizotinib (100 μM)	9.6 ±3.5	15.9 ± 0.4	1.65
crizotinib (10 μM at pH 6.4)	<LOQ	40.1 ± 5.4	nd
Paracellular Transport			
crizotinib (10 μM)	2.5 ± 0.8	nd	nd

Source: NDA submission Section 3.2.P.2.1 component of drug product

2.5.2 What moieties should be assessed in bioequivalence studies?

Crizotinib, the active ingredient of drug product, should be assessed in bioequivalence studies, based on the current knowledge. Also see Section 2.2.3.

2.5.3 What is the composition of the to-be-marketed formulation?

The commercial formulation is an immediate release formulated capsule (FC) for oral administration at 2 crizotinib dosage strengths of 200 mg and 250 mg. During the clinical development program, four additional crizotinib formulations (3 oral and 1 intravenous) were used: a powder in capsule (PIC), an immediate release (IR) tablet, an extemporaneously prepared oral suspension, and an intravenous (IV) solution.

The compositions of the to-be-marketed formulation (Formulated Capsule), PIC, IR, and IV formulations are listed in Table 22.

Table 22. Composition of clinical and to-be-marketed commercial crizotinib dosage forms

	Powder in Capsule (PIC)				Immediate Release (IR) Tablet		IV 5.0 mg/mL Solution[b]	Formulated Capsule		
Dosage Identification	D0502144	D0502145	D0804434	D0703126	D0904758	D0904759	D1005039	D1005259	D1005260	D1005261
Strength	10 mg	50 mg	50 mg	100 mg	50 mg	100 mg	5.0 mg/mL	150 mg	200 mg	250 mg
Drug Load	(b) (4)									
Crizotinib	10.00 mg	50.00 mg	50.00 mg	100.00 mg	50.00 mg	100.00 mg	5.02 mg/mL	150.00 mg	200.00 mg	250.00 mg
Excipients Colloidal Silicon Dioxide Microcrystalline Cellulose Anhydrous Dibasic Calcium Phosphate Sodium Starch Glycolate Magnesium Stearate (b) (4)	(b) (4)							(b) (4)		
Total										
Capsule Shell Description										
Capsule Shell Weight										
Total								361.0 mg	476.0 mg	596.0 mg

Source: Section 3.2.P.2.2 Drug Product
[a] The 10 mg PIC was shipped to A8081001 study sites but was not dispensed.
[b] Drug load refers to drug load of capsule fill
[c] Container closure for IV solution is a (b) (4)
Note: Study A8081009 dosed (b) (4)
(b) (4)
HG = hard gelatin

Source: NDA submission Section 3.2.P.2.2 drug product

2.5.4 What is the absolute bioavailability of crizotinib?

After oral dosing, crizotinib is absorbed with peak plasma concentration occurring between 4-6 hours under fasting conditions. The mean absolute bioavailability of a single dose of 250 mg oral crizotinib is 43% (range: 32% - 66%), when referring a single 50 mg dose of crizotinib administered via intravenous infusion over 2 hours (Trial 1010).

The absolute bioavailability crizotinib was evaluated an open-label, randomized, 2-period, 2-treatment, 2-sequence, crossover single-dose trial (Trial 1010). Each of fourteen healthy subjects received two treatments (A: 50-mg single IV dose of crizotinib administered as 200 mL of a 0.25 mg/mL IV solution over approximately 2 hours, B: 250-mg single oral dose of crizotinib administered in a fasted state with 240 mL of water) separated by a washout period of at least 14 days. The results for the crizotinib and active metabolite PF-06260182 are summarized in Table 23 and Table 24.

Table 23. Summary of plasma crizotinib pharmacokinetic parameters following 50 mg IV and 250 mg oral doses of crizotinib

	Parameter Summary Statistics[a] by Treatment	
Parameter (Units)	**Crizotinib 50 mg IV**	**Crizotinib 250 mg oral**
N[b]	14	14
AUC_{inf} (ng•hr/mL)	1067 (18)	2321 (34)
AUC_{last} (ng•hr/mL)	1007 (18)	2250 (35)
C_{max} (ng/mL)	155.0 (19)	99.60 (28)
T_{max} (hr)	1.92 (1.00 - 1.95)	5.00 (4.00 - 6.00)
$t_{1/2}$ (hr)	38.86 (16)	28.98 (10)
CL/F (L/hr)	NC	107.7 (32)
Vz/F (L)	NC	4478 (35)
CL (L/hr)	46.83 (18)	NC
Vss (L)	1772 (18)	NC
AUC_{inf}(dn) (ng•hr/mL/mg)	21.36 (18)	9.281 (34)
AUC_{last}(dn) (ng•hr/mL/mg)	20.14 (18)	8.998 (35)
C_{max}(dn) (ng/mL/mg)	3.101 (19)	0.3983 (28)

CV = coefficient of variation, hr = hour, NC = not calculated.
[a] Geometric mean (%CV) for all except: median (range) for T_{max} and arithmetic mean (%CV) for $t_{1/2}$.
[b] N = Number of subjects contributing to the mean.

Source: Table 13 of Trial 1010 final study report

Table 24. Summary of plasma PF-06260182 pharmacokinetic parameters following 50 mg IV and 250 mg oral doses of crizotinib

	Parameter Summary Statistics[a] by Treatment	
Parameter (Units)	**Crizotinib 50 mg IV**	**Crizotinib 250 mg oral**
N, n[b]	14	14, 13
AUC_{inf} (ng•hr/mL)	NC	360.4 (31)
AUC_{last} (ng•hr/mL)	35.61 (45)	342.7 (32)
C_{max} (ng/mL)	3.006 (45)	26.46 (24)
T_{max} (hr)	2.50 (1.92-4.02)	5.00 (5.00-6.07)
$MRAUC_{inf}$	NC	0.1440 (13)
$MRAUC_{last}$	0.03430 (31)	0.1477 (14)
MRC_{max}	0.01880 (36)	0.2577 (17)

CV = coefficient of variation, hr = hour, IV = intravenous, NC = not calculated.
[a] Geometric mean (%CV) for all except median (range) for T_{max}.
[b] N = Number of subjects in the treatment group, n = Number of subjects contributing to the mean.

Source: Table 15 of Trial 1010 final study report

2.5.5 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

The to-be-marketed formulation [formulated capsules (FC), also referred as commercial image capsule, (CIC)] is bioequivalent to both immediate release tablet (IRT) used in evaluating the MTD and safety of crizotinib (Trials 1001) and powder in capsule (PIC) used in trials 1001 and 1005.

Bioequivalence between CIC (250 mg strength) and IRT (50 mg and 100 mg strengths), CIC and PIC (50 mg and 100 mg strengths) were demonstrated in trial 1011, with a 4-period, 4-treatment (PIC, IRT, CIC under fasted state, and CIC under fed state), 4-sequence, cross-over design in 35 healthy adult subjects. The results are summarized in Table 25.

Table 25. Summary of the bioequivelence between commercial image capsule (CIC), and immediate release tablet (IRT), between CIC and powder in capsule (PIC) following 250 mg oral doses of crizotinib in 35 healthy subjects

	Adjusted Geometric Means			
Parameter (units)	Test	Reference	Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
Crizotinib CIC Fasted (Test) vs. Crizotinib IRT Fasted (Reference)				
AUC_{inf} (ng·hr/mL)	2886	2899	99.56	(91.49, 108.33)
AUC_{last} (ng·hr/mL)	2758	2769	99.60	(91.30, 108.66)
C_{max} (ng/mL)	134.6	125.9	106.97	(96.55, 118.51)
Crizotinib CIC Fasted (Test) vs. Crizotinib PIC Fasted (Reference)				
AUC_{inf} (ng·hr/mL)	2886	2699	106.93	(98.26, 116.35)
AUC_{last} (ng·hr/mL)	2758	2564	107.56	(98.58, 117.35)
C_{max} (ng/mL)	134.6	120.9	111.32	(100.47, 123.33)

CI=confidence interval; CIC = commercial image capsule; IRT = immediate-release tablet; PIC = powder-in-capsule
[a] The ratios (and 90% CIs) are expressed as percentages.

Source: Table 13 of Trial 1011 final study report

In addition, bioequivalence between IRT (50 mg and 100 mg strengths), and PIC (50 mg and 100 mg strengths) was demonstrated trial 1008, with a traditional 2-period, 2-treatment, 2-sequence, cross-over design in 24 healthy adult subjects. The results are summarized in Table 26.

Table 26. Summary of the bioequivelence between immediate release tablet (IRT), and powder in capsule (PIC) following 250 mg oral doses of crizotinib in healthy subjects

	Adjusted Geometric Means			
Parameter (units)	Test	Reference	Ratio (Test/Reference) of Adjusted Means [a]	90% CI for Ratio [a]
PF-02341066 IRT 250 mg (Test) vs PF-02341066 PIC 250 mg (Reference)				
AUC_{inf} (ng*hr/mL)	2722.51	2945.49	92.43	84.86, 100.68
AUC_{last} (ng*hr/mL)	2597.26	2804.51	92.61	84.84, 101.09
C_{max} (ng/mL)	112.11	113.35	98.91	90.18, 108.48

[a] The ratios (and 90% CIs) are expressed as percentages.
CI = confidence interval; PIC = powder-in-capsule; IRT = immediate-release tablet; AUC = area under the plasma concentration-time curve; AUC_{inf} = AUC from time 0 extrapolated to infinite time; AUC_{last} = AUC from time 0 to the time of the last quantifiable concentration; C_{max} = maximum observed concentration.

Source: Table 12 of trial 1008 final study report

2.5.6 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Compared to fasting state, a standard high-fat meal decreases the systemic exposure by an average of 15% following single 250 mg dose of crizotinib in patients with advanced solid tumors (Trial 1001) and in healthy subjects (Trial 1011). This magnitude of decrease in the bioavailability is not considered as clinically significant. Therefore, crizotinib may be taken with or without food.

Food effect in patients:

In the food effect sub-study of Trial 1001 using the CIC dosage form, 12 patients with solid tumors received a 250-mg dose of crizotinib under either the "fed" or "fasted" conditions on Day -7 and Cycle 1 Day 1. The evening dose of Cycle 1 Day 1 was cancelled for these patients. The fed/fasted ratios of the geometric means for crizotinib exposure were 84.64% (90% CI: 65.11%-110.05%) for AUC_{24hrs} and 87.65% (90% CI: 69.23%-110.98%) for C_{max} (Table 27).

Table 27. Summary of the effects of a standard high-fat meal on the pharmacokinetics parameters of crizotinib following a 250 mg oral dose of crizotinib in patients with advanced solid tumors

Parameters, Units	Parameter Summary Statistics[a] by Treatment	
	Fed	Fasted
N, n	11, 8	12, 10
AUC_{24}, ng*hr/mL	1213 (42)	1307 (31)
C_{max}, ng/mL	106 (45)	119 (23)
T_{max}, hr	4.18 (4.00-8.03)	4.00 (4.00-6.08)

Notes: N= number of patients; n= number of patients where AUC_{24} was determined.

Food effect in healthy subjects:

The effect of a standard high-fat meal on the single dose PK of crizotinib was evaluated in Trial 1011 using the CIC dosage form in 35 healthy subjects. Based on the ratios of the adjusted geometric means (fed/fasted), the coadministration of a high fat meal decreased both AUC_{inf} and C_{max} of approximately 14%. The ratios (fed/fasted) of geometric mean for AUC_{inf} and C_{max} were 85.76% with 90% CI [78.88%, 93.25%] and 86.22 with 90% CI [77.89%, 95.43%], respectively (Table 28).

Table 28. Summary of the effect of a standard high-fat meal on the pharmacokinetics of crizotinib following a 250 mg oral dose of crizotinib in healthy subjects

	Adjusted Geometric Means			
Parameter (units)	Test	Reference	Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
	Crizotinib CIC Fed (Test) vs. Crizotinib CIC Fasted (Reference)			
AUC_{inf} (ng·hr/mL)	2475	2886	85.76	(78.88, 93.25)
AUC_{last} (ng·hr/mL)	2359	2758	85.52	(78.45, 93.22)
C_{max} (ng/mL)	116.1	134.6	86.22	(77.89, 95.43)

Notes: CI=confidence interval; CIC = commercial image capsule; The ratios (and 90% CIs) are expressed as percentages.

Source: Table 13 of Trial 1011 final study report

See Section 2.5.5.

2.5.7 Has the applicant developed an appropriate dissolution method and specification that will assure *in-vivo* performance and quality of the product?

The dissolution method and specification were appropriate to assure the quality of the product, but were not predictive of *in vivo* performance. Please refer to biopharmaceutical review by Dr. Kareen Riviere for more information.

2.6 ANALYTICAL SECTION

(b) (4)

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

3 DETAILED LABELING RECOMMENDATIONS

Only relevant clinical pharmacology sections are included. Double underlines indicate the content that was added to the proposed label by the Agency and ~~strikethroughs~~ indicate content taken out from the proposed label by the Agency.

(b) (4)

6 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

4 PHARMACOMETRIC REVIEW

OFFICE OF CLINICAL PHARMACOLOGY:

PHARMACOMETRIC REVIEW

Application Number	NDA 202570
Submission Number (Date)	March 31, 2011
Compound (Dosing Regimen)	Crizotinib (250 mg orally BID)
Clinical Division	DDOP
Primary PM Reviewer	Anshu Marathe, Ph.D.
Secondary PM Reviewer	Christine Garnett, Pharm.D.

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following key questions.

1.1.1 Is there evidence of exposure-response relationship for objective response rate (ORR)?

Yes, there is evidence of exposure-response relationship for ORR in trials A8081005 and A8081001.

An exposure-response analysis was conducted for ORR in trials A8081005 and A8081001. Patients with pharmacokinetic samples (N=120 in A8081005, N=114 in A8081001) were divided into quartiles based on their steady state trough concentrations and the proportion of patients with response were determined for each quartile (Figure 1). Higher ORR of approximately 60% is observed in the patients with higher drug exposure in the upper quartiles compared to a lower response rate of 47% in the lower quartiles (Table 1) in A8081005. In A8081001, the ORR was 24% in the lowest quartile, while the response rate was 75% or greater in the upper three quartiles (Table 2). Similar results were obtained when the population predicted average steady state concentration (Cavg,ss) was used as the exposure measure (Table 16 and Table 17).

However, the difference in ORR is not only due to crizotinib concentrations but is also likely due to other confounding factors that are not balanced between the quartiles. The distribution of certain covariates in various concentration quartiles is shown in Table 3 and Table 4. Asian patients had higher drug exposures and thus there was a higher proportion of Asians in the highest quartile compared to the lowest quartile. Also there was a higher proportion patients with ECOG status 2 in the highest quartile compared to the lowest quartile. To account for these confounding factors, a logistic regression analysis was conducted that included all these factors. A step-wise logistic regression analysis identified log-transformed Ctrough as significant predictor of response in trial A8081001. In trial A8081005, log-transformed Cavg,ss was identified as a significant predictor of response (Table 5). Sponsor's analysis also identified these as significant predictors. In A8081005, use of CYP3 inhibitors was also found to be a predictor. However there was no effect of CYP3 inhibitors on drug concentrations and thus the mechanism for this finding is unclear.

Trial A8081005 Trial A8081001

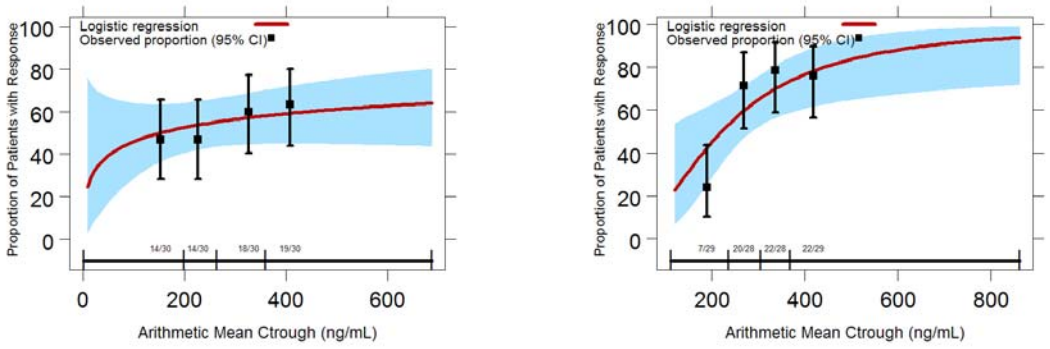


Figure 1: The proportion of patients with ORR versus mean steady state trough concentrations of Crizotinib in trial A8081005 and A8081001. Solid black symbols represent the observed percentage of patients responding to treatment in each C_{trough} quartile. The vertical black bars represent the 95% confidence interval. The exposure range in each C_{trough} quartile is denoted by the horizontal black line. Mean C_{trough} represents the arithmetic mean of the observed C_{trough} in various cycles after steady state was reached. *Source codes: CrizotinibER1005.ssc, CrizotinibER1001.ssc*

Table 1: ORR by mean steady state trough concentration quartiles in trial A8081005

Mean C_{trough} group*	Median Concentration (ng/ml)	Number of subjects	Number of responders	Response rate	Lower 95% CI	Upper 95 %CI
1	153	30	14	47	28	66
2	227	30	14	47	28	66
3	327	30	18	60	41	77
4	408	30	19	63	44	80

Mean C_{trough} represents the arithmetic mean of the observed C_{trough} in various cycles after steady state was reached. Source code: CrizotinibER1005.ssc

Table 2: ORR by mean steady state trough concentration quartiles in trial A8081001

Mean C_{trough} group*	Median Concentration (ng/ml)	Number of subjects	Number of responders	Response rate	Lower 95% CI	Upper 95%CI
1	189	29	7	24	10	44
2	269	28	20	71	51	87
3	336	28	22	79	59	92
4	418	29	22	76	56	90

** Mean C_{trough} represents the arithmetic mean of the observed C_{trough} in various cycles after steady state was reached. Source code: CrizotinibER1001.ssc*

Table 3: Summary of demographics by mean steady state trough concentration quartiles in trial A8081005

Demographics	**Concentration quartile1**	**Concentration quartile 2**	**Concentration quartile 3**	**Concentration quartile 4**
Continuous (Median)				
Age (years)	55	53	51	51
Wt (Kg)	69	71	65	60
Sum of longest diameters (mm) categorical	68	78	81	64
Categorical (% of subjects)				
Asian	17	27	40	53
Female	40	57	63	57
ECOG=0	37	33	23	20
ECOG=1	57	53	53	60
ECOG=2	7	13	23	20
Prior Therapy=1	10	10	7	17
Prior Therapy=2	37	17	37	27
Prior Therapy=3	20	30	33	27
Prior Therapy>=4	33	43	23	30
CYP3A Inhibitors	27	37	27	23
CYP3A Inducers	20	33	20	23
PPI	37	40	23	37

Source code: CrizotinibER1005.ssc

Table 4: Summary of demographics by mean steady state trough concentration quartiles in trial A8081001

Demographics	Concentration quartile1	Concentration quartile 2	Concentration quartile 3	Concentration quartile 4
Continuous (Median)				
Age (years)	49	48	58	55
Wt (Kg)	76	73	66	65
Sum of longest diameters (mm)	89	73	72	102
Categorical (% of subjects)				
Asian	10	14	21	72
Female	41	54	64	41
ECOG=0	45	32	43	17
ECOG=1	48	54	46	62
ECOG=2	3	14	11	21
ECOG=3	3	0	0	0
Prior Therapy=0	10	18	18	7
Prior Therapy=1	38	29	32	21
Prior Therapy=2	21	18	25	17
Prior Therapy=3	14	29	4	14
Prior Therapy>=4	17	7	21	41
CYP Inhibitors	34	32	29	24
CYP Inducers	38	25	25	17
PPI	52	39	61	28

Source code: CrizotinibER1001.ssc

Table 5: Parameter Estimates from Logistic Regression Analysis for ORR

Predictors	Parameter Estimate	Std Error	p-value	Odds ratio	Lower 95%CI	Upper 95%CI
Trial A8081005						
Log transformed Cavg,ss	1.15	0.51	0.02	3.17	1.16	8.63
Use of CYP3 Inhibitors	-0.41	0.20	0.04	0.44	0.20	0.97
Trial A8081001						
Log transformed C_{trough}	2.00	0.61	0.001	7.36	2.24	24.19

Source codes: ER_PFS_ORR_1005.sas, ER_PFS_ORR_1001.sas

1.1.2 Is there evidence of exposure-response for progression free survival (PFS)?

An exposure-response analysis was conducted for PFS in trials A8081005 and A8081001 (Figure 2). According to the Kaplan-Meir plots based on concentration quartiles, there is trend for increase in PFS with increasing exposure in A8081001 but this trend was not seen in A8081005. The analysis for trial A8081005 is considered preliminary because data are not fully mature at the time of cut-off. Thus this analysis will primarily focus on PFS data from trial A8081001.

In trial A8081001, a clear separation is observed between PFS of the lowest quartile and the upper three quartiles in Figure 2. The upper three quartiles overlap and show no clear separation, possibly suggesting saturation of response at those exposures. This is consistent with objective response rate where similar response rate of ~70% was observed for the upper three quartiles (Figure 1). The median PFS for trials A8081005 and A8081001 by concentration quartiles are shown in

Table 6 and Table 7. The median PFS in the lowest quartile in A8081001 is 7.1 months while the median PFS in the upper three quartiles is greater than 10 months. As mentioned previously the difference in PFS is not only due to exposure but also due to other confounding risk factors that might not be balanced between the lowest and upper quartiles. To account for these confounding risk factors, a Cox proportional model was developed. While numerically, it was observed that increasing exposure decreased hazard, this relation was not statistically significant. A likely reason for not seeing a statistically significant relationship is that while the lowest quartile was separated from others, there was overlap in the upper three quartiles which possibly suggests saturation. Thus, a stepwise Cox proportional analysis was done that included all likely demographic factors mentioned in Table 4 and concentration as a categorical covariate, *i.e.*, lowest quartile versus the combined upper three quartiles. The model suggested higher hazard in the lowest quartile compared to the upper three quartiles with a hazard ratio of 3.2 (90%CI: 1.62–6.36) (Table 8). ECOG status and concomitant use of PPI were other significant predictors in trial A8081001.

Trial A8081005 Trial A8081001

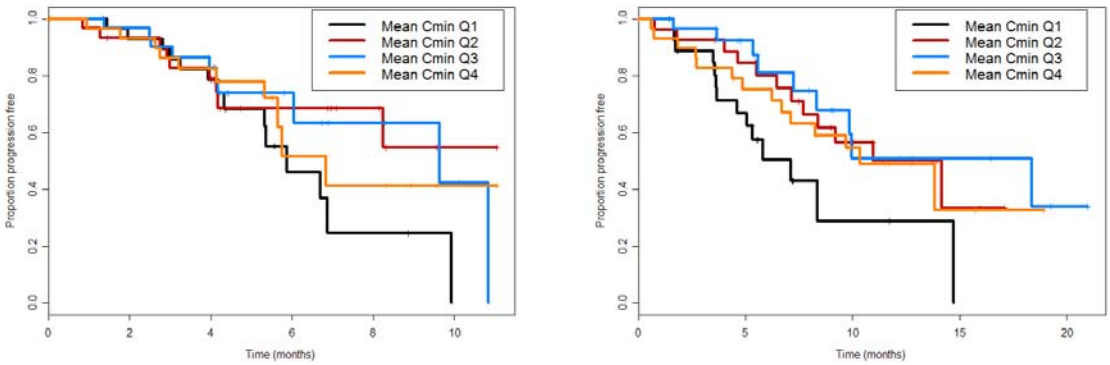


Figure 2: Kaplan-Meier plots for PFS for patients in various quartiles (Q1, Q2, Q3 and Q4) based on the mean steady state trough concentrations. C_{trough} represents the arithmetic mean of the observed C_{trough} in various cycles after steady state was reached.

Source codes: CrizotinibER1005.ssc, CrizotinibER1001.ssc

Table 6: Median PFS by mean steady state trough concentration quartiles in trial A8081005

Mean C_{trough} group*	Number of subjects	Median PFS (months)	Lower 95% CI	Upper 95 %CI
1	30	5.9	5.3	-
2	30	-	8.3	-
3	30	9.6	6.0	-
4	30	6.8	5.7	-

Source code: CrizotinibER1005.ssc

Table 7: Median PFS by mean steady state trough concentration quartiles in trial A8081001

Mean C_{trough} group*	Number of subjects	Median PFS (months)	Lower 95% CI	Upper 95 %CI
1	29	7.1	5.1	-
2	28	14.2	7.7	-
3	28	18.4	8.3	-
4	29	10.4	7.1	-

Source code: CrizotinibER1001.ssc

Table 8: Parameter Estimates of the Stepwise Cox Proportional Hazard Model

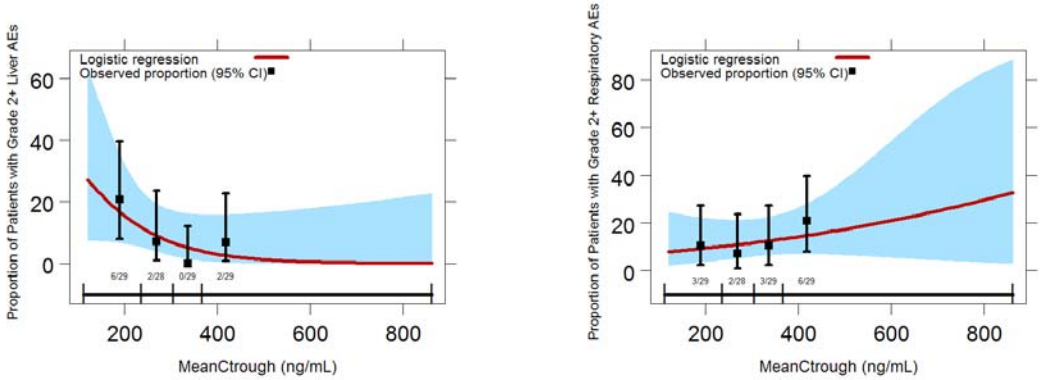
Predictor	Parameter Estimate	Std Error	p-value	Hazard ratio	Lower 95% CI	Upper 95%CI
Trial A8081001						
First quartile versus the combined upper three	1.17	0.35	0.0008	3.21	1.62	6.36
ECOG0 versus ECOG2	-2.02	0.47	<.0001	0.13	0.05	0.33
ECOG1 versus ECOG2	-1.03	0.35	0.0031	0.36	0.18	0.71
No PPI versus PPI	-0.91	0.31	0.0031	0.40	0.22	0.74

Source code: ER_PFS_ORR_1001.sas

1.1.3 Is there evidence of exposure-response for adverse events?

No meaningful exposure response relationship for respiratory and liver related adverse events was observed in trials A8081001 and A8081005 (Figure 3). Overall, the incidence of these adverse events for hematological toxicities, ALT and AST elevations and respiratory infections were low in trials A8081001 and A8081005 to conduct meaningful exposure-response analysis.

TRIAL A8081001



TRIAL A8081005

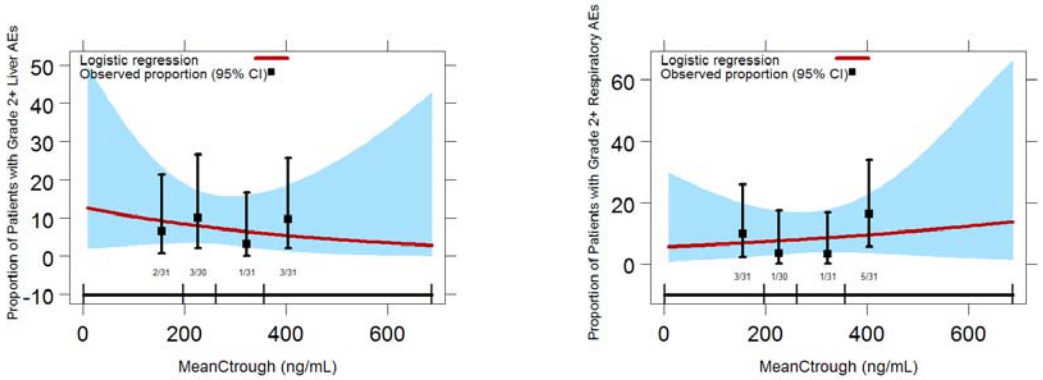


Figure 3: The probability of patients with A) Grade 2+ liver related AEs (left panel) and B) Grade 2+ respiratory related AEs (right panel)–steady state C_{trough} of crizotinib in trials A8081001 and A8081005. Solid black symbols represent the observed percentage of patients experiencing AEs in each C_{trough} quartile. The black bars represent the 95% confidence interval. The solid red line represents the mean logistic regression prediction. The shaded area represents the 95% confidence interval. The exposure range in each C_{trough} quartile is denoted by the horizontal black line. *Source codes: CrizotinibER1005_AE.ssc, CrizotinibER1001_AE.ssc*

1.1.4 Is the proposed dose of 250 mg BID appropriate?

Yes, based on the data collected in A8081005, the proposed dose of 250 mg BID seems reasonable. In contrast to A8081001, subjects in the lowest quartile had a response rate greater than 40% in A8081005 which is higher than the response rate (10-24%) of historical controls, *i.e.,* patients on standard of care. While subjects in the lowest quartile in A8081001 have 24% response rate, this was not consistent with the results from trial A8081005. In trial A8081005, patients with the same exposure range showed a response rate of 47%.

1.2 Recommendations

Division of Pharmacometrics finds the NDA 202570 acceptable from a clinical pharmacology perspective and recommends a PMC. The sponsor is requested to conduct exposure-response analysis for ORR, progression free survival, overall survival and safety endpoints utilizing data from their confirmatory trials, A8081007 and A8081014.
The goal of this analysis would be to justify the dose of 250 mg BID based on clinically meaningful endpoints such as progression free survival and overall survival in all patients. The basis of this recommendation is that an exposure-response relationship was observed in trials A8081001 and A8081005 for response rate. In trial A8081001, significantly low response of 24% was observed in patients with drug concentration levels of 112-235 ng/ml compared to greater than 70% response rate in patients with drug concentrations above 235 ng/ml. With the data submitted, it is not clear what factors are responsible for low exposures or low response rate in this subpopulation in trial A8081001 and the results are inconsistent with results from trial A8081005 where even for patients with drug concentration below 200 ng/ml, the response rate was 47% and less steep exposure-response curve was observed. Since A8081001 and A8081005 are small trials, exposure-response analysis is limited to address the discrepancies observed between the two trials and to conclusively determine if the dose is appropriate for all patients. Additionally, the PFS data from the pivotal trial A8081005 was not fully mature at the time of submission of this application to conduct a meaningful exposure-response relationship.

1.3 Label Statements

Not applicable because as per my understanding there are no labeling statements related to population PK.

2 PERTINENT REGULATORY BACKGROUND

This application is under consideration for an accelerated approval for ALK-positive advanced NSCLC patients based on Phase 1 trial A8081001 and Phase 2 trial A8081005. Type B meetings with FDA were held in April and July of 2010. Orphan drug status was granted in September 2010. Fast track, rolling review was granted on December 2010.

3 RESULTS OF SPONSOR'S ANALYSIS

3.1 Population PK Analysis

Sponsor performed population PK modeling utilizing data from trial A8081001 and A8081005. Primary objective of the population PK analysis was to describe effects of demographic factors and concomitant medications on the pharmacokinetic (PK) of crizotinib. Steady state average concentrations ($C_{AVG,SS}$) was predicted from the model that was further used for sponsor's exposure-response analyses.

3.1.1 Methods

PK data from a total of 250 subjects (3184 concentrations) was used for the analysis. This comprised of 165 subjects from trial A8081001 in the recommended Phase 2 dose (RP2D) cohort with 2849 concentrations and 85 from Study A8081005 with 335 concentrations. PK data were then fitted using Nonmem Version 7.1.2 (ICON Development Solutions, MD). All modeling work was done using the first order conditional method (FOCE) with interaction option.

3.1.2 Results

The population PK for crizotinib was described by a two-compartment model with first-order absorption, a lag time, and a decrease in apparent (oral) clearance (*CL/F*) after Cycle 1 Day 2. The model included weight, gender, race, and ECOG status as covariates on clearance, H_2-receptor antagonists and proton pump inhibitors on absorption rate (K_A) and weight on inter-distributional clearance (Q), volume of the central and peripheral compartments. The addition of all covariates resulted in only a small decrease (~6% relative change between base and final models) in unexplained variability in CL/F.

Table 9: Parameter Values from the Sponsor's Final Population PK Model

parameter	estimate	%RSE	CI
$CL/F(\theta_1)$	102 L/h	1.03	(91.6,112)
$\cdot(WT/70)^{\theta_6}$	0.402	31.3	(0.156,0.652)
$\cdot\theta_{11}CL/Fchg$	0.682	10.4	(0.633,0.737)
$\cdot\theta_{12}SEX2$	0.974	212	(0.89,1.07)
$\cdot\theta_{13}RACE2$	0.999	4390	(0.91,1.11)
$\cdot\theta_{14}RACE3$	1.05	214	(0.942,1.2)
$\cdot\theta_{15}RACE4$	1.18	51.9	(1.02,1.39)
$\cdot\theta_{16}RACE5$	0.922	102	(0.798,1.07)
$\cdot\theta_{17}RACE6$	0.828	37.1	(0.73,0.961)
$\cdot\theta_{18}RACE7$	1.07	148	(0.914,1.18)
$\cdot\theta_{19}RACE8$	0.841	136	(0.791,0.927)
$\cdot\theta_{20}ECOG1$	1	2430	(0.944,1.07)
$\cdot\theta_{21}ECOG234$	0.808	30.4	(0.696,0.897)
$V2/F(\theta_2)$	2390 L	0.559	(2170,2580)
$\cdot(WT/70)^{\theta_7}$	0.255	51.2	(0.0288,0.489)
$Q/F(\theta_3)$	44.4 L/h	2.79	(35.7,54.4)
$\cdot(WT/70)^{\theta_8}$	1.99	15.2	(1.36,2.55)
$V3/F(\theta_4)$	2200 L	1.27	(1820,2580)
$\cdot(WT/70)^{\theta_9}$	0.993	47.4	(0.28,1.61)
$Ka(\theta_5)$	0.817 h^{-1}	60.9	(0.625,1.16)
$\cdot\theta_{22}HRA2$	0.869	318	(0.554,1.31)
$\cdot\theta_{23}HRA4$	1.21	271	(0.432,4.33)
$\cdot\theta_{24}PPI1$	0.331	40.4	(0.141,0.824)
$\cdot\theta_{25}PPI2$	0.589	65.6	(0.262,0.996)
$\cdot\theta_{26}PPI3$	0.582	37.4	(0.408,0.884)
$\cdot\theta_{27}PPI4$	0.831	139	(0.563,1.27)
$Lag(\theta_{10})$	0.652 h	5.03	(0.566,0.759)
$\Omega^{1.1}CL/F$	0.0983 (%CV=31.4)	19.9	(0.0617,0.13)
$\Omega^{2.1}COV_{CL/F-V2}$	0.0904 (COR=0.598)	21.6	(0.0562,0.152)
$\Omega^{2.2}V2/F$	0.232 (%CV=48.2)	19.4	(0.144,0.334)
$\Omega^{3.1}COV_{CL/F-Ka}$	0.0677 (COR=0.169)	61.3	(-0.0151,0.181)
$\Omega^{3.2}COV_{V2/F-Ka}$	0.297 (COR=0.482)	28.4	(0.13,0.455)
$\Omega^{3.3}Ka$	1.64 (%CV=128)	16.2	(1.05,2.07)
$\Omega^{4.4}CL/Fchg$	0.0344 (%CV=18.5)	31.8	(0.0164,0.0589)
$\sigma^{1.1}prop1001$	0.11 (%CV=33.1)	6.59	(0.0973,0.122)
$\sigma^{3.3}prop1005$	0.0573 (%CV=23.9)	21	(0.0393,0.0796)

L/F = clearance, V2/F = central volume, Q/F = intercompartmental clearance, V3/F = peripheral volume, Ka = absorption rate constant, Lag = g time, CL/Fchg = change in CL/F after Day 8, WT = baseline weight, SEX2=female, RACE2=African American, RACE3=Hispanic, RACE4=Chinese, ACE5=Japanese, RACE6=Korean, RACE7=Other Asian, RACE8=Other, ECOG1=ECOG score of 1, ECOG234=ECOG score of 2, 3, or 4, HRA2=famotidine, RA4=ranitidine, PPI1=esomeprazole, PPI2=lansoprazole, PPI3=omeprazole, PPI4=pantoprazole, Ω = interindividual variance (%CV), σ = residual vari-ıce (proportional), CI = 95% confidence interval from non-parametric bootstrap, %RSE = relative standard error [=100*(asymptotic standard error of ıe estimate/point estimate)], %CV = percent coefficient of variation

(Source: Table 10 from Sponsor's Population Modeling Analysis Report- pmar-00192, page 39)

Intrinsic/Extrinsic Factors

Weight: Based on sponsor's analysis, distributions for *AUCss* values indicated that the probability for typical *AUCss* to fall outside the 80%–125% reference range was minimal when body weight was 50–110 kg. There was, however, 85% probability of having a typical *AUCss* greater than 125% of the value for the reference 70 kg individual when body weight is < 30 kg and an approximately 30% probability of falling outside the reference range when body weight is > 130 kg.

The remaining covariate effects (sex, race, and ECOG status) on *AUCss* demonstrated probability distributions for typical *AUCss* that fell within the 80%–125% reference range for the majority of categories except Korean race (25% probability that the typical *AUCss* would be greater than 125% of the reference *AUCss* value) and ECOG performance status of 2, 3, or 4 (42% probability that typical *AUCss* would be greater than 125% of the reference value). It should be noted, however, that the addition of all covariates resulted in only a small decrease (≈6% relative change between base and final models) in unexplained variability in *CL/F*.

Reviewer's comments on sponsor's population PK analysis:

- *Sponsor's population PK model is over parametrized as evidenced by the high RSE on the parameters estimates.*
- *Since inclusion of these covariates reduced the inter-individual variability on clearance by only 6%, there covariates are not likely to be clinically significant. The sponsor should reduce the model and retain only clinically meaningful covariates such that parameters are estimated with improved precision.*

3.2 Exposure-Response Analysis for Effectiveness

The sponsor conducted exposure-response analysis for objective response, PFS and safety endpoints.

3.2.1 Data

Data from trials A8081001 and A8081005 were utilized for this analysis.

3.2.2 Method and Results

Exposure-Response Analysis for Objective Response:

The exposure response relationship was explored for objective response in trial A8081005 and A8081001. Logistic regression model was used for objective response and Cox-proportional hazard model for PFS. The model for objective response is as follows:

$$\begin{aligned}\text{logit}(p_i) &= \theta_1 + \theta_2 \times Asian_i + \theta_3 \times I[ECOG_i = 1] + \theta_4 \times I[ECOG_i \geq 2] + \\ &\theta_5 \times Female_i + \theta_6 \times (BWT_i - 70) + \theta_7 \times (Age_i - 51) + \theta_8 \times I[\text{bs1ALT}_i \text{ not normal}] + \\ &\theta_9 \times CYP3A\_IND_i + \theta_{10} \times CYP3A\_INH_i + \theta_{11} \times PPI_i + \\ &\theta_{12} \times (SLD_i - 87) + \theta_{13} \times I[\#\text{Prior Met Reg}_i > 0] + \theta_{14} \times \ln(\text{exposure}_i)\end{aligned}$$

There is an apparent exposure-response relationship for response rate in both the trials. Log-transformed CAVGss and log-transformed C_{trough} were found to be significant predictor of response after adjusting for other confounding factors in trials A8081005 and A8081001 respectively (Table 10 and Table 11).

Table 10: Parameters of the Logistic Regression Analysis for Objective Response in Trial A8081005

	Unadjusted[1]		Adjusted[2]		
Model	Slope (SE)		Residual Deviance	Slope (SE)	95% CI[3]
CAVGss	0.00414 (0.00179)		144.8	0.00438 (0.00216)	(0.000144, 0.00861)
Log(CAVGss)	1.24 (0.508)		143.67	1.41 (0.621)	(0.192, 2.63)
Ctrough	0.00234 (0.00138)		148.18	0.00162 (0.00157)	(-0.00147, 0.0047)
Log(Ctrough)	0.207 (0.187)		148.79	0.141 (0.206)	(-0.264, 0.545)

1. Estimates of exposure-response not adjusted for potential confounders.
2. Estimates of exposure-response adjusted for potential confounders listed in Section 5.2
3. Confidence interval is a Wald CI using the asymptotic standard error.
Source: ePharm Artifact ID 4537576

(Source: Table 4 from Sponsor's Population Modeling Analysis Report- pmar-00243, page 17)

Table 11: Parameters of the Logistic Regression Analysis for Objective Response in Trial A8081001

	Unadjusted[1]		Adjusted[2]		
Model	Slope (SE)		Residual Deviance	Slope (SE)	95% CI[3]
CAVGss	0.00214 (0.00159)		127.01	-0.00143 (0.00203)	(-0.00541, 0.00255)
Log(CAVGss)	1.3 (0.563)		127.13	0.422 (0.683)	(-0.916, 1.76)
Ctrough	0.00479 (0.00191)		126.28	0.00245 (0.00227)	(-0.00199, 0.00689)
Log(Ctrough)	1.78 (0.534)		119.82	1.55 (0.612)	(0.346, 2.74)

1. Estimates of exposure-response not adjusted for potential confounders.
2. Estimates of exposure-response adjusted for potential confounders listed in Section 5.2
3. Confidence interval is a Wald CI using the asymptotic standard error.
Source: ePharm Artifact ID 4491917

(Source: Table 4 from Sponsor's Population Modeling Analysis Report- pmar-00242, page 18)

Reviewer's comments:

- *The sponsor's conclusion that there is an exposure-response relationship for objective response in both trials A8081005 and A80810001 is consistent with reviewer's conclusion in section 1.1.1.*

Exposure-Response Analysis for PFS:

The ER relationship for PFS was explored for only trial A8081001. This analysis was not conducted for trial A8081005 due to immature data at the time of sponsor's report.

The model for hazard is as follows:

$$h(t) = h_0(t)\exp\{\theta_2 \times Asian_i + \theta_3 \times I\left[ECOG_i = 1\right] + \theta_4 \times I\left[ECOG_i \geq 2\right] + \theta_5 \times Female_i + \theta_6 \times (BWT_i - 70) + \theta_7 \times (Age_i - 55) + \theta_8 \times I\left[bslALT_i\ not\ normal\right] + \theta_9 \times CYP3A4_i + \theta_{10} \times PPI_i\}$$

After adjusting for potential confounders, the model that provides the best fit to the data (based on lowest residual deviance) is the model using log-transformed Ctrough (Table 12). The estimated ER indicates that higher exposures (increased log-transformed

Ctrough) correspond to lower hazard and, thus, longer PFS; however, this relationship is not statistically significant at the 0.05 level, with the 95% CI including 0.

Reviewer's comments:

- *The sponsor's conclusion that there is decrease in hazard with increasing exposure; however the relationship is not significant when continuous measures of exposure is used is consistent with reviewer's analysis (see section 0). However, additional analysis revealed that exposure is significant when treated as a categorical variable with patients divided in low and high exposure groups. See section 0 for details.*

Table 12: Parameters of the Cox-Proportional Hazard Model for PFS in Trial A8081001

	Unadjusted[1]		Adjusted[2]		
Model	Slope (SE)		Residual Deviance	Slope (SE)	95% CI[3]
CAVGss	0.00183 (0.00128)		353.81	0.000755 (0.00154)	(-0.00226, 0.00377)
Log(CAVGss)	0.0612 (0.432)		353.25	-0.464 (0.509)	(-1.46, 0.535)
Ctrough	0.0000914 (0.00146)		354.01	0.000324 (0.00166)	(-0.00293, 0.00358)
Log(Ctrough)	-0.439 (0.320)		352.16	-0.532 (0.370)	(-1.26, 0.19300)

1. Estimates of exposure-response not adjusted for potential confounders.
2. Estimates of exposure-response adjusted for potential confounders listed in Section 5.2
3. Confidence interval is a Wald CI using the asymptotic standard error.
Source: ePharm Artifact ID 4502287

(Source: Table 6 from Sponsor's Population Modeling Analysis Report- pmar-00242, page 20)

4 RESULTS OF REVIEWER'S ANALYSIS

4.1 Objectives

The reviewer's analysis objectives are:

1. To determine if there is exposure-response relationship for efficacy endpoints, objective response and progression free survival
2. To determine if there is exposure-response relationship for safety endpoints.
3. To determine if the exposure-response relationship supports the proposed dose of 250 mg BID.

4.2 Methods

4.2.1 Data Sets

Data sets used are summarized in Table 13

Table 13: Analysis Data Sets.

Study Number	Name	Link to EDR
A8081001	pkpd.xpt	\\Cdsesub1\evsprod\NDA202570\0013\m5\datasets\pmar-00242\analysis\datasets
	advers.xpt	\\Cdsesub1\evsprod\NDA202570\0002\m5\datasets\a8081001\analysis
	pidflg.xpt	\\Cdsesub1\evsprod\NDA202570\0002\m5\datasets\a8081001\analysis
A8081005	pkpd.xpt	\\Cdsesub1\evsprod\NDA202570\0017\m5\datasets\pmar-00243\analysis\datasets
	advers.xpt	\\Cdsesub1\evsprod\NDA202570\0009\m5\datasets\a8081005\analysis
	pidflg.xpt	\\Cdsesub1\evsprod\NDA202570\0009\m5\datasets\a8081005\analysis

4.2.2 Software

SAS and S-PLUS were used for the reviewer's analyses.

4.3 Results

4.3.1 Population Pharmacokinetic Analysis

An independent analysis for population pharmacokinetics was not conducted. See reviewer's comments in section 3.1.

4.3.2 Exposure-Response Analysis

An exposure-response relationship was conducted for ORR and PFS for trials A8081001 and A8081005. See sections 1.1.1 and 0 for the results from the analysis. The exposure measure used for analysis in sections 1.1.1 and 0 was the arithmetic mean of the observed steady state trough concentrations of the drug as multiple trough samples were collected at steady state.

As a sensitivity analysis, additional analyses were conducted using the geometric mean of the trough concentrations. Also population predicted steady state average drug concentration is used as a measure of exposure ($C_{avg,ss}$). The results from these exposure measures are presented in this section.

Trial 1005 Trial 1001

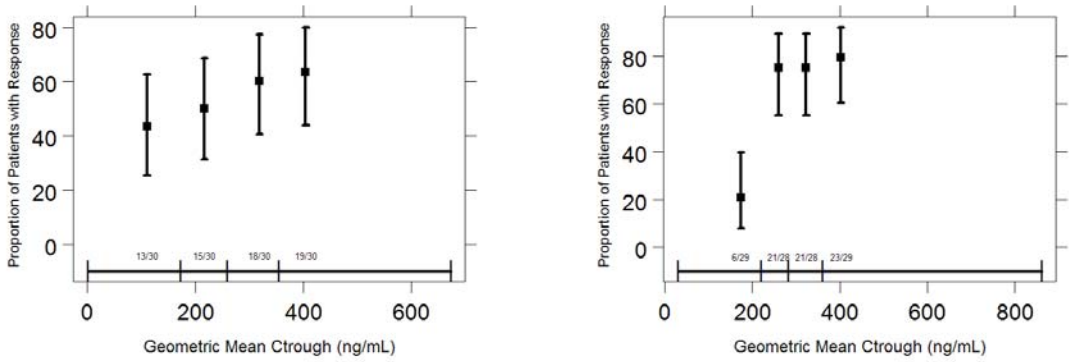


Figure 4: The proportion of patients with ORR versus mean steady state trough concentrations of crizotinib in trial A8081005 and A8081001. Solid black symbols represent the observed percentage of patients responding to treatment in each C_{trough} quartile. The vertical black bars represent the 95% confidence interval. The exposure range in each C_{trough} quartile is denoted by the horizontal black line. Mean C_{trough} represents the geometric mean of the observed C_{trough} in various cycles after steady state was reached. *Source codes: CrizotinibER1005.ssc, CrizotinibER1001.ssc*

Table 14: ORR by mean steady state trough concentration quartiles in A8081005

Mean C_{trough} group*	Median Concentration (ng/ml)	Number of subjects	Number of responders	Response rate	Lower 95% CI	Upper 95% CI
1	110	30	13	43	25	63
2	217	30	15	50	31	69
3	318	30	18	60	41	77
4	404	30	19	63	44	80

** Mean C_{trough} represents the geometric mean of the observed C_{trough} in various cycles after steady state was reached. Source code: CrizotinibER1005.ssc*

Table 15: ORR by mean steady state trough concentration quartiles in A8081001

Mean C_{trough} group*	Median Concentration (ng/ml)	Number of subjects	Number of responders	Response rate	Lower 95% CI	Upper 95% CI
1	174	29	6	21	8	40
2	260	28	21	75	55	89
3	323	28	21	75	55	89
4	403	29	23	79	60	92

* *Mean C_{trough} represents the geometric mean of the observed C_{trough} in various cycles after steady state was reached. Source code: CrizotinibER1001.ssc*

Trial 1005 Trial 1001

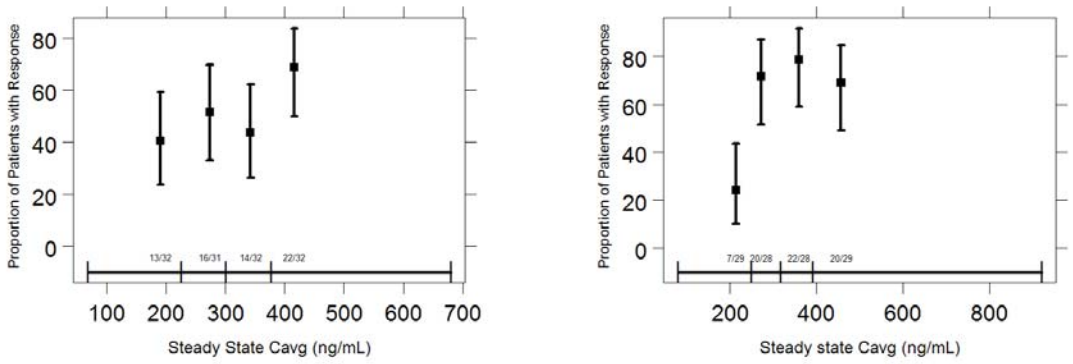


Figure 5: The proportion of patients with ORR versus the steady state average concentrations of crizotinib in trial A8081005 and A8081001. Solid black symbols represent the observed percentage of patients responding to treatment in each $C_{avg,ss}$ quartile. The vertical black bars represent the 95% confidence interval. The exposure range in each $C_{avg,ss}$ quartile is denoted by the horizontal black line. $C_{avg,ss}$ is predicted from the population PK model. *Source codes: CrizotinibER1005.ssc, CrizotinibER1001.ssc*

Table 16: ORR by steady state average concentration quartiles in A8081005

$C_{avg,ss}$ group	Median Concentration (ng/ml)	Number of subjects	Number of responders	Response rate	Lower 95% CI	Upper 95% CI
1	191	32	13	41	24	59
2	274	31	16	52	33	70
3	342	32	14	44	26	62
4	416	32	22	69	50	84

** $C_{avg,ss}$ is predicted from the population PK model. Source code: CrizotinibER1005.ssc*

Table 17: ORR by steady state average concentration quartiles in A8081001

$C_{avg,ss}$ group	Median Concentration (ng/ml)	Number of subjects	Number of responders	Response rate	Lower 95% CI	Upper 95% CI
1	214	29	7	24	10	44
2	272	28	20	71	51	87
3	360	28	22	79	59	92
4	457	29	20	69	49	85

**$C_{avg,ss}$ is predicted from the population PK model. Source code: CrizotinibER1001.ssc*

Trial A8081005 Trial A8081001

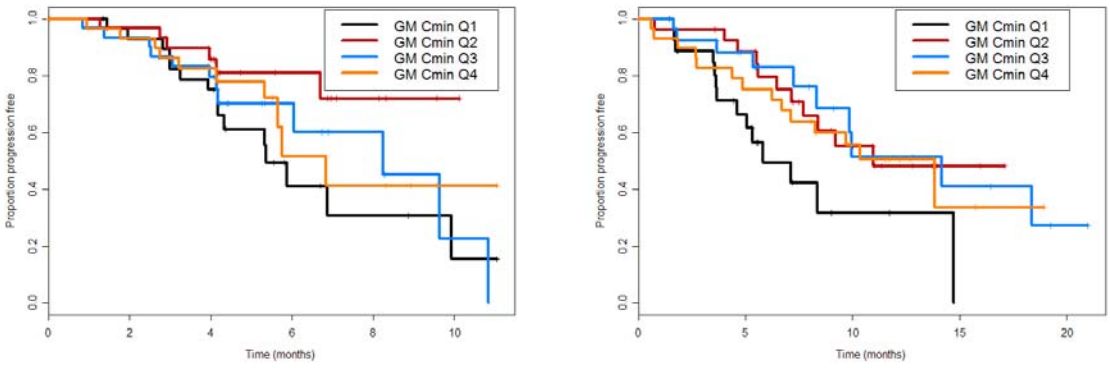


Figure 6: Kaplan-Meier plots for PFS for patients in various quartiles (Q1, Q2, Q3 and Q4) based on the mean steady state trough concentrations. C_{trough} represents the geometric mean of the observed C_{trough} in various cycles after steady state was reached. *Source codes: CrizotinibER1005.ssc, CrizotinibER1001.ssc*

Table 18: Median PFS by steady state trough concentration quartiles in A8081005

Mean C_{trough} group*	Number of subjects	Median PFS (months)	Lower 95% CI	Upper 95 %CI
1	30	5.4	4.3	-
2	30	-	-	-
3	30	8.3	6.0	-
4	30	6.8	5.7	-

** Mean C_{trough} represents the geometric mean of the observed C_{trough} in various cycles after steady state was reached. Source code: CrizotinibER1005.ssc*

Table 19: Median PFS by steady state trough concentration quartiles in A8081001

Mean C_{trough} group*	Number of subjects	Median PFS (months)	Lower 95% CI	Upper 95 %CI
1	29	5.8	4.6	-
2	28	11.0	7.7	-
3	28	14.2	8.3	-
4	29	13.8	7.1	-

** Mean C_{trough} represents the geometric mean of the observed C_{trough} in various cycles after steady state was reached. Source code: CrizotinibER1001.ssc*

Trial A8081005 Trial A8081001

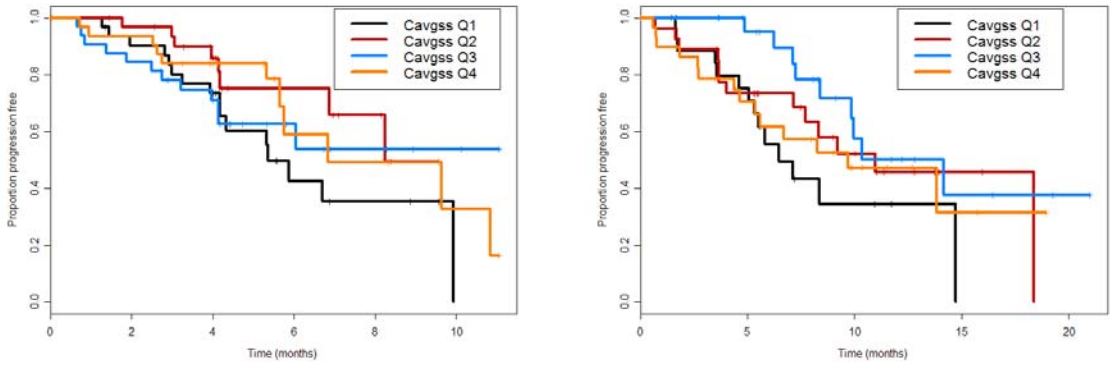


Figure 7: Kaplan-Meier plots for PFS for patients in various quartiles (Q1, Q2, Q3 and Q4) based on the mean steady state average concentrations. $C_{avg,ss}$ is predicted from the population PK model. *Source codes: CrizotinibER1005.ssc, CrizotinibER1001.ssc*

Table 20: Median PFS by steady state average concentration quartiles in A8081005

Mean $C_{avg,ss}$ group*	Number of subjects	Median PFS (months)	Lower 95% CI	Upper 95 %CI
1	32	5.4	4.2	-
2	31	8.3	6.9	-
3	32	-	4.1	-
4	32	6.8	5.7	-

** $C_{avg,ss}$ is predicted from the population PK model. Source code: CrizotinibER1005.ssc*

Table 21: Median PFS by steady state average concentration quartiles in A8081001

Mean $C_{avg,ss}$ group*	Number of subjects	Median PFS (months)	Lower 95% CI	Upper 95 %CI
1	29	6.5	5.3	-
2	28	11.0	7.7	-
3	28	14.2	9.9	-
4	29	9.7	5.6	-

$C_{avg,ss}$ is predicted from the population PK model. Source code: CrizotinibER1001.ssc

5 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
TRIAL A8081005		
CrizotinibER1005.ssc	Splus code to perform exposure-response analysis for ORR and PFS.	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Crizotinib_NDA202570_AM\ER Analyses\ER1005_SponsorDataSet
ORR_Cmin_Arithmetic_Pred.JPG ORR_Cmin_Geometric.JPG ORR_CAVGSS.JPG PFS_Cmin_Arithmetic.JPG PFS_Cmin_Geometric.JPG PFS_Cmin_CAVGSS.JPG	Output graphs from CrizotinibER1005.ssc	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Crizotinib_NDA202570_AM\ER Analyses\ER1005_SponsorDataSet\Graphs
ORR_Quartile_Cmin_Arithmetic.csv ORR_Quartile_Cmin_Geometric.csv ORR_Quartile_Cavgss.csv CatVar_Summary_ArithmeticCmin.csv ConVar_Summary_ArithmeticCmin.csv	Output tables from CrizotinibER1005.ssc	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Crizotinib_NDA202570_AM\ER Analyses\ER1005_SponsorDataSet\Tables
ER_PFS_ORR_1005.sas	Sas code to perform logistic regression and Cox-proportional hazard model	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Crizotinib_NDA202570_AM\ER Analyses\ER1005_SponsorDataSet
ORR_Logistic_1005.pdf	Output table from ER_PFS_ORR_1005.sas	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Crizotinib_NDA202570_AM\ER Analyses\ER1005_SponsorDataSet\Tables

CrizotinibER1005_AE.ssc	Splus code to perform exposure-response analysis for respiratory and liver related AEs.	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Crizotinib_NDA202570_AM\ER Analyses\ER1005_SponsorDataSet
ER_LiverGr3plus_ArithmeticMean_Pred.jpg ER_respGr3plus_ArithmeticMean_Pred.jpg	Output graphs from CrizotinibER1005_AE.ssc	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Crizotinib_NDA202570_AM\ER Analyses\ER1005_SponsorDataSet\Graphs
TRIAL A8081001		
CrizotinibER1001.ssc	Splus code to perform exposure-response analysis for ORR and PFS.	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Crizotinib_NDA202570_AM\ER Analyses\ER1001_SponsorDataSet
ORR_Cmin_Arithmetic_Pred.JPG ORR_Cmin_Geometric.JPG ORR_CAVGSS.JPG PFS_Cmin_Arithmetic.JPG PFS_Cmin_Geometric.JPG PFS_Cmin_CAVGSS.JPG	Output graphs from CrizotinibER1001.ssc	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Crizotinib_NDA202570_AM\ER Analyses\ER1001_SponsorDataSet\Graphs
ORR_Quartile_Cmin_Arithmetic.csv ORR_Quartile_Cmin_Geometric.csv ORR_Quartile_Cavgss.csv CatVar_Summary_ArithmeticCmin.csv ConVar_Summary_ArithmeticCmin.csv	Output tables from CrizotinibER1001.ssc	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Crizotinib_NDA202570_AM\ER Analyses\ER1001_SponsorDataSet\Tables

ER_PFS_ORR_1001.sas	Sas code to perform logistic regression and Cox-proportional hazard model	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Crizotinib_NDA202570_AM\ER Analyses\ER1001_SponsorDataSet
ORR_Logistic_1001.pdf ORR_CPH_1001.pdf	Output table from ER_PFS_ORR_1001.sas	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Crizotinib_NDA202570_AM\ER Analyses\ER1001_SponsorDataSet\Tables
CrizotinibER1001_AE.ssc	Splus code to perform exposure-response analysis for respiratory and liver related AEs.	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Crizotinib_NDA202570_AM\ER Analyses\ER1001_SponsorDataSet
ER_LiverGr3plus_ArithmeticMean_Pred.jpg ER_respGr3plus_ArithmeticMean_Pred.jpg	Output graphs from CrizotinibER1001_AE.ssc	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Crizotinib_NDA202570_AM\ER Analyses\ER1001_SponsorDataSet\Graphs

---

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

/s/

PENGFEI SONG
08/09/2011

ANSHU MARATHE
08/09/2011

CHRISTINE E GARNETT
08/09/2011

QI LIU
08/09/2011

NAM ATIQUR RAHMAN
08/10/2011

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 202-570	**Reviewer:** Kareen Riviere, PhD	
Submission Date:	March 30, 2010		
Division:	Division of Oncology Products	**Team Leader:** Angelica Dorantes, PhD	
Sponsor:	Pfizer	**Supervisor:** Patrick Marroum, PhD	
Trade Name:	Xalkori	**Date Assigned:**	March 30, 2010
Generic Name:	Crizotinib	**Date of Review:**	July 26, 2011
Indication:	For the treatment of anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC)	**Type of Submission:** Original New Drug Application	
Formulation/strengths	Capsules/ 200 and 250 mg		
Route of Administration	Oral		

THE SUBMISSION

This is a 505(b)(1) New Drug Application for an immediate release hard gelatin capsule containing 200 and 250 mg of Crizotinib, indicated for the treatment of anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC). This submission has Quality by Design elements for drug substance and drug product manufacturing.

BIOPHARMACEUTICS INFORMATION

1. Background

The Crizotinib commercial formulation was developed as an immediate release hard gelatin capsule to deliver 200 mg and 250 mg dose strengths. This was designed to meet criteria in the Quality Target Product Profile, which defined a target upper dose of 250 mg for twice daily dosing as a single unit dose. Three solid oral dosage forms of Crizotinib, powder in capsule (PIC), clinical tablet and formulated capsule have been evaluated in various clinical trials. Bioequivalence testing of these three solid dosage forms has also been completed.

Crizotinib has been categorized as a BCS 4 drug. Dissolution is designated a Critical Quality Attribute and is included in the Crizotinib Design Space.

Recommendations

This application is recommended for approval from a Biopharmaceutics standpoint.

- A waiver is granted for the CFR requirement to provide in vivo bioavailability data for the 200 mg strength capsule.
- The following dissolution method and specification for the 200 mg and 250 mg strength capsules are recommended:
    - Dissolution method: 0.1N HCl medium, Apparatus 1, 100 rpm agitation rate, 900 mL media volume.
    - Dissolution specification: Q= (b) (4) at 30 minutes.

2. Dissolution Method Development Report

The dissolution method for Crizotinib capsules is being used for quality control of the drug product and is not intended to correlate to the in vivo performance of the product. The dissolution method is designed to discriminate variations in the formulation and manufacturing process. There are no current plans to establish an IVIVC for Crizotinib capsules.

The dissolution method was designed (b) (4). The following parameters were investigated during the development of the dissolution test: dissolution medium, apparatus, agitation rate, and media volume. A summary of the different dissolution test conditions investigated by the Sponsor is outlined in Table 3.2.P.2.2-17.

Table 3.2.P.2.2-17. Dissolution Method Development Summary For Crizotinib Capsules. Reference Table 3.2.P.2.2-15 for Dissolution Method Test Conditions

Parameter	Range Investigated	Summary (see the following sections for in-depth discussion and conclusions)
(b) (4)		

A summary of the clinical studies to support the bioequivalence for the three solid oral dosage forms of Crizotinib are displayed in Table 3.2.P.2.2-14. The formulated capsule of Crizotinib is bioequivalent to the immediate release tablet as well as the powder in capsule (PIC) formulation that have been used in clinical studies.

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

The Sponsor is no longer proposing to include ranges of (b) (4) (b) (4) the drug product. They will maintain the (b) (4) (b) (4) described in Section 3.2.P.1 Description and Composition of the Drug Product.

Kareen Riviere, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Patrick Marroum, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

cc: Angelica Dorantes, Ph.D.

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

/s/

KAREEN RIVIERE
07/26/2011

PATRICK J MARROUM
07/26/2011

BIOPHARMACEUTICS REVIEW Office of New Drugs Quality Assessment			
Application No.:	NDA 202-570	**Reviewer:** Kareen Riviere, PhD	
Submission Date:	March 30, 2010		
Division:	Division of Oncology Products	**Team Leader:** Angelica Dorantes, PhD	
Sponsor:	Pfizer	**Supervisor:** Patrick Marroum, PhD	
Trade Name:		**Date Assigned:**	March 30, 2010
Generic Name:	Crizotinib	**Date of Review:**	May 16, 2011
Indication:	For the treatment of anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC)	**Type of Submission:** Original New Drug Application	
Formulation/strengths	Capsules/ 200 and 250 mg		
Route of Administration	Oral		

SUBMISSION:

This is a 505(b)(1) New Drug Application for an immediate release hard gelatin capsule containing 200 and 250 mg of Crizotinib, indicated for the treatment of anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC). This submission has Quality by Design elements for drug substance and drug product manufacturing.

BIOPHARMACEUTIC INFORMATION:

The Crizotinib commercial formulation was developed as an immediate release hard gelatin capsule to deliver 200 mg and 250 mg dose strengths. This was designed to meet criteria in the Quality Target Product Profile, which defined a target upper dose of 250 mg for twice daily dosing as a single unit dose. Three solid oral dosage forms of crizotinib, namely powder in capsule (PIC), clinical tablet and formulated capsule have been evaluated in various clinical trials. Bioequivalence testing of these three solid dosage forms has also been completed.

Crizotinib has been categorized as a BCS 4 drug. Dissolution is designated a Critical Quality Attribute and is included in the Crizotinib Design Space. The dissolution method for crizotinib capsules is being used for quality control of drug product and is not intended to correlate to the bioperformance of the product. The dissolution method is designed to discriminate variations in the formulation and manufacturing process. There are no current plans to establish an IVIVC for crizotinib capsules.

Proposed dissolution method and acceptance criterion:

	(b) (4)
Apparatus:	
Medium:	
Volume:	
Agitation Rate:	
Analytical End Analysis:	
Acceptance Criteria	

This submission includes a drug product development section, a dissolution development report with proposed dissolution specification and acceptance criterion, in vivo bioequivalence data of three solid oral dosage forms of Crizotinib, and comparative dissolution profiles for variant capsules formulations of Crizotinib.

The Biopharmaceutics review for this NDA will be focused on the evaluation and acceptability of the proposed dissolution methodology and acceptance criterion for Crizotinib as well as the suitability of the Design Space with regards to dissolution.

RECOMMENDATION:

The ONDQA/Biopharmaceutics team has reviewed NDA 202-570 for filing purposes. We found this NDA filable from a biopharmaceutics perspective. The sponsor has submitted a reviewable submission.

Kareen Riviere, PhD
Biopharmaceutics Reviewer
Office of New Drugs Quality Assessment

Angelica Dorantes, PhD
Biopharmaceutics Team Leader
Office of New Drugs Quality Assessment

cc: Patrick Marroum, PhD

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

/s/

KAREEN RIVIERE
05/16/2011

ANGELICA DORANTES
05/16/2011

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

NDA Number	202570	**Brand Name**	Xalkori®
DCP Division (I, II, III, IV, V)	V	**Generic Name**	Crizotinib (PF-02341066)
Medical Division	Oncology	**Drug Class**	Kinase inhibitor
OCP Reviewer	Pengfei Song, Ph.D.	**Indication(s)**	Treatment of Anaplastic Lymphoma Kinase (ALK)-Positive Advanced Non-Small Cell Lung Cancer (NSCLC).
OCP Team Leader	Qi Liu, Ph.D.	**Dosage Form / Strengths**	Capsules / 200 mg and 250 mg
Pharmacometric Reviewer	Anshu Marathe	**Dosing Regimen**	250 mg taken orally twice daily, continuously, with or without food
Pharmacometric Team Leader	Christine Garnett	**Route of Administration**	Oral
Sponsor	Pfizer Inc.	**Priority Classification**	Expedited Review
Date of Submission	30 March 2011	**Estimated Due Date of OCP Review**	15 June 2011
PDUFA Due Date	30 September 2011	**Division Due Date**	30 June 2011

Clinical Pharmacology Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**	**4**		• ***A8089001*** *LC/MS/MS for Studies A808100, addendum 1 for Studies 1008, 1009, Crizotinib in plasma, with a range of 0.02-200 ng/mL* • ***A8089002*** *LC/MS/MS for Study A8081009, crizotinib in urine only, with a range of 0.2-200ng/mL* • ***A8089003*** *LC/MS/MS for Studies A8081001(consented patients' samples for both crizotinib and active metabolite), 1005, 1010, 1011, 1015, 1016; Crizotinib and active metabolite PF-06260182 in plasma, with range 0.2-200 ng/mL* • ***A9009003*** *LC/MS/MS for Study A8081001, Midazolam in plasma, with a range of 0.05-50 ng/mL*
I. Clinical Pharmacology				
Mass balance:	**X**	**1**		**Study A8081009:** ^{14}C-Crizotinib in 6 healthy volunteers at 250 mg single dose. Within 20 days, 85.3% of radioactivity recovered in excreta, 63% in feces with 53% unchanged, 22% in urine with 1.3% unchanged. Active metabolite PF-06260182 accounts for 10% of the circulating radioactivity.
Metabolic profiling	**X**	**1**		**Study A8081009 Bioanalytical Report: Metabolic profiling of** ^{14}C-crizotinib in plasma, urine and feces (N=6),
Isozyme characterization:	**X**	**6**		• **PF02341066-PDM-018**: In Vitro Metabolic Stability and In Vitro and In Vivo Metabolite Profiles of PF-02341066 in Various Species • **PF02341066-PDM-024** Preliminary Evaluation of PF-02341066 Metabolism in Male and Female Rat and Human Liver S9 • **PF02341066-PDM-019** Identification of Human Cytochrome P450 Isoforms Involved in the Metabolism of PF-02341066 • **PF-02341066_09Sep10_163819** Assessment of In Vitro Metabolism of PF-02341066 by Recombinant Human Cytochrome P450 Enzymes • **PF-02341066_14Sep10_174623** Assessment of In Vitro Metabolism of PF-02341066 by Recombinant Human Cytochrome P450 3A4 and 3A5 Enzymes • **PF-02341066_10Sep10_145505** Involvement of P450 Isoforms and Aldehyde Oxidase in the Formation of Lactam- and Ether-Derived Metabolites of PF-02341066

Active Metabolites	**X**	**6**		○ PK results presented in Studies of A8081001, 1005, 1009, 1010, 1011, 1015, A8081016; No separate reports. ○ Study on the clinical relevance of this metabolite is ongoing. ○ Active metabolite: crizotinib lactam (M10, PF-06260182), forming 2 constituent diastereomers: PF-06270079 and PF-06270080), with approximately 3- to 8-fold less potent against ALK and 2.5- to 4-fold less potent against c-Met/HGFR, compared to crizotinib
Transporters	**X**	**6**		• **PF-02341066_11May10_141847:** In Vitro Study of P-Glycoprotein Inhibition by PF-02341066 in Caco-2 Cells • **PF-02341066_05Oct10_182103:** PF-02341066: BCRP Inhibtion Evaluation • **PF-02341066_28Jul10_181858:** In Vitro Inhibition of OATP1B1 by PF-02341066 • **PF-02341066_02Aug10_095303:** In Vitro Inhibition of OATP1B3 by PF-02341066 • **Absorption PF-02341066_03Aug10_174737:** MDR1 and BCRP Transport Evaluation of PF-02341066 • **PF-02341066_18Aug10_194244 PF-02341066:** In Vitro Assessment of Hepatic Uptake in Human Hepatocyte Suspensions
Blood/plasma ratio:	**X**	**1**		• **PF02341066-PDM-015:** Red Blood Cell Distribution of [3H]PF-02341066 in Whole Blood of Mouse, Rat, Dog, Monkey, and Human
Plasma protein binding:	**X**	**3**		• **Distribution PF02341066-PDM-014:** Equilibrium Dialysis Determination of Unbound Fraction of PF-02341066 in Rat, Mouse, Dog, Monkey, and Human Plasma • **PF-02341066_28Jul10_144558:** In Vitro Binding of PF-02341066 in Human Albumin and Human α1-Acid Glycoprotein • **PF-02341066_20Oct10_145554:** Determination of Protein Binding in Rat and Human Plasma for PF-06260182 and Its Diastereomers PF-06270079 and PF-06270080, Lactam Metabolites of PF-02341066
Pharmacokinetics (e.g., Phase I)				
Healthy volunteers-	**X**	**6**		• **A8081008**: Relative bioavailability study to compare two clinical formulations (IRT and PIC) • **A8081010**: Absolute bioavailability study to compare oral formulation (IRT) and intravenous formulation (50 mg IV, 250 mg oral) • **A8081011**: BE study of two clinical formulations used in A8081001 and A8081005 (IRT and PIC) and the final-market-image formulation, and a formal food effect study on the final-market-image formulation • **A8081009**: Mass balance study (250mg) • **A8081015**: Drug interaction study with ketoconazole on the single-dose (150 mg) PKof crizotinib • **A8081016**: Drug interaction study with rifampin on the single-dose (250 mg) PK of crizotinib
Patients-				
single dose:	**X**	**2**		**Study A8081001:** • Primary study to support the accelerated approval. • Ongoing, open-label, dose-escalation, single-arm study in patients with advanced cancer. • The study included a dose escalation phase and a RP2D phase including ALK-positive NSCLC, ALK-negative NSCLC and other tumor type groups. • Substudies: midazolam (MDZ) interaction at dose-escalation and RP2D cohorts, exploratory food effect at RP2D. **Study A8081005:** • Supportive study • Ongoing open-label, single-arm, Phase 2 study in 2nd setting patients with ALK-positive advanced NSCLC. • Sparse PK collected and used in population PK analysis.
multiple dose:	**X**			
Dose proportionality -	**X**			• Included in the Summary of Clinical Pharmacology
Drug-drug interaction studies				

In-vivo effects on primary drug:	**X**	**2**		• **Study A8081015 (CYP3A4 inhibitor):** 2x2 crossover design for ketoconazole on single dose of crizotinib in healthy volunteers. For crizotinib, $AUC_{inf, keto}/ AUC_{inf}$ =3, $C_{max, keto}/ C_{max}$ =1.4; For active metabolite PF-06260182, $AUC_{inf, keto}/ AUC_{inf}$ = 5, $C_{max, keto}/ C_{max}$ =1.6 • **Study A8081016 (CYP3A4 inducer):** 2x2 crossover design for rifampin on single dose of crizotinib in healthy volunteers. For crizotinib, $AUC_{inf, keto}/ AUC_{inf}$ =0.18, $C_{max, keto}/ C_{max}$ =0.31; For active metabolite PF-06260182, $AUC_{inf, keto}/ AUC_{inf}$ = 0.06, $C_{max, keto}/ C_{max}$ =0.11
In-vivo effects of primary drug on other drugs:	**X**	**1**		• **A8081001:** A 3.6-fold (90% CI: 2.7-4.9) increase in the oral midazolam AUC was observed following 28 days of crizotinib dosing at 250 mg BID.
In-vitro:	**X**	**3**		• **Study report 153034:** Evaluation of the inhibition of human liver microsomal CYP450 enzymes by crizotinib. IC50 for CYP3A: 7.3 uM for Testosterone 6-alpha-hydroxylase, • **Study report PDM-017:** Evaluation of time-dependent inhibition of CYP3A by crizotinib in human liver microsomes. Midazolam Ki=3 uM, Kinact=0.11 min^{-1} • **Study report 153446**: Induction effect on CYP1A2 and CYP3A mRNA expression and enzyme activities in three batches of fresh human hepatocytes
Subpopulation studies -				
Body size	**X**			**Population Modeling Analysis Report (PMAR-00192)**: o 250 patients receiving the 250 mg BID dosing regimen (165 from Study A8081001 in the RP2D cohort with 2849 concentrations; and 85 from Study A8081005 with 335 concentrations) o Crizotinib PK was described by a two-compartment model with first-order absorption, a lag time, and a decrease in apparent (oral) clearance (CL/F) after Cycle 1 Day 2. o The typical estimates of PK model parameters for the reference covariate effects (Caucasian, Male, 70 kg, ECOG performance status = 0, no proton-pump inhibitors or H2-receptor antagonists) were 102 L/hr, 0.682, 0.817 hr-1, and 0.652 hr for CL/F, proportional change in CL/F after Cycle 1 Day 2, absorption rate constant (ka), and absorption lag time (lag), respectively. o BW, PPI significant
Gender:	**X**			
Geriatrics:	**X**			
Renal Impairment:	**X**			
Race/Ethnicity:	**X**			
Hepatic Impairment:				NA
Pediatrics:				**NA**
PD:				
Phase 2:				
Phase 3:				
PK/PD:	**X**	**1**		**Study report of PMAR-00224 for QTc evaluation**
Population Analyses -				
Data rich:	**X**	**1**		**Population Modeling Analysis Report (PMAR-00192)**:
Data sparse:	**X**	**1**		• Pooled PK data from A8081001, 1005 • No healthy subject's data used
II. Biopharmaceutics				
Absolute bioavailability:	**X**	**1**		**Study A8081010:** 2x2 crossover design for 250 mg capsule vs 50 mg IV of crizotinib in 14 healthy volunteers. F=43% at 250 mg.
Relative bioavailability -	**X**	**1**		**Study A8081008:** 2x2 crossover design to compare the powder-in-capsule and immediate release tablet of PF-02341066 in healthy volunteers; o Treatment A (Ref): 1 x 50-mg and 2 x 100-mg PICs, o Treatment B (Test): 1 x 50-mg and 2 x 100-mg IRTs. $AUC_{inf\ ref}/ AUC_{inf\ ,test}$ = 92.43% (84.86%, 100.68%); $Cmax_{, ref}/ Cmax_{, test}$ = 98.91% (90.18%, 108.48%)
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -	**X**	**1**		**Study A8081011:** 4x4crossover design. The Commercial Image Capsule (CIC) crizotinib formulation demonstrated bioequivalence to both the crizotinib IRT and PIC formulations (references).

traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	**X**	**1**		**Study A8081011:** The coadministration of crizotinib with food resulted in a modest reduction (14%) in AUCinf and Cmax.
QT_C studies	**X**	**1**		**Study report of PMAR-00224:** o Data set of 326 patients contributing a total of 964 crizotinib concentration-ECG matched pairs from Studies A8081001 (640 pairs) and A8081005 (324 pairs). The study population consisted of 161 males and 165 females with weights ranging from 32 to 152 kg and 25.2% Asian patients.
In-Vitro Release BE				NA
(IVIVC):				NA
Bio-wavier request based on BCS				NA
BCS class				BCS IV
III. Other CPB Studies				
Genotype/phenotype studies:				NA; Ongoing
Chronopharmacokinetics				
Pediatric development plan				Requested waiver for rarity of the disease in pediatric population
Literature References				
Total Number of Studies		**8 PK-related clinical trial** **2 Pop PK-PD Study Reports** **24 in-vitro studies**		
Filability and QBR comments	**X**			
	"X" if yes	Comments		
Comments sent to firm?				
QBR questions (key issues to be considered)				
Other comments or information not included above				
Primary reviewer Signature and Date		**Pengfei Song, Ph D. 04/07/2011**		
Secondary reviewer Signature and Date		**Qi Liu, Ph.D. 04/07/2011**		

CC:
HFD-150 (CSO –Diane Hanner; **MTL –Virginia E Maher**; **MO – Shakun Malik)**
HFD-860 (Reviewer – P Song; **TL –** Q Liu; **DDD**-B Booth**; DD -** A Rahman**)**

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			

4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?		X		
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?		X		The sponsor requested a pediatric waiver, as the disease is very rare in pediatric patients

16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? _YES__

If the NDA/BLA is not fileable from the clinical pharmacology 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.

Pengfei Song 04/07/2011

Reviewing Clinical Pharmacologist Date

Qi Liu 04/07/2011

Team Leader/Supervisor Date

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

/s/

PENGFEI SONG
05/10/2011

QI LIU
05/11/2011