

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202570Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

PMR Description: 1789-1 Clinical trial report and datasets from A8081007: Phase 3, Randomized, Open-label Study of the Efficacy and Safety of PF-02341066 vs. Standard of Care (Pemetrexed or Docetaxel) in Patients with Advanced Non-Small Cell Lung Cancer Harboring a Translocation or Inversion Event Involving the Anaplastic Lymphoma Kinase Gene Locus

PMR/PMC Schedule Milestones:	Final Protocol Submission:	09//2009 (submitted)
	Study/Trial Completion:	12/2013
	Final Report Submission:	06//2014
	Other:	_____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

This randomized trial will provide additional information on the safety and efficacy of crizotinib in a comparative setting.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Crizotinib was approved on the basis of single arm studies in a population with non-small cell lung cancer. To fully determine the safety profile of this drug in a population with substantial pre-existing disease, it will be necessary to compare the adverse event profile of crizotinib to that of other drugs. Further, the efficacy of crizotinib in comparison to other drugs is an important safety concern since this will impact the patient’s ultimate outcome.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

This is an ongoing randomized clinical trial in patients with non-small cell lung cancer who have received one prior therapy.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
To ensure that the results of this study will be submitted regardless of the results of the primary analysis.

 - Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)

 - Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Are the objectives clear from the description of the PMR/PMC?
 - Has the applicant adequately justified the choice of schedule milestone dates?
 - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*
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PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

PMR Description: 1789-2 Clinical trial report and datasets from A8081014: Phase 3, Randomized, Open-label Study of the Efficacy and Safety of Crizotinib vs. Pemetrexed/Cisplatin or Pemetrexed/Carboplatin in Previously Untreated Patients with Non-Squamous Carcinoma of the Lung Harboring a Translocation or Inversion Event Involving the Anaplastic Lymphoma Kinase Gene Locus

PMR/PMC Schedule Milestones:	Final Protocol Submission:	06/2010 (submitted)
	Trial Completion:	12/2015
	Final Report Submission:	06/2016
	Other:	_____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

This study will provide comparative information on the safety and efficacy of crizotinib in patients with non-small cell lung cancer who have received no prior treatment. Since this population has less comorbid disease, the adverse event profile of crizotinib, seen in this comparative setting, will be more clearly delineated.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Crizotinib was approved on the basis of a surrogate endpoint in two small, single-arm trials. This study will provide additional safety data as well as information of the efficacy of crizotinib in this setting. Information on the efficacy of crizotinib is ultimately a safety concern since it may impact overall survival.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

An ongoing clinical trial in patients with untreated non-small cell lung cancer

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
Overall survival data from an ongoing clinical trial
 - Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Are the objectives clear from the description of the PMR/PMC?
 - Has the applicant adequately justified the choice of schedule milestone dates?
 - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

PMR Description: 1789-3 Submit the final report on the ongoing *in vitro* evaluations of induction potential of crizotinib on CYP2B and CYP2C enzymes.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	12/2011
	Study Completion:	12/2011
	Final Report Submission:	12/2011
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

As crizotinib induces CYP3A mRNA up to 23 fold, crizotinib may also induce CYP2B or CYP2C enzymes, which may subsequently decrease the drug concentrations of the substrates of these enzymes. The ongoing *in vitro* evaluations induction potential of crizotinib on CYP2B and CYP2C enzymes is therefore should be submitted for FDA's review.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

As crizotinib induces CYP3A mRNA up to 23 fold, crizotinib may also induce CYP2B or CYP2C enzymes, which may subsequently decrease the drug concentrations of the substrates of these enzymes. The ongoing *in vitro* evaluations induction potential of crizotinib on CYP2B and CYP2C enzymes may answer whether dose adjustments are needed for coadministration with CYP2B or CYP2C substrates with crizotinib.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The study is in vitro screening study using biomaterials such as hepatocytes.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial

- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

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NDA 202570 (Crizotinib)
PMR/PMC Ophthalmology

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

PMR Description: 1789-4 Clinical trial (existing trial or new clinical trial) in which at least 30 patients are studied. The following examinations should be performed in these patients at baseline, 2 and 6 weeks after drug administration and 2-8 weeks after discontinuation of the therapy (single visit post therapy).

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

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>10/2011</u>
	Trial Completion:	<u>12/2013</u>
	Final Report Submission:	<u>06/2014</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Additional ophthalmology examinations and tests will further clarify the significance and long term effects of these visual symptoms.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Visual disturbances associated with the use of crizotinib occurred in the majority of patients taking the drug product. These events have not been well characterized and included diplopia, photopsia, photophobia, vision blurred, visual field defect, visual impairment, vitreous floaters, visual brightness, and visual acuity reduced.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Clinical trial (existing trial or new clinical trial) in which at least 30 patients are studied.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- X **Primary safety study or clinical trial**
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- X Does the study/clinical trial meet criteria for PMRs or PMCs?
- X Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

PMR Description: 1789-5 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.

PMR/PMC Schedule Milestones:

Final Protocol Submission	09/2009 (submitted)
Trial Completion Date:	12/2013
Final Report Submission Date:	06/2014
Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Crizotinib appears to prolong the QTc interval. However, the QTc evaluation of crizotinib in trials A8081001 and A8081005 is inconclusive, due to ECG acquisition and interpretation issues. Large increases in QT interval (i.e., ~20 ms) can not be reliably excluded. The IRT-QTc review team recommends this PMR, based on previous agreement with the sponsor, to complete and submit a ongoing dedicated QTc assessment at 250 mg BID in the ECG sub-study in trial A8081007 to gain reliable estimation of QT effect size, especially if indications other than NSCLC with different benefit-risk balances are being pursued.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Based on the QTc evaluation of crizotinib in trials A8081001 and A8081005, crizotinib appears to be associated with concentration-dependent QT interval prolongation ($P < 0.001$).

The QT-IRT recommends a PMR to complete and submit an ongoing dedicated QTc assessment at 250 mg BID in the ECG-substudy in trial A8081007 to gain reliable estimation of QT effect size.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Time-matched PK/ECGs samples will be collected in 40 patients in the treatment Arm A (250 mg crizotinib BID) of Phase 3 trial 1007. In this ECG sub-study, all post-screening ECGs will be read in a blinded fashion by a central reader. The ECG recordings will be transferred digitally to a central reader where they will be stripped of any information which could permit identification of the patient, site, date or time. The ECGs will be evaluated for interval assessments including PR, QT, RR and QRS.

Based upon the standard deviation of change from baseline of QTc of 16 ms (Study A8081001), a total sample size of 40 patients from both Studies A8081007 (Arm A) and A8081005 should be sufficient for greater than 90% probability that all five boundaries of upper one-sided 95% confidence intervals for the change from baseline of QTc at all five QTc sampling time points on Cycle 2 Day 1 are under 20 ms, assuming the true change from baseline in QTc is 10 ms.

Required

- Observational pharmacoepidemiologic study
 Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 Thorough Q-T clinical trial
 Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 Pharmacokinetic studies or clinical trials
 Drug interaction or bioavailability studies or clinical trials
 Dosing trials
 Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 Immunogenicity as a marker of safety
 Other (provide explanation)

QT prolongation assessment using open-label, non-thorough QT study design.

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 Dose-response study or clinical trial performed for effectiveness
 Nonclinical study, not safety-related (specify)

-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The required drug-drug interaction trial will be a phase 1, crossover or parallel design to evaluate the effect of a CYP3A4 inhibitor, ketoconazole, on the pharmacokinetics of crizotinib at steady-state in humans.

Required

- Observational pharmacoepidemiologic study
 - Registry studies
- Continuation of Question 4*
- Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial

- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

PMR/PMC Description: 1789-7 Conduct a multiple dose trial in patients to determine how to adjust the crizotinib dose when it is coadministered with a strong CYP3A inducer (e.g., rifampin).

PMR/PMC Schedule Milestones: Final protocol Submission Date: 03/2012
/Clinical trial Completion Date: 01/2015
Final Report Submission Date: 07/2015
Other: _____ MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

NDA review indicated the need for 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). Crizotinib is extensively metabolized by CYP3A *in vitro*. Co-administration of single dose crizotinib with rifampin, a potent CYP3A inducer, decreases crizotinib AUC by 82% in healthy subjects. However, this result of a single-dose crizotinib interaction study can not be used to predict the effect of rifampin at the steady-state, due to the non-linear pharmacokinetics of crizotinib that was possibly caused by time-dependent inhibition of CYP3A. Therefore, a clinical drug interaction trial of crizotinib at steady-state with a strong CYP3A inducer, such as rifampin, is required to identify a safe dose when crizotinib is coadministered with CYP3A inducers.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Crizotinib is extensively metabolized by CYP3A. Thus, co-administration of rifampin, a potent CYP3A inducer, leads to a 82% decrease in crizotinib AUC in humans, which may subsequently lead to treatment failures. However, such single-dose drug interaction study can not be used to predict the effect of rifampin at the steady-state, due to the non-linear pharmacokinetics of crizotinib. A clinical drug interaction trial of crizotinib at steady-state with a potent CYP3A inducer, such as rifampin, is therefore required to determine the magnitude of crizotinib exposure changes when they are co-administered. Depending on the results, a safe dose of crizotinib may be identified for crizotinib when co-administered with potent CYP3A inducers.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

This required drug-drug interaction clinical trial will be a phase 1, crossover or parallel design to evaluate the effect of a strong CYP3A inducer (e.g., rifampin) on the pharmacokinetics of crizotinib at steady-state in humans.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety

- Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The required clinical trial will be a Phase 1 trial designed to assess the PK and safety of crizotinibi at steady-state in humans with mild, moderate and severe hepatic impairment.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety

- Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

This required clinical trial will be a phase 1 trial to evaluate the PK and safety of crizotinib in patients with severe renal impairment in order to identify a safe dose for such patient population.

Required

- Observational pharmacoepidemiologic study
 - Registry studies
- Continuation of Question 4*
- Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

This required clinical trial will be a phase 1, crossover or parallel design 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).

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial

- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

**NDA 202570 (Crizotinib)
PMR/PMC Development Template**

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

PMC Description: 1789-11 To assess the adequacy of the current cut-off, conduct a clinical trial to explore response to crizotinib in ALK-negative patients based on current assay cut-off. This should be compared to historic controls and to the response in ALK-positive patients. Additional biomarkers should be assessed in ALK-negative patients.

PMC Schedule Milestones:	Final Protocol Submission:	<u>10/2011</u>
	Trial Completion:	<u>05/2013</u>
	Final Report Submission:	<u>11/2013</u>
	Other:	<u>n/a</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

This requested trial will provide additional information on the safety and efficacy of crizotinib in a comparative setting of ALK negatives using the drug's companion diagnostic test (Abbott Molecular Vysis ALK Break Apart FISH probe assay).

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Crizotinib was approved on the basis of single arm studies in an ALK positive population with non-small cell lung cancer. Preliminary data from a small cohort of ALK negative patients shows that 5/19 patients (26.3%) who were classified as ALK negative (<15% of tumor cells positive for ALK gene rearrangement) who were enrolled into A8081001 showed a partial response to the drug similar to that as seen in the ALK positive cases at a similar time point. In addition, 2/19 patients (10.5%) were shown to have a best response of stable disease. It is necessary to further explore the response in patients determined to be ALK negative by the Vysis ALK Break Apart FISH probe assay to determine if crizotinib should be confined to the ALK positive population.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

An (exploratory/Phase II type) clinical trial in which the ALK negative patients are enrolled using the Vysis assay. The patient population should be comparable to those from A8081005. In addressing the bullets below attention will be needed for controlling for prescreening of patients prior to enrollment. The Sponsor (Pfizer, Inc.) is requested to propose a study designed to answer the following questions:

- Does the companion test divide the population into groups of patients who will respond better or worse (or not as well) when treated with crizotinib?
- Is crizotinib active in patients identified as ALK negative, based on the current established cut-off (<15%) using the Vysis ALK Break Apart FISH probe assay?
- In ALK negative patients, is the activity of crizotinib greater than the activity of standard lines of therapy for this patient population (compared to historical/currently known response rates)? (Pfizer may wish to refer to Jiang W, Friedlin B, and Simon R.

JNCI. 99(13):1036-1043. 2007.)

- Should other biomarkers, either in addition to or combination with ALK be taken into account when determining if treatment with crizotinib should be considered?

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Continuation of Question 4

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

Other

No pre-screening for ALK status should be performed. Patients should be tested with the Vysis ALK Break-Apart FISH assay only.

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

NDA 202570 (Crizotinib)
PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

PMC Description: 1789-12 To conduct exposure-response analysis for progression free survival, response rate, overall survival and safety endpoints utilizing data from confirmatory trial A8081007 and to submit the analysis plan for review.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>09/2009 (submitted)</u>
	/Trial Completion:	<u>12/2013</u>
	Final Report Submission:	<u>06/2014</u>
	Other: <u>Analysis Plan Submission</u>	<u>05/2012</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

There is an exposure-response relationship for objective response rate in trials A8081001 and A8081005. 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. However, further analysis is needed to address these issues and determine if the dose is optimal for this subpopulation or they are non-responders. In trial A8081005, even for patients with drug concentration below 200 ng/ml, the response rate was 47% and less steep exposure-response curve is 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. Thus, exposure-response analysis from confirmatory trials, A8081007 and A8081014 would be essential to determine if the 250 mg BID dose is optimal for all patients.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Based on analysis utilizing data from trial A8081001 and A8081005, there is exposure-response relationship for objective 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. However, further analysis is needed to address these issues and determine if the dose is optimal for all patients. Exposure-response analysis from confirmatory trials, A8081007 and A8081014 would be essential to determine if the 250 mg BID dose is optimal for all patients.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

An exposure-response analysis should be conducted for progression free survival, response rate, overall survival and safety endpoints such as pneumonitis and liver related toxicities utilizing data from confirmatory trials A8081007 and A8081014. The analysis should include all possible covariates that are likely to influence response. Since pharmacokinetic samples are being collected in these trials, both observed crizotinib concentrations and population PK model predicted concentrations should be used. The goal of this analysis should be to justify the dosing regimen in all patients.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

-
- Other
Exposure-response analysis utilizing data from confirmatory trials A8081007 and A8081014
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

NDA 202570 (Crizotinib)
PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

PMC Description: 1789-13 To conduct exposure-response analysis for progression free survival, response rate, overall survival and safety endpoints utilizing data from confirmatory trial A8081014 and to submit the analysis plan for review.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>06/2010 (submitted)</u>
	Trial Completion:	<u>12//2015</u>
	Final Report Submission:	<u>06//2016</u>
	Other: <u>Analysis Plan Submission</u>	<u>05/2012</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

There is an exposure-response relationship for objective response rate in trials A8081001 and A8081005. 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. However, further analysis is needed to address these issues and determine if the dose is optimal for this subpopulation or they are non-responders. In trial A8081005, even for patients with drug concentration below 200 ng/ml, the response rate was 47% and less steep exposure-response curve is 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. Thus, exposure-response analysis from confirmatory trials, A8081007 and A8081014 would be essential to determine if the 250 mg BID dose is optimal for all patients.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Based on analysis utilizing data from trial A8081001 and A8081005, there is exposure-response relationship for objective 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. However, further analysis is needed to address these issues and determine if the dose is optimal for all patients.

Exposure-response analysis from confirmatory trials, A8081007 and A8081014 would be essential to determine if the 250 mg BID dose is optimal for all patients.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

An exposure-response analysis should be conducted for progression free survival, response rate, overall survival and safety endpoints such as pneumonitis and liver related toxicities utilizing data from confirmatory trials A8081007 and A8081014. The analysis should include all possible covariates that are likely to influence response. Since pharmacokinetic samples are being collected in these trials, both observed crizotinib concentrations and population PK model predicted concentrations should be used. The goal of this analysis should be to justify the dosing regimen in all patients.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

-
- Other
Exposure-response analysis utilizing data from confirmatory trials A8081007 and A8081014
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

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/s/

DIANE C HANNER
08/24/2011

KATHERINE M FEDENKO
08/25/2011

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: August 12, 2011

TO: Dianne Hanner, Regulatory Project Manager
Shakun Malik, M.D., Ph.D., Medical Officer
Division of Drug Oncology Products

FROM: Robert Young
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Lauren Iacono-Connors, Ph.D.
Acting Team Leader, Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Jean Mulinde, M.D.
Acting Branch Chief, Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 202570

APPLICANT: Pfizer Inc
San Diego, CA

DRUG: Xalkori (crizotinib)

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority

INDICATION: Anaplastic lymphoma kinase positive advanced non-small cell lung cancer

CONSULTATION REQUEST DATE: March 31, 2011

Inspection Summary Goal Date: September 15, 2011 (Revised date)
DIVISION ACTION GOAL DATE: September 29, 2011 (Revised date)
PDUFA DATE: September 30, 2011

I. BACKGROUND:

Crizotinib is an inhibitor of the anaplastic lymphoma kinase (ALK) receptor tyrosine kinase (RTK) and its oncogenic variants. Crizotinib is also an inhibitor of the Hepatocyte Growth Factor Receptor (HGFR, c-Met) RTK. Crizotinib inhibits the kinase activity of ALK and c-Met in biochemical assays and inhibits phosphorylation and modulated kinase-dependent phenotypes in cell-based assays. Crizotinib demonstrates potent and selective growth inhibitory activity and induces apoptosis in tumor cell lines exhibiting ALK fusion events (including EML4-ALK and NPM-ALK) or exhibiting amplification of the ALK or MET gene locus. Crizotinib has cytoreductive antitumor activity, in mice bearing tumor xenografts that express ALK fusion proteins.

Protocol Study A8081001 was an open-label, dose escalation, safety, PD, PK, and antitumor activity study of crizotinib administered as a single oral agent to patients with advanced malignancies. It was carried out in eight sites in three countries including the US. This study was designed as a Phase 1 dose-escalation study in patients with any tumor type (except leukemia) followed by a expansion cohort to include at least 8, but no more than 15 patients, to further evaluate the safety and PK of the MTD of crizotinib. The starting dose was 50 mg daily.

Protocol Study A8081005 was an open-label, single-arm, Phase 2 study of crizotinib in patients with advanced (locally advanced or metastatic) NSCLC harboring a translocation or inversion event involving the ALK gene locus. The study was carried out at 57 sites in 12 countries including the US. Crizotinib 250 mg twice daily (BID) as a starting dose was administered orally continuously in 21-day cycles. Radiographic disease assessments for objective disease response and progression were to be performed at 6-week intervals (12-week intervals for bone scans) following the first dose of crizotinib. Study treatment was to be continued until the occurrence of disease progression or clinical deterioration, unacceptable toxicity, patient's withdrawal of consent, or protocol noncompliance. Crizotinib treatment could be continued after disease progression if the patient was considered to be benefitting clinically.

II. RESULTS (by Site):

All classifications are preliminary and based on preliminary review of Establishment Inspection Reports (EIR) of the clinical investigator audits, and written communications with the FDA field investigator who conducted the Pfizer sponsor inspection. These preliminary classifications are subject to revision based on final review of the relevant EIR and associated exhibits and responses to Form FDA 483 observations submitted by the inspected entity. An inspection summary addendum will be generated if conclusions change upon receipt and complete review of the EIRs

Name of CI (Site Number) or Sponsor	Protocol ## of Subjects	Inspection Date	Preliminary Classification
Jeffrey Clark (1002) Massachusetts General Hospital 55 Fruit St. Boston, MA 02114	A8081001/93	4/26 – 5/5/2011	NAI
Alice Shaw (1021) Massachusetts General Hospital 55 Fruit St. Boston, MA 02114	A8081005/13	5/3-10/2011	VAI
Dong-Wan Kim (1058) Seoul National University Hospital 28 Yongon-Dong, Chongno-Gu Seoul 110744 Korea	A8081005/23	4/16-20/2011	VAI
Yung-Jue Bang (1007) Seoul National University Hospital Department of Internal Medicine 28 Yongon-Dong, Chongno-gu Seoul, Korea 110-744	A8081001/37	5/23-27/2011	VAI
Pfizer Inc 10646 Science Center Drive San Diego, CA and Groton, CT	Sponsor/Monitor oversight of sites listed above was focused on during the inspection	6/6-9/2011	NAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and/or complete review of EIR is pending.

1. Jeffrey Clark

- a. What was inspected: The case histories of 30 subjects were reviewed for accuracy and completeness.
- b. General observations/commentary: No significant regulatory violations were found and a Form FDA 483 was not issued.
- c. Assessment of data integrity: The data from this site is acceptable in support of the pending application.

2. Alice Shaw

- a. What was inspected: Of the 13 subjects enrolled, 7 were transferred to other study sites leaving 6 at the inspected study site. The case histories of the latter were reviewed for accuracy and completeness.
- b. General observations/commentary: The records were well maintained and complete. Noted and reported on a Form FDA 483 was the failure to report to the sponsor all concomitant medications, which occurred because some medications were not entered into the electronic data capture system for transmission to the sponsor. For example, among the medications taken, but not reported was the use by several subjects of: Vitamin C, Vitamin D, homocysteine complex, prilosec, KCl, Oxycodone, Omeprazol, Guaifenesen, acetaminophen, etc. The clinical investigator replied to the issued Form FDA 483 acknowledging the lapse and putting into place a plan to avoid such lapses in the future. Additionally, the missing concomitant medications were entered into the data capture system.
- c. Assessment of data integrity: Although serious, the reporting lapse identified during the inspection appears to be isolated and the concomitant medications not reported are generally considered not to interact in a meaningful way with the investigational new drug or disease under consideration. There does not appear to be a general failure to report data from the study. The data from this site are acceptable in support of the pending application.

3. Dong-Wan Kim

- a. What was inspected: Of the 65 subjects screened, 31 were enrolled in the study. The case histories of 23 enrolled subjects were reviewed for accuracy and completeness.
- b. General observations/commentary: The records were generally in good order and the only regulatory violation identified and shared with the clinical investigator on a Form FDA 483 was the failure to include in several consent documents a statement of the possibility that the FDA might inspect the records. In his reply to the issued Form FDA 483, the investigator acknowledged the lapse and instituted a plan to avoid future violations.
- c. Assessment of data integrity: The deficiency identified during the inspection is not related to data integrity. The data generated by this site are acceptable in support of the pending application.

4. Yung-Jue Bang

- a. What was inspected: Of the 61 patients screened, 45 subjects were enrolled. The case histories of 24 enrolled subjects were reviewed for accuracy and completeness.

- b. General observations/commentary: The records were complete and accurate, and consistent with the investigational plan, except for the following observations noted on the Form FDA 483 issued to the clinical investigator:
- for one scheduled visit each, three subjects were evaluated by their family physician because of governmental air travel restrictions imposed when the H1N1 flu was declared pandemic;
 - for four subjects on day 1, cycle 1, the specific time of day of various sampling time points (e.g. hour 6, hour 9, etc), had not been entered in the Core Laboratory Log Book; and
 - in 8 different versions of the consent form there was no statement that the FDA might possibly inspect the study records.

The clinical investigator in his reply to the issued Form FDA 483 acknowledged the observations and instituted plans to avoid future violations.

- c. Assessment of data integrity: The first two deficiencies identified during the inspection appear to be minor and sporadic in nature; in addition, they are unlikely to significantly impact primary safety and efficacy analyses. The third item is not directly related to data integrity. The data generated by this site are acceptable in support of the pending application.

5. Pfizer Inc.

- a. What was inspected: This inspection was initially assigned for San Diego, CA, but as the records were in New London, CT; therefore, the assignment was transferred to CT. The Sponsor was inspected in accordance with the Sponsor/Monitor/CRO data validation compliance program, CP 7348.810. In addition to conduct of routine aspects of this program, the Sponsor's adequacy of oversight of the four audited clinical investigators above was specifically evaluated.
- b. General observations/commentary: Previous inspections (2005, 2008, and 2009) of the sponsor related to other applications were classified NAI and OAI (2009). During the 2009 inspection, it was identified that the sponsor had failed to ensure proper monitoring of the investigation and that the study was conducted according to the protocol, etc. Similar issues were not identified during the present inspection; there were no significant regulatory violations identified in relation to the conduct of studies submitted in support of the current application. A Form FDA 483 was not issued.
- c. Assessment of data integrity: Notwithstanding regulatory violations discussed in prior sections of this review, the data submitted from this sponsor to the agency as part and in support of NDA 202570 appear to be generally reliable.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Based on the review of preliminary inspectional findings for the sponsor (Pfizer), no regulatory violations have been identified in relation to their execution of Study A8081001 and Study A8081005, submitted in support of this application. The preliminary classification for the inspection of Pfizer is No Action Indicated (NAI). Based on the review of preliminary inspectional findings for the four audited clinical investigators above – Doctors Clark (NAI), Shaw (VAI), Kim (VAI), Bang (VAI) - survival data and toxicity data reported in the NDA appear reliable. Data from Study A8081001 and Study A8081005 are considered reliable in support of the requested indication.

Dr. Shaw did not report all concomitant medication usage to the sponsor, but the concomitant medications missed tended to be in the category of over the counter medications which probably had little impact on the investigational new drug and disease and consequently the study. The failures of Dr. Kim and Dr. Bang to identify on informed consent documents that the FDA might inspect the study records is not related to data integrity and is a technical deficiency. The substitution by Dr. Bang of a family physician evaluation of subjects when the subjects could not physically visit the study site was unavoidable given circumstances related to H1N1 restrictions, and the failure to capture the time of day related to each sampling point is considered a sporadic and minor deviation that is unlikely to significantly impact study results.

Note: All observations noted above are based on the preliminary communications provided by the FDA field investigators and preliminary review of available Form FDA 483, inspectional observations. An inspection summary addendum will be generated if conclusions change significantly upon receipt and complete review of the EIRs.

Follow-Up Actions: OSI will generate an inspection summary addendum if the conclusions change significantly upon final review of the EIRs and supporting inspection evidence and exhibits.

{See appended electronic signature page}

Robert Young
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCES: {See appended electronic signature page}

Lauren Iacono-Connors, Ph.D.
Acting Team Leader, Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

{ See appended electronic signature page }

Jean Mulinde, M.D.
Acting Chief, Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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/s/

ROBERT S K YOUNG
08/12/2011

LAUREN C IACONO-CONNORS
08/12/2011

JEAN M MULINDE
08/15/2011

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/s/

AMARILYS VEGA
08/11/2011

CLAUDIA B KARWOSKI
08/11/2011
concur

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

PATIENT LABELING REVIEW

Date: August 11, 2011

To: Robert Justice MD, Director
Division of Drug Oncology Products (DDOP)

Through: LaShawn Griffiths, RN, MSHS-PH, BSN
Acting Team Leader, Patient Labeling Reviewer
Division of Risk Management (DRISK)

Barbara Fuller, RN, MSN, CWOCN
Acting Team Leader, Patient Labeling Reviewer
Division of Risk Management

From: Latonia M. Ford, RN, BSN, MBA
Patient Labeling Reviewer
Division of Risk Management

Subject: DRISK Review of Patient Labeling (Patient Package Insert)

Drug Name (established name): Tradename (crizotinib)

Dosage Form and Route: Capsules, oral

Application Type/Number: NDA 202570

Applicant: Pfizer Inc.

OSE RCM #: 2011-1135

1 INTRODUCTION

This review is written in response to a request by the Division of Drug Oncology Products (DDOP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Patient Package Insert (PPI) for Tradename (crizotinib) Capsules.

On January 4, 2011, Pfizer Inc. submitted original New Drug Application (NDA), 202570 for Tradename (crizotinib) Capsules. The Applicant seeks accelerated approval for the proposed indication of the treatment of anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC).

2 MATERIAL REVIEWED

- Draft Tradename (crizotinib) Capsules, oral Patient Package Insert (PPI), received on March 30, 2011, and received by DRISK on August 3, 2011.
- Draft Tradename (crizotinib) Capsules, oral prescribing information (PI) received March 30, 2011 revised by the Review Division throughout the current review cycle, and received by DRISK on August 3, 2011.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APhont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 11.

In our review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the prescribing information (PI)
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DRISK on the correspondence.
- Our annotated (tracked and clean) versions of the PPI are appended to this memo. Consult DRISK regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI

Please let us know if you have any questions.

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

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/s/

LATONIA M FORD
08/10/2011

LASHAWN M GRIFFITHS
08/11/2011

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY

DATE: 10 August 2011

FROM: John R. Senior, M.D., Associate Director for Science, Office of Pharmacovigilance and Epidemiology (OPE), Office of Surveillance and Epidemiology (OSE)

TO: Robert Justice, M.D., Director, Division of Drug Oncologic Products (DDOP)
Shakun Malik, M.D., Medical Safety Officer, DDOP
V. Ellen Maher, M.D., Medical Team Leader, DDOP

VIA: Gerald Dal Pan, M.D., Director, OPE

SUBJECT: Possible hepatotoxicity of crizotinib (Pfizer); NDA 202570, assigned OSE tracking number 2011-1341.

Documents reviewed:

- 1) Consultation request dated 26 April 2011 from Diane Hanner, project manager DDOP, requesting my review regarding the liver toxicity of this drug
- 2) Copies of narrative summaries for one case selected by Dr. Malik, and two others found in the sponsor's report as adverse events resulting in discontinuation of drug
- 3) Labeling for other members of the drug class of tyrosine kinase inhibitors (TKIs)
- 4) Medical literature on crizotinib, and other TKIs.

Crizotinib (TKI-258, Novartis) is being developed as an anti-neoplastic agent for treating non-small cell lung cancer (NSCLC). Its NDA 202570 was received 30 March 2011, and was granted priority review. The agent is another member of the tyrosine kinase receptor inhibitors, of which many have been approved for targeted attack on several types of advanced cancers:

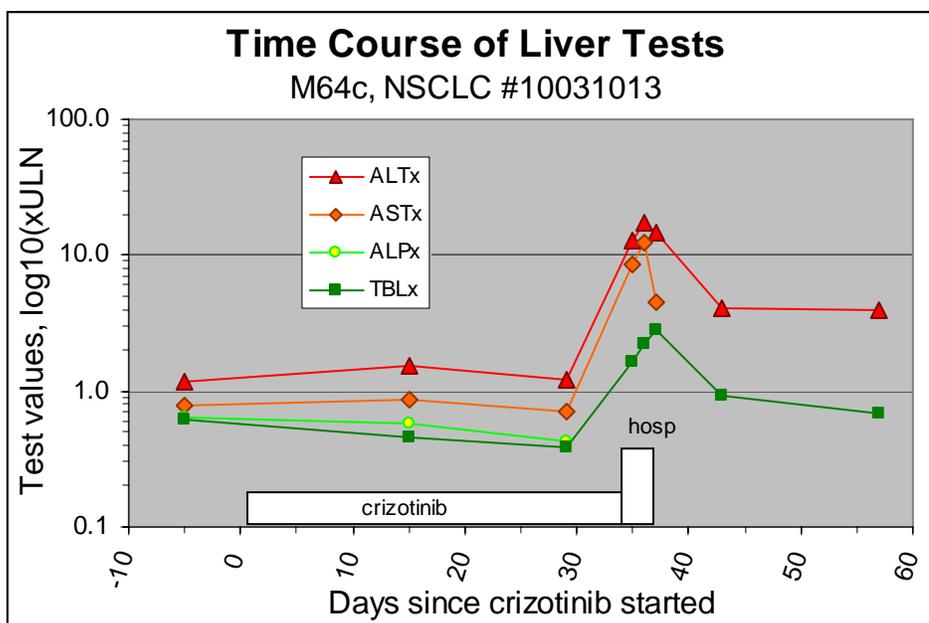
imatinib (GLEEVEC®, Novartis, NDA 21-335, 10 May 2001),
gefitinib (IRESSA®, AstraZeneca, NDA 21-399, 5 May 2003),
erlotinib (TARCEVA, Genentech, NDA 21-743, 18 November 2004),
sorafenib (NEXAVAR®, Bayer Pharmaceuticals, NDA 21-923, 20 December 2005),
sunitinib (SUTENT®, Pfizer, NDA 21-968, 25 January 2006),
dasatinib (SPRYCEL, BristolMyersSquibb, NDA 21-986, 28 June 2006),
lapatinib (TYKERB, SmithKlineBeecham, 13 March 2007),
nilotinib (TASIGNA, Novartis, NDA 22-068, 29 October 2007),
pazopanib (VOTRIENT®, GlaxoSmithKline, NDA 22-465, 19 October 2009),
vandetanib (CAPRELSA®, AstraZeneca, NDA 22-405, 6 April 2011),

and there may have been more. Some are still under investigation:

(b) (4)

including this drug, crizotinib. Several of them already have boxed warnings about severe and fatal hepatotoxicity associated with their use, with recommendations for assessment of liver status before starting treatment and careful monitoring on treatment. It would be prudent to look for possible hepatotoxicity in any member of this class of agents.

The index case of concern about possible drug-induced serious hepatotoxicity was reported from the University of Colorado, site 1003 (Dr. Ross Camidge), to the sponsor on 8 December 2010 and from them to us 10 January 2011. The adverse effect occurred in a 64-year-old man (date of birth (b) (6)) subject 1013 diagnosed with non-small cell lung cancer, brain metastases and electrolyte depletion. He had a history of hypertension since September 2009 and had been on lisinopril and dexamethasone since then, ranitidine since January 2010, potassium supplements, temazepam and diphenhydramine since March 2010. He started taking oral crizotinib 250 mg twice daily on 4 May 2010 and continued until 5 June. He developed abdominal pain on (b) (6), with angioedema, and was advised by a nurse practitioner to take 2 mg dexamethasone and report to the emergency room. He was given more dexamethasone and diphenhydramine, with some benefit, but the next day his lips were swollen, and the pain was so severe at times that he fell to the floor. He couldn't eat, and had fullness and bloating but no nausea or vomiting. He went back to the emergency room with worsening angioedema and was admitted on the evening of (b) (6). Distended gallbladder with stones and sludge were noted by ultrasound, and patchy right lower lung nodular consolidation and mass by x-ray. His serum lipase was elevated to 713 (11.3 times the upper limit of the normal range (xULN)). Acute pancreatitis was diagnosed, but no further tests of lipase were done. In hospital it was noted that serum aminotransferase enzyme activities were elevated markedly and his serum bilirubin was rising.

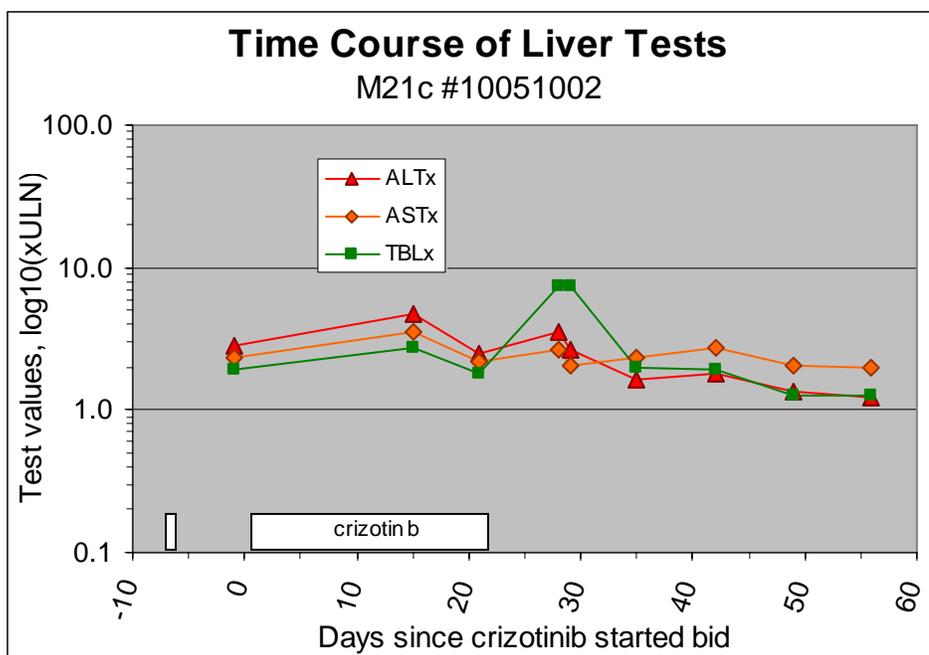


The serum alanine aminotransferase (ALT) activity rose to a peak of 17.1 times the upper limit of the normal range (xULN), aspartate aminotransferase (AST) to 12.3 xULN on (b) (6), and total bilirubin (TBL) to 3.6 mg/dL (2.8 xULN) on the (b) (6), when he was discharged from the hospital as “recovered,” according to the narrative summary provided. No further testing of pancreatic enzymes was done; no additional alkaline phosphatase (ALP) enzyme activity or AST measures were done. He was eating, had no abdominal pain, and was sent home for care by his daughter. The serum ALT values were still elevated but slowly subsiding on the 15th and 29th of June, by which time the TBL had returned to normal. No further crizotinib was given.

Comment: The investigators seemed quite unsure of what was going on, attributing the problem first to acute pancreatitis and then switching to “elevated liver enzymes” or “transaminitis” that were “possibly related” to study drug, but not really following closely or making firm diagnosis. The data suggest that this sequence of events involved both acute edematous pancreatitis and fairly serious but not severe hepatocellular injury with borderline clinical jaundice, probably drug-induced by crizotinib.

Among the other reports of potential interest regarding hepatotoxicity in the report of the phase I safety study done according to protocol A8081001, there were two patients reported from center 1005 (Dr. R. G. Maki, Memorial Sloan Kettering Cancer Research Center, New York). They are summarized briefly below:

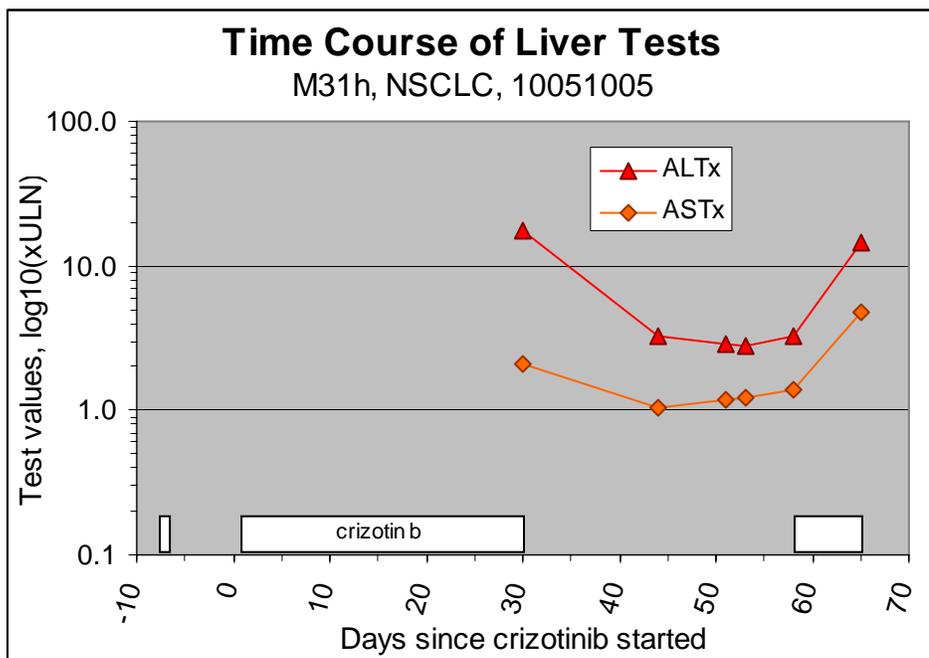
Patient 10051002 was withdrawn from crizotinib 250 mg b.i.d. because of “increased blood bilirubin.” He was a 21-year-old male with inflammatory myofibroblastic tumor, given a single dose of crizotinib orally on 24 July 2008, then started on twice-daily crizotinib 250 mg from 31 July to 21 August. Elevated serum total bilirubin (TBL) at 2.7 mg/dL was found on 14 August, rising to 7.5 mg/dL on 27 and 28 August, after crizotinib had been stopped on the 21st.



He had a history of acute cholecystitis in 2007 with biliary obstruction and jaundice for which a biliary drain had been inserted. At screening he was said to have had an acneiform skin rash with red vesicles on the face and back (but no jaundice was noted). At the time of finding the elevated serum TBL he was reported to have fatigue, dark urine, anorexia, nausea, weight loss, dizziness, neuropathy, cough, low grade fever, and elevated AST and ALP. He was treated with penicillin and cetirizine, and had biliary catheter exchanges on (b) (6). The opinion of the investigator was that the TBL increase was related to study drug.

Comment: The data provided are sparse and confusing, but do not support a conclusion that the bilirubin increases were drug-induced, and it was unclear what exactly was going on. The young man had a chronic biliary obstructive process that was not well characterized in the report, but did not appear crizotinib-induced. No ALP values were reported in the narrative summary, and two different laboratories with wildly different normal ranges were used, and the results jumbled together. No testing was done before the single dose of crizotinib given a week before the daily regimen started. Very unclear report, but the problems described were unlikely to have been caused by crizotinib.

The second case reported from that center was that of a 31-year-old Hispanic male (10051005) with anaplastic lymphoma kinase-positive NSCLC given a single oral dose of crizotinib 250 mg on 8 June 2009, then started on twice daily crizotinib 250 mg in 15 June. Elevated serum activity of alanine aminotransferase (ALT) to 17.4 times the upper limit of the normal range (xULN) was found on 14 July, 30 days later, and crizotinib treatment was interrupted. Slight elevation of aspartate aminotransferase (AST) to 2.1 xULN was also noted. The ALT levels fell back to about 3xULN and crizotinib was restarted 11 August, but stopped permanently when recurrent ALT to 14.6xULN and AST to 4.8xULN were found a week later.



The patient had a history of appendectomy in 1986, bronchitis and central venous catheterization in 2009. At the time of finding the elevated ALT levels in mid-July he had been taking a large number of other medications, including salbutamol, dexamethasone, guaifensin with codeine, Robitussin DM, Centrum Silver (multivitamins), montelukast, benzonatate, aprepitant, EMLA cream, papadeine, and Orthoxicol, and he complained of fatigue, cough, mild wound dehiscence, nausea and vomiting. The investigator concluded that the increased ALT was crizotinib-related.

Comment: It is unclear whether the mild symptoms reported by the patient were related to his disease, or to adverse effects of crizotinib, but the ALT increase seem very likely crizotinib-induced. No testing was reported before crizotinib was started, but recurrence after rechallenge was strong evidence for probable or very likely drug-induced hepatocellular injury. No test results for bilirubin or alkaline phosphatase were provided, and virtually no work-up of the problem seems to have been done.

These cases indicate a potential for crizotinib to cause at least some patients to show liver injury that is probably or very likely drug-induced. The first case (10031013) was the most serious, but resolved gradually after withdrawal of crizotinib. The second case was probably due to biliary tract disease, and the third case reflected only serum enzyme increases (although no measures of true liver function were done). Given the modest number of patients exposed to crizotinib, and the approaching due date for priority decision on approval, at least some mention of the cases should be included in the labeling to warn physicians about the possibility. Benefits of treating their very serious advanced of metastatic cancers may outweigh the modest risk of serious harm from hepatotoxicity of this agent, as has been done in labeling of other TKIs.

Recommendations:

1. Include some warning about possible hepatotoxicity of crizotinib, and advice to work up and investigate patients showing serum ALT or AST rises to determine the severity and probable cause of the problem.
2. We may see additional cases as more patients are exposed, but it is difficult to estimate or extrapolate the extent from the limited exposure data available now.

John R. Senior, M.D.

cc: OSE consultation #2011-1341
S. Malik, DDOP
V.E. Maher, DDOP
G. Dal Pan, OSE

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/s/

JOHN R SENIOR
08/12/2011

Internal Consult

Pre-decisional Agency Information

To: Diane Hanner, RPM, Division of Drug Oncology Products, (DDOP)

From: Marybeth Toscano, Regulatory Reviewer Officer
Richard Lyght, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications
(DDMAC)

CC: Karen Rulli, Professional Review Group II Leader, DDMAC
Amy Toscano, DTC Review Group IV Leader, DDMAC

Date: August 9, 2011

Re: Comments on draft labeling (Package Insert) for crizotinib
capsules, oral
NDA 202570

In response to your consult request dated March 31, 2011, we have reviewed the draft version of the Package Insert for crizotinib capsules. We offer the following comments. Please note some of these comments may have been addressed during labeling meetings.

Section	Statement from draft	Comment
• 1 Indications and Usage and Highlights	Tradenname is a kinase inhibitor indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive [REDACTED] (b) (4) [REDACTED]	Please add "in patients with locally advanced or metastatic NSCLC"
• 14 Clinical Studies	Study A The median response duration was 41.9 weeks Study B	These statements may be used in promotion. Was the response a PR, CR, etc.? Please provide a clarification.

	The median response duration was 48.1 weeks	
<ul style="list-style-type: none"> 14 Clinical Studies 	<p>Study A</p> <p>Based on (b) (4) investigator assessments, there were 1 complete and (b) (4) partial responses for an ORR of 50% (95% CI: (b) (4)%, (b) (4)%). (b) (4)</p> <p>Study B</p> <p>Based on (b) (4) investigator assessments, there were 2 complete and 69 partial responses for an ORR of 61% (95% CI: 52%, 70%). (b) (4)</p>	Please include CR and PR values for the independent reviews.

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

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/s/

MARYBETH TOSCANO
08/09/2011

RICHARD A LYGHT
08/09/2011

Hanner, Diane

From: Hanner, Diane
Sent: Monday, August 08, 2011 10:07 AM
To: 'Domingo, Ron '
Subject: FDA clarifications regarding PMRs

Hi,

Per your August 03, 2011, request regarding the clinical pharmacology PMRs, FDA has the following clarifications:

PMR 2. 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).

PMR 3. 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).

Applicant's response to PMR 2 and 3:

Due to the likely difficulties associated with the conduct of the proposed studies, Pfizer would like to discuss the trials with the FDA. The conduct of multiple-dose studies in healthy volunteers is not feasible due to crizotinib's adverse event profile. Additionally, performing multiple-dose CYP3A inhibition and induction studies in cancer patients will be very difficult to recruit and complete. The conduct of multiple-dose CYP3A inhibition and induction studies in ALK-positive NSCLC patients poses concerns with regards to the possibility of sub-therapeutic and supratherapeutic crizotinib exposures. As the proposed USPI advises patients to avoid the concomitant use of crizotinib with strong CYP3A inhibitors or inducers, Pfizer does not believe that formal drug-drug interaction studies would be necessary.

Please provide more clarity on the population in which the Agency proposes that Pfizer conduct these CYP3A drug interaction trials. Additionally, please provide the draft labeling sections related to the CYP3A inhibitors/inducers so that we can consider the FDA's request in light of the marked-up product label.

FDA clarification:

We agree with you that strong CYP3A inducers and inhibitors should be avoided at this time. However, in order to determine the dose adjustments in patients who have to take crizotinib with CYP3A inducers or inhibitors, a multiple dose trial with a strong CYP3A inducer (e.g., rifampin) or a strong CYP3A inhibitor (e.g., ketoconazole) must be conducted in patients with cancers. We recommend that you use PBPK modeling and simulations (or other useful tools) and real-time PK to help the study design and conduct so that the exposure can be matched in the test condition to that in the reference condition (250 mg BID without coadministration of strong CYP3A inhibitors or inducers).

Draft labeling language will be available after August 11, 2011.

PMR 6. 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).

Applicant Response:

Pfizer does not believe it is possible to conduct a multiple-dose study in healthy volunteers due to crizotinib's adverse event profile. Pfizer believes that a popPK/PD approach would be a proper alternative to evaluate how to dose crizotinib with regard to gastric pH elevating agents.

Please provide clarity on the population in which the Agency proposes that Pfizer conduct this trial with a pH-elevating agent. Additionally, please provide the draft labeling sections related to pH-elevating agents so that we can consider the FDA's request in light of the marked-up product label.

FDA clarification:

This multiple dose trial should be conducted in patients with cancers to explicitly determine how to dose crizotinib with regard to gastric pH elevating agents. Single dose trial in healthy subjects or a population PK/PD approach may not provide explicit conclusions on the dosing strategies with regard to gastric pH elevating agents, though they may provide helpful information on the study design of the multiple dose trial in patients with cancers.

Draft labeling language will be available after August 11, 2011.

Regards,

Diane

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/s/

DIANE C HANNER
08/08/2011

Medical Officer's Consultative Review of NDA 202570
Ophthalmology Consult

NDA 202570
Ophthalmology Consult

Submission date: 3/30/11
Review date: 7/28/11

Sponsor: Pfizer

Drug: XALKORI™ (crizotinib)

Pharmacologic Category: Tyrosine kinase inhibitor

Proposed Indication: Treatment of anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC)

Background: This is a new NME application that has been submitted, and DDOP is requesting that a review be done regarding the following ophthalmology concern:

Question: Pts on crizotinib have a 53% incidence of a grade 1 visual disorder described primarily as flashing lights or peripheral lines/haziness. 44% of events have resolved with continuation of crizotinib. Visual acuity, slit lamp examination, and fundoscopy have been done in a limited # of pts and results were described as normal/abnormal. We are considering a PMR to further characterize these events. Would you recommend a PMR? If so, what testing would you recommend?

Clinical Review Material: [Module 2 SCS](#), [Module 5 CSR A8081001](#), [Module 5 CSR A8081005](#), [Sequence 0009](#), [60-Day Clinical Data Update](#)

Reported Adverse Events:

The following ocular adverse events have been reported in the clinical trials. Many have been included by the applicant in the “cluster” of vision disorders.

Reviewer's Comments: *There are additional adverse events which should be included in the vision disorder cluster.*

PID	AECASEID	CLUSTER	AEDECD1	AETERM
A8081001	1003 10031023		Periorbital edema	Intermittent Periorbital Edema
A8081001	1003 10031020		Periorbital edema	Periorbital Edema
A8081001	1003 10031035		Periorbital edema	Periorbital Edema
A8081001	1002 10021071		Periorbital edema	Periorbital Edema
A8081001	1003 10031014		Periorbital edema	Periorbital Edema
A8081001	1003 10031016		Periorbital edema	Periorbital Edema
A8081001	1003 10031030		Periorbital edema	Periorbital Edema
A8081001	1002 10021084		Periorbital edema	Symmetric Periorbital Edema
A8081001	1002 10021088		Periorbital edema	Trace Periorbital Edema.
A8081001	1008 10081002		Horner's syndrome	Left Sided Horner's Syndrome
A8081001	1002 10021089	Should include in cluster of vision disorder	Vision loss	Visual Loss

PID	AECASEID	CLUSTER	AEDECD1	AETERM
A8081001	1007 10071027		Cataract	Cataract
A8081001	1007 10071034		Cataract (right)	Right Eye Cataract
A8081005	1009 10091001	Vision disorder	Eye floaters	Eye Disorder Floaters
A8081005	1021 10211005	Vision disorder	Floaters	Floaters
A8081005	1193 11931001	Vision disorder	Floaters	Floaters
A8081001	1002 10021069	Vision disorder	Floaters	Vision Alteration. She Has Ribbon-Like Floaters In Her Peripheral Vision Occasio
A8081001	1002 10021057	Vision disorder	Floaters	Visual Changes: Floaters
A8081005	1025 10251002	Vision disorder	Floaters	Visual Disturbances/Floaters
A8081001	1003 10031031		Subconjunctival hemorrhage	Subconjunctival Hemorrhage In The Left Eye
A8081005	1058 10581008		Conjunctival congestion	Conjunctival Congestion
A8081001	1008 10081001		Conjunctivitis	Conjunctivitis
A8081005	1013 10131002		Ptosis	Right Ptosis
A8081001	1007 10071045		Head pain	Lt Eye Side Pain(Head Pain Beside Lt Eye)
A8081001	1007 10071045		Head pain	Lt Eye Side Pain(Head Pain Beside Lt Eye)
A8081005	1057 10571001		Iritis	Iritis
A8081005	1043 10431003		Dry eyes	Bilateral Dry Eyes
A8081005	1021 10211012		Dry eyes	Dry Eyes
A8081001	1001 10011049		Teary eyes	Tearful Eyes
A8081001	1002 10021051		Edema eyelid	Edema Right Eyelid
A8081005	1119 11191002	Vision disorder	Peripheral vision defective	Peripheral Vision Changes
A8081001	1002 10021085	Vision disorder	Vision peripheral defective	Peripheral Vision Haze
A8081005	1131 11311002	Vision disorder	Visual field defect	Visual Alterations (Stripes On Visual Field)
A8081001	1003 10031040	Vision disorder	Peripheral vision defective	Visual Changes With Shadows Of Periphery Of Vision
A8081001	1001 10011049	Vision disorder	Peripheral vision defective	Visual Peripheral Lines
A8081001	1007 10071031		Eye edema	Eye Edema
A8081005	1174 11741001		Eye pain	Left Eye Pain
A8081005	1130 11301005	Should include in cluster of vision disorder	Eye disorder	Ocular Disturbance
A8081001	1007 10071027		Eye redness	Eye Redness
A8081005	1018 10181007		Irritation of eyes	Irritated Eyes
A8081005	1042 10421001		Red eye	Red Eyes
A8081005	1042 10421001	Should include in cluster of vision disorder	Eye strain	Eye Strain
A8081005	1074 10741005	Should include in cluster of vision disorder	Eye strain	Eye Strain
A8081005	1129 11291010	Should include in cluster of vision disorder	Photophobia	Light Photophobia
A8081005	1129 11291012	Should include in cluster of vision disorder	Photophobia	Light Photophobia
A8081005	1129 11291015	Should include in cluster of vision disorder	Photophobia	Light Photophobia
A8081005	1030 10301007	Should include in cluster of vision disorder	Light sensitivity to eye	Light Sensitivity - Eyes
A8081005	1018 10211008	Should include in cluster of vision disorder	Light sensitivity to eye	Visual Changes, Increased Sensitivity To Light
A8081001	1007 10071016	Should include in cluster of vision disorder	Dilatation pupillary	Right Eye Pupillary Dilatation
A8081001	1005 10051006	Should include in cluster of vision disorder	Presbyopia	Presbyopia
A8081005	1053 10211003	Should include in cluster of vision disorder	Aura	Visual Changes: Aura Of Light Around Moving Objects
A8081005	1196 11961001	Vision disorder	After images	After Image
A8081005	1106 11061001	Vision disorder	Diplopia	Bilateral Diplopia
A8081001	1006 10061093	Vision disorder	Blurred vision	Blurred Vision
A8081001	1008 10081004	Vision disorder	Blurred vision	Blurred Vision
A8081001	1008 10081005	Vision disorder	Blurred vision	Blurred Vision
A8081001	1003 10031031	Vision disorder	Blurred vision	Blurred Vision
A8081001	1002 10021040	Vision disorder	Blurred vision	Blurred Vision

PID	AECASEID	CLUSTER	AEDECD1	AETERM
A8081001	1005 10051006	Vision disorder	Blurred vision	Blurred Vision
A8081005	1012 10121002	Vision disorder	Blurred vision	Blurred Vision
A8081001	1003 10031036	Vision disorder	Blurred vision	Blurred Vision In Right Eye
A8081001	1005 10051010	Vision disorder	Blurry vision	Blurry Vision
A8081005	1042 10421001	Vision disorder	Blurry vision	Blurry Vision
A8081001	1003 10031016	Vision disorder	Abnormal vision	Changes In Vision
A8081001	1003 10031042	Vision disorder	Abnormal vision	Changes In Vision
A8081005	1003 10031002	Vision disorder	Double vision	Double Vision
A8081005	1018 10181002	Vision disorder	Double vision	Double Vision
A8081005	1177 11771001	Vision disorder	After images	Eye Disorder(After Image)
A8081005	1054 10541003	Vision disorder	Photopsia	Eye Flashes
A8081005	1050 10501010	Vision disorder	Flashing lights	Flashing In Eyes
A8081001	1003 10031028	Vision disorder	Flashing lights	Flashing Lights
A8081005	1105 11051029	Vision disorder	Flashing lights	Flashing Lights
A8081005	1105 11051040	Vision disorder	Flashing lights	Flashing Lights
A8081001	1003 10031032	Vision disorder	Visual disturbance	Ghost-Like Shadows In Vision
A8081005	1019 10191007	Vision disorder	Blurred vision	Increased Blurred Vision
A8081001	1003 10031023	Vision disorder	Visual disturbance	Intermittent Dark To Light Visual Changes (Patient Refers To As Sparkles)
A8081001	1003 10031031	Vision disorder	Diplopia	Intermittent Diplopia
A8081005	1011 10111002	Vision disorder	Visual disturbance	Intermittent Eye Disorders Other: (Ghost Shadows Visual Disturbance)
A8081001	1003 10031034	Vision disorder	Flashing lights	Intermittent Flashing Lights In The Periphery Of Vision
A8081005	1050 10501004	Vision disorder	Flashing vision	Intermittent Flashing Spots In Eyes When Wa king From Dark To Light
A8081005	1011 10111002	Vision disorder	Visual disturbance	Intermittent Ocular/Visual Other: Ghost Shadows Visual Disturbance
A8081001	1003 10031036	Vision disorder	Visual disturbance	Intermittent Vision Changes- Ghost Like Images When Lights Are Dim
A8081001	1003 10031021	Vision disorder	Visual disturbance	Intermittent Visual Changes
A8081001	1003 10031014	Vision disorder	Visual disturbance	Intermittent Visual Disturbance
A8081001	1003 10031019	Vision disorder	Visual disturbance	Intermittent Visual Disturbance
A8081001	1003 10031029	Vision disorder	Visual disturbance	Intermittent Visual Disturbance
A8081001	1007 10071045	Vision disorder	Blurred vision	Left Eye Blurred Vision
A8081001	1007 10071045	Vision disorder	Blurred vision	Left Eye Blurred Vision
A8081001	1007 10071045	Vision disorder	Blurred vision	Left Eye Blurred Vision
A8081001	1007 10071045	Vision disorder	Blurred vision	Left Eye Blurred Vision
A8081001	1002 10021060	Vision disorder	Subjective visual disturbances	Ocular/Visual Shadows With Movement When Going From Low Light To Regular Light
A8081005	1077 10771007	Vision disorder	Visual disturbance	Overnight Visual Disturbance
A8081001	1002 10021051	Vision disorder	Vision blurred	Right Eye Blurriness
A8081001	1007 10071032	Vision disorder	Visual disturbance	Rt Visual Disturbance
A8081001	1005 10051015	Vision disorder	Visual disturbances	Transient Visual Disturbances
A8081001	1005 10051013	Vision disorder	Visual disturbance	Transient Wavy Vision
A8081001	1003 10031020	Vision disorder	Visual disturbance	Vision Changes
A8081005	1002 10021003	Vision disorder	Visual disturbance	Vision Changes
A8081005	1021 10211004	Vision disorder	Visual disturbance	Vision Changes
A8081005	1039 10391005	Vision disorder	Visual disturbance	Vision Changes
A8081001	1002 10021076	Vision disorder	Flashing lights	Vision Changes - Flashing Of Light
A8081001	1002 10021058	Vision disorder	Flashing lights	Vision Changes: Flashes Of Bright Lights In Both Eyes
A8081005	1052 10521002	Vision disorder	Visual disturbance	Vision Changes-Seeing Shadows
A8081005	1004 10041005	Vision disorder	Flashing lights	Vision Flashing Lights
A8081005	1175 11751001	Vision disorder	Visual disturbance	Visual Change
A8081005	1001 10011002	Vision disorder	Visual disturbance	Visual Change- Shadow
A8081005	1003 10031020	Vision disorder	Visual disturbance	Visual Changes
A8081001	1002 10021039	Vision disorder	Visual disturbance	Visual Changes

PID	AECASEID	CLUSTER	AEDECD1	AETERM
A8081001	1003 10031017	Vision disorder	Visual disturbance	Visual Changes
A8081001	1003 10031025	Vision disorder	Visual disturbance	Visual Changes
A8081001	1005 10051012	Vision disorder	Visual disturbance	Visual Changes
A8081005	1001 10011009	Vision disorder	Visual disturbance	Visual Changes
A8081005	1012 10121001	Vision disorder	Visual disturbance	Visual Changes
A8081005	1012 10121002	Vision disorder	Visual disturbance	Visual Changes
A8081005	1012 10121003	Vision disorder	Visual disturbance	Visual Changes
A8081005	1021 10211012	Vision disorder	Visual disturbance	Visual Changes
A8081001	1002 10021091	Vision disorder	Flashing lights	Visual Changes (Flashing Lights, Streaking Lights)
A8081001	1002 10021071	Vision disorder	Vision double	Visual Changes (Sees Double)
A8081005	1018 10211008	Vision disorder	Near vision disturbance	Visual Changes Difficulty With Near Vision After Getting New Glasses
A8081001	1002 10021080	Vision disorder	Flashing lights	Visual Changes, Flashing Light
A8081005	1053 10211003	Vision disorder	Visual disturbance	Visual Changes: Light/Dark
A8081001	1002 10021057	Vision disorder	Photopsia	Visual Changes: Scintillations Of Bright Light
A8081005	1021 10211018	Vision disorder	Visual disturbance	Visual Changes: Waves In Vision
A8081001	1002 10021072	Vision disorder	Double vision	Visual Changes-Double Vision
A8081001	1007 10071032	Vision disorder	Visual disturbance	Visual Defect
A8081005	1059 10591011	Vision disorder	Visual disturbance	Visual Disturbance
A8081005	1059 10591016	Vision disorder	Visual disturbance	Visual Disturbance
A8081001	1002 10021079	Vision disorder	Visual disturbance	Visual Disturbance
A8081001	1003 10031027	Vision disorder	Visual disturbance	Visual Disturbance
A8081001	1003 10031030	Vision disorder	Visual disturbance	Visual Disturbance
A8081001	1003 10031035	Vision disorder	Visual disturbance	Visual Disturbance
A8081001	1005 10051017	Vision disorder	Visual disturbance	Visual Disturbance
A8081001	1006 10061023	Vision disorder	Visual disturbance	Visual Disturbance
A8081001	1006 10061036	Vision disorder	Visual disturbance	Visual Disturbance
A8081001	1006 10061038	Vision disorder	Visual disturbance	Visual Disturbance
A8081001	1006 10061071	Vision disorder	Visual disturbance	Visual Disturbance
A8081001	1007 10071026	Vision disorder	Visual disturbance	Visual Disturbance
A8081001	1007 10071030	Vision disorder	Visual disturbance	Visual Disturbance
A8081001	1007 10071031	Vision disorder	Visual disturbance	Visual Disturbance
A8081001	1007 10071032	Vision disorder	Visual disturbance	Visual Disturbance
A8081001	1007 10071033	Vision disorder	Visual disturbance	Visual Disturbance
A8081001	1007 10071034	Vision disorder	Visual disturbance	Visual Disturbance
A8081001	1007 10071035	Vision disorder	Visual disturbance	Visual Disturbance
A8081001	1007 10071036	Vision disorder	Visual disturbance	Visual Disturbance
A8081001	1007 10071037	Vision disorder	Visual disturbance	Visual Disturbance
A8081001	1007 10071038	Vision disorder	Visual disturbance	Visual Disturbance
A8081001	1007 10071039	Vision disorder	Visual disturbance	Visual Disturbance
A8081001	1007 10071041	Vision disorder	Visual disturbance	Visual Disturbance
A8081001	1007 10071042	Vision disorder	Visual disturbance	Visual Disturbance
A8081001	1007 10071043	Vision disorder	Visual disturbance	Visual Disturbance
A8081001	1007 10071044	Vision disorder	Visual disturbance	Visual Disturbance
A8081001	1007 10071045	Vision disorder	Visual disturbance	Visual Disturbance
A8081001	1007 10071046	Vision disorder	Visual disturbance	Visual Disturbance
A8081001	1007 10071047	Vision disorder	Visual disturbance	Visual Disturbance
A8081001	1007 10071050	Vision disorder	Visual disturbance	Visual Disturbance
A8081001	1008 10081001	Vision disorder	Visual disturbance	Visual Disturbance
A8081001	1008 10081004	Vision disorder	Visual disturbance	Visual Disturbance
A8081001	1008 10081005	Vision disorder	Visual disturbance	Visual Disturbance
A8081005	1030 10301001	Vision disorder	Visual disturbance	Visual Disturbance
A8081005	1058 10581001	Vision disorder	Visual disturbance	Visual Disturbance
A8081005	1058 10581003	Vision disorder	Visual disturbance	Visual Disturbance
A8081005	1058 10581003	Vision disorder	Visual disturbance	Visual Disturbance

PID	AECASEID	CLUSTER	AEDECD1	AETERM
A8081005	1058 10581010	Vision disorder	Visual disturbance	Visual Disturbance
A8081005	1058 10581011	Vision disorder	Visual disturbance	Visual Disturbance
A8081005	1058 10581015	Vision disorder	Visual disturbance	Visual Disturbance
A8081005	1058 10581019	Vision disorder	Visual disturbance	Visual Disturbance
A8081005	1058 10581032	Vision disorder	Visual disturbance	Visual Disturbance
A8081005	1058 10581033	Vision disorder	Visual disturbance	Visual Disturbance
A8081005	1058 10581034	Vision disorder	Visual disturbance	Visual Disturbance
A8081005	1058 10581035	Vision disorder	Visual disturbance	Visual Disturbance
A8081005	1058 10581037	Vision disorder	Visual disturbance	Visual Disturbance
A8081005	1058 10581040	Vision disorder	Visual disturbance	Visual Disturbance
A8081005	1059 10591021	Vision disorder	Visual disturbance	Visual Disturbance
A8081005	1059 10591037	Vision disorder	Visual disturbance	Visual Disturbance
A8081005	1145 11451001	Vision disorder	Visual disturbance	Visual Disturbance
A8081005	1196 11961002	Vision disorder	Visual disturbance	Visual Disturbance
A8081005	1057 10571001	Vision disorder	Flashing lights	Visual Disturbance - Flashing Lights
A8081005	1176 11761001	Vision disorder	After images	Visual Disturbance (After Images)
A8081005	1053 10211017	Vision disorder	Flashing lights	Visual Disturbance: Transient Flickers Of Light In Peripheral Vision At Night
A8081001	1002 10021038	Vision disorder	Visual disturbance	Visual Disturbance-Aura Around Lights
A8081001	1002 10021088	Vision disorder	Visual disturbances	Visual Disturbances
A8081001	1005 10051017	Vision disorder	Visual disturbances	Visual Disturbances
A8081001	1006 10061084	Vision disorder	Visual disturbances	Visual Disturbances
A8081001	1006 10061119	Vision disorder	Visual disturbances	Visual Disturbances
A8081005	1021 10211016	Vision disorder	Visual disturbances	Visual Disturbances
A8081005	1039 10391002	Vision disorder	Visual disturbances	Visual Disturbances
A8081005	1039 10391003	Vision disorder	Visual disturbances	Visual Disturbances
A8081005	1039 10391004	Vision disorder	Visual disturbances	Visual Disturbances
A8081005	1039 10391006	Vision disorder	Visual disturbances	Visual Disturbances
A8081001	1002 10021090	Vision disorder	Flashing lights	Visual Disturbances (Light Flashes)
A8081001	1002 10021084	Vision disorder	Visual disturbance	Visual Disturbances (Light Traces)
A8081001	1002 10021073	Vision disorder	Flashing lights	Visual Disturbances (Strobe Lights)
A8081001	1002 10021081	Vision disorder	Visual disturbance	Visual Disturbances (Waves And White Circles)
A8081001	1002 10021063	Vision disorder	Flashing lights	Visual Disturbances- Flashing Lights
A8081005	1042 10421004	Vision disorder	Visual disturbance	Visual Disturbance-Sees Tracers
A8081001	1002 10021067	Vision disorder	Visual disturbance	Visual Disturbances-Visual Streamers
A8081001	1002 10021059	Vision disorder	Visual disturbance	Visual Perception Alterations At Night
A8081005	1185 11851001	Vision disorder	Visual disturbance	Visual Shadows
A8081001	1008 10081003	Vision disorder	Visual disturbance	Visual Symptoms
A8081005	1053 10211011	Vision disorder	Visual disturbance	Visual Symptoms
A8081005	1053 10211003	Vision disorder	Visual disturbance	Visual Symptoms Light/Dark
A8081005	1119 11191001	Vision disorder	Visual disturbance	Visual Tracer
A8081005	1013 10131003	Should include in cluster of vision disorder	Vision halo	Visual Changes - Halos Around Light
A8081001	1002 10021093	Should include in cluster of vision disorder	Visual brightness	Visual Changes Bright Lights
A8081005	1004 10041002	Should include in cluster of vision disorder		Visual Flashing Lights/Floaters

Reviewer's Comments on Need for Additional Testing: *It is unclear why the drug product appears to cause these visual events. Additional ocular testing is recommended to further characterize these events. It is recommended that a Phase 4 clinical trial be conducted in which at least 30 patients are studied on the drug product and the following examinations are included at baseline, at 2 and 6 weeks after drug administration, and after 2-8 weeks after discontinuation of the drug product:*

1. *Best corrected distance visual acuity*
2. *Refractive error associated with best corrected distance visual acuity*
3. *Pupil size under standardized lighting conditions*
4. *Slit lamp biomicroscopy of the anterior segment*
5. *Intraocular pressure*
6. *Ocular coherence tomography of the macula*
7. *Dilated fundus photography of the retina.*

Labeling: In their proposed package insert, the applicant has included the following paragraph to describe the visual adverse events observed in the clinical trials:

6.1. Visual Effects

Vision disorder including diplopia, photopsia, vision blurred, visual impairment and vitreous floaters was experienced by 74 (62%) patients in Study A and 80 (59%) patients in Study B. Greater than 98% of these patients had events that were mild in severity with median times to onset of 13 and 7 days in Studies A and B, respectively. Ophthalmological evaluation should be considered if vision disorder persists or worsens in severity. None of the patients in Studies A and B required dosing interruption, dose reduction, or permanent discontinuation from treatment for vision disorder, except 1 patient in Study B had temporary treatment discontinuation for Grade 2 diplopia. Caution should be exercised when driving or operating machinery by patients who experience vision disorder [*see Patient Counseling Information (17)*]

17.2. Visual Effects

Patients should be informed that Grade 1 visual changes such as perceived flashes of light, blurry vision, and double vision was a commonly reported adverse event. These events began most commonly during the first two weeks of treatment [*see Adverse Reactions (6)*].

17.3. Effects on Ability to Drive and Use Machines

No studies on the effect of XALKORI on the ability to drive and use machines have been performed. However, caution should be exercised when driving or operating machinery by patients who experience vision disorder, dizziness, or fatigue while taking XALKORI [*see Adverse Reactions (6)*].

Reviewer's Comments: *The language proposed for the package insert is problematic. Photopsia and vitreous floaters are classic signs of traction by the vitreous on the retina and/or signs of retinal holes which could lead to a retinal detachment. They are the warning signs that signal when patients should be examined so that impending retinal detachments can be treated promptly before noticeable visual impairment occurs. Language which instructs patients to ignore these warning signs should be avoided.*

It is recommended that the labeling be changed as suggested below:

6.1. Visual Effects

Vision disorder including diplopia, photophobia, photopsia, vision blurred, visual impairment and vitreous floaters was experienced by the majority of patients in clinical trials. These events generally started within two weeks of drug administration. Ophthalmological evaluation should be considered particularly if patients experience photopsia, or experience new or increased vitreous floaters. Caution should be exercised when driving or operating machinery by patients who experience vision disorder [*see Patient Counseling Information (17)*]

17.2. Visual Effects

Patients should be informed that visual changes such as perceived flashes of light, blurry vision, light sensitivity, floaters and double vision were a commonly reported adverse event. These events began most commonly during the first two weeks of treatment [*see Adverse Reactions (6)*].

17.3. Effects on Ability to Drive and Use Machines

No studies on the effect of XALKORI on the ability to drive and use machines have been performed. However, caution should be exercised when driving or operating machinery by patients who experience vision disorder, dizziness, or fatigue while taking XALKORI [*see Adverse Reactions (6)*].

Conclusions:

1. Visual disturbances associated with the use of crizotinib occurred in the majority of patients taking the drug product. These events have not been well characterized. It is recommended that a Phase 4 clinical trial be conducted in which at least 30 patients taking the drug product are studied and the following examinations are included at baseline, at 2 and 6 weeks after drug administration ,and after 2 8 weeks after discontinuation of the drug product:
 1. Best corrected distance visual acuity
 2. Refractive error associated with best corrected distance visual acuity
 3. Pupil size under standardized lighting conditions
 4. Slit lamp biomicroscopy of the anterior segment
 5. Intraocular pressure
 6. Ocular coherence tomography of the macula
 7. Dilated fundus photography of the retina.

2. The applicant's proposed labeling minimizes the ocular events. It is recommended that the Adverse Event and Patient Information section of the proposed labeling be revised to include:

6.1. Visual Effects

Vision disorder including diplopia, photophobia, photopsia, vision blurred, visual impairment and vitreous floaters was experienced by the majority of patients in clinical trials. These events generally started within two weeks of drug administration. Ophthalmological evaluation should be considered, particularly if patients experience photopsia or experience new or increased vitreous floaters. Caution should be exercised when driving or operating machinery by patients who experience vision disorder [*see Patient Counseling Information (17)*]

17.2. Visual Effects

Patients should be informed that visual changes such as perceived flashes of light, blurry vision, light sensitivity, floaters and double vision were a commonly reported adverse event. These events began most commonly during the first two weeks of treatment [*see Adverse Reactions (6)*].

Wiley A. Chambers, M.D.
Supervisory Medical Officer, Ophthalmology

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/s/

WILEY A CHAMBERS
08/01/2011

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Date: July 26, 2011

To: Robert Justice, MD, Director
Division of Drug Oncology Products

Through: Todd Bridges, RPh, Team Leader
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis

From: Kimberly DeFronzo, RPh, Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s) and Strength: Xalkori (crizotinib) Capsules
200 mg, 250 mg

Application Type/Number: NDA 202570

Applicant: Pfizer Inc.

OSE RCM #: 2011-1169

1 INTRODUCTION

This review evaluates the proposed container labels and insert labeling for Xalkori (NDA 202570) for areas of vulnerability that could lead to medication errors.

2 MATERIAL REVIEWED

Using Failure Mode and Effects Analysis, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the product container labels and insert labeling submitted on March 30, 2011 to identify vulnerabilities that may lead to medication errors. See Appendix A for the draft container labels for 200 mg and 250 mg strengths.

3 CONCLUSIONS AND RECOMMENDATIONS

Our Label Risk Assessment indicates that the presentation of information on the container labels and insert labeling introduces vulnerability to confusion that could lead to medication errors. The risks we have identified can be addressed and mitigated prior to drug approval. We provide recommendations for the insert labeling in Section 3.1 and recommendations for the container labels in Section 3.2.

Please copy the Division of Medication Error Prevention and Analysis on any communication to Pfizer, Inc. with regard to this review. If you have further questions or need clarifications, please contact Sarah Simon, OSE Safety Regulatory Project Manager, at 301-796-5205.

3.1 COMMENTS TO THE DIVISION ON INSERT LABELING

A. General Comment

We recognize that the Applicant uses abbreviations (e.g., c-Met, *MET*, EML4-ALK, NPM-ALK), symbols (e.g., >, <), and trailing zeros (e.g., >5.0 x ULN) in the labeling.

Generally, the Agency does not approve labeling with the use of abbreviations because they may be misinterpreted. On June 14, 2006, the Agency, in conjunction with ISMP, launched a campaign to warn healthcare practitioners and consumers not to use error prone abbreviations, acronyms, dose designations such as trailing zeros, or symbols. As part of this campaign, FDA agreed not to use such error prone designations in their approved product labeling because they are carried onto the prescribing practice.

However, we recognize that the use of abbreviations for disease processes is common practice in oncology, and none of these abbreviations appear on the Institute of Safe Medication Practices (ISMP) list of Error-Prone Abbreviations, Symbols, and Dose Designations¹. Therefore, we find it acceptable to use these abbreviations if each abbreviation is fully defined once at its first use.

¹ ISMP's List of Error Prone Abbreviations, Symbols and Dose Designations <http://www.ismp.org/Tools/errorproneabbreviations.pdf>

Because the symbols > and < appear on the ISMP list of Error-Prone Abbreviations, Symbols, and Dose Designations, we recommend using the terms “greater than” or “less than” instead of the symbols as they have been mistaken as the opposite of its intended meaning and practitioners have mistakenly used the incorrect symbol.

Similarly, since the use of trailing zeros is also error-prone and can result in ten-fold dosing error if the decimal is not seen (i.e. ‘1.0’ is misinterpreted as ‘10’); thus, we recommend removing the trailing zeros where they appear in the insert labeling.

B. Section 16. How Supplied/Storage and Handling

We recommend not using the hyphen between the numbers since a hyphen can be misinterpreted as a negative sign. Therefore, please revise (b) (4) to read 15° to 30°C (59° to 86°F) for improved clarity and to be consistent with the current USP designations.

C. Section 17. Patient Counseling Information

We recommend you add a discussion on:

1. How to handle “missed doses”
2. How to properly administer or handle the product
(e.g., capsules should be swallowed whole, do not dissolve or open capsules, maybe taken with or without food, etc.)
3. Do not eat or drink grapefruit products while taking this product
4. Avoiding pregnancy while on Xalkori

3.2 COMMENTS TO THE APPLICANT ON CONTAINER LABELS

Container Label

1. Ensure the size of the established name (including dosage form) is at least half as large as the letters comprising the proprietary name and has a prominence consistent with the proprietary name (type, size, color, font) in accordance with 21 CFR 201.10 (g)(2).
2. Unbold and relocate the “Rx only” wording to bottom of label from top right corner to decrease clutter in this top corner and increase visibility of the NDC number.
3. Change the wording on the left side panel to read 15° to 30°C (59° to 86°F) rather than (b) (4) for improved clarity and to be consistent with the current USP designations.

4 REFERENCE

1. *OSE Review # 2011-1168*, Proprietary Name Review for Xalkori

APPENDIX A

Container Label (in CRC packaging) (DRAFT)



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

/s/

KIMBERLY A DEFRONZO
07/26/2011

TODD D BRIDGES
07/26/2011

CAROL A HOLQUIST
07/26/2011

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 202570 BLA#	NDA Supplement #:S- N/A BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Established/Proper Name: Crizotinib Dosage Form: Capsule Strengths: 200 mg and 250 mg		
Applicant: Pfizer Inc Agent for Applicant (if applicable):		
Date of Application: March 30, 2011 Date of Receipt: March 30, 2011 Date clock started after UN:		
PDUFA Goal Date: TBD (tentative August 29, 2011)		Action Goal Date (if different): September 30, 2011
Filing Date: May 30, 2011		Date of Filing Meeting: May 2, 2011
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed indication(s)/Proposed change(s): ALK-positive advanced Non-small cell lung cancer (NSCLC)		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification:	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input checked="" type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		

<input checked="" type="checkbox"/> Fast Track <input checked="" type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>): CDRH/OIVD/DIHD				
List referenced IND Number(s): 073544				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>																				
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>																				
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i></p>																				
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)?</p> <p>Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1451 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</p>		<p>X</p>																		

<p>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>				
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested: 5</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>	X			
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>		X		
<p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>				

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>				
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).</p>	X			
<p>Index: Does the submission contain an accurate comprehensive index?</p>	X			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p>	X			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?				
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, “Form 3674.”</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature?	X			

<p>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</p> <p>Note: Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</p>				
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</p> <p>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</p>			X	

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff :</i></p>			X	

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</p>	X			
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>		X		Not required since this is an orphan-designated indication.

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>			X	
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>			X	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>		X		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	X			
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/ DCRMS via the DCRMSRMP mailbox</i>				
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request in 74-day letter.</i>	X			
Is the PI submitted in PLR format? ⁴	X			

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

⁴ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request PLR format in 74-day letter.</i>			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	X			CDRH 3-31-11 IRT-QT-3-31-11 OSE – 4-26-11 DMEPA 4-25-11 DRISK 3-31-11 DDMAC 3-31-11 OSE-Safety 4-26-11 DAIP- 6-28-11
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s) Date(s): May 22, 2009	X			

<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): EOP3 meeting 4/28/10	X			
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s): May 28, 2009	X			5-28-09
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: May 2, 2011

BLA/NDA/Supp #: 202570

PROPRIETARY NAME:

ESTABLISHED/PROPER NAME: crizotinib

DOSAGE FORM/STRENGTH: 200 mg. and 250 mg.

APPLICANT: Pfizer Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): TRADENAME is indicated for the treatment of anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC).

BACKGROUND: Filing Meeting May 2, 2011

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	CDR Diane Hanner, M.P.H., M.S.W., Senior Program Management Officer	Y
	CPMS/TL:	CAPT. Frank Cross Jr., M.A., MT (ASCP), Chief, Project Management Staff	N
Cross-Discipline Team Leader	V. Ellen Maher, M.D., Clinical Team Leader		Y

(CDTL)			
Clinical	Reviewer:	Shakun Malik, M.D., Medical Officer	Y
	TL:	V. Ellen Maher, M.D., Clinical Team Leader Anthony Murgo, M.D., M.S., FACP, Associate Director OODP IO, Acting Deputy Director DDOP	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	NONE	
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	NONE	
	TL:		
Clinical Pharmacology	Reviewer:	Pengfei Song, Ph.D., Clinical Pharmacology Reviewer, DCP5	Y
	TL:	Qi Liu, Ph.D., Team Leader, Office of Clinical Pharmacology, DCP5	Y
Biostatistics	Reviewer:	Lijun Zhang, Ph.D., Math Statistician, DB 5	Y
	TL:	Shenghui Tang, Ph.D., Team Leader, DB 5	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Brenda Gehrke, Ph.D., Pharmacologist/Toxicologist	Y
	TL:	Whitney Helms, Ph.D., Acting Supervisory Pharmacologist	Y
Statistics (carcinogenicity)	Reviewer:	NONE	
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	NONE	
	TL:		
Product Quality (CMC)	Reviewer:	Debasis Ghosh, M. Pharm., Ph.D., ONDQA, CMC	Y

		Reviewer, Division 3, Branch 5 ZeDong Dong., Ph.D., ONDQA, CMC Reviewer, Division 3, Branch 5	
	TL:	Haripada Sarker, Ph.D., Pharmaceutical Assessment Lead, Branch 5/DPAMS/ONDQA	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	NONE	
	TL:		
CMC Labeling Review	Reviewer:	Debasis Ghosh, M. Pharm., Ph.D., ONDQA, CMC Reviewer, Division 3, Branch 5 ZeDong Dong., Ph.D., ONDQA, CMC Reviewer, Division 3, Branch 5	Y
	TL:	Haripada Sarker, Ph.D., Pharmaceutical Assessment Lead, Branch 5/DPAMS/ONDQA	Y
Facility Review/Inspection	Reviewer:	Derek Smith Shawn Gould	Y
	TL:	Lori Gorski	N
OSE/DMEPA (proprietary name)	Reviewer:	Latonia Fond Denise Baugh	Y-by phone
	TL:	Barbara Fuller	
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/DCRMS (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (DSI)	Reviewer:	Robert Young, Ph.D.	Y
	TL:	Tejashri Purohit-Sheth, Ph.D.	N
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers:			
Other reviewers			
Other reviewers			
Other reviewers	Other reviewers		Other reviewers
Other attendees			

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable
CLINICAL	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO

<p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> To be determined Reason: <ul style="list-style-type: none"> ○ <i>the clinical study design was acceptable</i>
<ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY And Pharmacometrics</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE

<p>Comments:</p>	<input type="checkbox"/> Review issues for 74-day letter
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments: Since the applicant provided a statement which claim a categorical exclusion to the EA requirement, there is no EA to be reviewed.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO

<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<input type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Richard Pazdur, M.D.</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <p>Comments:</p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter. <input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input type="checkbox"/> Standard Review <input checked="" type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter/ NONE
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

DIANE C HANNER
06/30/2011

Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

IND or NDA	NDA 202570
Brand Name	Not determined
Generic Name	Crizotinib
Sponsor	Pfizer Inc.
Indication	ALK-positive advanced non-small cell lung cancer (NSCLC)
Dosage Form	Tablet
Drug Class	Small molecule inhibitor
Therapeutic Dosing Regimen	250 mg b.i.d.
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	250 mg b.i.d.
Submission Number and Date	SDN 004
Review Division	DDOP / HFD 150

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

Crizotinib appears to be associated with concentration-dependent QT interval prolongation ($P < 0.001$). Because of ECG acquisition and interpretation issues (please refer to Section 1.2), large increases in QT interval (i.e., ~20 ms) cannot be reliably excluded. From two clinical trials (Study A8081001 and Study A8081005) of crizotinib, three of 306 patients (<1%) were found to have QTcF (corrected QT by the Fridericia method) ≥ 500 ms and 9 of 286 patients (3%) had an increase from baseline QTcF ≥ 60 ms by automated machine-read evaluation of ECG.

Safety ECGs were collected at 0 and 6 hours post-dose at steady state in clinical trials following the treatment of crizotinib in two clinical trials - Study A8081001 and Study A8081005.

Study A8081001 was a Phase 1, open label, single arm, dose-escalation trial to determine appropriate Phase 2 dosage with amendments to evaluate additional patients based on observed antitumor activity and safety. The dose escalation portion included 8 and 6 subjects at crizotinib 250 mg b.i.d. and 300 mg b.i.d., respectively. In the expanded portion, a total of 167 subjects received 250 mg b.i.d.

Study A8081005 was a Phase 2, open-label single arm study to evaluate the efficacy and safety of crizotinib in patients with non-small cell lung cancer (NSCLC) with a translocation or inversion at the anaplastic lymphoma kinase (ALK) gene locus. Crizotinib was administered at 250 mg b.i.d., and 136 subjects with safety ECGs were available for analysis.

1.2 QT INTERDISCIPLINARY REVIEW TEAM’S COMMENTS

- Pdf files of paper ECGs were submitted for review. These ECGs appear inadequate to exclude effects around 20 ms or greater due to the following reasons:
 - On review of subset at random, some copies were of poor quality (see examples in section 5.4.2).
 - No interval annotations were available.
 - These were not centrally read ECGs.
 - Overall, these ECGs appear adequate for categorical analysis (i.e., percentage of subjects with absolute QTc over 500 ms or over 60 ms change from baseline but not for interval quantification).
- In earlier submissions to the QT-IRT under IND 73544 the sponsor had indicated that they would conduct a dedicated QT assessment at the MTD with centrally read ECGs collected in replicates and with time-matched ECG/PK sampling. We recommend this study as a PMR to gain reliable estimation of QT effect size, especially if indications other than NSCLC with different benefit-risk balances are being pursued.

2 PROPOSED LABEL

2.1 THE SPONSOR PROPOSED LABEL

The sponsor proposed the following labeling language.

Highlights of Prescribing Information:

8. Use in Specific Populations

- QT Interval Prolongation: (b) (4)
 patients who have a history of or predisposition for QTc prolongation, or who are taking medications that are known to prolong the QT interval (b) (4)
 (b) (4) periodic monitoring with electrocardiograms and electrolytes should be considered. (5.2)

Section 2.2: Dose Modification:

Table 2: TRADENAME Dose Modification – Non-Hematologic Toxicities

CTCAE ^a Grade	TRADENAME Dosing
Grade 3 (b) (4)	Withhold until recovery to Grade (b) (4) then resume

(b) (4)	(b) (4)
(b) (4)	

Section 5: Warning and Precautions:

5.2: QT INTERVAL PROLONGATION

(b) (4)

Section 12 Clinical Pharmacology:

12.4. CARDIAC ELECTROPHYSIOLOGY

The QT interval prolongation potential of crizotinib was assessed in all patients who received TRADENAME 250 mg twice daily. Serial ECGs in triplicate were collected following a single dose and at steady state to evaluate the effect of crizotinib on QT intervals. Three of 30^(b) patients^{(b)(4)} were found to have QTcF (corrected QT by the Fridericia method)^{(b)(4)} 500 msec and^{(b)(4)} patients^{(b)(4)} had an increase from baseline QTcF^{(b)(4)} 60 msec by automated machine-read evaluation of ECG.^{(b)(4)}

[see Warnings and Precautions (5.2)].

Reviewer's comments:

QT-IRT provided labeling recommendations on W&P statement and study description. Please refer to Section 2.2.

2.2 QT-IRT PROPOSED LABEL

We have the following label recommendations which are suggestions only. We defer the final labeling decisions to the review division. We agree with the proposed dose modification for QT prolongation (table 2 in the proposed PI)

8. Use in Specific Populations

- QT Interval Prolongation: (b) (4) In patients who have a history of or predisposition for QTc prolongation, or who are taking medications that are known to prolong the QT interval, (b) (4) periodic monitoring with electrocardiograms and electrolytes should be considered. (5.2)

5.2 QT INTERVAL PROLONGATION

(b) (4)

Section 12.4.

The QT interval prolongation potential of crizotinib was assessed in all patients who received TRADENAME 250 mg twice daily. Serial ECGs in triplicate were collected following a single dose and at steady state to evaluate the effect of crizotinib on QT intervals. Three of 30 (b) (4) patients (b) (4) were found to have QTcF (corrected QT by the Fridericia method) (b) (4) 500 msec and (b) (4) patients (b) (4) had an increase from baseline QTcF (b) (4) 60 msec by automated machine-read evaluation of ECG. (b) (4)

(b) (4) -A pharmacokinetic/ pharmacodynamic analysis suggested a concentration-dependent (b) (4)

3 BACKGROUND

Also see QT-IRT reviews dated April 22, 2009, July 2, 2009, July 20, 2010 and August 25, 2010 under IND 73544.

3.1 PRODUCT INFORMATION

Crizotinib (PF-02341066) is a selective small-molecule inhibitor of the anaplastic lymphoma kinase (ALK) receptor tyrosine kinase (RTK) and its oncogenic variants (i.e.,

ALK fusion events and selected ALK mutations). Crizotinib is also an inhibitor of the hepatocyte growth factor receptor (HGFR, c-Met) RTK. Crizotinib has the molecular formula of C₂₁H₂₂Cl₂FN₅O and a molecular weight of 450.34. This application seeks approval for crizotinib for the treatment of ALK-positive advanced non-small cell lung cancer (NSCLC). The recommended dose and schedule is 250 mg taken orally twice daily continuously.

3.2 MARKET APPROVAL STATUS

Crizotinib is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

Source: IB dated January 2008

“Cardiovascular Effects: In vivo cardiovascular effects were observed in the safety pharmacology study in anesthetized dogs. PF-0234 1066 administration was associated with decreases in heart rate and increases in LVEDP at 84 and 164 ng/mL free plasma concentration. There were also statistically significant differences compared with vehicle treated animals in myocardial contractility (LV+dP/dt) at 164 ng/mL free plasma concentration. Although there was a statistically significant decrease in myocardial contractility, it should be noted that the actual myocardial contractility values in the treated animals were similar to the pre-dose values. The main effects of PF-02341066 on ECG parameters were statistically significant increases in PR interval, QRS, and QT interval at 84 and 164 ng/mL free plasma concentration. The prolongation of PR-interval, QRS, and QT interval is probably due to the reduction in heart rate observed at these doses. Monophasic action potential duration during cardiac pacing is a heart rate-independent index of cardiac repolarization. There were statistically significant increases in MAPD₁₀₀ at sinus rhythm at 84 and 164 ng/mL free plasma concentration. The increases in MAPD₁₀₀ at sinus rhythm were consistent with the decreases observed in heart rate. The plasma concentrations of PF-02341066 achieved in this study were up to 44 times the free efficacious plasma level predicted in humans (8.1 nM or 3.7 ng/mL).

“In vitro, PF-02341066 blocked potassium currents or hERG channel conduction with IC₅₀ and IC₂₀ values of 1.1 μ M (495 ng/mL) and 0.3 μ M (135 ng/mL), respectively. In the rat aortic tension model, in vitro dog isolated Purkinje fibers, and in freshly isolated Guinea pig ventricular myocytes, PF-02341066 produced effects consistent with calcium channel antagonism. The hERG assay, rat aortic model, Guinea pig myocyte assay, and Purkinje fiber data suggest that PF-02341066 is mixed-channel blocker and this may explain the lack of effect on MAPD₁₀₀ during pacing in this study. The decrease in diastolic blood pressure observed at a free plasma concentration of 164 ng/mL may reflect the calcium channel antagonist effects observed in the rat isolated aorta model. The nonclinical data suggest that free plasma concentrations greater than or equal to 84 ng/mL may produce changes in the heart rate and at higher free plasma concentrations (164 ng/mL) changes in diastolic blood pressure.”

8.1. Nonclinical Safety Tables

Table 17. Safety Pharmacology Studies (Study Nos. PF02341066HERG, PF0234066AORTA, 04-2796-01, PF02341066/CG/003/04, PF02341066/IC/001/04, 3660, 3622)

In vitro				
Type of Test	Test Cells/Tissues	Tested Concentrations	Results	GLP compliance
hERG Patch Clamp	HEK-293 cells expressing hERG channels	0.1, 0.3, 1, 3, 10 μ M	hERG IC ₅₀ = 1.1 μ M; hERG IC ₂₀ = 0.30 μ M	No
Cardiac Action Potential	Isolated dog Purkinje fibers	0.01, 0.1, 1, 10 μ M	No effects on cardiac action potential at concentrations up to 1 μ M. At 10 μ M, effects on cardiac action potential were consistent with calcium channel antagonism. A reduction in APD ₅₀ was observed with 10 μ M PF-02341066 at all stimulation frequencies. The largest reduction in APD ₅₀ observed was -18.4 \pm 2.9% at 3 Hz. A reduction in APD ₉₀ was observed with 10 μ M PF-02341066 at stimulation frequencies of 3 and 1 Hz but not at 0.3 Hz. The largest reduction in APD ₉₀ observed was -8.1 \pm 1.7% at 3 Hz.	Yes
Isometric Tension Assay	Rat thoracic aorta segments	0.1, 1, 10 μ M	Apparent steady-state decreases in tension achieved within 90 minutes. Concentration-dependent relaxation of a 45 mM potassium chloride induced contraction was observed with an IC ₅₀ of 0.83 μ M.	No
Calcium Channel Current	Freshly isolated guinea pig ventricular myocytes	1, 3, 10, 30, 100 μ M	At 1, 3, 10, 30, and 100 μ M, L-type calcium channel was inhibited by 9.3 \pm 0.5, 17.3 \pm 2.7, 36.0 \pm 1.9, 67.7 \pm 7.8, and 95.6 \pm 3.6%, respectively. IC ₅₀ of 14.6, Hill coefficient 1.1.	No

HERG = Human ether-a-go-go; APD = Action Potential Duration; Hz = hertz; GLP = Good laboratory practice

In vivo						
Organ Systems Evaluated	Species/ Strain	Method of Administration	Doses (mg/kg)	Gender and No. per Group	Noteworthy Findings	GLP Compliance
Cardiovascular	Dog/ Beagle	IV (under Isoflurane Anesthesia)	0 (vehicle), 0.134, 0.295, 1.192, 1.907 mg/kg ^a	4 M	<p>Animals given 1.192 and 1.907 mg/kg followed by 0.0834 and 0.134 mg/kg/min infusion rate, respectively had decreased heart rate and increased LVEDP. Increased PR, QRS, and QT-interval and increased MAPD₁₀₀ at sinus rhythm were likely secondary to the decreased heart rate at these doses.</p> <p>Animals given 1.907 mg/kg followed by 0.134 mg/kg/min had decreased myocardial contractility, decreased arterial blood pressure, and decreased diastolic blood pressure.</p> <p>Mean Plasma Concentration: Post 10-minute loading of 0.134, 0.295, 1.192, and 1.907 mg/kg were 218, 521, 2210, and 3363 ng/mL, respectively. Post maintenance of 0.00939, 0.0207, 0.0834, and 0.134 mg/kg/min were 196, 557, 1963, and 3817 ng/mL, respectively. Steady-state free plasma concentrations were 8.4, 24, 84, and 164 ng/mL or 19, 53, 187, and 364 nM.</p>	Yes

GLP = Good laboratory practice; min = Minutes; M = males; IV = intravenous; MAPD = Monophasic action potential duration; LVEDP = Left ventricular end diastolic pressure

^a Delivered over 10 minutes followed by maintenance infusions of 0.00939, 0.0207, 0.0834, and 0.134 mg/kg/min for approximately 25 minutes, respectively, and compared with time-matched IV vehicle infusions give total mg/kg dose over 35 minutes.

Reviewer's Comment: Decrease in heart rate and diastolic BP, in vivo prolongation of PR, QRS, QT and increased MAPD₁₀₀ and in vitro inhibition of hERG occurred at concentrations well within total C_{max} (503 ng/ml) observed in patients in multiple dose studies. Although IC₅₀s for hERG and calcium are close, it is unclear if the mixed ion channel blockade (hERG and Calcium channel) may be protective against pro-arrhythmia based on the varying results observed in different in-vitro studies and QT prolongation noted in vivo.

3.4 PREVIOUS CLINICAL EXPERIENCE

Source: Summary of Clinical Safety, eCTD 2.7.4

The safety data is mainly from 2 ongoing patient studies of crizotinib administered at 250 mg orally BID:

- Pivotal Study A8081001 (Study 1001), an ongoing multicenter, multinational, open-label, single-arm study evaluating the safety, pharmacokinetics, pharmacodynamics, and antitumor activity of oral crizotinib in patients with advanced cancer, including a

recommended Phase 2 dose (RP2D) cohort of patients with ALK-positive advanced NSCLC and

- Supportive Study A8081005 (Study 1005), an ongoing multicenter, multinational, open label, single-arm, Phase 2 study evaluating the safety and efficacy of oral crizotinib in patients with ALK-positive advanced NSCLC.

Overall, 450 subjects had received crizotinib in 8 studies as of the database snapshot dates and are included in the safety analysis. Of these subjects, 255 had ALK-positive locally advanced or metastatic NSCLC (hereafter referred to as ‘ALK-positive advanced NSCLC’) and received crizotinib 250 mg orally twice daily in Studies A8081001 and A8081005, comprising the target population and the recommended dosing regimen for crizotinib treatment. One hundred ten of the 450 subjects were healthy volunteers enrolled in clinical pharmacology studies, and 85 were patients with advanced cancer enrolled in Study A8081001 but who did not represent the target population and/or did not receive the recommended dosing regimen.

Twenty-two of the 255 patients (8.6%) died within 28 days after the last dose of crizotinib (defined as deaths on study), and 13 (5.1%) patients died during long-term follow-up. The most common cause of death was disease under study. Two deaths (pneumonitis, death of unknown cause) were considered related to study treatment by the Investigator.

Table 9. Summary of Deaths: Study 1001 ALK-Positive NSCLC Cohort and Study 1005

Deaths	Number (%) of Patients	
	Study 1001 ALK-positive NSCLC Cohort (N=119)	Study 1005 (N=136)
Patients who died	23 (19.3)	12 (8.8)
Within 28 days after last dose of study drug	13 (10.9)	9 (6.6)
More than 28 days after last dose of study drug	10 (8.4)	3 (2.2)
Cause of death*		
Disease under study	17 (14.3)	9 (6.6)
Unknown/not reported	1 (0.8)	1 (0.7)
Study treatment toxicity	0	2 (1.5)
Other	5 (4.2)	2 (1.5)

*More than 1 cause of death may be reported for a single patient.

Source: Study 1001 CSR Table 13.6.6.2b and Study 1005 CSR Table 13.6.6.2

Cardiac disorders reported are bradycardia (5% of subjects in study 1001 and 4% of subjects in study 1005) and QT prolongation. One (0.8%) patient in Study 1001 and 2 (1.5%) patients in Study 1005 had on-treatment QTcF intervals ≥ 500 ms on at least 1 assessment. Nine patients in these 2 studies (3.8%) had maximum changes in QTcF of ≥ 60 ms. One patient in each of Studies 1001 and 1005 had both QTcF ≥ 500 ms and a maximum change from baseline in QTcF of ≥ 60 ms (discussed further in section 4.2.8.3)

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of crizotinib's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the ECG assessment and data analysis plan under IND 73544. The sponsor submitted the study report for Study A8081001 and Study A8081005 for crizotinib, including electronic datasets and ECGs submitted as pdf files.

4.2 QT STUDIES

4.2.1 Title

A8081001

Phase 1 Safety, Pharmacokinetic and Pharmacodynamic Study of PF-02341066, A c-Met/HGFR Selective Tyrosine Kinase Inhibitor, Administered Orally to Patients with Advanced Cancer

A8081005

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

4.2.2 Protocol Number

A8081001

A8081005

4.2.3 Study Dates

A8081001

Initiation: April 19, 2006

Completion: Ongoing

A8081005

Initiation: January 7, 2010

Completion: Ongoing

4.2.4 Objectives

A8081001

The objectives of this study were to:

- Determine the safety profile of crizotinib including identification of dose-limiting toxicity (DLT) and maximum tolerated dose (MTD);

- Determine the recommended Phase 2 doses (RP2D) and regimens of crizotinib;
- Determine pharmacokinetic (PK) profile of crizotinib following oral administration including the effect of food;
- Perform initial evaluation of crizotinib related cytochrome P450 3A4 (CYP3A4) inhibition using midazolam (MDZ) as a probe;
- Perform exploratory evaluation of c-Met/hepatocyte growth factor receptor (HGFR) genotype and expression, pharmacodynamic (PD) endpoints, and biomarkers for crizotinib; and
- Document any evidence of anti-tumor activity of crizotinib.

A8081005

Primary Objectives:

- To assess the antitumor efficacy of oral single-agent crizotinib administered to patients with advanced NSCLC after failure of at least 1 line of chemotherapy and harbor a translocation or inversion event involving the ALK gene locus as measured by ORR; and
- To assess the safety and tolerability of oral crizotinib.

Secondary Objectives:

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

4.2.5 Study Description

4.2.5.1 Design

A8081001

This was an open-label, multicenter, multinational, dose escalation, safety, PD, PK, and antitumor activity study of crizotinib administered as a single oral agent to patients with advanced malignancies. This study was originally designed as a Phase 1 dose-escalation study in patients with any tumor type (except leukemia) followed by a RP2D expansion cohort to include at least 8, but no more than 15 patients, to further evaluate the safety

and PK of the MTD of crizotinib. With the high responder rate observed, the trial was expanded to include 167 ALK positive NSCLC patients administered with 250-mg b.i.d dosing.

A8081005

This is an ongoing, multicenter, multinational, open-label, single-arm, Phase 2 study of crizotinib in patients with advanced (locally advanced or metastatic) NSCLC harboring a translocation or inversion event involving the ALK gene locus. Crizotinib 250 mg twice daily (BID) as a starting dose was to be administered orally continuously in 21-day cycles. Routine safety evaluations have included monitoring for AEs and periodic physical examinations, hematology and chemistry evaluations, and electrocardiograms (ECGs).

4.2.5.2 Controls

The sponsor did not use placebo or positive controls (moxifloxacin) in these studies.

4.2.5.3 Blinding

Treatment arms were not blinded in either of these studies.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

A8081001

Crizotinib was administered orally once daily (q.d.) or b.i.d. The starting dose for crizotinib was 50 mg q.d. in the first cohort of patients enrolled in this study. Each dose level cohort initially included a minimum of 3 evaluable patients for assessment of toxicity within the first cycle, i.e., first 4 weeks of dosing. Dose escalation occurred in 100% increments until either of the following occurred:

- drug-related toxicity of Grade 2 severity occurred in 2 or more patients within a dose level
- mean unbound area under the concentration-time profile from zero time to 24-hr postdose (AUC_{0-24}) exceeded $2.4 \mu\text{g}\cdot\text{h}/\text{mL}$ (the highest unbound area under the concentration-time profile [AUC] tested in the 1-month toxicology studies).

Escalation increments were then to become 40%. In any cohort, if 1 patient experienced a DLT, 3 additional patients were enrolled to that dose level. If 2 of 3 or 2 of 6 patients experienced a DLT, no further dose escalation occurred.

Patients enrolled in the RP2D cohorts received crizotinib 250 mg b.i.d. with a cycle length of 3 or 4 weeks depending on the cohort.

A8081005

Crizotinib 250 mg (administered as two 100-mg tablets and one 50-mg tablet) was administered orally BID at approximately the same time each day on a continuous dosing

schedule. Cycles were defined in 21-day treatment periods to facilitate scheduling of visits and assessments.

4.2.6.2 Sponsor's Justification for Doses

A8081001

The starting dose for crizotinib was 50 mg q.d. in the first cohort of patients enrolled in this study. Dose escalation occurred in 100% increments until either of the following occurred:

- drug-related toxicity of Grade 2 severity occurred in 2 or more patients within a dose level
- mean unbound area under the concentration-time profile from zero time to 24-hr postdose (AUC_{0-24}) exceeded 2.4 $\mu\text{g}\cdot\text{h}/\text{mL}$ (the highest unbound area under the concentration-time profile [AUC] tested in the 1-month toxicology studies).

Escalation increments were then to become 40%. In any cohort, if 1 patient experienced a DLT, 3 additional patients were enrolled to that dose level. If 2 of 3 or 2 of 6 patients experienced a DLT, no further dose escalation occurred.

The highest dose evaluated was 300 mg b.i.d. where two grade 3 fatigue events were observed. Based on these observations, the dose-escalation was terminated, and patients enrolled in the RP2D cohorts received crizotinib 250 mg b.i.d. with a cycle length of 3 or 4 weeks depending on the cohort.

A8081005

The use of crizotinib 250 mg b.i.d. is supported by the dose-escalation study A8081001. Only therapeutic doses were evaluated in this study.

Reviewer's Comment: The dose of 250 mg b.i.d. represents the highest therapeutic dose and is acceptable for QT evaluation. The sponsor's have not provided adequate intrinsic/extrinsic drug interaction data to identify if the highest dose from A8081001 (300 mg b.i.d.) addresses the high exposure scenario. However, as 250 mg b.i.d. was the highest dose tolerated from A8081001, this is an appropriate dose for initial exploration of efficacy.

4.2.6.3 Instructions with Regard to Meals

Doses were administered orally on an empty stomach.

Reviewer's Comment: The impact of food on crizotinib was studied in a subset of patients from A8081001. Patients administered a high-fat meal had slightly lower C_{max} (ratio: 0.84 high-fat versus fasted) and AUC_{0-24} (ratio: 0.85 high-fat versus fasted) exposures. Based on this substudy, dosing on an empty stomach is appropriate.

4.2.6.4 ECG and PK Assessments

A8081001

PK Assessments

Blood samples for crizotinib PK analysis were collected into appropriately labeled tubes at times listed in the protocol. Blood samples were collected on Day 1 of Cycle 1, Day 15 of Cycle 1, and Day 1 of Cycle 2 with matching ECGs at the following time points: 0 (predose), 6, and 24 hr (only Day 1 of Cycle 1) postdose.

Safety Assessments

Time-matched, triplicate ECG assessments were obtained at the scheduled PK sampling points described. Three consecutive 12-lead ECGs were performed at least 2 min apart during the screening period; Cycle 1 Day 1 at pre-dose (0 hr), 6 hr post-dose (C_{max}), and 24 hr post-dose; Cycle 1 Day 15 and Cycle 2 Day 1 at pre-dose and 6 hr (C_{max}) post-dose. ECGs were performed prior to PK blood draws at respective time points.

A8081005

PK Assessments

Blood samples for crizotinib PK analysis were collected on Day 1 of Cycle 1, Day 15 of Cycle 1, and Day 1 of Cycle 2 with matching ECGs at the following time points: 0 (predose) and 6 hr postdose.

Safety Assessments

Time-matched, triplicate ECG assessments were obtained at the scheduled PK sampling points described. Three consecutive 12-lead ECGs were performed at least 2 min apart on Cycle 1 Day 1 and Cycle 2 Day 1 at pre-dose (0 hr) and 2-6 hr postdose.

Reviewer's Comment: Based on the sponsor's multiple dose observations (Table 12), Day 15 of Cycle 1 and Day 1 of Cycle 2 will be at steady-state crizotinib concentrations. Also, based on the sponsor's dense PK sampling shown in Figure 1, sampling at 6 hr postdose will occur approximately at C_{max} following crizotinib administration. These samplings are appropriate to approximate QT prolongation from crizotinib 250 mg b.i.d., but are not optimal for characterization of a precise QT prolongation.

4.2.6.5 Baseline

Day 1 of Cycle 1 at time zero is used as the baseline.

4.2.7 ECG Collection

Triplicate 12-lead (with a 10-second rhythm strip) tracing was used for all ECGs. It was preferable that the machine used had a capacity to calculate the standard intervals automatically. The sponsor reports that (foot notes of table 13.9.1 in the CSR-A8081001) that QTc readings are taken directly from the ECG machine.

Reviewer's Comment: ECG methodology was not optimal for accurate quantification of QT effect.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

A8081001

Patients with advanced malignancies were enrolled into either the QD dose-escalation or RP2D cohorts (Table 1 and Table 2). Subjects with ongoing cardiac dysrhythmias of National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE Version 3.0) Grade ≥ 2 , uncontrolled atrial fibrillation of any grade, or QT interval, corrected (QTc) interval >470 ms were excluded. Subject disposition is summarized by the sponsor as follows for the dose-escalation and RP2D cohorts.

Table 1: Summary of Patient Disposition by Dose Level for the Dose-Escalation Cohort

Number (%) of Patients	Crizotinib 50 mg QD	Crizotinib 100 mg QD	Crizotinib 200 mg QD	Crizotinib 200 mg BID	Crizotinib 250 mg BID	Crizotinib 300 mg BID	Total
Assigned to study treatment	3	4	9	7	9	6	38
Treated	3	4	8	7	8	6	36
Ongoing at database snapshot date	0	0	0	1 (14.3)	0	0	1 (2.8)
Discontinued from treatment	3 (100)	4 (100)	8 (88.9)	6 (85.7)	8 (88.9)	6 (100)	35 (97.2)
AE	0	0	0	1 (14.3)	2 (25.0)	1 (16.7)	4 (11.1)
Progressive disease	2 (66.7)	2 (50.0)	5 (62.5)	3 (42.9)	6 (75.0)	4 (66.7)	22 (61.1)
Patient no longer willing to participate in study	1 (33.3)	1 (25.0)	2 (25.0)	1 (14.3)	0	0	5 (13.9)
Other ^a	0	1 (25.0)	1 (12.5)	1 (14.3)	0	1 (16.7)	4 (11.1)

Source: Tables 13.1.1 and 13.1.3.1 and Appendix B1.1.

Abbreviations: QD=daily; BID=twice daily; AE=adverse event

^aOther included physician's discretion (n=1) and clinical progression (n=3).

Note: Treated included all enrolled patients who received at least 1 dose of crizotinib starting on Cycle 1 Day 1 (ie, patients who only received a single dose of crizotinib on Day -7 were not included).

Percentages for reasons for discontinuation based on treated patients only.

Source: CSR for Study A8081001

Table 2: Summary of Patient Disposition for the RP2D Cohorts

Number (%) of Patients	ALK-Positive NSCLC 250 mg BID	ALK-Negative NSCLC 250 mg BID	RP2D Other 250 mg BID
Assigned to study treatment	119	5	50 ^a
Treated	119	5	44
Ongoing at database snapshot date	77 (64.7)	3 (60.0)	7 (14.0)
Discontinued	42 (35.3)	2 (40.0)	37 (84.1)
Adverse event	3 (2.5)	0	3 (6.8)
Progressive disease	25 (21.0)	1 (20.0)	24 (54.5)
Patient died	8 (6.7)	1 (20.0)	1 (2.3)
Patient no longer willing to participate in study	1 (0.8)	0	2 (4.5)
Other ^b	5 (4.2)	0	7 (15.9)

Source: Tables 13.1.1b and 13.1.3.1b and Appendix B1.1

Abbreviations: RP2D=recommended Phase 2 dose; NSCLC=non-small cell lung cancer; ALK=anaplastic lymphoma kinase; BID=twice daily; RECIST=Response Evaluation Criteria in Solid Tumors

^aOne patient (Patient 10071024) was enrolled but not treated and is not included in Appendix B1.1 because no demography data were collected.

^bOther included patients who had clinical progression not consistent with RECIST.

Note: Treated included all enrolled patients who received at least 1 dose of crizotinib starting on Cycle 1 Day 1 (ie, patients who only received a single dose of crizotinib on Day -7 were not included).

Percentages for reasons for discontinuation based on treated patients only.

Source: CSR for Study A8081001

A8081005

Patients with ALK positive NSCLC were enrolled in Study A8081005 (Table 3).

Table 3: Summary of Patient Disposition at End of Treatment (Safety Analysis Population)

Number of Patients	Crizotinib 250 mg BID N=136 n (%)
Ongoing at date of database snapshot (29 October 2010)	119 (87.5)
Discontinued from the study	
Adverse event	3 (2.2)
Global deterioration of health status	1 (0.7)
Lost to follow-up	0
Objective progression or relapse	8 (5.9)
Protocol violation	0
Study terminated by Sponsor	0
Patient died	5 (3.7)
Patient no longer willing to continue treatment for reason other than AE	0
Other	0
Total discontinued from the study	17 (12.5)

Source: [Table 13.1.3.1.1](#)

Data regarding discontinuations due to AEs in this table are from the End of Treatment page of the case report form ([Appendix A2](#)).

Abbreviations: AE = adverse event, BID = twice daily, N/n = number of patients

Source: CSR for Study A8081005

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

A8081001

The mean changes from baseline for QTcF ranged from 1.5 to 5.7 ms during Cycle 1 Day 15 and Cycle 2 Day 1 (crizotinib at steady state concentrations) (Table 4). The highest upper bound of two-sided 90% CI (UCI) for QTcF was 9.7 ms, across these measured time points (Cycle 1 Day 15 and Cycle 2 Day 1).

Table 4: ECG Change from Baseline (A8081001)

QTcF INTERVAL (FRIDERICIA'S CORRECTION) (msec)

Cycle		ALK+ NSCLC, 250 mg BID	ALK- NSCLC, 250 mg BID	RP2D Other, 250 mg BID
Cycle1/D1- 6H	N	101	5	38
	Mean	3.3	15.9	1.9
	Std. Dev.	11.48	16.09	9.36
	Median	4.0	18.0	3.8
	90% CI	1.4 , 5.2	0.6 , 31.3	-0.7 , 4.4
	Min	-35	-7	-20
	Max	35	35	18
Cycle1/D1-24H	N	81	3	33
	Mean	0.1	-2.0	1.7
	Std. Dev.	14.07	10.41	15.25
	Median	1.0	-7.3	-0.3
	90% CI	-2.5 , 2.7	-19.6 , 15.6	-2.8 , 6.2
	Min	-35	-9	-27
	Max	59	10	46
Cycle1/D15-0H	N	77	2	34
	Mean	2.8	19.8	2.1
	Std. Dev.	18.21	18.15	16.34
	Median	1.3	19.8	4.2
	90% CI	-0.7 , 6.2	-61.2 , 100.9	-2.7 , 6.8
	Min	-27	7	-35
	Max	61	33	46
Cycle1/D15-6H	N	82	2	31
	Mean	5.7	25.0	5.6
	Std. Dev.	17.80	24.04	21.01
	Median	4.7	25.0	6.7
	90% CI	2.5 , 9.0	-82.3 , 132.3	-0.8 , 12.0
	Min	-31	8	-39
	Max	61	42	58
Cycle2/D1-0H	N	77	1	26
	Mean	1.5	2.0	3.2
	Std. Dev.	19.87		21.24
	Median	0.0	2.0	3.0
	90% CI	-2.3 , 5.3		-3.9 , 10.4
	Min	-42	2	-51
	Max	89	2	38
Cycle2/D1-6H	N	82	1	23
	Mean	5.3	3.0	2.2
	Std. Dev.	18.72		16.76
Cycle2/D1-6H	Median	2.2	3.0	3.7
	90% CI	1.8 , 9.7		-3.8 , 8.2
	Min	-52	3	-36
	Max	95	3	32

Sponsor's a8081005-interim-report-body.pdf, pg 2201

A8081005

The central tendency analysis included summary statistics with 90% confidence limits of changes from baseline for QTcF for all patients (Table 5). The mean changes from baseline for QTcF ranged from 7.2 to 10.3 ms, respectively, at time points on Cycle 2 Day 1, where crizotinib concentrations had reached the steady state. The highest upper bound of two-sided 90% CI (UCI) for was 13.3 ms, respectively, across these measured time points. All UCIs for the QTcF change from baseline were <20 ms (Table 5)

Table 5: ECG Change from Baseline (Safety Analysis Population – A8081005)

Cycle/ Hours Postdose	Parameter	Crizotinib 250 mg BID
QTcF interval (msec)		
Baseline/ 0 hour	N	128
	Mean	409.6
	Std Dev	23.72
	Median	408.3
	90% CI	405.3, 413.8
	Maximum	474
Change from baseline at Cycle 1 Day 1/ 6 hours	N	121
	Mean	2.8
	Std Dev	13.22
	Median	1.3
	90% CI	0.8, 4.8
	Maximum	68
Change from baseline at Cycle 2 Day 1/ 0 hour	N	107
	Mean	7.2
	Std Dev	17.61
	Median	6.3
	90% CI	4.4, 10.1
	Maximum	77
Change from baseline at Cycle 2 Day 1/ 6 hours	N	105
	Mean	10.3
	Std Dev	18.48
	Median	8.3
	90% CI	7.3, 13.3
	Maximum	78

Sponsor’s a8081005-interim-report-body.pdf, pg 107

Reviewer’s comments: The quality of ECGs collected from Study A8081001 and Study A8081005 is poor. Safety ECGs are not sufficient to exclude large increase in QT interval (i.e., ~ 20 ms).

4.2.8.2.2 Assay Sensitivity

Moxifloxacin was not included in either study.

Reviewer’s Comments: Assay sensitivity is not applicable to either Study A8081001 or A8081005.

4.2.8.2.3 Categorical Analysis

A8081001

A summary of categorization of maximum postdose ECG data is provided for the dose escalation cohort in Table 6 and the ALK-positive NSCLC patients in Table 7. Zero patients in the dose-escalation group and one patient in the ALK-positive NSCLC group (0.8%) had a maximum postdose QTcF \geq 480 ms. Three patients in the dose escalation cohort (8.6%) and twelve patients in the ALK-positive NSCLC group (10.2%) had a maximum postdose QTcF 450 to <480 ms. One patient in the ALK-positive NSCLC group (0.8%) had a maximum postdose QTcF >500 ms.

Table 6: Categorization of Maximum Postdose ECG Data: Dose-Escalation Cohort (Safety Analysis Population – A8081001)

Maximum QTcF	N	Total
		n (%)
<450 msec	35	32 (91.4)
450 to <480 msec	35	3 (8.6)
480 to <500 msec	35	0
≥500 msec	35	0

Sponsor's a8081001-interim-report-body.pdf, pg 137

Table 7: Categorization of Maximum Postdose QTcF: ALK-Positive NSCLC (Safety Analysis Population – A8081001)

Maximum QTcF	N	ALK-Positive NSCLC 250 mg BID
		n (%)
<450 msec	118	104 (88.1)
450 to <480 msec	118	12 (10.2)
480 to <500 msec	118	1 (0.8)
≥500 msec	118	1 (0.8)

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A summary of categorization of QTcF maximum increase from baseline is provided in Table 8 and Table 9. One patient in the dose-escalation cohort (3%) and 9 patients in the ALK-positive NSCLC group (8.5%) had a maximum increase from baseline in QTcF of ≥60 ms.

Table 8: Categorization of QTcF Interval Maximum Increase from Baseline: Dose-Escalation Cohort (Safety Analysis Population – A8081001)

Maximum Increase from Baseline in QTcF (msec)	N	Total
		n (%)
<30	33	32 (97.0)
30 ≤ Change <60	33	0
Change ≥60	33	1 (3.0)

Sponsor's a8081001-interim-report-body.pdf, pg 137

Table 9: Categorization of QTcF Interval Maximum Increase from Baseline: ALK-Positive NSCLC (Safety Analysis Population – A8081001)

Maximum Increase from Baseline in QTcF (msec)	N	ALK-Positive NSCLC 250 mg BID
		n (%)
<30	106	93 (87.7)
30 ≤ Change <60	106	9 (8.5)
Change ≥60	106	4 (3.8)

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A8081005

In the current study, QTcF was reported as the primary QT Correction. The majority of patients had maximum postdose QTcF intervals <450 ms (119 [89.5%] patients). Two patients (1.5%) had QTcF intervals \geq 500 ms (Table 10).

Table 10: Categorization of ECG Data (Safety Analysis Population – A8081005)

Parameter	Criteria	Crizotinib 250 mg BID	
		N	n (%)
Maximum QTcF interval (msec)	<450	133	119 (89.5)
	450 to <480	133	9 (6.8)
	480 to <500	133	3 (2.3)
	\geq 500	133	2 (1.5)

Sponsor's a8081005-interim-report-body.pdf, pg 104

The majority of patients (87.5%) had a change in QTcF interval of <30 msec. A total of 5 (3.9%) patients had maximum QTcF interval change from baseline of \geq 60 ms (Table 11).

Table 11: Categorization of Maximum Increase From Baseline (Safety Analysis Population – A8081005)

Parameter (Increase From Baseline)	Criteria	Crizotinib 250 mg BID	
		N	n (%)
Maximum QTcF interval change from baseline (msec)	Change <30	128	112 (87.5)
	Change \geq 30 to <60	128	11 (8.6)
	Change \geq 60	128	5 (3.9)

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4.2.8.3 Safety Analysis

Cardiac AEs discussed in section 3.4. Narratives for QTcF outliers are discussed below. Event of concern per ICH E-14 guidelines are discussed in section 5.4.1.

A8081001

Patient 10031009 was a 29-year-old white male patient with previously treated Ewing's sarcoma who received crizotinib 300 mg BID on study, was evaluated by ECG on Days 1, 15, and 29 per protocol, and was observed to have 1 mean reading with prolonged QTcF (68 ms increase over 382 ms) during the 6-hour postdose assessment on Cycle 1 Day 15. Serum potassium and calcium remained within normal limits throughout the study. No AEs relevant to prolonged QTcF were reported around the time of the QT interval prolongation.

Patient 10071046, a 56-year-old Asian male, was evaluated by ECG predose and postdose on study treatment Days 1, 13, and 27 and was observed to have 1 mean reading with prolonged QTcF (61 ms increase over 402 ms baseline) during the pre-dose assessment on Day 13. Serum potassium and calcium levels were within normal limits during the ECG monitoring period.

Patient 10081003, a 43-year-old, white, male, was evaluated by ECG predose and postdose on study treatment Days 1, 15, and 29 and was observed to have 1 mean reading with prolonged QTcF (61 ms increase over 357 ms baseline) during the post-dose assessment on Day 15 (reported as normal). The individual values for QTcF for the Day 15, 6-hour post-dose tracings were 386, 381, and 487 ms; thus, the mean was greater than 60 ms over baseline due to the outlying value of 487 ms. Serum potassium and calcium levels were within normal limits during the ECG monitoring period.

Patient 10081006, a 61-year-old white female, was evaluated by ECG predose and postdose on Days 1, 15, and 29 and was observed to have 1 mean reading with prolonged QTcF (84 ms increase over 413 ms baseline) during the pre-dose assessment on Day 29, which was reported by the investigator to be normal. The 3 sets of measurements obtained predose on Day 29 vary widely: heart rates of 68, 119, and 46 bpm, PR intervals of 216, 144, and 137 ms, and QTcF of 454, 579, and 460 ms. Serum potassium values reported during the study ranged from 3.6 to 4.3 mmol/L (normal range 3.5-5.0 mmol/L); calcium was 2.16, 1.84, and 2.04 mmol/L on Days 0, 15 and 29, respectively (normal range 2.1-2.6 mmol/L).

Patient 10021071 was evaluated by ECG predose and postdose on study treatment Days 1, 15, and 29 (Cycle 2 Day 1). Screening ECGs revealed sinus bradycardia with a mean heart rate of 60 bpm, a mean QTcF of 407 ms, and an incomplete right bundle branch block (Cycle 1 Day 15). His QTcF remained normal during his first 2 weeks on treatment, though he remained bradycardic. On Cycle 1 Day 15, pre-dose QTcF was 466 ms (Grade 2 prolongation) with a concurrent heart rate of 48 bpm; 6-hour post-dose values were 434 ms and 50 bpm, respectively. He was asymptomatic, but his metoprolol was stopped that day. On Day 29 (Cycle 2 Day 1), the pre-dose QTcF was 504 ms with a heart rate of 44 bpm, and 6-hour post-dose values were 510 ms and 44 bpm, respectively, and reported by the investigator to be clinically significant. A final single ECG was recorded on Day 33 and demonstrated a QTcF of 457 ms with a heart rate of 50 bpm. The patient's reported serum potassium remained between 4.0 and 5.0 mmol/L and his serum calcium remained within normal limits throughout the period of ECG assessment (magnesium levels were not collected in the study). There were no crizotinib dose modifications made as a result of these ECG changes, but the lisinopril dosage was lowered on Day 43 when the patient was reported as having Grade 2 bradycardia with an associated AE of Grade 1 Dizziness. The patient had been on study for 393 days and remained on study at the time of data snapshot.

A80081005:

Patient 10311003 was evaluated by ECG predose on Cycle 1 Day 1 and postdose on Cycle 1 Day 5 and was observed to have the mean reading with prolonged QTcF (68 ms increase over 313 ms baseline) during the post-dose assessment on Cycle 1 Day 5. Laboratory values obtained on Cycle 1 Day 1 revealed low-normal potassium (3.3

mmol/L), normal serum calcium (2.13 mmol/L), and normal magnesium (0.8 mmol/L). There were no reported symptoms associated with the change in QTc.

Patient 11741001 was evaluated by ECG pre- and postdose on Cycle 1 Day 1 and Day 22 (Cycle 2 Day 1) and was observed to have mean readings with prolonged QTcF (77 ms and 78 ms increase over 339 ms baseline, respectively) during the pre-dose and 6-hour post-dose ECGs on Day 22 (Cycle 2 Day 1), reported by the investigator to be not clinically significant. Laboratory values from the same day (ie, Cycle 2 Day 1) revealed normal potassium (4.3 mmol/L), normal magnesium (0.85 mmol/L), and low calcium (1.88 mmol/L). There were no AEs associated with the QTcF changes on Day 22 (Cycle 2 Day 1) and no changes in study treatment were made. Subsequently, on Day 65 (Cycle 4 Day 2) the patient experienced an SAE of Grade 1 Palpitations that lasted 2 days. Absolute QTcF or ECG on that day is unavailable.

Patient 11771001 was evaluated by ECG pre- and postdose on Cycle 1 Day 1 and postdose on Day 22 (Cycle 2 Day 1) and was observed to have 1 mean reading with prolonged QTcF (73 ms increase over 417 ms at baseline) during 6-hour post-dose ECG on Cycle 1 Day 20. At baseline and on Day 22 (Cycle 2 Day 1), serum potassium, magnesium, and calcium were within normal range. There were no associated symptoms.

Patient 11961002 was evaluated by ECG pre- and postdose on Cycle 1 Day 1 and Day 22 (Cycle 2 Day 1) and was observed to have 1 mean reading with prolonged QTcF (67 ms increase over 394 ms at baseline) during the 6-hour post-dose ECGs on Day 22 (Cycle 2 Day 1). Laboratory studies done the same day as the QTcF prolongation demonstrated normal serum potassium and magnesium (4.4 and 0.80 mmol/L, respectively) and a mildly decreased calcium of 2.08 mmol/L (normal range 2.1 to 2.58 mmol/L).

Patient 10581044 was evaluated by ECG at screening and predose on Day 22 (Cycle 2 Day 1), when prolonged QTcF of 511 ms was observed. Serum chemistry results on Day 22 (Cycle 2 Day 1) are not yet available. The patient had no reported symptoms associated with QTcF prolongation, but study treatment was interrupted.

Patient 10641047 was evaluated by ECG pre- and postdose on Cycle 1 Day 1 and Day 22 (Cycle 2 Day 1) and was observed at the 6-hour post-dose ECG on Day 22 to have mean QTcF of 501 ms (75 ms increase over 426 ms baseline) representing a Grade 3 QTc prolongation. At baseline and on Day 22 (Cycle 2 Day 1), serum potassium, magnesium, and calcium values were within normal range.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

A8081001

As of 13 September 2010, crizotinib PK data were available for a total of 204 patients, 37 of whom were from the dose-escalation cohort, and 167 of whom were from the RP2D cohorts. After repeated (b.i.d. or q.d.) oral administration, plasma concentrations of crizotinib appeared to reach steady state within 15 days. Patients receiving doses in the range of 100 to 200 mg q.d. and 200 to 300 mg b.i.d. appeared to demonstrate dose proportional increases in geometric mean $AUC_{0-\tau}$ and C_{max} with single or multiple dose administration. However, greater than dose proportional increases were observed in crizotinib $AUC_{0-\tau}$ and C_{max} over the dose range of 50 to 100 mg q.d..

Median plasma concentration-time profiles for crizotinib following multiple oral dose administration (Day 15 of Cycle 1 and Day 1 of Cycle 2) in the dose escalation cohort are shown in Figure 1 for the dose-escalation cohort. Pharmacokinetic parameters for crizotinib are summarized in Table 12.

Figure 1: Median Plasma Crizotinib Concentration-Time Profiles Following Multiple Oral Administration of Crizotinib; Cycle 1 Day 15 (left) and Cycle 2 Day 1 (right), in the Dose-Escalation Cohort

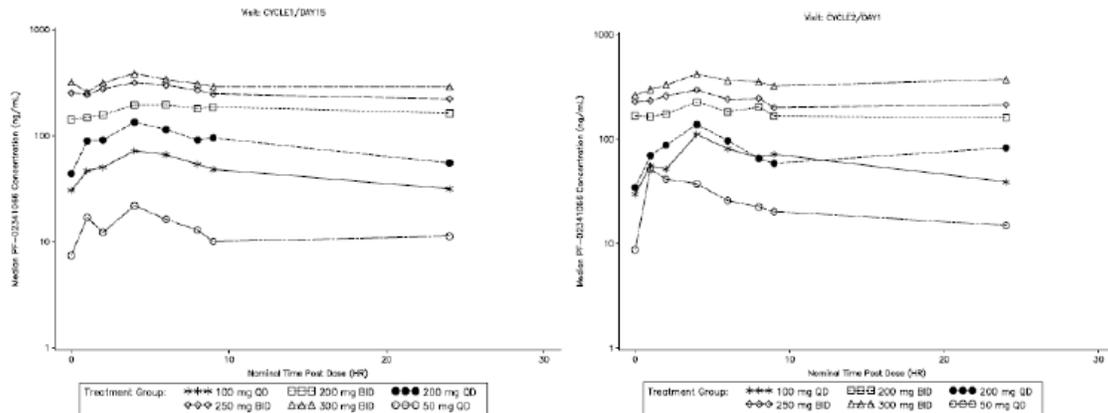


Table 12: Descriptive Summary of Plasma Pharmacokinetic Parameters of Crizotinib in the Dose-Escalation Cohort (A8081001)

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

Cycle 1 Day 15 (multiple doses)						
N	3	4	8	4	5	4
T _{max} , hr	2.00 (1.00-4.00)	2.51 (0.00-6.08)	4.07 (1.00-6.00)	5.01 (2.08-8.03)	4.00 (0.97-6.07)	4.99 (3.98-6.22)
C _{max} , ng/mL	24.4 (52) 7.47	85.7 (69) 30.6	149 (27) 44.1	189 (48)	327 (25) 259	420 (48) 279
C _{trough} , ng/mL	(4.81-10.8)	(23.5-52.4)	(30.8-160)	132; 183 ^b	(159-356) ^c	(183-403)
AUC _t , ng*hr/mL	206 (64)	1087 (37)	2047 (48)	1780 (61)	3084 (32)	4067 (55)
CL/F, L/hr	243 (63) 1.61	91.8 (27) 2.36	97.8 (44) 2.80	112 (61) 4.85	81.0 (28) 4.53	73.7 (42) 4.87
R _{ac}	(0.72-2.89)	(2.20-2.61)	(1.12-25.8)	(3.74-18.7)	(4.36-8.70)	(3.39-7.47)
Cycle 2 Day 1 (multiple doses)						
N	3	3	5	3	5	3
T _{max} , hr	1.02 (1.00-4.00)	3.98 (2.00-4.02)	4.00 (2.00-4.17)	4.00 (3.95-4.00)	4.00 (4.00-6.00)	4.05 (3.98-9.00)
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 _t , ng*hr/mL	426 (40)	1596 (31)	1719 (63)	2256 (13)	3054 (32)	3240; 4100 ^b
CL/F, L/hr	117 (51) 3.79	62.6 (26) 3.39	116 (51) 1.62	88.5 (14) 4.65	81.8 (25) 5.27	73.3; 92.6 ^b 3.94
R _{ac}	(1.98-3.97)	(3.14-3.83)	(1.46-3.13)	(4.18-4.88)	(3.73-8.77)	(3.75-4.13)

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In the RP2D cohort, Crizotinib plasma concentrations appeared to reach steady state within 15 days with repeated 250-mg b.i.d. dosing (Table 13). The median trough concentrations of crizotinib were 319 and 301 ng/mL for C1D15 and Cycle 2 Day 1, respectively.

Table 13: Descriptive Summary of Plasma Pharmacokinetic Parameters Following 250-mg BID Dosing of Crizotinib in the RP2D Cohort (A8081001)

Parameters, Units	Parameter Summary Statistics ^a by Visit			
	Single dose		Multiple dose	
	Day -7	Cycle 1 Day 1	Cycle 1 Day 15	Cycle 2 Day 1
N	46	98	24	18
T _{max} , hr	4.00 (2.00-9.33)	4.05 (1.00-9.08)	4.00 (0.00-9.03)	4.00 (0.00-9.02)
C _{max} , ng/mL	108 (38)	98.9 (45)	411 (44)	478 (38)
C _{trough} , ng/mL	0.00 (0.00-32.6) ^b	0.00 (0.00-517) ^c	319 (1.57-1030) ^d	301 (3.17-849) ^e
AUC _t , ng*hr/mL	742 (40)	663 (45) ^f	3880 (36) ^g	4164 (38) ^h
AUC _{inf} , ng*hr/mL	2489 (51) ⁱ	NA	NA	NA
CL/F, L/hr	100 (50) ⁱ	NA	64.5 (56) ^g	60.1 (44) ^h
V _z /F, L	5946 (63) ⁱ	NA	NA	NA
t _{1/2} , hr	42.4 (21) ^j	NA	NA	NA
R _{ac}	NA	NA	4.84 (3.06-13.1) ^h	4.78 (2.75-15.4) ^k

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An exploratory evaluation of the effect of food (a standard high-fat meal v.s. overnight fast) on crizotinib PK was conducted in 12 patients receiving a single 250-mg crizotinib dose (Table 14). The fed/fasted ratios of the geometric means for crizotinib exposure were 85% (90% CI: 65%-110%) for AUC₀₋₂₄ and 88% (90% CI: 69%-111%) for C_{max}. The results of this assessment indicated that coadministration of crizotinib with a standard high-fat meal did not markedly affect systemic exposure to orally administered crizotinib.

Table 14: Summary of Statistical Comparison of Crizotinib PK Parameters in Fed versus Fasted State in the RP2D Cohorts (A8081001)

Parameters, Units	Fed		Fasted		Ratio (Fed/Fasted) %	90% Confidence Intervals %
	N	Adjusted Geometric Mean	N	Adjusted Geometric Mean		
AUC ₂₄ , ng*hr/mL	8	1125	10	1329	84.64	(65.11, 110.05)
C _{max} , ng/mL	11	104	12	119	87.65	(69.23, 110.98)

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A8081005

The PK samples collected before and on 15 September 2010 were analyzed and reported in the preliminary report. 85 patients, each of whom had at least 1 measured plasma concentration (including below the limit of quantitation) of crizotinib or PF-06260182, were included in the PK dataset.

Crizotinib appeared to reach the steady state within the first cycle (21 days per cycle) after repeated oral administration of crizotinib at 250 mg b.i.d. The median predose concentrations of crizotinib were 280, 255, and 242 ng/mL on Cycle 2 Day 1, Cycle 3 Day 1, and Cycle 5 Day 1, respectively (Table 15). Similar to crizotinib, the steady state plasma concentrations of its metabolite, PF-06260182, also appeared to be achieved within the first cycle. The median predose concentrations of PF-06260182 following 250-mg BID dosing of crizotinib were 58.6, 54.9, and 66.5 ng/mL on Cycle 2 Day 1, Cycle 3 Day 1, and Cycle 5 Day 1, respectively (Table 15). The mean (%CV) predose concentration ratios of PF-06260182 to crizotinib were 0.234 (44%), 0.204 (46%), and 0.211 (39%) at Cycle 2 Day 1, Cycle 3 Day 1, and Cycle 5 Day 1, respectively (Table 15).

Table 15: Summary of Predose Concentrations of Crizotinib and its Metabolite PF-06260182, Following 250-mg BID Oral Dosing (A8081005)

Parameter	Predose Plasma Concentration* (ng/mL)			
	Cycle 1 Day 1	Cycle 2 Day 1	Cycle 3 Day 1	Cycle 5 Day 1
<i>All Patients</i>				
N	74	36	24	14
Crizotinib	BLQ	280 (1.38-622)	255 (0.803-475)	242 (55.1-857)
PF-06260182	BLQ	58.6 (0.00-329)	54.9 (0.00-162)	66.5 (4.28-164)
PF-06260182 to crizotinib ratio	NA	0.234 (44)	0.204 (46)	0.211 (39)
<i>Asian Patients</i>				
N	28	15	7	3
Crizotinib	BLQ	320 (1.58-622)	373 (220-475)	381 (77.3-575)
PF-06260182	BLQ	76.4 (34.0-148)	97.2 (44.4-162)	131 (9.14-148)
PF-06260182 to crizotinib ratio	NA	0.237 (20)	0.257 (24)	0.233 (47)
<i>Non-Asian Patients</i>				
N	46	21	17	11
Crizotinib	BLQ	196 (1.38-523)	219 (0.803-400)	233 (55.1-857)
PF-06260182	BLQ	44.9 (0.00-329)	41.6 (0.00-162)	62.6 (4.28-164)
PF-06260182 to crizotinib ratio	NA	0.232 (37)	0.183 (53)	0.205 (39)

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4.2.8.4.2 Exposure-Response Analysis

A preliminary PK/PD analysis has been conducted to explore the QT/QTc and plasma crizotinib concentration relationship for Study A8081001 by using graphical methods and mixed effects linear modeling. A total of 62 patients were available for this analysis. Of these, 53 patients had at least 1 set of baseline measurements and at least 1 post dose set of values. Most patients had at least 5 measurements post dose. The commonly used Fridericia's (QTcF) correction was applied. Figure 2 presents QTcF versus crizotinib concentrations by sex with the mixed effects linear model regression lines.

The results from the mixed effects linear modeling of QTcF is shown in Table 16. The estimated slope is 0.020 ms per ng/mL indicating that QTcF interval increases as crizotinib concentration increases. The 90% confidence limits (0.006, 0.034) indicate that the slope for concentration-QTcF relationship is not zero. Based on the model, the drug induced increase in QTcF at the mean C_{max} (380 ng/mL for 250 mg b.i.d.) is 7.5 ms (90% conf. limits: 2.3, 12.8 ms).

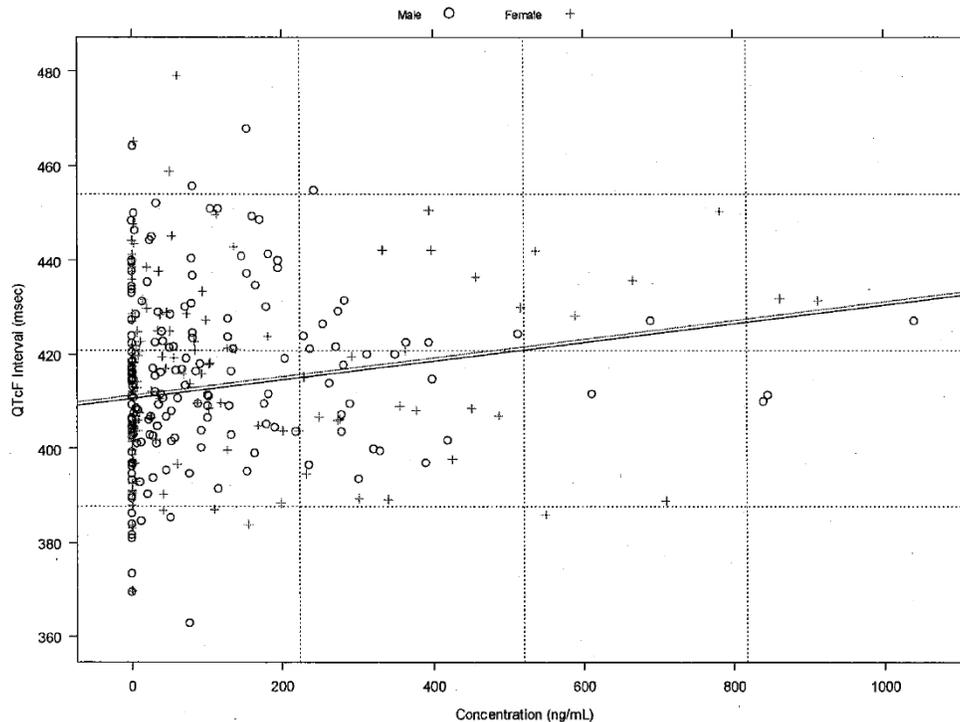
Table 16: Linear Model Results for Crizotinib Concentration Versus QTcF Interval (A8081001)

Parameter	Estimate	SE	RSE%
Intercept, males (msec)	411	3.05	0.7
Intercept, females (msec)	411	3.15	0.8
Slope (msec/ng/mL)	0.0198	0.00844	42.6
Between Subject Effect , Intercept	252	50.3	20.0
Between Subject Effect , Slope	0.00068	0.000707	103.4
Residual Error, singlet (msec)	8.1	1.72	21.3
Residual Error, triplicate (msec)	10.0	1.00	10.0

SE = standard error; RSE% = relative standard error (percent);

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Figure 2: Crizotinib Concentration Versus Mean QTcF by Sex (A8081001)



IND73544 SDN039 _ Protocol_IB & ClinPharmTable.PDF, pg 302

Reviewer's Analysis: A significant concentration- Δ QTcF relationship was identified by the sponsor and is supported by the reviewer's analysis. Anticipated QT prolongation at the crizotinib 250 mg b.i.d. based on observations from A8081001 and A8081005 are shown in the reviewer's analysis.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

We evaluated the appropriateness of the correction methods (QTcF and QTcI). Data from both A8081001 and A8081005 were combined in this analysis. Patients receiving 250 mg b.i.d. were combined as a single group from A8081001. Baseline values were excluded in the validation. Ideally, a good correction QTc would result in no relationship of QTc and RR intervals.

We used the mixed model of the pooled post-dose data of QTcF and QTcI distinguished by an indicator of correction method to evaluate the linear relationships between different correction methods and RR. The model included RR, correction type (QTcF and QTcI), and the interaction term of RR and correction type. The slopes of QTcF and QTcI versus RR are compared in magnitude as well as statistical significance in difference. As shown in Table 17, it appears that QTcI had smaller absolute slopes than QTcF. However, closer inspection of the data indicates that crizotinib may also impact heart rate. Due to the sparse data, study setting in which these ECG measurements were obtained (i.e., safety monitoring), and evidence of drug-induced heart rate changes, the reviewer has selected QTcF as the correction method for the study data, which is consistent with the sponsor's primary correction method.

Table 17: Comparison of QTcF and QTcI Using the Mixed Model

Treatment Groups	Slope of QTcF	Slope of QTcI
All	0.028 (p-value <0.001)	-0.008 (p-value 0.20)

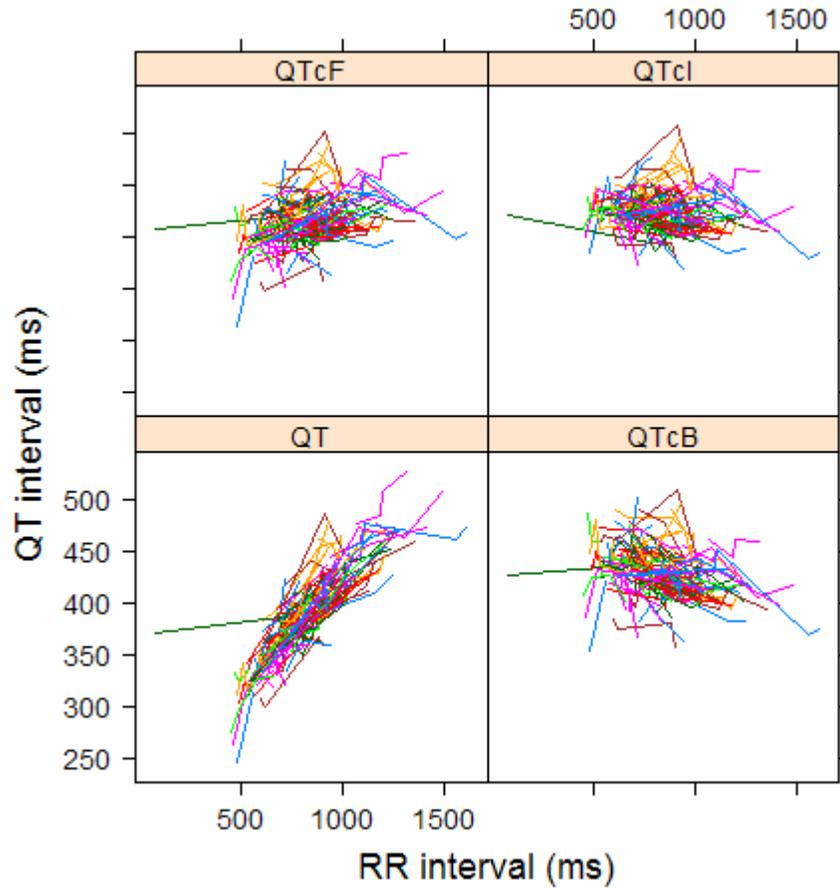
We also confirmed this conclusion by using the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based on the results listed in Table 18, it also appears that QTcF is the best correction method. Therefore, this reviewer used QTcF for the primary statistical analysis. This is consistent with the sponsor's choice of QTcF for their primary analysis.

Table 18: Average of Sum of Squared Slopes for Different QT-RR Correction Methods

Treatment Group	QTcF		QTcI	
	N	MSSS	N	MSSS
All	326	0.0011	326	0.0005

The relationship between different correction methods and RR is presented in Figure 3.

Figure 3: QT, QTcB, QTcF, and QTcI vs. RR (Each Subject's Data Points are Connected with a Line)



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for Crizotinib

The analysis results are listed in the following tables (Table 19).

Table 19: Analysis Results of Δ QTcF for Crizotinib 250 mg b.i.d. and 300 mg b.i.d. from A8081001 and Crizotinib 250 mg b.i.d. from A8081005

Treatment	Visit	Time (hr)	Mean (ms)	Standard Error (ms)	Lower 90% CI	Upper 90% CI
250 mg b.i.d. A8081001	Day 1 Cycle 1	6	3.3	1.0	1.6	4.9
	Day 1 Cycle 1	24	0.5	1.3	-1.6	2.6
	Day 15 Cycle 1	0	3	1.6	0.4	5.7
	Day 15 Cycle 1	6	5.3	1.7	2.6	8.1
	Day 1 Cycle 2	0	2.6	2.0	-0.8	6.0
	Day 1 Cycle 2	6	4.8	1.8	1.7	7.8

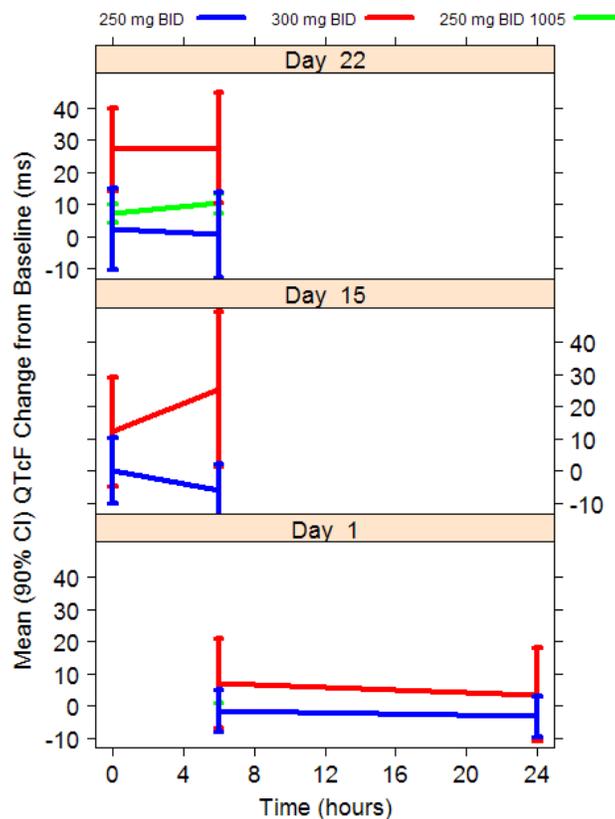
300 mg b.i.d. A8081001	Day 1 Cycle 1	6	6.8	8.5	-7.2	20.8
	Day 1 Cycle 1	24	3.5	8.9	-11.2	18.2
	Day 15 Cycle 1	0	12.3	10.3	-4.7	29.2
	Day 15 Cycle 1	6	25.4	14.6	1.3	49.6
	Day 1 Cycle 2	0	27.2	7.8	14.3	40.2
	Day 1 Cycle 2	6	27.7	10.4	10.5	44.8
250 mg b.i.d. A8081005	Day 1 Cycle 1	6	4.2	1.4	1.8	6.5
	Day 1 Cycle 2	0	7.5	1.9	4.3	10.6
	Day 1 Cycle 2	6	9.5	1.8	6.5	12.4

The largest upper bounds of the 2-sided 90% CI for the mean change from baseline for crizotinib 250 mg b.i.d. and crizotinib 300 mg b.i.d. from A8081001 was 8.1 and 49.6 ms, respectively. Likewise, the largest upper bound of the 2-sided 90% CI for the mean change from baseline for crizotinib 250 mg b.i.d. for A8081005 was 12.4 ms.

5.2.1.2 Graph of Δ QTcF Over Time

Figure 4 displays the time profile of Δ QTcF for different treatment groups.

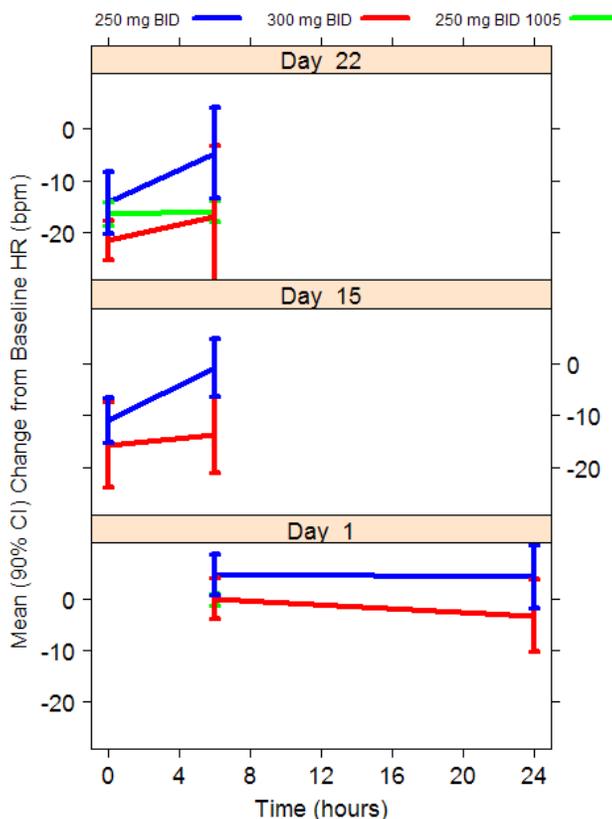
Figure 4: Mean and 90% CI Δ QTcF Timecourse for Crizotinib



5.2.1.3 Graph of Change from Baseline in Heart Rate (Δ HR) Over Time

Figure 5 displays the time profile of Δ HR for different treatment groups.

Figure 5: Mean and 90% CI ΔHR Timecourse for Crizotinib



5.2.1.4 Categorical Analysis

Table 20 lists the number of subjects as well as the number of observations whose QTcF values are ≤ 450 ms, between 450 ms and 480 ms. Two subjects from A8081001 and five subjects from A8081005 receiving crizotinib 250 mg b.i.d. had QTcF was above 480 ms. Two subjects with baseline (Day 1 Cycle 1) data available and one additional subject with only Day 1 Cycle 2 data available had QTcF>500 ms. The categorical analysis results match the sponsor reported values in the label.

Table 20: Categorical Analysis for QTcF

Treatment Group	Total N		Value \leq 450ms		450<Value \leq 480ms		Value>480ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
100 mg q.d. (A8081001)	4	28	4 (100%)	28 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
200 mg b.i.d (A8081001)	7	35	5 (71.4%)	31 (88.6%)	2 (28.6%)	4 (11.4%)	0 (0%)	0 (0%)
200 mg q.d. (A8081001)	8	40	8 (100%)	40 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

250 mg b.i.d. (A8081001)	166	930	144 (86.7%)	885 (95.2%)	20 (12%)	42 (4.5%)	2 (1.2%)	3 (0.3%)
300 mg b.i.d. (A8081001)	6	29	6 (100%)	29 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
50 mg q.d. (A8081001)	3	20	3 (100%)	20 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
250 mg b.i.d. (A8081005)	135	472	119 (88.1%)	446 (94.5%)	11 (8.1%)	21 (4.4%)	5 (3.7%)	5 (1.1%)

Table 21 lists the categorical analysis results for Δ QTcF. Four subjects from A8081001 and five subjects from A8081005 receiving crizotinib 250 mg b.i.d. had QTcF change from baseline above 60 ms.

Table 21: Categorical Analysis of Δ QTcF

Treatment Group	Total N		Value \leq 30ms		30<Value \leq 60ms		Value>60ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
100 mg q.d. (A8081001)	4	23	4 (100%)	23 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
200 mg b.i.d. (A8081001)	6	26	6 (100%)	26 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
200 mg q.d. (A8081001)	8	32	8 (100%)	32 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
250 mg b.i.d. (A8081001)	158	750	140 (88.6%)	714 (95.2%)	14 (8.9%)	31 (4.1%)	4 (2.5%)	5 (0.7%)
300 mg b.i.d. (A8081001)	5	23	4 (80%)	18 (78.3%)	0 (0%)	4 (17.4%)	1 (20%)	1 (4.3%)
50 mg q.d. (A8081001)	3	17	3 (100%)	17 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
250 mg b.i.d. (A8081005)	128	333	112 (87.5%)	311 (93.4%)	11 (8.6%)	16 (4.8%)	5 (3.9%)	6 (1.8%)

5.2.2 PR Analysis

The outlier analysis results for PR are presented in Table 22.

Table 22: Categorical Analysis for PR

Treatment Group	Total N		Value>200ms	
	# Subj.	# Obs.	# Subj.	# Obs.
100 mg q.d. (A8081001)	4	27	1 (25%)	1 (3.7%)
200 mg b.i.d. (A8081001)	7	33	1 (14.3%)	5 (15.2%)
200 mg q.d. (A8081001)	8	37	0 (0%)	0 (0%)
250 mg b.i.d. (A8081001)	165	913	11 (6.7%)	49

				(5.4%)
300 mg b.i.d (A8081001)	6	29	1 (16.7%)	2 (6.9%)
50 mg q.d. (A8081001)	3	20	0 (0%)	0 (0%)
250 mg b.i.d. (A8081005)	134	468	7 (5.2%)	18 (3.8%)

5.2.3 QRS Analysis

The outlier analysis results for QRS are presented in Table 23.

Table 23: Categorical Analysis for QRS

Treatment Group	Total N		Value>110ms	
	# Subj.	# Obs.	# Subj.	# Obs.
100 mg q.d. (A8081001)	4	27	0 (0%)	0 (0%)
200 mg b.i.d (A8081001)	7	33	0 (0%)	0 (0%)
200 mg q.d. (A8081001)	8	37	0 (0%)	0 (0%)
250 mg b.i.d (A8081001)	166	921	8 (4.8%)	30 (3.3%)
300 mg b.i.d (A8081001)	6	29	0 (0%)	0 (0%)
50 mg q.d. (A8081001)	3	20	0 (0%)	0 (0%)
250 mg b.i.d. (A8081005)	135	472	4 (3%)	8 (1.7%)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The mean drug concentration-time profile is illustrated in Figure 1. Metabolite concentrations (PF-06260182) were only available from patients in A8081005 and were only observed at predose and at 6 hr post-dose. Due to the limited samples and the sponsor's Table 15 that demonstrates a metabolite to crizotinib ratio ranging between 0.20-0.23, only crizotinib concentrations were evaluated in the exposure-response analysis.

The relationship between $\Delta QTcF$ and crizotinib concentrations was investigated by linear mixed-effects modeling.

The following three linear models were considered:

Model 1 is a linear model with an intercept

Model 2 is a linear model with mean intercept fixed to 0 (with variability)

Model 3 is a linear model with no intercept

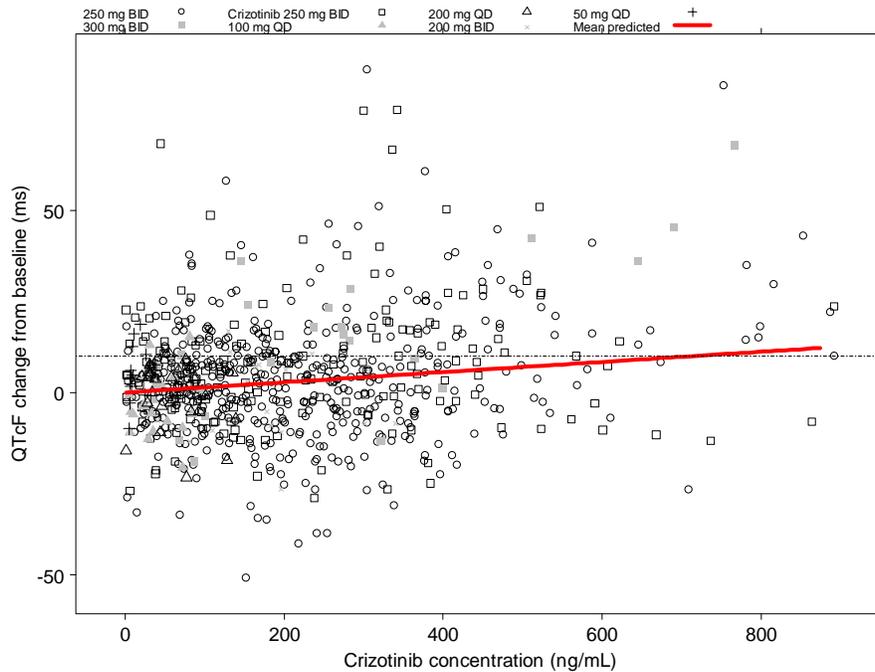
Table 24 summarizes the results of the crizotinib concentration - $\Delta QTcF$ analyses. Model 2 was used for further analysis since the model with intercept fixed to zero was found to fit the data best.

Table 24: Exposure-response Analysis of Crizotinib Associated Δ QTcF Prolongation

	Parameter	Estimate	P-value	Interindividual Variability (CV %)
Model 1: Δ QTcF = Intercept + slope * Crizotinib Concentration				
	Intercept (ms)	0.6 (-0.9; 2.1)	0.51	8
	Slope (ms per ng/mL)	0.012 (0.005; 0.019)	0.009	42
	Residual Variability (ms)	9.5		
Model 2: Δ QTcF = Intercept + slope * Crizotinib Concentration				
	Intercept (ms)	0		8
	Slope (ms per ng/mL)	0.014 (0.008; 0.020)	<0.001	41
	Residual Variability (ms)	9.65		
Model 3: Δ QTcF = slope * Crizotinib Concentration				
	Slope (ms per ng/mL)	0.014 (0.007; 0.021)	<0.001	52
	Residual Variability (ms)	10.8		

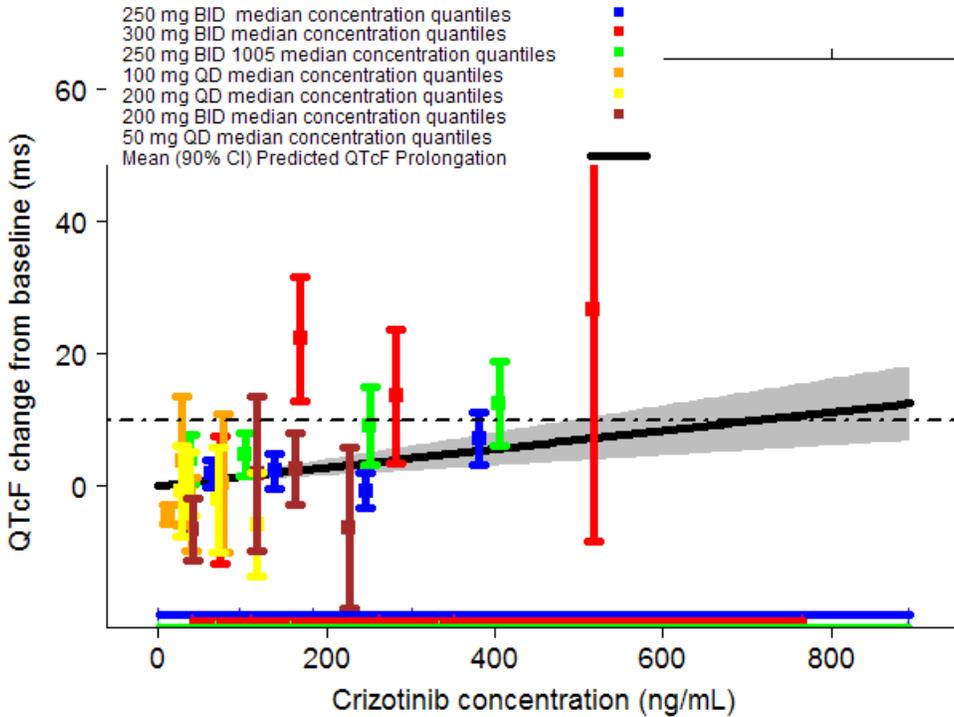
The relationship between Δ QTcF and crizotinib concentrations is visualized in Figure 6.

Figure 6: Observed Δ QTcF vs. Crizotinib Concentration Together with the Population Predictions (solid red line).



The goodness-of-fit plot in Figure 7 shows the observed median-quantile crizotinib concentrations and associated mean (90% CI) Δ QTcF (90% CI) together with the mean (90% CI) predicted Δ QTcF.

Figure 7: Observed Median-Quantile Crizotinib Concentrations and Associated Mean (90% CI) Δ QTcF (color dots) Together with the Mean (90% CI) Predicted Δ QTcF (black line with shaded grey area).



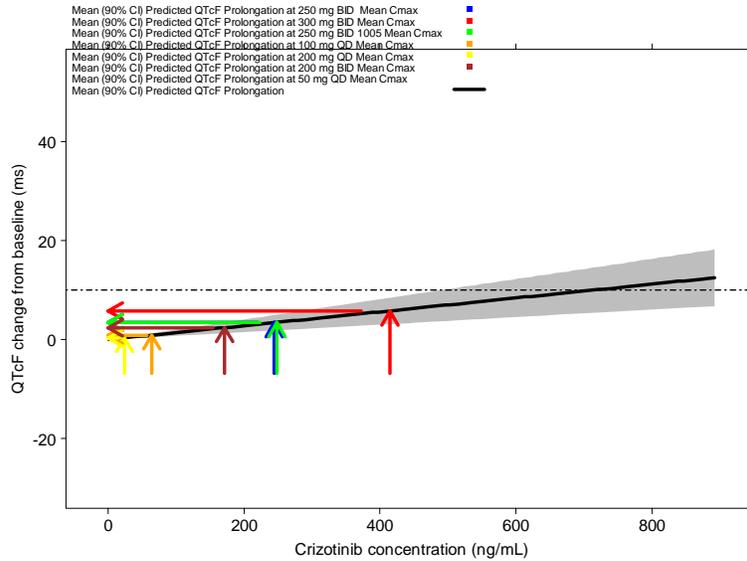
The predicted Δ QTcF at the geometric mean peak Crizotinib concentrations can be found in Table 25 and visualized in Figure 8.

Table 25: Predicted Δ QTcF Interval at Geometric Mean Peak Crizotinib Concentration Using Model 2

Treatment	Geometric C_{max} (ng/mL)	Predicted Δ QTcF (ms)	90% Confidence Interval
250 mg b.i.d. A8081001	244	3.4	(1.9; 5.0)
300 mg b.i.d. A8081001	414	5.8	(3.1; 8.4)

250 mg b.i.d. A8081005	248	3.5	(1.9; 5.1)
---------------------------	-----	-----	------------

Figure 8: Mean (90% CI) Predicted Δ QTcF at Geometric Mean C_{max}



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

Events identified to be of clinical importance per the ICH E 14 guidelines:

A8081001

4 subjects had syncope with no reported association with QT prolongation. One patient (Patient 10021039) experienced nausea 40-50 minutes after dosing on Day -7, followed by a Grade 3 Presyncope that was associated with Grade 2 Electrocardiogram QT prolonged. There were 4 reports of seizure in patients with brain metastasis.

A8081005

3 subjects experienced syncope, one of these was classified as Grade 3 and resulted in study drug discontinuation. ECG and lab data on the day of the event are unavailable. There were no reports of seizure in this study.

Reviewer's comments: Sudden death and cardiac disorders are discussed under section 3.4.

5.4.2 ECG assessments

These were not centrally read ECGs and, as shown in examples below timing of ECGs relative to treatment was known. Pdf files of paper ECGs were submitted. On review of subset at random, some copies were of poor quality (see examples below). No interval annotations are available. These ECGs seem inadequate to quantify effects ≤ 20 ms based

on review of these pdf copies. Overall, these ECGs appear adequate for outlier analysis but not for any quantification of QT effect size.

10011001

Cydel Dayl

10-MAY-2006 14:24:11

(b) (6) HEMOC ROUTINE RETRIEVAL

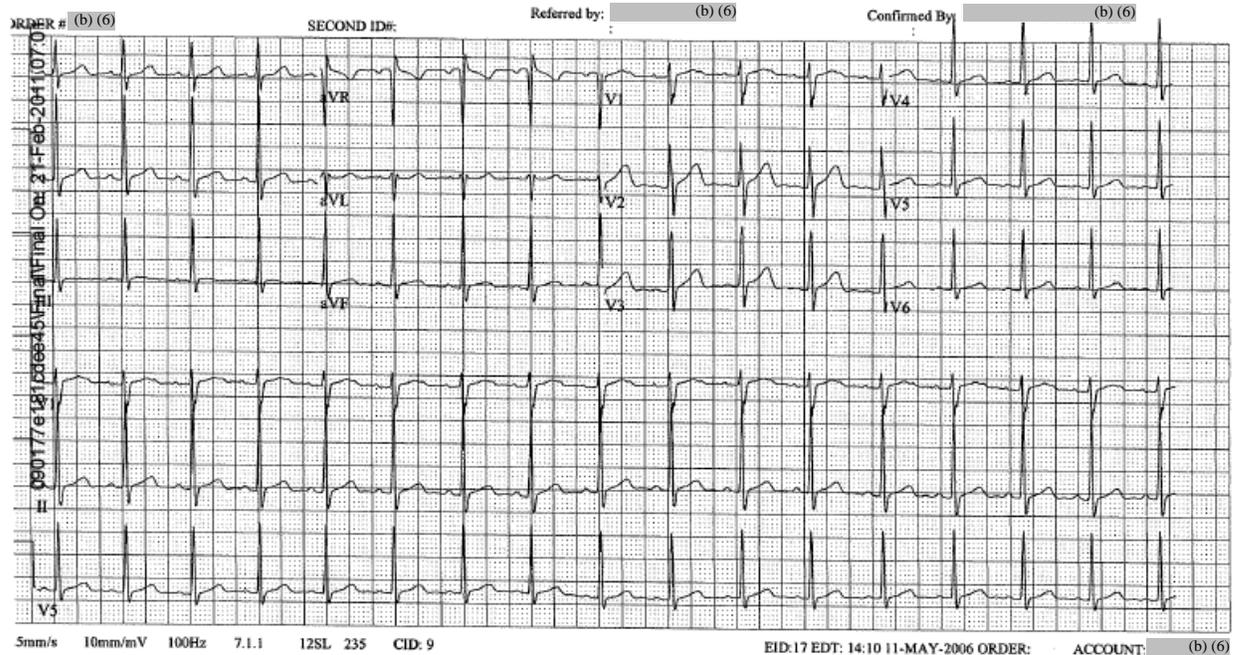
██████████
██████████
██████████
toom:
oe:13

Vent. rate	99	BPM
PR interval	140	ms
QRS duration	88	ms
QT/QTc	350/449	ms
P-R-T axes	49 76 47	

I have reviewed the test strips and agree with the findings.
Normal sinus rhythm
Normal ECG
When compared with ECG of 10-MAY-2006 14:22, (unconfirmed)
No significant change was found
Hema/onc, Edited by: Mm

FEB 09 2011

Technician: (b) (6)
Test ind: V58.69



Page 1 of 1

[Redacted]

10011003

ID: (b) (6)

29-Jun-2006 8:22:39

(b) (6)

Room:
Loc: 13

Vent. rate 58 bpm
PR interval 202 ms
QRS duration 94 ms
QT/QTc 406/398 ms
P-R-T axes 72 68 57

Sinus bradycardia
Otherwise normal ECG

CIDr

JAN 19 2011

Technician: 7
Test ind: V58.69

91



1002103 /

[Redacted]

ID: [Redacted]

15-APR-2009 16:00:28

(b) (6)

[Redacted]
[Redacted]

Vent. rate	84	BPM
PR interval	140	ms
QRS duration	82	ms
QT/QTc	360/425	ms
P-R-T axes	79 85 62	

Normal sinus rhythm
 Nonspecific ST abnormality
 Abnormal ECG
 When compared with ECG of 15-APR-2009 08:38, (unconfirmed)
 No significant change was found

Loc:5

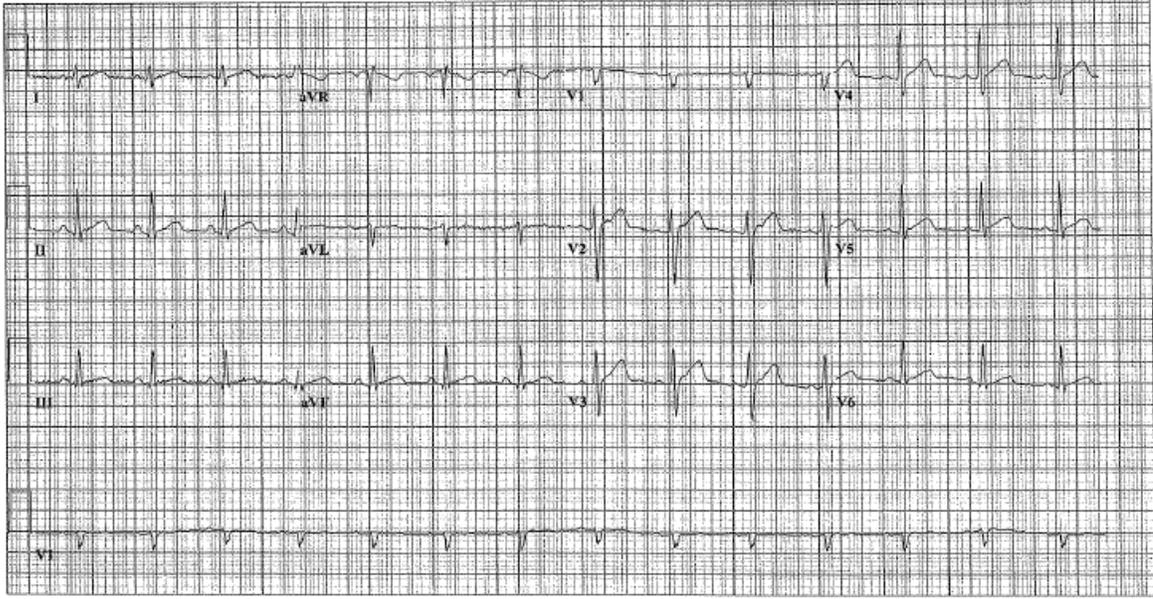
JAN 21 2009

Technician: (b) (6)

Referred by: (b) (6)

Confirmed By: (b) (6)

090177e181ced23d\Final\Final On: 22-Feb-2011 15:44



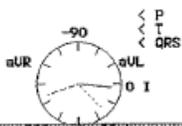
25mm/s 10mm/mV 40Hz 005E 12SL 235 CID: 10

EID:12 EDT: 08:27 21-APR-2009 ORDER:

Page 1 of 1

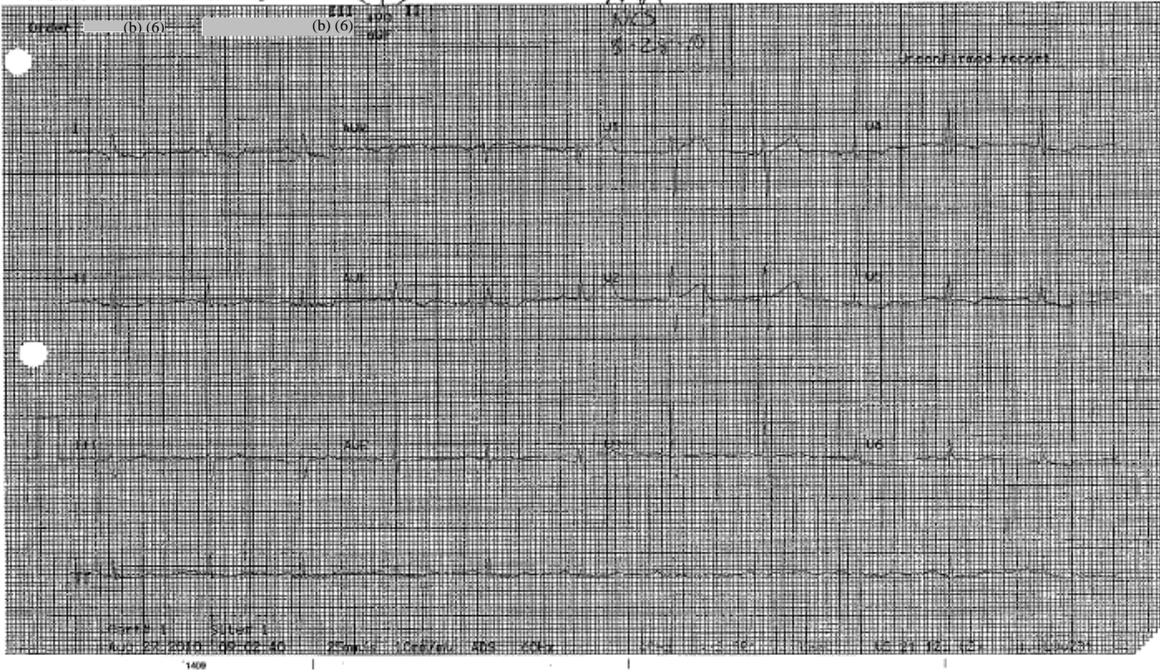
Measurement Results:

QRS	102 ms
QT/QTcB	392 / 414 ms
PR	182 ms
P	116 ms
RR/PP	880 / 895 ms
P/QRS/T	47° / 7° / 160 degrees



Interpretation:
 *** Age and gender specific ECG analysis ***
 Normal sinus rhythm
 ST & T wave abnormality, consider lateral ischemia
 Abnormal ECG

090177e181cdf73FinalFinal On: 21-Feb-2011 07:20



1005

10011002
C2D1
6/24/10
13:24

PIPR: 104/168 ms sinus rhythm (slow)
QRS: 96 ms Normal ECG
QT/QTc: 452/436 ms
P/QRS/T Axis: 77/39/49 deg
Heart Rate: 56 BPM

Unconfirmed Report



090177e181d3b00fFinal On: 03-Mar-2011 07:41

25 mm/s 10 mm/mV Frequency Response [0.5-35] Hz 60 Hz 6/24/2010 13:24:17

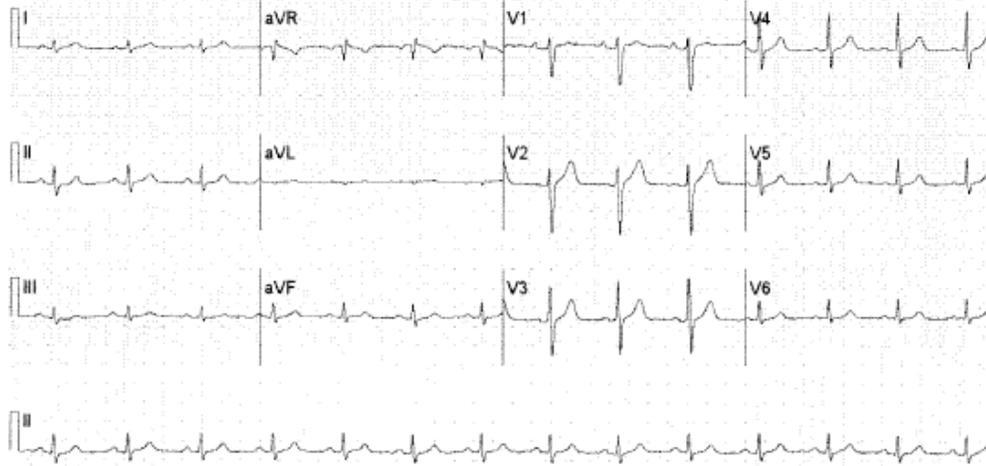
Version 2.4.0

09/23/2010 08:32:32

Vent rate: 93 Sinus rhythm
 RR : 720
 -- Durations -- Normal ECG
 P : 114
 QRS: 90 Unchanged from PREVIOUS TRACING: 09/13/2010 10:43
 -- Intervals --
 PR : 166
 QT : 346
 QTc: 386
 QTd: 90
 -- Axes --
 P : 66
 QRS: 73
 T : 53
 Confirmed By: (b) (6)

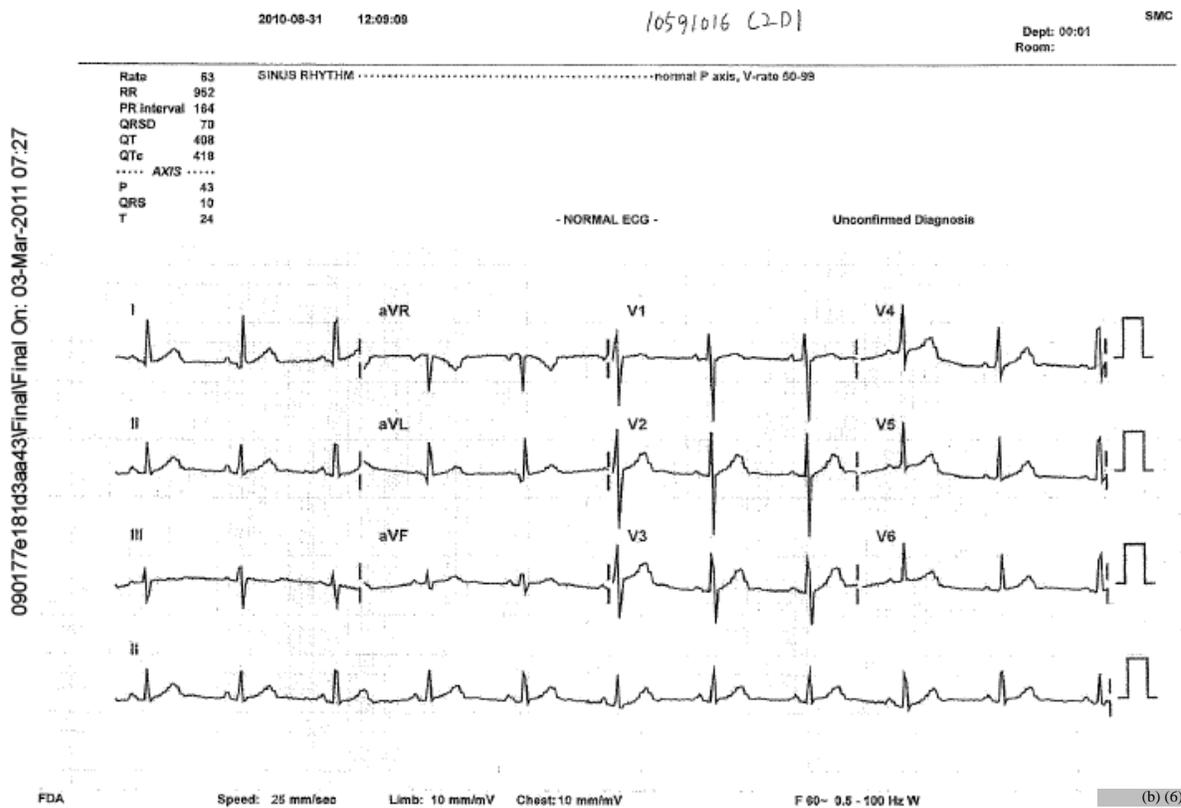
10011020
 (b) (6)
 9123110
 8:32

Dept : CA2 Room: OP
 Date : 09/23/2010 Time: 08:32:46
 Speed: 25 mm/s Limb Lead Gain: 10.0 mm/mV Chest Lead Gain: 10.0 mm/mV Filters(s): Notch 60 Hz Artifact 40 Hz Stable On



(b) Printed 09/23/2010 14:12:29 Transcribed By: (b) (6) 09/23/2010 14:11:25
 CONFIRM PRGM: PREMIER12.7/3.25/26.3/2.3 0001109 QTcH (ModGea) Page 1 of 1

A808100



5.4.3 PR and QRS Interval

A8081001:

There were no clinically relevant effects in the PR & QRS intervals. Subjects with a post-baseline PR over 200 ms had an elevated PR at baseline with change from baseline less than 25%.

Patient 10021096, a 44-year-old white female, with clear cell sarcoma, who had a history of mitral valve prolapse, was evaluated by ECG on Cycle 1 Day 1, Cycle 1 Day 15, and Cycle 1 Day 29. The ECG on Day Cycle 1 Day 29 revealed an increase in the QRS complex from the baseline mean of 76 ms to 119 ms predose and 117 ms at 6 hours postdose, reported by the investigator as not clinically significant. On Days -1 and 15, serum potassium was 3.1 and 3.2 mmol/L (normal range 3.6-5.0 mmol/L) and calcium was 8.6 and 8.3 mg/dL (normal range 8.4-10.2 mg/dL), respectively. The QRS prolongation was part of a right bundle branch block reported as a Grade 1 treatment related AE, which was ongoing 2 weeks later, at the time of the patient's discontinuation from study for disease progression.

A8081005:

The sponsor reports 4 patients with a maximum QRS complex increase from baseline of $\geq 50\%$ and a baseline value of < 100 ms. Narratives are not provided. Based on our review and analysis of the datasets provided, no subject with a mean QRS interval post-treatment over 110 ms had a change from baseline over 25%.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	250 mg BID	
Maximum tolerated dose	250 mg BID	
Principal adverse events	Most common AEs regardless of causality ($\geq 20\%$): nausea, fatigue, vomiting, diarrhea, constipation, anorexia, cough, back pain, dyspnea, dyspepsia; Dose limiting Toxicities: G3 fatigue (2 patients at 300 mg BID); G3 \uparrow ALT (1 patient at 200 mg QD)	
Maximum dose tested	Single Dose	300 mg
	Multiple Dose	300 mg BID for >28 days
Exposures Achieved at Maximum Tested Dose	Single Dose	C_{max} : 130 ng/mL (n=1) AUC_{0-12hr} : 2525 ng.hr/mL (n=1)
	Multiple Dose	Mean C_{max} (CV): 503 ng/mL (43%) Mean AUC_{0-12hr} (CV): 5085 ng.hr/mL (49%)
Range of linear PK	PK linearity in tested doses ranging from 100 mg QD to 200 mg QD and from 200 mg BID – 300 mg BID	
Accumulation at steady state	Mean accumulation ratio (CV) = 5.0 (31%) at 250 mg BID for 28 days	
Metabolites	Unknown	
Absorption	Absolute/Relative Bioavailability	To be done
	Tmax	Median (range): 4 hours (1-9 hours) following 250 mg BID
Distribution	Vd/F	Mean (CV): 9892 L (39%) following a single dose of 250 mg
	% bound	Mean: 90.7% (in vitro assay at 0.5 to 20 μ M)
Elimination	Route	<ul style="list-style-type: none"> • Primary via CYP3A metabolism; percent dose eliminated unknown • Others including CYP2D6 metabolism and hepatic conjugation • Negligible renal recovery of unchanged
	Terminal t_{1/2}	Mean (CV): 53 hours (28%) following a single dose of 250 mg
	CL/F	Mean (CV): 129 L/hr (36%) following a single dose of 250 mg
Intrinsic Factors	Age	Unknown
	Sex	Unknown
	Race	Unknown
	Hepatic & Renal Impairment	Unknown
Extrinsic Factors	Drug interactions	28-day treatment of PF-02341066 (250 mg BID) increased oral midazolam AUC by a mean of 3.6-fold (90%CI: 2.7 – 4.9).
	Food Effects	To be done
Expected High Clinical Exposure Scenario	The worst case scenario would be when PF-02341066 is administered with potent CYP3A inhibitors. By using SIMCYP simulation, ketoconazole (400 mg QD) is predicted to increase PF-02341066 AUC by a mean of 3-fold. Clinical studies for such drug interactions have not been done. However, the worst supra-therapeutic exposure is not expected to occur as potent CYP3A4 inhibitors are not allowed for patients who are on PF-02341066 treatment.	

* All information are based on the preliminary data from the ongoing first-in-patient study A8081001, unless otherwise indicated.

Protocol Activity	Screening	Lead-in PK Period***	Cycle 1 = 28 Days**		Cycle 2 = 28 Days**		Every 4 Weeks** (after Cycle 2-Cycle 5)	Every 8 Weeks*****	End of Treatment
	Day -14 to Day 0	Day -7	Day 1 (Predose)	Day 15	Day 1 (Predose)	Day 15	Day 1		
Page 1 of 4									
Informed consent ^a	X								
Medical history ^b	X								
Physical examination ^c	X		X		X		X		X
Weight, height, temperature, blood pressure, pulse ^d	X		X		X		X		X
ECOG performance status ^e	X		X		X		X		X
12-Lead electrocardiogram ^f	X		X	X	X				
Registration/hematology ^g	X		(X)	X	X		X		X
Chemistry ^h	X		(X)	X	X		X		X
Coagulation tests ⁱ	X		(X)	X	X				
Urinalysis ^j	X		(X)		X		X		
Ophthalmology examination ^k	X								
Safety assessment (adverse events) ^l	X		X	X	X	X	X		X
Tumor assessment ^{mm}	X							X	X
Survival ⁿ			Until at least 1 year after the final dose						
Concomitant medications ^o	X		X	X	X	X	X		
Pregnancy test ^p	X								X
Special laboratory studies									
Plasma sampling for full crizotinib PK in patients not participating in the MDZ study ^q		X	X	X	X				
Plasma sampling for full crizotinib PK in patients participating in the MDZ study ^q			X	X	X				
2 plasma sampling points for crizotinib PK ^r						X	X (up to Cycle 5)		
Plasma sampling for full MDZ PK ^s		X			X				
Blood sample for crizotinib metabolite profiling ^t				X					
Blood sample for pharmacogenomics ^u	X								
24-hour urine collection for crizotinib ^v				X					
Urine sample for 6βOHC/C ratio ^w			X	X	X				
Serum/plasma soluble markers assessments ^x			X	X	X	X	X (up to Cycle5)		
Tumor samples (paraffin block) ^y	X								
Fresh tumor biopsy ^z	X				X				X
[¹⁸ F]-FLT-PET and [¹⁸ F]-FDG-PET ^{aa}	X				X				
Crizotinib treatment ^{bb}		X	Once a day or twice a day continuously						
MDZ Treatment for patients participating in the MDZ study ^{cc}		X			X				

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

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

/s/

HAO ZHU
05/31/2011

JEFFRY FLORIAN
05/31/2011

SUCHITRA M BALAKRISHNAN
06/01/2011

NORMAN L STOCKBRIDGE
06/01/2011

DSI CONSULT: Request for Clinical Inspections

Date: March 31, 2011

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1
Tejashri Purohit-Sheth, M.D., Branch Chief (Acting), GCP2
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: Shakun Malik, M.D., Ph.D., Clinical Reviewer, DDOP
V. Ellen Maher, M.D., Clinical Team Leader, DDOP
Robert L. Justice, M.D. M.S., Division Director, DDOP

From: Diane Hanner, RPM, DDOP

Subject: Request for Clinical Site Inspections

I. General Information

Application# NDA 202570 (IND 73544)
Applicant: Pfizer: (PF-02341066) (Crizotinib)
Contact information: Ron Domingo, (858-622-3234) (ron.domingo@pfizer.com)
NME: YES
Study Population: NSCLC patients with tumors harboring an ELM4-ALK fusion
Study Population includes < 17 years of age (Yes)
Is this for Pediatric Exclusivity (No)

Proposed Indication: Crizotinib is indicated for anaplastic lymphoma kinase positive advanced non-small cell lung cancer

PDUFA: September 30, 2011 (HIGH PRIORITY)

Target Date: June 30, 2011

Inspection Summary Goal Date: **May 31, 2011 by the DSI**

II. Background Information

Pfizer has submitted a New NDA for accelerated approval application under Subpart H for Crizotinib. Pfizer has indicated that the size of the safety database will include 200 to 250 patients from nonrandomized studies at the time of the NDA submission. The study design for a first-line study in metastatic ALK positive NSCLC was previously agreed upon. The DSI consult is now being formally submitted since the DSI involvement began prior to the actual NDA submission. DSI has been involved in site selection.

III. Protocol/Site Identification

Site # (Name, Address, Phone number, email, fax#)	Protocol #	Number of Subjects	Comments
Site #1007 Dr. Yung-Jue Bang Seoul National University Hospital / Department of Internal Medicine 28 Yongon-dong Chongno-gu Seoul 110-744	A8081001	42	
Site #1058 Seoul National University Hospital / Department of Internal Medicine 101 Daehang-ro, Jongno-gu Seoul 110-744	A8081005	23	
Site # 1002 Jeffery Clark Massachusetts General Hospital 55 Fruit Street Boston, MA 02114 Tel. 617-724-0786 FAX 617-724-3166 Email: jclark@partners.org	A8081001	80	
Site # 1021 Alice Shaw Massachusetts General Hospital 55 Fruit Street Boston, MA 02114 Tel. 617-724-2000 FAX 617-724-0599	A8081005	17	

IV. Site Selection/Rationale

This NDA is based on data from 2 single arm trials. This NDA also has a companion diagnostic component. Sites selected are based on the highest enrollment numbers. CDRH is

also interested in looking into concordance rates for the ALK mutation results that have been used to enroll these patients.

Domestic Inspections:

We have requested inspections because (please check all that apply):

- Enrollment of large numbers of study subjects**
High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making**
There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify): a high rate of detection of prostate cancer relative to other centers. One local site was selected since medical reviewers are interested in attending the inspection.

International Inspections:

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify) This would be the first approval of this new drug and most of the limited experience with this drug has been at a foreign site in Korea and at Massachusetts General Hospital in the US. CDRH is interested in inspecting the Massachusetts General site for information about a site-specific assay and for concordance with the companion diagnostic.**

V. Tables of Specific Data to be Verified (if applicable)

Should you require any additional information, please contact Diane Hanner (regulatory project manager) at 301-796-4058 or Dr. Malik (medical reviewer).

Concurrence: (as needed)

Shakun Malik _____ Medical Reviewer
V. Ellen Maher _____ Medical Team Leader
Robert Justice _____ Division Director (for foreign inspection requests only)

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

/s/

DIANE C HANNER
04/08/2011

SHAKUNTALA M MALIK
04/08/2011

VIRGINIA E MAHER
04/08/2011

ANTHONY J MURGO
04/08/2011
Anthony J. Murgo, M.D., M.S.
Acting Deputy Division Directory