

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**202570Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 202570

SUPPL #

HFD # 150

Trade Name Xalkori Capsules, 200 mg and 250 mg.

Generic Name crizotinib

Applicant Name Pfizer Inc.

Approval Date, If Known August 26, 2011

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES  NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES  NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES  NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5

e) Has pediatric exclusivity been granted for this Active Moiety?

YES  NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES  NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)  
IF "YES," GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES  NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES  NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES  NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES  NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES  NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigation, identify the NDA in which a



Explain:

! Explain:

Investigation #2

!

!

YES

! NO

Explain:

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

=====

Name of person completing form: Frank Cross  
Title: Chief, Project Management Staff  
Date: 8/23/11

Name of Office/Division Director signing form: Robert L. Justice, M.D., M.S.  
Title: Director, Division of Drug Oncology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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DIANE C HANNER  
08/26/2011

FRANK H CROSS  
08/26/2011

ROBERT L JUSTICE  
08/26/2011

**NDA 202570**

**Crizotinib**

**DEBARMENT CERTIFICATION**

**[FD&C Act 306(k)(1)]**

Pfizer 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.

**Ron C. Domingo**

Reason: I attest to the accuracy and integrity of this document.  
Location: San Diego, CA  
Date: 02-Mar-2011 15:21:50 -0500

02Mar2011

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Signature of Company Representative

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Date

PFIZER CONFIDENTIAL

# ACTION PACKAGE CHECKLIST

## APPLICATION INFORMATION<sup>1</sup>

NDA # 202570 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Xalkori Established/Proper Name: Crizotinib Dosage Form: Capsule 200 and 250 mg		Applicant: Pfizer Inc Agent for Applicant (if applicable):
RPM: Diane Hanner		Division: DDOP
<p><b>NDA:</b>                  NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1)   <input type="checkbox"/> 505(b)(2)                  Efficacy Supplement:   <input type="checkbox"/> 505(b)(1)   <input type="checkbox"/> 505(b)(2)</p> <p>(A 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). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p><b>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</b>                  Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>If no listed drug, explain.</p> <p><input type="checkbox"/> This application relies on literature.  <input type="checkbox"/> This application relies on a final OTC monograph.  <input type="checkbox"/> Other (explain)</p> <p><b><u>Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></b></p> <p><b><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></b></p> <p><input type="checkbox"/> No changes   <input type="checkbox"/> Updated   Date of check:</p> <p><b>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</b></p>
❖ Actions		
<ul style="list-style-type: none"> <li>• Proposed action</li> <li>• User Fee Goal Date is <u>September 30, 2011</u></li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>• Previous actions (<i>specify type and date for each action taken</i>).</li> </ul>		<input checked="" type="checkbox"/> None

The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received?          Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a>). If not submitted, explain _____</p>	<p><input type="checkbox"/> Received</p>
<p>❖ Application Characteristics <sup>2</sup></p> <p>Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority          Chemical classification (new NDAs only):</p> <p><input checked="" type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch  <input checked="" type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch  <input checked="" type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDAs: Subpart H <span style="margin-left: 200px;">BLAs: Subpart E</span>  <input checked="" type="checkbox"/> Accelerated approval (21 CFR 314.510) <span style="margin-left: 100px;"><input type="checkbox"/> Accelerated approval (21 CFR 601.41)</span>  <input type="checkbox"/> Restricted distribution (21 CFR 314.520) <span style="margin-left: 100px;"><input type="checkbox"/> Restricted distribution (21 CFR 601.42)</span></p> <p>Subpart I <span style="margin-left: 200px;">Subpart H</span>  <input type="checkbox"/> Approval based on animal studies <span style="margin-left: 100px;"><input type="checkbox"/> Approval based on animal studies</span></p> <p><input type="checkbox"/> Submitted in response to a PMR <span style="margin-left: 200px;">REMS: <input type="checkbox"/> MedGuide</span>  <input type="checkbox"/> Submitted in response to a PMC <span style="margin-left: 100px;"><input type="checkbox"/> Communication Plan</span>  <input type="checkbox"/> Submitted in response to a Pediatric Written Request <span style="margin-left: 100px;"><input type="checkbox"/> ETASU</span>  <span style="margin-left: 400px;"><input type="checkbox"/> REMS not required</span></p> <p>Comments:</p>	
<p>BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<p><input type="checkbox"/> Yes, dates</p>
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> <li>• Office of Executive Programs (OEP) liaison has been notified of action</li> </ul>	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p>
<ul style="list-style-type: none"> <li>• Press Office notified of action (by OEP)</li> </ul>	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p>
<ul style="list-style-type: none"> <li>• Indicate what types (if any) of information dissemination are anticipated</li> </ul>	<p><input type="checkbox"/> None  <input checked="" type="checkbox"/> HHS Press Release  <input type="checkbox"/> FDA Talk Paper  <input type="checkbox"/> CDER Q&amp;As  <input checked="" type="checkbox"/> Other BURST &amp; Information Advisory</p>

<sup>2</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Exclusivity	
<ul style="list-style-type: none"> <li>Is approval of this application blocked by any type of exclusivity?</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> <li>NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date 10-year limitation expires: _____
<b>❖ Patent Information (NDAs only)</b>	
<ul style="list-style-type: none"> <li>Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.</li> </ul>	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> <li>Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.</li> </ul>	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> <li>[505(b)(2) applications] If the application includes a <b>paragraph III</b> certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).</li> </ul>	<input type="checkbox"/> No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> <li>[505(b)(2) applications] For <b>each paragraph IV</b> certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i></li> </ul>	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner’s receipt of the applicant’s notice of certification?

Yes       No

(Note: The date that the patent owner received the applicant’s notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

*If “Yes,” skip to question (4) below. If “No,” continue with question (2).*

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant’s notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes       No

*If “Yes,” there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

*If “No,” continue with question (3).*

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes       No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

*If “No,” the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes       No

*If “Yes,” there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).*

*If “No,” continue with question (5).*

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes    <input type="checkbox"/> No</p>
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**CONTENTS OF ACTION PACKAGE**

<p>❖ Copy of this Action Package Checklist<sup>3</sup></p>	<p>Yes</p>
<b>Officer/Employee List</b>	
<p>❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)</p>	<p><input checked="" type="checkbox"/> Included</p>
<p>Documentation of consent/non-consent by officers/employees</p>	<p><input type="checkbox"/> Included</p>
<b>Action Letters</b>	
<p>❖ Copies of all action letters (<i>including approval letter with final labeling</i>)</p>	<p>Action(s) and date(s) AP letter dated (8/26/11)</p>
<b>Labeling</b>	
<p>❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)</p>	
<ul style="list-style-type: none"> <li>• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	<p>Yes (3-30-11)</p>
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	<p>N/A</p>

Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling ( <i>write submission/communication date at upper right of first page of each piece</i> )	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> <li>Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	Yes 3-30-11
<ul style="list-style-type: none"> <li>Example of class labeling, if applicable</li> </ul>	N/A
❖ Labels ( <b>full color</b> carton and immediate-container labels) ( <i>write submission/communication date on upper right of first page of each submission</i> )	
<ul style="list-style-type: none"> <li>Most-recent draft labeling</li> </ul>	Container labeling only 3-30-11
❖ Proprietary Name <ul style="list-style-type: none"> <li>Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> <li>Review(s) (<i>indicate date(s)</i>)</li> </ul>	Proprietary name review Acceptable 8-3-11
❖ Labeling reviews ( <i>indicate dates of reviews and meetings</i> )	<input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEPA (6-27-11) & (8-3-11) Proprietary name And 7-26-11 (label review)  <input checked="" type="checkbox"/> DRISK 8-11-11 <input type="checkbox"/> DDMAC 8-09-11 <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
<b>Administrative / Regulatory Documents</b>	
❖ Administrative Reviews ( <i>e.g., RPM Filing Review<sup>1</sup>/Memo of Filing Meeting</i> ) ( <i>indicate date of each review</i> )	
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment ( <i>indicate date</i> )	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary ( <i>signed by Division Director</i> )(8/26/11)	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	
<ul style="list-style-type: none"> <li>Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>This application is on the AIP           <ul style="list-style-type: none"> <li>If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input type="checkbox"/> No  <input type="checkbox"/> Not an AP action
❖ Pediatrics ( <i>approvals only</i> ) <ul style="list-style-type: none"> <li>Date reviewed by PeRC _____ If PeRC review not necessary, explain: orphan designated indication</li> <li>Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>)</li> </ul>	<input type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent ( <i>include certification</i> )	<input checked="" type="checkbox"/> Verified, statement is acceptable

Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

Outgoing communications ( <i>letters (except action letters), emails, faxes, telecons</i> )	Yes
❖ Internal memoranda, telecons, etc.	Yes
❖ Minutes of Meetings	
• Regulatory Briefing ( <i>indicate date of mtg</i> )	<input type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting ( <i>indicate date of mtg</i> )	<input type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting ( <i>indicate date of mtg</i> ) EOP3 meetings	<input type="checkbox"/> No mtg 8/27/10
• EOP2 meeting ( <i>indicate date of mtg</i> )	<input type="checkbox"/> No mtg 5/22/09
• Other milestone meetings (e.g., EOP2a, CMC pilots) ( <i>indicate dates of mtgs</i> )	CMC Pre NDA Mtg 11/12/10; CDRH mtg 6/24/10 EOP 3 mtg. 4/28/10
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available ( <i>do not include transcript</i> )	
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 8/11/11
PMR/PMC Development Templates ( <i>indicate total number</i> ) PMR=11, PMC=2	<input type="checkbox"/> None
<b>Clinical Information<sup>5</sup></b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )	See the CDTL dated 8/11/11
• Clinical review(s) ( <i>indicate date for each review</i> )	8/13/11
• Social scientist review(s) (if OTC drug) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	See Clinical review dated 8/13/11
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input type="checkbox"/> None Ophthalmology- 8/1/11; CDRH (DRAFT)
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management	
• REMS Documents and Supporting Statement ( <i>indicate date(s) of submission(s)</i> )	<input type="checkbox"/> None  DRISK-8-11-11 Epidemiology 8-12-11
• REMS Memo(s) and letter(s) ( <i>indicate date(s)</i> )	
• Risk management review(s) and recommendations (including those by OSE and CSS) ( <i>indicate date of each review and indicate location/date if incorporated into another review</i> )	

Filing reviews should be filed with the discipline reviews.

❖ DSI Clinical Inspection Review Summary(ies) (include copies of DSI letters to investigators)	<input type="checkbox"/> 8/15/11
<b>Clinical Microbiology</b> <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Microbiology Review(s) (indicate date for each review)	<input type="checkbox"/> None 8/1/11
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None 8/5/11
Statistical Review(s) (indicate date for each review)	<input type="checkbox"/> None 8/5/11
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None
Clinical Pharmacology review(s) (indicate date for each review) Pharmacometric Review 8/10/11 with the Clin Pharm Review & Genomics Review	<input type="checkbox"/> None 8/10/11 Genomics Review 8/26/11
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)	<input type="checkbox"/> None
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None 8/11/11
• Supervisory Review(s) (indicate date for each review)	<input type="checkbox"/> None 8/10/11
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	<input type="checkbox"/> None 8/10/11
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None
❖ DSI Nonclinical Inspection Review Summary (include copies of DSI letters)	<input checked="" type="checkbox"/> None requested
<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	<input type="checkbox"/> None 8/4/11
• Branch Chief/Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Product quality review(s) including ONDQA biopharmaceutics reviews (indicate date for each review)	<input type="checkbox"/> 8/2/11(2), Analytical and Drug Product, 8/3/11 Drug Substance
❖ Microbiology Reviews <input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (indicate date of each review) <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) (indicate date of each review)	<input type="checkbox"/> Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)	<input type="checkbox"/> None Biostatistical Review 7/27/11 BPH Review 7/26/11

❖ Environmental Assessment (check one) (original and supplemental applications)	
<input type="checkbox"/> Categorical Exclusion ( <i>indicate review date</i> )( <i>all original applications and all efficacy supplements that could increase the patient population</i> )	See CMC DP Review dated 8/2/11
<input type="checkbox"/> Review & FONSI ( <i>indicate date of review</i> )	
<input type="checkbox"/> Review & Environmental Impact Statement ( <i>indicate date of each review</i> )	
❖ Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout) ( <i>date completed must be within 2 years of action date</i> ) ( <i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>6</sup></i> )	Date completed: 8/4/11 (see Div. Dir. Review 8/4/11 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER ( <i>date of most recent TB-EER must be within 30 days of action date</i> ) ( <i>original and supplemental BLAs</i> )	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation ( <i>check box only, do not include documents</i> )	<input type="checkbox"/> Completed <input checked="" type="checkbox"/> Requested- See approval letter <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

<sup>6</sup>e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

## Appendix to Action Package Checklist

An NDA or NDA supplemental 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) **Or** 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.
- (3) **Or** 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) **And** 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.
- (3) **And** 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) **Or** 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.
- (3) **Or** 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 ODE's ADRA.

**Hanner, Diane**

---

**From:** Hanner, Diane  
**Sent:** Tuesday, August 23, 2011 12:09 PM  
**To:** 'Domingo, Ron'  
**Subject:** RE: NDA 202570 IR

Hi,  
I believe since we have deleted the IRR responses from the label that we will no longer need you to e-mail the tables.  
Regards,  
Diane

---

**From:** Domingo, Ron [mailto:Ron.Domingo@pfizer.com]  
**Sent:** Tuesday, August 23, 2011 9:52 AM  
**To:** Hanner, Diane  
**Subject:** RE: NDA 202570 IR

Hi Diane,

Do you still need us to email the IRR DR tables today? Based on the FDA's labeling feedback yesterday it seemed as though it may not be needed anymore. Please confirm.

Thanks,  
Ron

Ron Domingo, MS, RAC  
Worldwide Regulatory Strategy

Global Research & Development  
La Jolla Laboratories, Pfizer Inc.  
10646 Science Center Drive (CB10)  
San Diego, CA 92121  
Phone: 858-622-3234  
Cell: 858-722-3065  
Fax: 877-481-0933  
Email: [ron.domingo@pfizer.com](mailto:ron.domingo@pfizer.com)

---

**From:** Hanner, Diane [mailto:Diane.Hanner@fda.hhs.gov]  
**Sent:** Monday, August 22, 2011 12:26 PM  
**To:** Domingo, Ron  
**Subject:** FW: NDA 202570 IR

Hi,  
I was instructed to convey the following:

It is acceptable to submit IRR duration of response information tomorrow.

Regards,  
Diane

---

**From:** Domingo, Ron [mailto:Ron.Domingo@pfizer.com]  
**Sent:** Monday, August 22, 2011 3:12 PM  
**To:** Hanner, Diane  
**Subject:** FW: NDA 202570 IR

Hi Diane,

In response to your query below please see the attached files for studies 1001 and 1005. This information will be submitted to the NDA tomorrow.

Can you please confirm if the Agency still needs the IRR Duration of Response output?

Thanks,  
Ron

Ron Domingo, MS, RAC  
Worldwide Regulatory Strategy

Global Research & Development  
La Jolla Laboratories, Pfizer Inc.  
10646 Science Center Drive (CB10)  
San Diego, CA 92121  
Phone: 858-622-3234  
Cell: 858-722-3065  
Fax: 877-481-0933  
Email: [ron.domingo@pfizer.com](mailto:ron.domingo@pfizer.com)

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**From:** Hanner, Diane [mailto:Diane.Hanner@fda.hhs.gov]  
**Sent:** Monday, August 22, 2011 10:38 AM  
**To:** Domingo, Ron  
**Subject:** NDA 202570 IR  
**Importance:** High

Hi,  
Please address the following Information Request regarding NDA 202570:

**Patients who are not evaluable for IRR due to missing scans should be included in response rate calculation. IRR response rate should be based on 136 treated patients. We note that the patient (ID 11051040), who was not response-evaluable by investigator, was included in the 128 IRR response-evaluable population.**

**Please submit IRR response rate with 95% CI and response duration for both studies by 3:00pm today.**

**Please submit SAS dataset for IRR response data including response duration for both studies by COB August 23, 2011.**

Thank you.  
Regards,  
Diane

CDR Diane Hanner  
Senior Program Management Officer  
FDA/CDER/OODP/DDOP  
10903 New Hampshire Avenue  
Bldg. 22/Room 2119  
Silver Spring, Maryland 20993  
(301) 796-2330  
FAX (301) 796-9845  
E-mail: [diane.hanner@fda.hhs.gov](mailto:diane.hanner@fda.hhs.gov)

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/s/  
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DIANE C HANNER  
08/25/2011



FOOD AND DRUG ADMINISTRATION

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**Meeting Date and Time:** August 22, 2011 3:30 p.m.  
**Meeting Type:** Teleconference  
**Meeting Category:** N/A  
**Meeting Location:** Bldg. 22, Room 2376  
**Application Number:** NDA 202570  
**Product Name:** Crizotinib  
**Received Briefing Package** N/A  
**Sponsor Name:** Dr. Udayan Guha (SGE)  
**Meeting Requestor:** CDR Diane Hanner  
**Meeting Chair:** Shakun Malik, M.D., Medical Officer, DDOP  
**Meeting Recorder:** CDR Diane Hanner, Senior Program Management Officer, DDOP

**Meeting Attendees:**

**Attendee from NIH**

- Udayan Guha, M.D.

**FDA Attendees**

- Robert Justice, M.D., M.S., Director DDOP
- Anthony J. Murgo, M.D., M.S., FACP., Associate Director for Regulatory Science
- Shakun Malik, M.D., Ph.D., Medical Officer
- CDR Diane Hanner, M.P.H., M.S.W., Senior Program Management Officer, DDOP

**BACKGROUND**

Pfizer originally submitted NDA 202570 to the Division of Oncology Drug Products for NSCLC on March 30, 2011. On August 22, 2011, the Division of Oncology Drug Products and Dr. Guha Special Government Employee (SGE), held a teleconference to discuss his advice regarding his consultative review of crizotinib.

**DISCUSSION:**

FDA solicited the advice from the consultants regarding the following:

FDA asked Dr. Udayan Guha to discuss the benefit: risk ratio of crizotinib for the treatment of patients with locally advanced or metastatic ALK-positive non-small cell lung cancer (NSCLC) based on response rate and the toxicities noted in two single arm nonrandomized clinical trials.

Dr. Guha responded that based on the ORR and the toxicities presented in the two single arm nonrandomized studies, the benefit/risk ratio of crizotinib for the treatment of locally advanced or metastatic ALK rearrangement-positive NSCLC is favorable. However, the existing randomized Phase III trials will eventually demonstrate whether crizotinib will be beneficial to current standard of care. At this time there is no treatment available that is specific to the ALK rearranged patients.

An ORR of more than 40% is a significant improvement to current treatments available.

He was however, concerned about the standardization of the diagnostic test. The FDA responded that we at the OODP believe that the test will be readily available to the community physicians soon after the approval. We will confirm this after consulting with the CDRH team and then convey it to Dr Guha.

Dr Guha believed that he as a physician will not have any hesitations in using Crizotinib as first line therapy in patients who are found to have ALK positive NSCLC unless they fit in a clinical trial. He believed that the toxicity profile and the high response rate is clinically meaningful in these patients.

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/s/  
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DIANE C HANNER  
08/23/2011

SHAKUNTALA M MALIK  
08/23/2011



FOOD AND DRUG ADMINISTRATION

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**Meeting Date and Time:** August 19, 2011 12:00 p.m.  
**Meeting Type:** Teleconference  
**Meeting Category:** N/A  
**Meeting Location:** Bldg. 22, Room 2376  
**Application Number:** NDA 202570  
**Product Name:** Crizotinib  
**Received Briefing Package** N/A  
**Sponsor Name:** Dr. Wyndaham Wilson (SGE)  
**Meeting Requestor:** Diane Hanner  
**Meeting Chair:** Shakun Malik, M.D., Medical Officer, DDOP  
**Meeting Recorder:** Diane Hanner, Senior Program Management Officer, DDOP

**Meeting Attendees:**

**Attendee from NIH**

- Wyndaham Wilson, M.D.

**FDA Attendees**

- Richard Pazdur, M.D., Office Director, OODP
- Robert Justice, M.D., M.S., Director DDOP
- Shakun Malik, M.D., Ph.D., Medical Officer
- Diane Hanner, M.P.H., M.S.W., Senior Program Management Officer, DDOP

**BACKGROUND**

Pfizer originally submitted NDA 202570 to the Division of Oncology Drug Products for NSCLC on March 30, 2011. On August 19, 2011, the Division of Oncology Drug Products and Dr. Wilson, Special Government Employee (SGE), held a teleconference to discuss his advice regarding his consultative review of crizotinib.

**DISCUSSION:**

FDA solicited the advice from the consultants regarding the following:

FDA asked Dr. Wilson to discuss the benefit: risk ratio of crizotinib for the treatment of patients with locally advanced or metastatic ALK-positive non-small cell lung cancer (NSCLC) based on response rate and the toxicities noted in two single arm nonrandomized clinical trials.

Dr. Wilson responded that the response rate (50% - 61%), and the duration of response in patients with locally advanced or metastatic ALK-positive NSCLC, treated with crizotinib is clinically meaningful. Therefore, I support accelerated approval of crizotinib.

The toxicity spectrum is a bit worrisome especially pneumonitis, vision disorders and hepatic toxicities. However, it is not possible to differentiate if pneumonitis was caused by the underlying lung cancer or if it was drug related. Most of the liver and visual toxicities noted were reversible.

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/s/  
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DIANE C HANNER  
08/22/2011

SHAKUNTALA M MALIK  
08/22/2011

**Hanner, Diane**

---

**From:** Hanner, Diane  
**Sent:** Friday, August 12, 2011 10:13 AM  
**To:** 'Domingo, Ron'  
**Subject:** FDA response regarding NDA 202570  
**Follow Up Flag:** Follow up  
**Flag Status:** Red

Hi,

I have been instructed to convey the following regarding NDA 202570:

You plan to accrue 20 patients with ALK negative NSCLC (the majority of patients with lung cancer) over a 33 month period. Given the RR demonstrated in the 23 patients with ALK negative NSCLC treated with crizotinib, we do not think it will be difficult to recruit these patients. From your previous response, the reason for this long period of accrual is unclear. Please state the number of sites that will conduct this protocol, the number of patients with ALK negative NSCLC seen at those sites each month, and the number of patients that are estimated to participate in this trial. Please reply by **Friday, August 12**.

Regards,  
Diane

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/s/  
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DIANE C HANNER  
08/25/2011

## Hanner, Diane

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**From:** Hanner, Diane  
**Sent:** Thursday, August 18, 2011 2:56 PM  
**To:** 'Domingo, Ron'  
**Subject:** Label revisions regarding NDA 202570

**Attachments:** Crizotinib USPI\_FDA comments 8-3-11 and 8-11-11\_final tracked.doc

Hi,  
Please click on the attachment and view the latest version of the Crizotinib (NDA 202570) label.

I need you to pay particular attention to the following regarding the attached label changes located in Section 6; Table 3:

"Please revise the table to include treatment emergent as well as treatment adverse reactions in more than 10% of patients all grades as well grades 3 and 4."

Please let me know if you have any questions and please send back the final label by c.o.b. **Friday, 8/19**, tomorrow. Also, please remember to send me a clean and tracked version of the label.

Regards,  
Diane



Crizotinib  
\_FDA commen

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/s/  
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DIANE C HANNER  
08/25/2011

**Hanner, Diane**

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**From:** Hanner, Diane  
**Sent:** Thursday, August 11, 2011 3:14 PM  
**To:** 'Domingo, Ron'  
**Subject:** RE: FDA clarifications regarding PMRs

Hi,  
CDER would like an explanation for why the timeline for their ELK negative PER (two years of accrual) is so long? Also, please clarify where the ELK testing would be taking place.  
Thank you.  
Regards,  
Diane

---

**From:** Domingo, Ron [mailto:Ron.Domingo@pfizer.com]  
**Sent:** Thursday, August 11, 2011 9:48 AM  
**To:** Hanner, Diane  
**Subject:** RE: FDA clarifications regarding PMRs

Dear Diane,

Please see the attached document for our responses to the queries received on August 9, 2011. This information will be submitted to the NDA later today. Please contact me if you have any questions.

Regards,  
Ron

Ron Domingo, MS, RAC  
Worldwide Regulatory Strategy

Global Research & Development  
La Jolla Laboratories, Pfizer Inc.  
10646 Science Center Drive (CB10)  
San Diego, CA 92121  
Phone: 858-622-3234  
Cell: 858-722-3065  
Fax: 877-481-0933  
Email: [ron.domingo@pfizer.com](mailto:ron.domingo@pfizer.com)

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**From:** Hanner, Diane [mailto:Diane.Hanner@fda.hhs.gov]  
**Sent:** Monday, August 08, 2011 7:08 AM  
**To:** Domingo, Ron  
**Subject:** FW: FDA clarifications regarding PMRs  
**Importance:** High

Please verify that you have received this e-mail.  
Thanks.  
Diane

---

1e

August 08, 2011 10:07 AM

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/  
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DIANE C HANNER  
08/16/2011

**Hanner, Diane**

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**From:** Hanner, Diane  
**Sent:** Thursday, August 11, 2011 2:34 PM  
**To:** 'Domingo, Ron'  
**Subject:** FW: NDA 202570- Crizotinib

Hi,

Below is the FDA response to your inquiry regarding the rationale for changing the Pregnancy Category from (b) (4) to D.

Pregnancy Category D was considered appropriate for this drug for the following reasons:

- Positive findings of post-implantation loss and low fetal weight in animals at exposures similar to the clinical exposure—based on an ODAC discussion in which it was agreed that based on mechanism of action (targeting rapidly dividing cells and targets that are important in embryogenesis) that Category D was appropriate for many cancer drugs despite the lack of human data.
- The importance of ALK in neural development which would not be reflected well in the embryo-fetal development studies—while embryo-fetal studies are the only reproductive toxicology studies required for a drug in this patient population, pregnancy categories are based on an assumption of the full battery of reproductive toxicology studies being performed
- Other kinase inhibitors including erlotinib and imatinib are category D as well with similar reproductive findings.

Regards,  
Diane

---

**From:** Domingo, Ron [mailto:Ron.Domingo@pfizer.com]  
**Sent:** Saturday, August 06, 2011 1:38 AM  
**To:** Hanner, Diane  
**Subject:** RE: NDA 202570- Crizotinib

Hi Diane,

Can you tell us about the rationale for changing the Pregnancy Category from (b) (4) to D?

Thanks,  
Ron

Ron Domingo, MS, RAC  
Worldwide Regulatory Strategy

Global Research & Development  
La Jolla Laboratories, Pfizer Inc.  
10646 Science Center Drive (CB10)  
San Diego, CA 92121  
Phone: 858-622-3234  
Cell: 858-722-3065  
Fax: 877-481-0933  
Email: [ron.domingo@pfizer.com](mailto:ron.domingo@pfizer.com)

---

**From:** Hanner, Diane [mailto:Diane.Hanner@fda.hhs.gov]  
**Sent:** Friday, August 05, 2011 8:26 AM  
**To:** Domingo, Ron  
**Subject:** FW: NDA 202570- Crizotinib

Hi,

Please see the FDA responses below to your questions regarding NDA 202570:

#### Adverse Event Summary and Table

1. How did FDA define treatment emergent AEs?

**FDA Response:** TEAEs were events which occurred after day 1. This was based on FACTDAT = ne and EMERGE = 1 in the datasets.

2. Were clustered AEs presented in Table 3 defined solely based on the events included in the footnote?

**FDA Response:** Yes

3. What was the criteria for including AEs in Table 3

**FDA Response:** TEAEs that occurred in at least 10% of patients.

4. Does the summary of common AEs and Grade 3/4 AEs in the opening paragraph to this section report treatment emergent AEs or treatment related AEs?

**FDA Response:** This refers to TEAEs.

#### Clinical Studies Section

Can FDA clarify the source used for median duration of response in study 1005 and how it was calculated?

**FDA Response:** The median duration of response was calculated using Kaplan-Meier method based on 60-day updated data but patient 10391003 was not considered as a responder per FDA review .

Regards,  
Diane

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/s/  
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DIANE C HANNER  
08/16/2011

## Hanner, Diane

---

**From:** Hanner, Diane  
**Sent:** Tuesday, August 09, 2011 12:36 PM  
**To:** 'Domingo, Ron'  
**Subject:** NDA 202570 Timeline Request for an analysis plan

Hi,

I have been instructed to convey the following regarding the exposure response PMC:

It has been noticed that Pfizer has not provided a date when they would submit the exposure-response analysis plan to us. We would like Pfizer to submit their analysis plan for both trials 1007 and 1014 by May 2012.

Regards,  
Diane

CDR Diane Hanner  
Senior Program Management Officer  
FDA/CDER/OODP/DDOP  
10903 New Hampshire Avenue  
Bldg. 22/Room 2119  
Silver Spring, Maryland 20993  
(301) 796-2330  
FAX (301) 796-9845  
E-mail: [diane.hanner@fda.hhs.gov](mailto:diane.hanner@fda.hhs.gov)

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/s/  
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DIANE C HANNER  
08/16/2011

**Hanner, Diane**

---

**From:** Hanner, Diane  
**Sent:** Tuesday, August 02, 2011 10:14 AM  
**To:** 'Domingo, Ron'  
**Subject:** Crizotinib NDA 202570

Hi,

I have been instructed to request the following regarding NDA 202570:

Please send death narratives on the following patients:

**Study 1001**

10061148

10061160:

**Study 1005**

10301003

Thank you,  
Regards,  
Diane

CDR Diane Hanner  
Senior Program Management Officer  
FDA/CDER/OODP/DDOP  
10903 New Hampshire Avenue  
Bldg. 22/Room 2119  
Silver Spring, Maryland 20993  
(301) 796-2330  
FAX (301) 796-9845  
E-mail: diane.hanner@fda.hhs.gov

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/s/  
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DIANE C HANNER  
08/02/2011

**Hanner, Diane**

---

**From:** Hanner, Diane  
**Sent:** Monday, August 01, 2011 5:47 PM  
**To:** 'Domingo, Ron'  
**Subject:** NDA 202570 -Crizotinib- DRAFT PMRs.  
**Importance:** High

Hi Ron,

Please provide your feedback (where requested) regarding these **DRAFT** PMRs & PMCs listed below and please be sure to include the Date of Final Protocol Submission, Date of Trial Completion, and Date of Final Report Submission information.

This list is the a Re-cap of the [DRAFT](#) - PMRs that I know about to date:

- [Clinical Study A8081007 \(No additional input needed at this time from Pfizer\)](#)

Date of Final Protocol Submission Final Protocol: September 11, 2009

Amendment 9: January 25, 2011

Projected Date of Trial Completion December 2013

Projected Date of Final Report Submission June 2014

- [Clinical Study A8081014 \(No additional input needed at this time from Pfizer\)](#)

Date of Final Protocol Submission Final Protocol: June 15, 2010

Amendment 4: July 18, 2011

Projected Date of Trial Completion December 2015

Projected Date of Final Report Submission June 2016

- [Ophthalmology \(Input needed from Pfizer\)](#)

- 1) **Ophthalmology PMR**

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. Please conduct a 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

## 2) Follow-up on PMR (study of ALK –ive NSCLC patients)

As Pfizer is aware that SWOG in collaboration with CTEP has contacted the FDA regarding their interest in the trial of ALK negative patients with additional correlative markers. This was discussed in a t-con that Maurizio Voi from Pfizer had attended. FDA will be supportive of this collaborative effort if it will meet the PMR requirements for ALK negative NSCLC trial and if it can be conducted in a timely manner.

## 3) Follow-up on corrected data submission for Laboratory values

Please provide a definitive timeline.

- **CDRH (Revised- PMRs) (Input needed from Pfizer)**

- A 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 there another cut-off such that crizotinib is not active in ALK negative patients? (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?

\*\*\*\*\*

- A 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:
  - 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? (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?

- **Clin Pharm (Input needed from Pfizer)**

### PMRs:

- Complete the ECG sub-study in trial A8081007 and submit the final report, along with a thorough review of cardiac safety data, for the potential of crizotinib on QTc interval prolongation in humans.
- 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).
- 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).
- Conduct a multiple dose trial to determine the appropriate crizotinib dose in patients with various degrees of hepatic impairment.
- Conduct a multiple dose trial to determine the appropriate crizotinib dose in patients with severe renal impairment.
- 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).

- Submit the study report on the ongoing in vitro evaluations induction potential of crizotinib on CYP2B and CYP2C enzymes

**PMCs:**

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

Please let me know if you have any questions.  
Thank you.

Diane

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/s/  
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DIANE C HANNER  
08/01/2011

## Hanner, Diane

---

**From:** Hanner, Diane  
**Sent:** Monday, August 01, 2011 3:34 PM  
**To:** 'Domingo, Ron'  
**Subject:** NDA 202570 Crizotinib Label Comments

Hi,

Please address the following IR regarding NDA 202570:

### ***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.

Regards,  
Diane

CDR Diane Hanner  
Senior Program Management Officer  
FDA/CDER/OODP/DDOP  
10903 New Hampshire Avenue  
Bldg. 22/Room 2119  
Silver Spring, Maryland 20993  
(301) 796-2330  
FAX (301) 796-9845  
E-mail: [diane.hanner@fda.hhs.gov](mailto:diane.hanner@fda.hhs.gov)

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/s/  
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DIANE C HANNER  
08/01/2011

**Hanner, Diane**

---

**From:** Hanner, Diane  
**Sent:** Monday, August 01, 2011 11:05 AM  
**To:** 'Domingo, Ron'  
**Subject:** NDA 202570 Crizotinib Protocol A8081012

Hi,

I was instructed to request that you please address the following IR regarding NDA 202570:

Please provide the SimCYP modeling and simulation report that you used in the study design of Protocol A8081012.

Thanks  
Diane

---

**From:** Domingo, Ron [mailto:Ron.Domingo@pfizer.com]  
**Sent:** Friday, July 29, 2011 3:40 PM  
**To:** Hanner, Diane  
**Subject:** Crizotinib Clinical Pharmacology Protocol A8081012

Dear Diane,

Please see attached documents regarding our proposal for a study in patients with impaired hepatic function. As agreed to by the agency, we are requesting the review of the protocol and feedback from the Clinical Pharmacology Review team within 30 days. Please contact me if you have any questions.

Regards,  
Ron

Ron Domingo, MS, RAC  
Worldwide Regulatory Strategy

Global Research & Development  
La Jolla Laboratories, Pfizer Inc.  
10646 Science Center Drive (CB10)  
San Diego, CA 92121  
Phone: 858-622-3234  
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Fax: 877-481-0933  
Email: [ron.domingo@pfizer.com](mailto:ron.domingo@pfizer.com)

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DIANE C HANNER  
08/01/2011

**Hanner, Diane**

---

**From:** Hanner, Diane  
**Sent:** Friday, July 22, 2011 11:19 AM  
**To:** 'Domingo, Ron'  
**Subject:** NDA 202570 Crizotinib IR

Hi,  
Please provide the following information for studies 1007 and 1014 regarding NDA 202570 (Crizotinib).

Date of Final Protocol Submission  
Date of Trial Completion  
Date of Final Report Submission

Thank you,

Regards,  
Diane

CDR Diane Hanner  
Senior Program Management Officer  
FDA/CDER/OODP/DDOP  
10903 New Hampshire Avenue  
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Silver Spring, Maryland 20993  
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DIANE C HANNER  
07/22/2011

**Hanner, Diane**

---

**From:** Hanner, Diane  
**Sent:** Monday, July 18, 2011 4:33 PM  
**To:** 'Domingo, Ron'  
**Subject:** NDA 202570 (Xalkori) IR for impurity qualification issue

Hi,

Below is the FDA response regarding the impurity qualification for impurity (b) (4):

Impurity (b) (4) is not qualified based on calculations comparing the human dose of the impurity at the proposed specification of NMT (b) (4) to the rat dose of the impurity in the one month toxicology study (b) (4) using body surface area. Your justification for the proposed specification of impurity (b) (4) using calculations with doses in mg/kg/day is not adequate. The specification for impurity (b) (4) needs to be lowered to the ICH qualification threshold of 0.15% or a non-clinical study will need to be conducted as a PMR to qualify the impurity at the proposed specification of NMT (b) (4).

Regards,  
Diane

CDR Diane Hanner  
Senior Program Management Officer  
FDA/CDER/OODP/DDOP  
10903 New Hampshire Avenue  
Bldg. 22/Room 2119  
Silver Spring, Maryland 20993  
(301) 796-2330  
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DIANE C HANNER  
07/18/2011

**Hanner, Diane**

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**From:** Hanner, Diane  
**Sent:** Tuesday, July 12, 2011 5:28 PM  
**To:** 'Domingo, Ron'  
**Subject:** Crizotinib NDA 202570

Hi,  
Please provide investigator tumor response data sets for Sub 10031042 and 10051017 from study 1001 by the end of the day July 13<sup>th</sup> 2011.

Regards,  
Diane

CDR Diane Hanner  
Senior Program Management Officer  
FDA/CDER/OODP/DDOP  
10903 New Hampshire Avenue  
Bldg. 22/Room 2119  
Silver Spring, Maryland 20993  
(301) 796-2330  
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DIANE C HANNER  
07/12/2011

## Hanner, Diane

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**From:** Hanner, Diane  
**Sent:** Tuesday, July 12, 2011 10:59 AM  
**To:** 'Domingo, Ron'  
**Subject:** NDA 202570 Xalkori

Hi,  
I have been asked to request that you please confirm that the NDA 202570- Xalkori package will have a container closure that is child resistant.  
Thank you.  
Regards,  
Diane

CDR Diane Hanner  
Senior Program Management Officer  
FDA/CDER/OODP/DDOP  
10903 New Hampshire Avenue  
Bldg. 22/Room 2119  
Silver Spring, Maryland 20993  
(301) 796-2330  
FAX (301) 796-9845  
E-mail: [diane.hanner@fda.hhs.gov](mailto:diane.hanner@fda.hhs.gov)

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/s/  
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DIANE C HANNER  
07/12/2011

**Hanner, Diane**

---

**From:** Hanner, Diane  
**Sent:** Tuesday, July 12, 2011 9:48 AM  
**To:** 'Domingo, Ron'  
**Subject:** NDA 202570-Information Request

Hi,  
Please address the following regarding NDA 202570:

For Subject 10581008 from Study 1005 the cause of death in (b) (6) day updated CSR on pg 11 table 5 is reported as PD. Please clarify and send a response by the end of the day July 13<sup>th</sup>.

Regards,  
Diane

CDR Diane Hanner  
Senior Program Management Officer  
FDA/CDER/OODP/DDOP  
10903 New Hampshire Avenue  
Bldg. 22/Room 2119  
Silver Spring, Maryland 20993  
(301) 796-2330  
FAX (301) 796-9845  
E-mail: [diane.hanner@fda.hhs.gov](mailto:diane.hanner@fda.hhs.gov)

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/s/  
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DIANE C HANNER  
07/12/2011

## Hanner, Diane

---

**From:** Hanner, Diane  
**Sent:** Monday, July 11, 2011 12:31 PM  
**To:** 'Domingo, Ron'  
**Subject:** NDA 202570- Crizotinib Information request

**Importance:** High

Hi,  
I have been instructed to convey the following regarding NDA 202570:

There appear to be some errors in the duration of dose interruption in dose.xpt for Study 1001 in amendment 2. Using the variable INTDURW, several pts had dosing interruptions of 3, 4, and 7 wks. 1 pt has a dose interruption of 52 wks. It may be that these values are recorded in days. Please correct these discrepancies and send back the corrected dataset by [7-18-11](#).

Thank you.

Regards,  
Diane

CDR Diane Hanner  
Senior Program Management Officer  
FDA/CDER/OODP/DDOP  
10903 New Hampshire Avenue  
Bldg. 22/Room 2119  
Silver Spring, Maryland 20993  
(301) 796-2330  
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/s/  
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DIANE C HANNER  
07/11/2011

## Hanner, Diane

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**From:** Hanner, Diane  
**Sent:** Wednesday, July 06, 2011 3:40 PM  
**To:** 'Domingo, Ron'  
**Subject:** NDA 202570 (Crizotinib)

Hi,  
I was instructed to convey the following regarding NDA 202570(Crizotinib):

As noted in our June 30, 2011 communication, there are a substantial number of CTC grades which have been assigned incorrectly in the lab.xpt dataset for study 1005 (amendment 9). For example, among the 39 rows in which CTC grade 4 is assigned, 21 appear to be incorrect. Please investigate this further. One possible solution is to reassess the laboratory dataset. Another is to limit laboratory analyses to laboratories obtained at your central lab. However, we are unable to locate the variable MAINLAB. Further, the number of laboratories run by the central laboratory vs. those run by the local laboratory is unclear. Please determine a course of action and discuss it with us.

Since we have not yet worked with the laboratory dataset for study 1001. Please provide instructions for its use.

Please reply by July 8.

Thank you.  
Regards,  
Diane

CDR Diane Hanner  
Senior Program Management Officer  
FDA/CDER/OODP/DDOP  
10903 New Hampshire Avenue  
Bldg. 22/Room 2119  
Silver Spring, Maryland 20993  
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/s/  
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DIANE C HANNER  
07/06/2011



NDA 202570

**INFORMATION REQUEST**

Pfizer Inc.  
Attention: Ron Domingo, Manager  
10646 Science Center Drive  
San Diego, CA 92121

Dear Mr. Domingo:

Please refer to your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Crizotinib Capsule.

We reviewed your Chemistry, Manufacturing, and Controls information and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Drug Substance

1. Your justification for the proposed specification of impurities, (b) (4), in drug substance is not adequate. Revise the specification to meet ICH recommendations or provide justification for any other proposed limits.
2. Your proposed plan in section S.2.6 to mitigate the risk associated with the change of supplier, manufacturing site and (b) (4) process used to produce starting materials appears to be scientifically justified. Provide a statement that any such change will follow current guidance for changes to an approved application.
3. Your process description for achieving the particle size of the drug substance is inadequate. Update your process description for the drug substance. Include detailed descriptions (b) (4) procedures based on the proposed commercial manufacturing plan. In addition, clarify why (b) (4) is considered optional.
4. You have stated in Sec S.2.6.5.3, "*A follow-up study demonstrated that crizotinib is stable* (b) (4).  
(b) (4) However, no supporting data are provided in the submission (e.g. stress studies) to confirm the stability of crizotinib (an aryl-alkyl ether) (b) (4). Provide the supporting data to justify the stability of crizotinib in the proposed conditions.

5. The stress testing of crizotinib (b) (4) is not adequate. Based on ICH Q1A, stress testing should include the effect of temperature. Provide stress testing data for the drug substance with both acid and base, conducted at or above the accelerated stability temperature.

Drug Product



10. Note that to support the approval of the 200 mg strength capsule, in vivo bioavailability (BA) data are needed for this strength. If BA information was provided, please indicate where this information is located in your submission. If not, you may request a waiver for the CFR requirement to provide BA data for this strength. The following information would be needed to support a biowaiver request:
  - a. Acceptable in vivo BA data for the highest strength.
  - b. The composition of 250mg and 200mg strengths should be proportionally similar in their active and inactive ingredients.

- c. *In vitro* comparative dissolution profile data and similarity f2 values (n=12) in three media: 0.1 N HCl and phosphate buffers pH 4.5 and 6.8, using the same dissolution testing conditions.

11. Provide [REDACTED] (b) (4) batches (9807033000, 9807033001, 9807033002, 9807083000). Also, provide the tablet content uniformity analysis results for the stratified in-process samples for the three registration batches for 150 mg strength.
12. [REDACTED] (b) (4)
13. In the proposed post-approval stability protocol for shelf life confirmation and annual lots, revise the sampling time points for the first year to every three months, every six months for the second year, and every twelve months thereafter.
14. In accordance with CFR 314.50, a complete description of the commercial scale drug product manufacturing processes is required and should include all process parameters. Therefore, include a master batch record and/or a detailed manufacturing process description in P.3.3 (drug product) of the application that also includes information about batch size and equipment type. The Agency understands your approach for handling changes to non-critical process parameters would be managed under your quality system without the need for regulatory review and approval prior to implementation, as outlined in section 3.2.P.2.3. Note that notification of all changes including changes to process parameters should be provided in accordance with 21CFR 314.70.
15. Describe your approach to scale up process parameter ranges (e.g. [REDACTED] (b) (4)) from pilot to commercial scale [REDACTED] (b) (4). Provide any available data for verification of the design space at commercial scale.
16. [REDACTED] (b) (4)
17. [REDACTED] (b) (4)
18. [REDACTED] (b) (4)

19.

(b) (4)

20.

21.

22.

23.

Analytical Methods

24.

(b) (4)

25.

26.

27.

(b) (4)

28.

29.

30.

If you have any questions, call Don Henry, Regulatory Project Manager, at (301) 796-4227.

Sincerely,

*{See appended electronic signature page}*

Sarah Pope Miksinski, Ph.D.  
Branch Chief  
Division of New Drug Quality Assessment II  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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/s/  
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SARAH P MIKSINSKI  
07/06/2011

## Mwidau, Jamila

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**From:** Mwidau, Jamila  
**Sent:** Tuesday, July 05, 2011 7:36 AM  
**To:** 'Ron.Domingo@Pfizer.com'  
**Cc:** Hanner, Diane  
**Subject:** Information Request - Crizotinib (NDA202570)

**Attachments:** DEATHS 1005.doc IR.doc

Dear Ron,

Attached is information request from our clinical reviewer. Also, please provide a response to both this request and the request sent on June 27<sup>h</sup> by July 15<sup>th</sup>. Kindly acknowledge receipt of this email.



DEATHS 1005.doc  
IR.doc (35 KB)...

Sincerely, Jamila (for CDR Diane Hanner)

Jamila A. Mwidau, RN,BSN,MPH  
Regulatory Health Project Manager  
FDA/CDER/OND/OODP/DDOP  
10903 New Hampshire Ave.  
WO22 Rm 2133  
Silver Spring, MD 20993  
Tel: 301-796-4989  
Fax: 301-796-9845

**DEATHS WITHIN 30 DAYS PROTOCOL A8081005**  
**Among 261 patients treated 32 deaths reported. 26 within 30 days**

Please provide **DATA SETS of Tumor measurements** for the following patients

10181012  
10371016  
10391011  
10391012  
10551010  
10741013  
10771032  
10771056  
12051019  
12151001

Please provide **death narratives** for the following patients

10371016  
10741013  
10551010 (Narrative provided for this patient does not include the death narrative)

**Please address following.**

**10581008:** 50 yr old male started study drug in May 31st 2010. The patient was admitted to the hospital with labored breathing and pneumonia. The culture results provided for sputum and endo tracheal aspirate may be contaminants ( staph aureus, rare Yeast and acinetobacter baumannii ). No blood cultures available to review. CT report showed decreasing tumor size and pneumonia. Not reported what kind of pneumonic pattern was seen.

*Please provide with the blood culture, full sputum and tracheal culture reports (including # of colonies and sensitivity results) and laboratory values. Please provide a full report of CT scan at the time of the event and hospital records.*

*Please clarify why the PI and the Pfizer did not think that the event was drug related if blood cultures and pathogenic cultures from the sputum are negative.*

**11051012:** 39 yrs old female, started study drug on July 22nd 2010. (b)(6) drug was stopped due to Increased LFT's Hospitalized with dyspnea on (b)(6) died on (b)(6). On Ultrasound of chest the patient was noted to have increased pleural effusion. SD on data set.

*Please provide a copy of the Ultrasound report.*

**11261013:** 67 yr old male started study drug on May 21st 2010. Patient was admitted to the hospital with worsening dyspnea on (b)(6). CT scan was stable. Pleural effusion showed staph. aureus.

***Please provide full culture reports (including # of colonies and sensitivity results) and laboratory values. Please provide a full report of CT scan at the time of the event and hospital records.***

**11851001** PD 40 Male was treated with the study drug daily since 20Jul2010. patient was admitted to the hospital with pneumonia on (b)(6) and grade 3 elevated ALT. Patients LFT's and pneumonia improved after stopping the study drug ( although he received antibiotics as well) On September 27th the patient restarted the study drug and developed pneumonia like symptoms again on re-challenge on (b)(6). Liver enzyme results are not provided. The patient later died.

***Please provide full culture reports (including # of colonies and sensitivity results), hospital records and laboratory values including LFT's for both events. . Please provide a full report of CT scan at the time of the events.***

***Please provide a rationale for patients Gr 3 ALT elevation to pneumonia and not drug related.***

***Please clarify why the PI and the Pfizer did not think that the event could be drug related toxicity.***

***Please provide a rationale as PD for the final cause for patient's death.***

**10181012** Cardiovascular 64 yr Male started the study drug on October 29th 2010. Developed dyspnea on (b)(6) and died the same day. Patient had no h/o cardiac disease and was not on any cardiac meds except for Norvasc for hypertension. Please provide a rationale for final cause of death as Cardiovascular.

***Please clarify why the PI and the Pfizer did not think that the event could be drug related pulmonary toxicity.***

**10391011** PD A 43-year-old, female started study drug on 22Oct2010. The subject's mother called the clinic on 04Nov2010 to inform clinicians that the subject passed away on (b)(6) due to disease progression.

***Please clarify why the PI and the Pfizer did not think that the event could be drug related toxicity. Please provide all medical records of this patient***

**10771032** Worsening of Dyspnea A 63-year-old male started study drug on 12Nov2010. On 29Dec2010 the subject developed worsening of dyspnea The subject died on (b)(6) On (b)(6) a computerized tomogram (CT) scan showed pulmonary embolism.

***Please clarify why the PI and the Pfizer did not think that the event could be related to pulmonary embolism and or drug related toxicity.***

**12051019** Hypoxemia A 45-year-old male started the study drug on 23Dec2010 developed symptoms of hypoxemia on 28th and died on (b)(6).

***Please clarify why the PI and the Pfizer did not think that the event Hypoxia could be drug related pulmonary toxicity.***

**12151001** 35-year-old male started to receive study medication on 29Dec2010. His ECOG PS score was 2. He was admitted to local hospital [REDACTED] with hypoxia and died on [REDACTED].

***Please clarify why the PI and the Pfizer did not think that the event Hypoxia could be drug related pulmonary toxicity. Please provide all medical records including hospital records for this patient***

10771056: A 49-year-old, female subject started to receive study drug on 05Jan2011. On [REDACTED] the subject died at home due to disease progression. No laboratory data were available. An autopsy was not performed.

***Please provide all medical records and explanation of the death event. Please clarify why the PI and the Pfizer did not think that the event could be drug related.***

Please provide the IR and the IR sent on June 27<sup>th</sup> by July 15<sup>th</sup> 2011.

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/s/  
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JAMILA MWIDAU  
07/05/2011

**Hanner, Diane**

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**From:** Hanner, Diane  
**Sent:** Friday, July 01, 2011 11:03 AM  
**To:** 'Ron.domingo@pfizer.com'  
**Cc:** 'Donnelly, Erling'  
**Subject:** Information Request - Crizotinib (NDA202570)

Hi,

I have been instructed to request the following regarding NDA 202570 -Crizotinib

Please provide the source code for generating Tables 14, 15 and 16 in your Population Modeling Analysis Report (pmar-00242).

Please provide the source code for generating Tables 16 and 17 in your Population Modeling Analysis Report (pmar-00243).

We respectfully request that this information to be submitted by **July 7, 2011**.

Thank you.  
Regards,  
Diane

CDR Diane Hanner  
Senior Program Management Officer  
FDA/CDER/OODP/DDOP  
10903 New Hampshire Avenue  
Bldg. 22/Room 2119  
Silver Spring, Maryland 20993  
(301) 796-2330  
FAX (301) 796-9845  
E-mail: diane.hanner@fda.hhs.gov

<b>Tracking:</b>	<b>Recipient</b>	<b>Delivery</b>
	'Ron.domingo@pfizer.com'	
	'Donnelly, Erling'	
	Maher, Virginia E.	Delivered: 7/1/2011 11:03 AM
	Mal k, Shakun	Delivered: 7/1/2011 11:03 AM
	Marathe, Anshu	Delivered: 7/1/2011 11:03 AM

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/s/  
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DIANE C HANNER  
07/01/2011

## Hanner, Diane

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**From:** Hanner, Diane  
**Sent:** Thursday, June 30, 2011 4:21 PM  
**To:** 'Domingo, Ron'  
**Subject:** Crizotinib IR (NDA 202570)

**Importance:** High

Hi,  
Please respond to the following information request by July 6th,

If I use LAB\_STD, MIN\_STD, and MAX\_STD, the grading does not seem to be correct for many of the laboratory values. For example, pt A8081005 1077 10741006 has a calcium value of 37.6. This seems unlikely, but is listed as gr 4 with a nml range of 8.4-10.2. Alternatively, pt A8081005 1105 11051012 has a calcium of 5.04 with a nml range of 4.64-5.28. This is listed as gr 4, but appears to be in the nml range. These findings are not isolated to serum calcium. Please provide instructions for the use of the laboratory datasets, labs.xpt.

There appears to be a large amount of missing data in the laboratory datasets. For example, labs.xpt for study 1005 in amendment 9 has 272 rows listed as LABEVALC = Failed text to numeric conversion, 1171 rows with LABEVALC = failed unit conversion, and 2630 rows with LABEVALC listed as LABCVTXT-SPECIFIED NON-EVALUABLE RESULT. A similar problem is seen in the dataset for study 1001 found in amendment 2. Please state whether data from these rows can be made available. If not, please state the number of patients and timepoints affected as well as the reason for this problem.

On study 1005, the CRF for patient 11741001 in amendment 9 does not contain the adverse event motor neuropathy. However, this AE is listed in the dataset included with amendment 9. Please explain this discrepancy and provide information on the extent of this problem (data not included in CRFs). Please also provide further information on the development and resolution of motor neuropathy in this pt.

Thank you.  
Regards,  
Diane

CDR Diane Hanner  
Senior Program Management Officer  
FDA/CDER/OODP/DDOP  
10903 New Hampshire Avenue  
Bldg. 22/Room 2119  
Silver Spring, Maryland 20993  
(301) 796-2330  
FAX (301) 796-9845  
E-mail: [diane.hanner@fda.hhs.gov](mailto:diane.hanner@fda.hhs.gov)

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/s/  
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DIANE C HANNER  
06/30/2011

## REQUEST FOR CONSULTATION

TO (Division/Office):  
**CDER DAIP CONSULT-(Ophthalmology Issue)**  
-Attn: Wiley Chambers

FROM: HFD-150/Diane Hanner  
RPM-DDOP  
(301) 796-4058

DATE 6-28-11	IND NO. 073544	NDA NO. 202570	TYPE OF DOCUMENT Electronic link dated 3/30/11 \\CDSESUB1\EVSPROD \NDA202570\202570.enx	DATE OF DOCUMENT 3-30-11
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NAME OF DRUG <b>Crizotinib</b>	PRIORITY CONSIDERATION <b>High Priority (Pending final decision at filing meeting)</b>	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE <b>Before 8/29/11</b>
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NAME OF FIRM: Pfizer Inc., 10646 Science Center Drive, San Diego, CA 92121

### REASON FOR REQUEST

#### I. GENERAL

- |  |  |   |
|--|--|---|
| <input type="checkbox"/> NEW PROTOCOL<br><input type="checkbox"/> PROGRESS REPORT<br><input type="checkbox"/> NEW CORRESPONDENCE<br><input type="checkbox"/> DRUG ADVERTISING<br><input type="checkbox"/> ADVERSE REACTION REPORT<br><input type="checkbox"/> MANUFACTURING CHANGE/ADDITION<br><input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> PRE--NDA MEETING<br><input type="checkbox"/> END OF PHASE II MEETING<br><input type="checkbox"/> RESUBMISSION<br><input checked="" type="checkbox"/> SAFETY/EFFICACY<br><input type="checkbox"/> PAPER NDA<br><input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER<br><input type="checkbox"/> FINAL PRINTED LABELING<br><input type="checkbox"/> LABELING REVISION<br><input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE<br><input type="checkbox"/> FORMULATIVE REVIEW<br><input type="checkbox"/> OTHER (SPECIFY BELOW): |
|--|--|---|

#### II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):	<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):

#### III. BIOPHARMACEUTICS

- |   |  |
|---|--|
| <input type="checkbox"/> DISSOLUTION<br><input type="checkbox"/> BIOAVAILABILITY STUDIES<br><input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE<br><input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS<br><input type="checkbox"/> IN-VIVO WAIVER REQUEST |
|---|--|

#### IV. DRUG EXPERIENCE

- |  |   |
|--|---|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL<br><input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES<br><input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)<br><input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY<br><input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE<br><input type="checkbox"/> POISON RISK ANALYSIS |
|--|---|

#### V. SCIENTIFIC INVESTIGATIONS

- |  |                                      |
|--|--------------------------------------|
| <input checked="" type="checkbox"/> CLINICAL | <input type="checkbox"/> PRECLINICAL |
|--|--------------------------------------|

COMMENTS/SPECIAL INSTRUCTIONS. 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 funduscopy 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?

Suggest Section 2.7.4.2.1.5.4.1 of Summary of Clinical Safety

EDR Location: \\CDSESUB1\EVSPROD\NDA202570\202570.enx

356H Form: \\CDSESUB1\EVSPROD\NDA202570\0002\m1\us\356h.pdf

Cover Letter: \\CDSESUB1\EVSPROD\NDA202570\0002\m1\us\cover.pdf

\*Team PMR and labeling meeting: Monday, July 11, 2011, 4:00 p.m. to 5:00 p.m. in Room CDER WO 2205

**PDUFA DATE:** August 29, 2011

**ATTACHMENTS**

HFD-150/RPM Diane Hanner

HFD- /Reviewers and Team Leaders **Medical Officers: Shakun Malik and Virginia E. Maher (T.L)**

NAME AND PHONE NUMBER OF REQUESTER

Diane Hanner 301-796-4058

METHOD OF DELIVERY (Check one)

DFS ONLY

MAIL

HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

5/28/05

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/s/  
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DIANE C HANNER  
06/28/2011

## Hanner, Diane

---

**From:** Hanner, Diane  
**Sent:** Monday, June 27, 2011 4:02 PM  
**To:** 'Domingo, Ron'  
**Cc:** 'Donnelly, Erling'  
**Subject:** NDA 202570 (Crizotinib) Information Request 6-27-11

Hi Ron,

Please address the following information request regarding NDA 202570:

### **PROTOCOL 1001 DEATHS WITHIN 30 days**

1. SUB ID: 10021061: 41 never smoker dev hypoxia 13 days after starting the study drug as 2<sup>nd</sup> line therapy for his NSCLC. He died on (b) (6) day after starting the study drug. Imaging showed interval worsening of multifocal airspace opacities, particularly within the lower lobes since starting the study drug. Cardiac work up for CHF and enzymes were negative. His culture reports provided were negative and he failed to respond to broad spectrum antibiotics.  
*Please clarify the reason why the PI and Pfizer did not believe this could be drug related.*
2. SUB ID: 10021063: 44 yrs old male developed brain mets on therapy Pts last imaging had revealed new brain mets and stable other lesions. He was clinically stable after receiving whole brain XRT when the drug was restarted. (b) (6) days later patient died suddenly.  
*Please clarify PD as final cause of his death.*
3. SUB ID: 10021080: **IR sent Pending response**
4. SUB ID: 10051010: 75 F on study drug was hospitalized and treated with chest subcutaneous abscess drainage on (b) (6). Pleural culture was positive for staphylococcus aureus. CT on (b) (6) showed Fluid component nearly completely resolved. The patient passed away on (b) (6). Patient has documented PR on the last scan on May 15<sup>th</sup> 2010 as per data set.  
*Please clarify PD as final cause of his death.*
5. SUB ID: 10051015: 71 yrs old male received study drug from 24Feb2010 to 10Mar2010. The subject was admitted to hospital on (b) (6) for worsening dyspnea. He died on (b) (6). Patient developed dyspnea within 15 days and died on (b) (6) day. No scan was done after symptom development.  
*Please clarify the reason to note the final cause of death as PD and why the PI and Pfizer did not believe this could be drug related.*
6. SUB ID: 10051016: 78 yrs old female diagnosed with drug relate radiation pneumonitis later died on (b) (6). Last data set provided dated July 27<sup>th</sup> 2010 showed a PR.  
*Please provide a death narrative and clarify the reason to note the final cause of death as PD.*
7. SUB ID: 10061036 48 yrs old female has documented PR and SD on the last scan on (b) (6). Patient continued treatment till (b) (6) before her death.  
*Please provide a death narrative and clarify the reason to note the final cause of death as PD.*
8. SUB ID: 10061082: 57 yrs old male on study drug developed acute respiratory failure needing intubation resulting in death. Last imaging in data set on (b) (6) on the day of the hospitalization

showed stable disease. Patient was diagnosed of septic shock and ARDS and died on (b) (6). All the cultures available for review were not significantly positive.

***Please clarify the reason to note the final cause of death as PD and why the PI and Pfizer did not believe this could be drug related.***

9. SUB ID: 10061087: 60yrs old female on study drug was admitted to the hospital with syncope. All the scans were stable. She died later without resolution of syncope

***Please clarify PD as the cause of her death***

10. SUB ID: 10061093: 32 yrs old female has a documented PR as per data set on 8/31. The patient continued therapy till Oct 13th and died (b) (6).

***Please provide a death narrative and clarify the reason to note the final cause of death as PD.***

11. SUB ID: 10061166: 63yrs old male started study drug on 23Nov2010. On (b) (6) the subject was hospitalized due to pneumonia which resulted in death.

Patient underwent nuclear medicine whole body gallium exam on (b) (6) which showed patchy activity in chest suspicious for inflammatory process.

***Please clarify if the gallium scan showed inflammation in lungs and patient did not respond to antibiotics (culture results not provided) why the investigator and Pfizer did not believe that the event could be drug related. 10071021***

12. SUB ID: 10071021: 63 female started study drug on March 2<sup>nd</sup> 2009. She died with acute massive pulmonary HYG on (b) (6). Chest X-RAY and bronchoscope results provided showed no change.

***Please clarify the reason why the PI and Pfizer did not believe this could be drug related and why the PI thinks the patient had massive bleed e.g. did the patient have an endo-bronchial lesion?***

13. **SUB ID: 10071026:** 49 yrs old male has documented PR on 4/3/2010. He took his last dose of study drug on June 14th and died (b) (6).

***Please clarify the reason why the PI believes that the final cause of death is PD.***

14. **SUB ID: 10071037:** 52 F started study drug on 16Sep2009. The subject presented with general weakness, cough, sputum, and fever on 04Dec2009. Chest CT showed pneumonia in the both lungs and pulmonary embolism. Last Scan on 11/17 noted a PR. She expired on (b) (6). The patient did not respond to antibiotics.

***Please clarify the reason why the PI believes that the final cause of death is PD and why the PI and Pfizer did not believe this could be drug related.***

Regards,  
Diane

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/s/  
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DIANE C HANNER  
06/27/2011



NDA 202570

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Pfizer Inc.  
10646 Science Center Drive  
San Diego, California 92121

ATTENTION: Ron C. Domingo, MS, RAC  
Manager, Worldwide Regulatory Strategy

Dear Mr. Domingo:

Please refer to your New Drug Application (NDA) dated March 30, 2011, received March 30, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Crizotinib Capsules, 200 mg and 250 mg.

We also refer to your March 31, 2011, correspondence, received on March 31, 2011, requesting reconsideration of your proposed proprietary name, Xalkori. We have completed our review of the proposed proprietary name, Xalkori and have concluded that it is acceptable.

The proposed proprietary name, Xalkori will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your March 31, 2011, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Sarah Simon, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5205. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Diane Hanner at (301) 796-4058.

Sincerely,

*{See appended electronic signature page}*

Kellie Taylor, PharmD, MPH  
Associate Director  
Division of Medication Error Prevention and Analysis  
Office of Medication Error Prevention and Risk  
Management  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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/s/  
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TODD D BRIDGES  
06/24/2011

KELLIE A TAYLOR  
06/27/2011

## Hanner, Diane

---

**From:** Hanner, Diane  
**Sent:** Wednesday, June 22, 2011 2:25 PM  
**To:** 'Donnelly, Erling'  
**Cc:** 'Domingo, Ron'  
**Subject:** Crizotinib NDA 202570 IR

Hi,

From Study 1005, please provide a list of the 43 patients who had a response by IRR. Please state why patients 10501004 and 10771004 are or are/not included in this group. Please respond by Friday, June 24th.

Thank you.  
Regards,  
Diane

CDR Diane Hanner  
Senior Program Management Officer  
FDA/CDER/OODP/DDOP  
10903 New Hampshire Avenue  
Bldg. 22/Room 2119  
Silver Spring, Maryland 20993  
(301) 796-2330  
FAX (301) 796-9845  
E-mail: [diane.hanner@fda.hhs.gov](mailto:diane.hanner@fda.hhs.gov)

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/s/  
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DIANE C HANNER  
06/22/2011

**Hanner, Diane**

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**From:** Hanner, Diane  
**Sent:** Tuesday, June 21, 2011 11:04 AM  
**To:** 'Donnelly, Erling'  
**Cc:** Domingo, Ron  
**Subject:** IR NDA 202570 Crizotinib  
**Importance:** High

Hi,

I have been instructed to request that you please address the following information request and provide clarification regarding NDA 202570 Crizotinib study reports, etc. by c.o.b. tomorrow, June 22, 2011.

**1) Study Report table for Study 1001/1005 reports**

**Study 1001**

Total Safety Population =136

Total Deaths 40

**Deaths within 30 days 19**

Deaths >30 days 21

We have 20 patients Sub ID who died on this study within 30 days based on data sets

Please clarify

- |     |                 |                            |
|-----|-----------------|----------------------------|
| 1.  | 10021061        | Hypoxia                    |
| 2.  | 10021063        | Disease progression        |
| 3.  | 10021079        | Disease progression        |
| 4.  | 10021080        | Disease progression        |
| 5.  | 10051010        | Disease progression        |
| 6.  | 10051014        | Disease progression        |
| 7.  | 10051015        | Disease progression        |
| 8.  | <b>10051016</b> | <b>Disease progression</b> |
| 9.  | <b>10061036</b> | <b>Disease progression</b> |
| 10. | 10061082        | Respiratory failure        |
| 11. | 10061087        | Disease progression        |
| 12. | <b>10061093</b> | <b>Disease progression</b> |
|     |                 | <b>Subcutaneous</b>        |
| 13. | <b>10061133</b> | <b>emphysema</b>           |
| 14. | <b>10061166</b> | <b>Pneumonia</b>           |
| 15. | 10071021        | Pulmonary hemorrhage       |
| 16. | 10071026        | Disease progression        |
| 17. | 10071037        | Pneumonia                  |
| 18. | <b>10071055</b> | <b>DIC</b>                 |
| 19. | <b>10081002</b> | <b>Disease progression</b> |
| 20. | 10081005        | Disease progression        |

**Study 1005**

Total Safety Population =136

Total Deaths 21

**Deaths within 30 days 16**

Deaths >30 days 5

**We have following 15 patients from data sets with deaths, please clarify**

1. 10021002 Disease progression
2. 10041001 Pneumonia
3. 10051003 Disease progression
4. 10131003 Alanine aminotransferase increased
5. 10181002 Disease progression
6. 10211001 Pneumonitis
7. 10301003 Sepsis
8. 10311003 Disease progression
9. 10581008 Septic shock
10. 11051012 Disease progression
11. 11261013 Pyothorax
12. 11281001 Death  
Disease progression/ Pulmonary
13. 11411001 embolism
14. 11741001 Disease progression
15. 11961001 Disease progression

**Protocol: A8081001**

1) 10051004: 28 y.o., male Started study drug on 19Feb2009 and developed Grade 3 hypoxia resulting in hospitalization on [REDACTED] Study drug stopped permanently on 25Feb2009 Patient died on [REDACTED] from Infection/sepsis.

- The reason for Patient's death is reported as fatal PD. Please clarify.

2) 10071037. 52 yr female 16, Started study drug on (11Sep2009) developed weakness, cough, fever resulting in hospitalization on [REDACTED] Study drug stopped. CXR showed pneumonia1. Patient died on [REDACTED].  
CT SCAN on 11Nov2009 showed significant improvement in all facets of disease from baseline.

Scan on 04Dec2009revealed significant and severe deterioration; extensive bilateral GGOs were not present before. The IRC determined that the event was likely both infection as well as pulmonary embolism.

- Please provide a CT report of December 4<sup>th</sup>. Any hospital records, bronchoscope and culture reports and the reason why IRC did not think that it was drug related.

**Protocol: A8081005:**

1) Subject ID10041001: 29 y.o., male Started study drug on 06Apr2010 and developed hypoxia resulting in hospitalization on [REDACTED].

18Apr2010: CT chest showed multifocal pneumonia, no PE, possible lymphangitic disease Patient died

(b) (6)

The IRC committee felt that while ILD, infection, progression of disease or a combination of these factors were all possibilities, the fact that the patient had extensive pre-existing lung cancer, had no documented infection despite bronchoscopy, was afebrile and nontoxic appearing on presentation of her event, that it was reasonable to conclude that her event was related to progression of disease.

- The patient was admitted with a fever and IRC had no scans to review. Please provide a rationale for their conclusion.
- Please provide scan reports and hospital records at the time of event

4) Protocol: A8081005: Subject ID 10431012: The IRC committee felt that it was difficult to ascertain with certainty the etiology of pulmonary event given the lack of a baseline chest CT to review.

- Please provide the Scan reports.

Thank you.  
Regards,  
Diane

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/s/  
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DIANE C HANNER  
06/21/2011

## Hanner, Diane

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**From:** Hanner, Diane  
**Sent:** Friday, June 10, 2011 9:47 AM  
**To:** 'Donnelly, Erling'  
**Cc:** 'Domingo, Ron'  
**Subject:** Crizotinib/ Pfizer study recommendation ( NDA 202570)

**Importance:** High

Hi,

I have been instructed to inform you that it will become problematic if Pfizer uses 1001 as the principal study for the approval of Crizotinib (NDA 202570) because Abbott will then need to redo the concordance study. Therefore, FDA strongly recommends that Pfizer use the 1005 study as the "primary" or principal study and that 1001 be used as a supportive study.

Regards,  
Diane

CDR Diane Hanner  
Senior Program Management Officer  
FDA/CDER/OODP/DDOP  
10903 New Hampshire Avenue  
Bldg. 22/Room 2119  
Silver Spring, Maryland 20993  
(301) 796-2330  
FAX (301) 796-9845  
E-mail: [diane.hanner@fda.hhs.gov](mailto:diane.hanner@fda.hhs.gov)

<b>Tracking:</b>	<b>Recipient</b>	<b>Delivery</b>
	'Donnelly, Erling'	
	'Domingo, Ron'	
	Mahe r, Virginia E.	Delivered: 6/10/2011 9:47 AM
	Mal k, Shakun	Delivered: 6/10/2011 9:47 AM
	Bijwaard, Karen E	Delivered: 6/10/2011 9:47 AM

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/s/  
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DIANE C HANNER  
06/10/2011

## Hanner, Diane

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**From:** Hanner, Diane  
**Sent:** Tuesday, June 07, 2011 1:48 PM  
**To:** 'Domingo, Ron'  
**Subject:** Crizotinib IR NDA 202570

**Importance:** High

Hi Ron,

I have been instructed to convey the following information request regarding NDA 202570, and I'm requesting that you please respond by **June 9th**:

1. In Table 13.4.6.2 in Amendment 9 (5-25-11) to your NDA, the population for the IRR response assessment is N = 136 and 105 (when the 31 pts not included in the IRR RE are removed). In Table 13.4.6.3 from the same amendment, the population is N = 102. In dataset xtmx.xpt, 115 pts have baseline scans, 109 pts have baseline target lesions, and 99 pts have subsequent scans.

A. Please clarify, with patient numbers, the differences between these populations.

B. Please state the population you have chosen for analysis of the IRR reading and the reason you have chosen this population. We are considering using 136 for all assessments.

C. Please provide a listing of missing scans and information on your efforts to retrieve these scans.

2. Pts 10501004, 10771004, and 11051040 are not in the Investigator's response evaluable population. These pts are included in the IRR response evaluable population. Please state why they are not included/included in these populations.

3. You have presented both the Investigator and Investigator-derived response. The Investigator-derived response appears to more strictly apply the RECIST criteria. We have the following questions concerning differences in the responders between these assessments.

A. Pt 10521002 had PD between 2 assessments of PR. Further, not all the non-target lesions are commented on in post baseline exams. This pt is not considered a responder in the INV assessment, but is considered a responder in the INV-derived assessment. Please provide your rationale.

B. Pt 10211022 had a PR by the INV and SD in the INV-derived response. Please state why this pt was classified as SD.

C. Pt 10471003 had a PR in the INV and an Indeterminate response in the INV-derived assessment. This pt had an Indeterminate response between assessments of PR due to a missing head CT. Please provide your rationale for the assessment of SD.

D. Pt 10391004 had a PR by INV and an assessment of Indeterminate by the INV-derived response. Please state why this pt was classified as Indeterminate.

E. Pt 11291010 had a PR by INV and an assessment of SD by the INV-derived response. Please state why this pt was classified as SD.

4. The variable RIST is included in dataset xtmx.xpt in Amendment 9 and its value ranges from 0.8 to 6. Please provide the units for these measurements.

5. In dataset xtmx.xpt in Amendment 9, 27.9% of scans required adjudication (this counts 1 scan at each time point per pt). Please state the number of pts in which adjudication was required in the assessment of best response.

Thank you,  
Diane

CDR Diane Hanner  
Senior Program Management Officer  
FDA/CDER/OODP/DDOP  
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/s/  
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DIANE C HANNER  
06/07/2011

## Hanner, Diane

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**From:** Hanner, Diane  
**Sent:** Friday, June 03, 2011 11:24 AM  
**To:** 'Domingo, Ron'  
**Subject:** IR-crizotinib NDA 202570

Hi,

Please provide narratives on the following patients from Study 1001 (NDA 202570).

10061166 (pneumonia)  
10071055 (DIC)  
1001149 (SOB and UE edema leading to discon)  
10031025 (pregnancy in partner and miscarriage)  
10051013 (NSCLC-GI perforation)  
10021111 (NSCLC-GI perforation leading to discon)  
10081009 (infection with OI)

Thank you,  
Regards,  
Diane

CDR Diane Hanner  
Senior Program Management Officer  
FDA/CDER/OODP/DDOP  
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E-mail: [diane.hanner@fda.hhs.gov](mailto:diane.hanner@fda.hhs.gov)

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/s/  
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DIANE C HANNER  
06/03/2011

## Hanner, Diane

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**From:** Hanner, Diane  
**Sent:** Thursday, June 02, 2011 2:59 PM  
**To:** 'Domingo, Ron'  
**Subject:** NDA 202570~ Crizotinib IR

**Attachments:** 1005.Possible Discrepancies in # Prior Regimens.xls

Hi Ron,

Please provide, by June 9, a dataset containing the investigator response assessments for the 25 ALK negative NSCLC patients.

In Study 1005, there are 30 pts in which the # of prior chemotherapy regimens appear to be incorrect. See attached spreadsheet. Please provide your rationale, by June 9, for the # of prior regimens listed in the dataset for these patients.



1005.Possibl  
iscrepancies i

Thank you.  
Regards,  
Diane

CDR Diane Hanner  
Senior Program Management Officer  
FDA/CDER/OODP/DDOP  
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E-mail: [diane.hanner@fda.hhs.gov](mailto:diane.hanner@fda.hhs.gov)

Pt #	Prior Meds	Start Date	Stop Date	# regimens	# regimens FDA v. Dataset	Crizotinib Start	Reason
1	A8081005 1025 10251002 ADJUVANT CARBOPLATIN/PACLITAXEL	12/1/1996	4/1/1997	0		8/17/2010	> 5 y
	A8081005 1025 10251002 ADVANCED/METASTATIC MUC-1	3/1/2000	9/1/2000	0			> 5 y
	A8081005 1025 10251002 ADVANCED/METASTATIC GEMCITABINE HYDROCHLORIDE	9/1/2000	11/2/2000	0			> 5 y
	A8081005 1025 10251002 ADVANCED/METASTATIC GEFITINIB	10/1/2001	3/25/2004	0			> 5 y
	A8081005 1025 10251002 ADVANCED/METASTATIC ERLOTINIB HYDROCHLORIDE	1/1/2005	7/2/2007	1			
	A8081005 1025 10251002 ADVANCED/METASTATIC PEMETREXED	3/1/2007	6/29/2010	2	2 v. 11		
2	A8081005 1021 10211032 ADVANCED/METASTATIC PACLITAXEL	4/12/2007	11/3/2007	1		8/30/2010	
	A8081005 1021 10211032 ADVANCED/METASTATIC BEVACIZUMAB	4/12/2007	11/3/2007	1			
	A8081005 1021 10211032 ADVANCED/METASTATIC CARBOPLATIN	4/12/2007	11/3/2007	1			
	A8081005 1021 10211032 ADVANCED/METASTATIC BEVACIZUMAB	12/4/2007	8/15/2008	2			
	A8081005 1021 10211032 ADVANCED/METASTATIC ERLOTINIB	12/4/2007	8/15/2008	2			
	A8081005 1021 10211032 ADVANCED/METASTATIC PACLITAXEL	8/15/2008	12/4/2008	3			
	A8081005 1021 10211032 ADVANCED/METASTATIC BEVACIZUMAB	8/15/2008	12/4/2008	3			
	A8081005 1021 10211032 ADVANCED/METASTATIC CARBOPLATIN	8/15/2008	12/4/2008	3			
	A8081005 1021 10211032 ADVANCED/METASTATIC PEMETREXED	12/4/2008	4/10/2009	4			
	A8081005 1021 10211032 ADVANCED/METASTATIC BEVACIZUMAB	12/4/2008	4/10/2009	4			
	A8081005 1021 10211032 ADVANCED/METASTATIC DOCETAXEL	4/10/2009	6/10/2009	5			
	A8081005 1021 10211032 ADVANCED/METASTATIC VINORELBINE	6/19/2009	12/15/2009	6			
	A8081005 1021 10211032 ADVANCED/METASTATIC CETUXIMAB	6/19/2009	12/15/2009	6			
	A8081005 1021 10211032 ADVANCED/METASTATIC GEMCITABINE	12/18/2009	12/18/2009	7			
	A8081005 1021 10211032 ADVANCED/METASTATIC GEMCITABINE	2/19/2010	4/23/2010	7			
	A8081005 1021 10211032 ADVANCED/METASTATIC TEMOZOLOMIDE	3/22/2010	7/15/2010	not in crf			
	A8081005 1021 10211032 ADVANCED/METASTATIC GEMCITABINE	5/17/2010	7/14/2010	8			
	A8081005 1021 10211032 ADVANCED/METASTATIC CISPLATIN	5/17/2010	7/14/2010	8	8 v 10		
3	A8081005 1077 10771004 ADVANCED/METASTATIC CISPLATIN	8/14/2004	12/2/2004	0		9/9/2010	> 5 yr
	A8081005 1077 10771004 ADVANCED/METASTATIC GEMCITABINE	8/14/2004	12/2/2004	0			> 5 yr
	A8081005 1077 10771004 ADVANCED/METASTATIC GEFITINIB	3/22/2005	3/20/2007	1			
	A8081005 1077 10771004 ADVANCED/METASTATIC CARBOPLATIN	4/12/2007	9/13/2007	2			
	A8081005 1077 10771004 ADVANCED/METASTATIC PEMETREXED	4/12/2007	9/13/2007	2			
	A8081005 1077 10771004 ADVANCED/METASTATIC ERLOTINIB	12/22/2008	3/5/2009	3			
	A8081005 1077 10771004 ADVANCED/METASTATIC BLINDED THERAPY	3/27/2009	5/29/2009	4			
	A8081005 1077 10771004 ADVANCED/METASTATIC DOCETAXEL	6/10/2009	10/7/2009	5			
	A8081005 1077 10771004 ADVANCED/METASTATIC GEMCITABINE	6/10/2009	10/7/2009	5			
	A8081005 1077 10771004 ADVANCED/METASTATIC GEMCITABINE	10/27/2009	1/7/2010	6			
	A8081005 1077 10771004 ADVANCED/METASTATIC CISPLATIN	5/21/2010	7/30/2010	7			
	A8081005 1077 10771004 ADVANCED/METASTATIC PEMETREXED	5/21/2010	7/30/2010	7	7 v 8		
4	A8081005 1021 10211016 ADVANCED/METASTATIC GEMCITABINE	5/1/2006	8/1/2006	1		5/13/2010	
	A8081005 1021 10211016 ADVANCED/METASTATIC CARBOPLATIN	5/1/2006	8/1/2006	1			
	A8081005 1021 10211016 ADVANCED/METASTATIC ERLOTINIB	2/1/2007	8/1/2007	2			
	A8081005 1021 10211016 ADVANCED/METASTATIC PACLITAXEL	9/1/2007	2/1/2008	3			
	A8081005 1021 10211016 ADVANCED/METASTATIC BEVACIZUMAB	9/1/2007	6/1/2008	3			
	A8081005 1021 10211016 ADVANCED/METASTATIC CARBOPLATIN	9/1/2007	2/1/2008	3			
	A8081005 1021 10211016 ADVANCED/METASTATIC PEMETREXED	7/1/2008	2/1/2009	4			
	A8081005 1021 10211016 ADVANCED/METASTATIC OXALIPLATIN	7/1/2008	2/1/2009	4			
	A8081005 1021 10211016 ADVANCED/METASTATIC CETUXIMAB	7/1/2008	2/1/2009	4			
	A8081005 1021 10211016 ADVANCED/METASTATIC IRINOTECAN	3/1/2009	8/1/2009	5			
	A8081005 1021 10211016 ADVANCED/METASTATIC VINORELBINE	8/1/2009	8/30/2009	6			
	A8081005 1021 10211016 ADVANCED/METASTATIC GEMCITABINE	8/1/2009	8/30/2009	6			
	A8081005 1021 10211016 ADVANCED/METASTATIC SUBEROYLANILIDE HYDROXAMIC	10/1/2009	4/7/2010	7			
	A8081005 1021 10211016 ADVANCED/METASTATIC CARBOPLATIN	10/1/2009	4/7/2010	7			
	A8081005 1021 10211016 ADVANCED/METASTATIC DOCETAXEL	10/1/2009	4/7/2010	7	7 v 6		
5	A8081005 1042 10421011 The # in the dataset are not consistent with those in the CRF and this is uninterpretable.					9/17/2010	
6	A8081005 1043 10431003 ADVANCED/METASTATIC CARBOPLATIN	2/12/2004	4/21/2004	0		6/9/2010	> 5 yrs
	A8081005 1043 10431003 ADVANCED/METASTATIC GEMCITABINE	2/12/2004	4/21/2004	0			> 5 yrs
	A8081005 1043 10431003 ADVANCED/METASTATIC GEFITINIB	11/20/2004	1/10/2005	0			> 5 yrs
	A8081005 1043 10431003 ADVANCED/METASTATIC PEMETREXED	1/10/2005	12/1/2007	1			
	A8081005 1043 10431003 ADVANCED/METASTATIC BEVACIZUMAB	12/2/2007	8/15/2008	2			
	A8081005 1043 10431003 ADVANCED/METASTATIC PEMETREXED	12/2/2007	8/15/2008	2			
	A8081005 1043 10431003 ADVANCED/METASTATIC DOCETAXEL	7/13/2009	9/2/2009	3			
	A8081005 1043 10431003 ADVANCED/METASTATIC CARBOPLATIN	9/3/2009	12/2/2009	4			
	A8081005 1043 10431003 ADVANCED/METASTATIC GEMCITABINE	9/3/2009	5/20/2010	4	4 v 6		
7	A8081005 1057 10571002 ADJUVANT PACLITAXEL	9/3/2004	11/2/2004	0		7/9/2010	> 5 yrs
	A8081005 1057 10571002 ADJUVANT CARBOPLATIN	9/3/2004	11/2/2004	0			> 5 yrs

A8081005	1057	10571002	ADVANCED/METASTATIC	VINORELBINE	11/15/2006	2/15/2007	1		
A8081005	1057	10571002	ADVANCED/METASTATIC	CISPLATIN	11/15/2006	2/15/2007	1		
A8081005	1057	10571002	ADVANCED/METASTATIC	ERLOTINIB	8/7/2007	11/13/2008	2		
A8081005	1057	10571002	ADVANCED/METASTATIC	PEMETREXED	11/24/2008	1/2/2009	3		
A8081005	1057	10571002	ADVANCED/METASTATIC	CISPLATIN	11/24/2008	1/2/2009	3		
A8081005	1057	10571002	ADVANCED/METASTATIC	GEMCITABINE	2/3/2009	10/13/2009	4		
A8081005	1057	10571002	ADVANCED/METASTATIC	CISPLATIN	2/3/2009	10/13/2009	4		
A8081005	1057	10571002	ADVANCED/METASTATIC	BEVACIZUMAB	2/3/2009	10/13/2009	4		
A8081005	1057	10571002	ADVANCED/METASTATIC	PACLITAXEL	11/2/2009	7/1/2010	5		
A8081005	1057	10571002	ADVANCED/METASTATIC	CARBOPLATIN	11/2/2009	7/1/2010	5		
A8081005	1057	10571002	ADVANCED/METASTATIC	BEVACIZUMAB	11/2/2009	7/1/2010	5	5 v 6	
8	A8081005	1002	10021002	ADVANCED/METASTATIC	PACLITAXEL	7/25/2006	8/15/2006	1	8/3/2010
	A8081005	1002	10021002	ADVANCED/METASTATIC	FIGITUMUMAB	7/25/2006	8/15/2006	1	
	A8081005	1002	10021002	ADVANCED/METASTATIC	CARBOPLATIN	7/25/2006	8/15/2006	1	
	A8081005	1002	10021002	ADVANCED/METASTATIC	PEMETREXED	10/3/2006	3/6/2007	2	
	A8081005	1002	10021002	ADVANCED/METASTATIC	DOCETAXEL	10/3/2006	3/6/2007	2	
	A8081005	1002	10021002	ADVANCED/METASTATIC	SELICICLIB	10/20/2007	11/20/2007	3	
	A8081005	1002	10021002	ADVANCED/METASTATIC	PEMETREXED	12/14/2007	12/4/2008	4	
	A8081005	1002	10021002	ADVANCED/METASTATIC	DOCETAXEL	12/14/2007	4/24/2008	4	
	A8081005	1002	10021002	ADVANCED/METASTATIC	PEMETREXED	10/26/2009	1/7/2010	5	
	A8081005	1002	10021002	ADVANCED/METASTATIC	VINORELBINE	2/4/2010	3/20/2010	6	
	A8081005	1002	10021002	ADVANCED/METASTATIC	DOCETAXEL	4/8/2010	7/1/2010	7	7 v 5
9	A8081005	1013	10131001	ADVANCED/METASTATIC	CARBOPLATIN	9/1/2001	12/31/2001	0	4/26/2010 > 5 yrs
	A8081005	1013	10131001	ADVANCED/METASTATIC	PACLITAXEL	9/1/2001	12/31/2001	0	> 5 yrs
	A8081005	1013	10131001	ADVANCED/METASTATIC	CARBOPLATIN	1/7/2008	4/30/2008	1	
	A8081005	1013	10131001	ADVANCED/METASTATIC	BEVACIZUMAB	1/7/2008	9/30/2008	1	
	A8081005	1013	10131001	ADVANCED/METASTATIC	PACLITAXEL	1/7/2008	4/30/2008	1	
	A8081005	1013	10131001	ADVANCED/METASTATIC	ERLOTINIB HYDROCHLORIDE	4/7/2008	9/30/2008	2	
	A8081005	1013	10131001	ADVANCED/METASTATIC	PEMETREXED	3/1/2009	12/31/2009	3	3 v 5
10	A8081005	1013	10131003	ADJUVANT	CARBOPLATIN	8/1/2006	12/31/2006	1	8/16/2010
	A8081005	1013	10131003	ADJUVANT	PACLITAXEL	8/1/2006	12/31/2006	1	
	A8081005	1013	10131003	ADJUVANT		12/1/2006	3/31/2007	2	
	A8081005	1013	10131003	ADVANCED/METASTATIC	BEVACIZUMAB	9/1/2007	3/31/2009	3	
	A8081005	1013	10131003	ADVANCED/METASTATIC	PEMETREXED	9/1/2007	3/31/2009	3	
	A8081005	1013	10131003	ADVANCED/METASTATIC	ERLOTINIB HYDROCHLORIDE	4/20/2009	10/31/2009	4	
	A8081005	1013	10131003	ADVANCED/METASTATIC	CARBOPLATIN	11/1/2009	11/30/2009	5	
	A8081005	1013	10131003	ADVANCED/METASTATIC	GEMCITABINE HYDROCHLORIDE	11/1/2009	11/30/2009	5	
	A8081005	1013	10131003	ADVANCED/METASTATIC	CARBOPLATIN	12/29/2009	3/22/2010	6	
	A8081005	1013	10131003	ADVANCED/METASTATIC	PEMETREXED	12/29/2009	3/22/2010	6	6 v 5
11	A8081005	1043	10431019	ADJUVANT	ETOPOSIDE	1/1/1997	12/31/1997	0	9/3/2010 > 5 yrs
	A8081005	1043	10431019	ADJUVANT	CISPLATIN	1/1/1997	12/31/1997	0	> 5 yrs
	A8081005	1043	10431019	ADVANCED/METASTATIC	ERLOTINIB HYDROCHLORIDE	10/1/2009	10/15/2009	1	
	A8081005	1043	10431019	ADVANCED/METASTATIC	BEVACIZUMAB	11/24/2009	2/17/2010	2	
	A8081005	1043	10431019	ADVANCED/METASTATIC	CARBOPLATIN	11/24/2009	2/17/2010	2	
	A8081005	1043	10431019	ADVANCED/METASTATIC	PACLITAXEL	11/24/2009	2/17/2010	2	
	A8081005	1043	10431019	ADVANCED/METASTATIC	PEMETREXED	3/17/2010	5/19/2010	3	
	A8081005	1043	10431019	ADVANCED/METASTATIC	VINORELBINE	6/9/2010	7/27/2010	4	4 v 5
12	A8081005	1058	10581037	ADJUVANT	GEMCITABINE	12/8/2004	12/8/2004	0	9/16/2010 > 5 yrs
	A8081005	1058	10581037	ADJUVANT	TEGAFUR URACIL	4/1/2005	1/31/2006	1	.
	A8081005	1058	10581037	ADVANCED/METASTATIC	GEMCITABINE	8/16/2006	10/25/2006	2	.
	A8081005	1058	10581037	ADVANCED/METASTATIC	CISPLATIN	8/16/2006	10/25/2006	2	.
	A8081005	1058	10581037	ADVANCED/METASTATIC	GEFITINIB	11/15/2006	12/31/2007	3	.
	A8081005	1058	10581037	ADVANCED/METASTATIC	PEMETREXED	6/14/2007	2/10/2010	4	4 v 5
13	A8081005	1058	10581039	ADJUVANT	VINORELBINE	1/7/2005	4/18/2005	0	9/13/2010
	A8081005	1058	10581039	ADJUVANT	CISPLATIN	1/14/2005	4/18/2005	0	
	A8081005	1058	10581039	ADVANCED/METASTATIC	GEMCITABINE	8/31/2006	11/13/2006	1	
	A8081005	1058	10581039	ADVANCED/METASTATIC	CISPLATIN	9/7/2006	11/13/2006	1	
	A8081005	1058	10581039	ADVANCED/METASTATIC	ERLOTINIB	11/1/2006	3/21/2007	2	
	A8081005	1058	10581039	ADVANCED/METASTATIC	DOCETAXEL	3/22/2007	9/19/2007	3	
	A8081005	1058	10581039	ADVANCED/METASTATIC	PEMETREXED	1/2/2008	7/21/2010	4	4 v 5
14	A8081005	1162	11621001	ADVANCED/METASTATIC	GEMCITABINE	7/18/2007	1/31/2008	1	8/25/2010
	A8081005	1162	11621001	ADVANCED/METASTATIC	CARBOPLATIN	7/18/2007	1/31/2008	1	
	A8081005	1162	11621001	ADVANCED/METASTATIC	PEMETREXED	1/1/2008	3/31/2008	2	

A8081005	1162	11621001	ADVANCED/METASTATIC	DOCETAXEL	3/27/2008	5/31/2008	3		
A8081005	1162	11621001	ADVANCED/METASTATIC	BEVACIZUMAB	3/27/2008	5/31/2008	3		
A8081005	1162	11621001	ADVANCED/METASTATIC	DOCETAXEL	9/1/2008	5/31/2009	4		
A8081005	1162	11621001	ADVANCED/METASTATIC	BEVACIZUMAB	9/1/2008	5/31/2009	4		
A8081005	1162	11621001	ADVANCED/METASTATIC	FIGITUMUMAB	10/27/2009	12/7/2009	5		
A8081005	1162	11621001	ADVANCED/METASTATIC	PF-00299804	10/27/2009	12/7/2009	5		
A8081005	1162	11621001	ADVANCED/METASTATIC	ERLOTINIB HYDROCHLORIDE	12/17/2009	3/9/2010	6 6 v 5		
15	A8081005	1019	10191007	ADVANCED/METASTATIC	PACLITAXEL	7/7/2008	7/28/2008	1	6/29/2010
	A8081005	1019	10191007	ADVANCED/METASTATIC	CISPLATIN	7/28/2008	10/2/2008	2 .	
	A8081005	1019	10191007	ADVANCED/METASTATIC	ETOPOSIDE	8/18/2008	10/2/2008	2 .	
	A8081005	1019	10191007	ADVANCED/METASTATIC	VINORELBINE	10/23/2008	12/4/2008	3 .	
	A8081005	1019	10191007	ADVANCED/METASTATIC	PEMETREXED	12/23/2008	9/30/2009	4 .	
	A8081005	1019	10191007	ADVANCED/METASTATIC	BEVACIZUMAB	12/23/2008	9/30/2009	4 .	
	A8081005	1019	10191007	ADVANCED/METASTATIC	DOCETAXEL	11/2/2009	4/19/2010	5 .	
	A8081005	1019	10191007	ADVANCED/METASTATIC	GEMCITABINE HYDROCHLORIDE	5/17/2010	6/14/2010	6 6 v 4	
16	A8081005	1021	10211001	ADVANCED/METASTATIC	BEVACIZUMAB	10/1/2008	2/1/2009	1	
	A8081005	1021	10211001	ADVANCED/METASTATIC	CARBOPLATIN	10/1/2008	2/1/2009	1 .	
	A8081005	1021	10211001	ADVANCED/METASTATIC	PEMETREXED	10/1/2008	2/1/2009	1 .	
	A8081005	1021	10211001	ADVANCED/METASTATIC	BEVACIZUMAB	2/6/2009	7/29/2009	2 .	
	A8081005	1021	10211001	ADVANCED/METASTATIC	PEMETREXED	2/6/2009	7/29/2009	2 .	
	A8081005	1021	10211001	ADVANCED/METASTATIC	ERLOTINIB	11/15/2009	11/23/2009	3 3 v 4	
17	A8081005	1042	10421001	ADJUVANT	CISPLATIN	2/18/2004	5/13/2004	0	5/21/2010
	A8081005	1042	10421001	ADJUVANT	DOCETAXEL	2/18/2004	5/13/2004	0 .	
	A8081005	1042	10421001	ADVANCED/METASTATIC	ERLOTINIB HYDROCHLORIDE	3/3/2005	2/1/2007	1 .	
	A8081005	1042	10421001	ADVANCED/METASTATIC	pemetrexed	2/7/2008	7/24/2008	2 .	
	A8081005	1042	10421001	ADVANCED/METASTATIC	GEMCITABINE	4/3/2009	5/21/2009	3 .	
	A8081005	1042	10421001	ADVANCED/METASTATIC	TRIAPIINE	4/3/2009	5/21/2009	3 3 v 4	
18	A8081005	1129	11291015	ADVANCED/METASTATIC	GEMCITABINE	11/1/2008	1/31/2009	1	
	A8081005	1129	11291015	ADVANCED/METASTATIC	CISPLATIN	11/1/2008	1/31/2009	1 .	
	A8081005	1129	11291015	ADVANCED/METASTATIC	BEVACIZUMAB	11/1/2008	1/31/2009	1 .	
	A8081005	1129	11291015	ADVANCED/METASTATIC	DOCETAXEL	1/1/2009	4/30/2009	2 .	
	A8081005	1129	11291015	ADVANCED/METASTATIC	CISPLATIN	1/1/2009	4/30/2009	2 .	
	A8081005	1129	11291015	ADVANCED/METASTATIC	ERLOTINIB HYDROCHLORIDE	1/20/2010	6/24/2010	3 3 v 4	
19	A8081005	1002	10021003	ADVANCED/METASTATIC	CISPLATIN	1/22/2009	1/22/2009	1	
	A8081005	1002	10021003	ADVANCED/METASTATIC	PEMETREXED	1/22/2009	1/22/2009	1 .	
	A8081005	1002	10021003	ADVANCED/METASTATIC	ERLOTINIB HYDROCHLORIDE	3/14/2009	4/30/2009	2 .	
	A8081005	1002	10021003	ADVANCED/METASTATIC	CARBOPLATIN	4/21/2009	5/19/2009	3 .	
	A8081005	1002	10021003	ADVANCED/METASTATIC	PACLITAXEL	4/21/2009	5/19/2009	3 .	
	A8081005	1002	10021003	ADVANCED/METASTATIC	PEMETREXED	6/26/2009	8/7/2009	4 .	
	A8081005	1002	10021003	ADVANCED/METASTATIC	DOCETAXEL	8/29/2009	12/29/2009	5 5 v 3	
20	A8081005	1004	10041005	ADVANCED/METASTATIC	PACLITAXEL	1/1/2009	12/31/2009	1	Could make a reasonable argue
	A8081005	1004	10041005	ADVANCED/METASTATIC	CARBOPLATIN	1/1/2009	12/31/2009	1 .	
	A8081005	1004	10041005	ADVANCED/METASTATIC	BEVACIZUMAB	1/1/2009	12/31/2009	1 .	
	A8081005	1004	10041005	ADVANCED/METASTATIC	BEVACIZUMAB	1/1/2009		1 .	
	A8081005	1004	10041005	ADVANCED/METASTATIC	PACLITAXEL	7/30/2009	10/9/2009	2 .	
	A8081005	1004	10041005	ADVANCED/METASTATIC	BEVACIZUMAB	7/30/2009	10/9/2009	2 .	
	A8081005	1004	10041005	ADVANCED/METASTATIC	CARBOPLATIN	7/30/2009	10/9/2009	2 2 v 3	
21	A8081005	1030	10301003	ADVANCED/METASTATIC	ERLOTINIB	1/4/2007	4/9/2007	1	> 1 yr between pemetrexed
	A8081005	1030	10301003	ADVANCED/METASTATIC	GEMCITABINE	4/19/2007	4/26/2007	2	
	A8081005	1030	10301003	ADVANCED/METASTATIC	CARBOPLATIN	4/19/2007	4/26/2007	2	
	A8081005	1030	10301003	ADVANCED/METASTATIC	PEMETREXED	5/24/2007	3/6/2008	3	
	A8081005	1030	10301003	ADVANCED/METASTATIC	PEMETREXED	4/17/2009	5/7/2010	4 4 v 3	
22	A8081005	1042	10421003	ADVANCED/METASTATIC	PACLITAXEL	6/1/2005	1/31/2006	1	> 1 yr between pemetrexed
	A8081005	1042	10421003	ADVANCED/METASTATIC	CARBOPLATIN	6/1/2005	1/31/2006	1 .	
	A8081005	1042	10421003	ADVANCED/METASTATIC	ERLOTINIB	1/1/2006	8/31/2006	2 .	
	A8081005	1042	10421003	ADVANCED/METASTATIC	PEMETREXED	8/1/2006	6/30/2008	3 .	
	A8081005	1042	10421003	ADVANCED/METASTATIC	PEMETREXED	8/3/2009	5/10/2010	4 4 v 3	
23	A8081005	1141	11411001	ADVANCED/METASTATIC	DOCETAXEL	12/12/2007	1/28/2008	1	
	A8081005	1141	11411001	ADVANCED/METASTATIC	CISPLATIN	12/12/2007	1/29/2008	1	
	A8081005	1141	11411001	ADVANCED/METASTATIC	CISPLATIN	10/27/2008	12/30/2008	2	
	A8081005	1141	11411001	ADVANCED/METASTATIC	PEMETREXED	10/27/2008	12/30/2008	2	

	A8081005 1141 11411001	ADVANCED/METASTATIC BEVACIZUMAB	10/27/2009	12/30/2009	2 2 v 3	
24	A8081005 1002 10021001	ADVANCED/METASTATIC DOCETAXEL	1/8/2008	6/17/2008	1 .	Addition of another drug counted e
	A8081005 1002 10021001	ADVANCED/METASTATIC CARBOPLATIN	1/8/2008	5/13/2008	1 .	
	A8081005 1002 10021001	ADVANCED/METASTATIC BEVACIZUMAB	2/13/2008	6/17/2008	2 .	
	A8081005 1002 10021001	ADVANCED/METASTATIC PEMETREXED	6/3/2008	9/2/2008	3 .	
	A8081005 1002 10021001	ADVANCED/METASTATIC CISPLATIN	8/11/2008	9/2/2008	4 .	
	A8081005 1002 10021001	ADVANCED/METASTATIC CISPLATIN	3/25/2009	5/4/2009	5 .	
	A8081005 1002 10021001	ADVANCED/METASTATIC PEMETREXED	3/25/2009	2/1/2010	5 .	
	A8081005 1002 10021001	ADVANCED/METASTATIC BEVACIZUMAB	4/13/2009	2/1/2010	6 .	
	A8081005 1002 10021001	ADVANCED/METASTATIC GEMCITABINE	5/19/2009	6/15/2009	7 7 v 2	
25	A8081005 1004 10041001	ADVANCED/METASTATIC ERLOTINIB HYDROCHLORIDE	7/1/2009	7/31/2009	1 .	Erlotinib counted twice for 4 regim
	A8081005 1004 10041001	ADVANCED/METASTATIC PACLITAXEL	8/13/2009	9/29/2009	2 .	
	A8081005 1004 10041001	ADVANCED/METASTATIC CARBOPLATIN	8/13/2009	9/29/2009	2 .	
	A8081005 1004 10041001	ADVANCED/METASTATIC ERLOTINIB HYDROCHLORIDE	9/29/2009	2/5/2010	3 .	
	A8081005 1004 10041001	ADVANCED/METASTATIC PEMETREXED	12/23/2009	2/5/2010	4 4 v 2	
26	A8081005 1021 10211018	ADJUVANT CARBOPLATIN	3/1/2006	5/31/2006	1	4/21/2010
	A8081005 1021 10211018	ADJUVANT PACLITAXEL	3/1/2006	5/31/2006	1	
	A8081005 1021 10211018	ADVANCED/METASTATIC ERLOTINIB	9/1/2008	12/31/2008	2	
	A8081005 1021 10211018	ADVANCED/METASTATIC PEMETREXED	1/1/2009	9/30/2009	3 3 v 2	
27	A8081005 1042 10421004	ADVANCED/METASTATIC CISPLATIN	1/1/2005	11/30/2006	1	6/14/2010
	A8081005 1042 10421004	ADVANCED/METASTATIC ETOPOSIDE	1/1/2005	11/30/2006	1	
	A8081005 1042 10421004	ADVANCED/METASTATIC DOCETAXEL	11/1/2006	1/31/2007	2	
	A8081005 1042 10421004	ADVANCED/METASTATIC CARBOPLATIN	1/1/2007	4/30/2007	3	
	A8081005 1042 10421004	ADVANCED/METASTATIC PEMETREXED	1/1/2007	4/30/2007	3 3 v 2	
28	A8081005 1105 11051040	ADVANCED/METASTATIC CARBOPLATIN	5/12/2009	9/3/2009	1	Addition of cetuximab counted as :
	A8081005 1105 11051040	ADVANCED/METASTATIC PACLITAXEL	5/12/2009	9/3/2009	1	
	A8081005 1105 11051040	ADVANCED/METASTATIC CETUXIMAB	6/30/2009	9/17/2009	2	
	A8081005 1105 11051040	ADVANCED/METASTATIC BEVACIZUMAB	9/25/2009	12/23/2009	3	
	A8081005 1105 11051040	ADVANCED/METASTATIC PEMETREXED	1/14/2010	7/1/2010	4 4 v 2	
29	A8081005 1106 11061001	ADVANCED/METASTATIC PEMETREXED	10/20/2008	1/31/2010	1	Pemetrexed/Carbo and pemetrexe
	A8081005 1106 11061001	ADVANCED/METASTATIC CARBOPLATIN	10/20/2008	12/31/2008	1	
	A8081005 1106 11061001	ADVANCED/METASTATIC ERLOTINIB HYDROCHLORIDE	2/23/2009	1/31/2010	2	
	A8081005 1106 11061001	ADVANCED/METASTATIC DOCETAXEL	1/1/2010	3/26/2010	3	
	A8081005 1106 11061001	ADVANCED/METASTATIC GEMCITABINE	3/26/2010	4/2/2010	4	
30	A8081005 1039 10391008	ADVANCED/METASTATIC ERLOTINIB	5/29/2009	8/16/2009	1	
	A8081005 1039 10391008	ADVANCED/METASTATIC PEMETREXED	9/1/2009	11/24/2009	2 .	
	A8081005 1039 10391008	ADVANCED/METASTATIC BEVACIZUMAB	9/1/2009	11/24/2009	2 .	
	A8081005 1039 10391008	ADVANCED/METASTATIC CARBOPLATIN	9/1/2009	11/24/2009	2 .	
	A8081005 1039 10391008	ADVANCED/METASTATIC DOCETAXEL	1/12/2010	5/15/2010	3 .	

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/s/  
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DIANE C HANNER  
06/02/2011

**Hanner, Diane**

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**From:** Hanner, Diane  
**Sent:** Wednesday, June 01, 2011 3:34 PM  
**To:** 'Domingo, Ron'  
**Subject:** NDA 202570 (Crizotinib) IR-Questions

Hi,  
Please address the following information request regarding NDA 202570 (Crizotinib):

**Study 1007**

Please submit narratives for the following patients from study 1007

11021019, 11841043, and 11921004

**Study 1005**

Patient 11151001 received radiation therapy during treatment with crizotinib. Please state the areas that received irradiation and the indication for radiation therapy. We note that patient 11151001 had a new lesion with an increase in 2 of 4 target lesions, yet had radiation therapy on crizotinib. Please explain.

For the 136 pts treated on Study 1005

In dataset SURGER, there are 80 rows in which Surgery Study Period (SGSTUPER) is blank, but in which there is a surgery date (CTRSTSDT). In 79/80 instances, CTTERM is blank. All surgery dates (CTRSTSDT) are after the initiation of crizotinib. Did surgery occur and, if so, did it occur during treatment with crizotinib? If these surgeries did occur during treatment with crizotinib, please provide an updated dataset containing this information.

Please submit narratives for the following patients from study 1005

10021002  
10041001  
10181012  
10391011  
10391012  
10551010  
10771032  
10771056  
12051019  
12151001

**Study 1001**

Please see the attached FDA review of prior therapies .We have separated the patients who had received prior Adjuvant and or neoadjuvant only. As noted some of them have had a long duration from the prior therapy. We have noted a number of entries twice for the same agent within 6 months (e.g. subject A8081001 1003 10031014 Carboplatin/Paclitaxel was added for 7/25/2000 and 11/1/2000 within 4 months twice). In addition

there were a number of entries for non-chemotherapeutic agent Zoledronic Acid e.g. subject A8081001 1007 10071035.

No chemo	Adjuv/Noead only	one	Two	Three	Four	Five	Six	Seven
8	7	32	16	23	14	12	5	2

Duration from Adjuvant therapy

Sub ID	Adjuvant/neo therapy	Treatment	Duration from adjuvant
1002 10021039	05/11/2007	10/02/2008	17m
1002 10021057	01/01/2004	03/31/2009	>5yrs
1002 10021072	10/24/2004	08/12/2009	App. 5 yrs
1002 10021088	01/01/2008	03/03/2010	>2yrs
1003 10031019	05/13/2008	08/11/2009	15 months
1006 10061084	05/15/2006	03/11/2010	App 4yrs
1007 10071038	10/07/2008	09/30/2009	App 1yr

Thank you.

Regards,

Diane

CDR Diane Hanner  
 Senior Program Management Officer  
 FDA/CDER/OODP/DDOP  
 10903 New Hampshire Avenue  
 Bldg. 22/Room 2119  
 Silver Spring, Maryland 20993  
 (301) 796-2330  
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 E-mail: [diane.hanner@fda.hhs.gov](mailto:diane.hanner@fda.hhs.gov)

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/s/  
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DIANE C HANNER  
06/01/2011

## Hanner, Diane

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**From:** Hanner, Diane  
**Sent:** Wednesday, June 01, 2011 11:49 AM  
**To:** 'Domingo, Ron'  
**Subject:** FW: IR for updated PK dataset of NDA 202570 (Crizotinib)  
**Importance:** High

Hi Ron,

I have been instructed to request the following regarding NDA 202570:

Please submit the updated PK dataset of Study A8081005 containing concentrations of crizotinib and active metabolite PF-06260182 in "\*.xpt" files by **June 2, 2011**. The dataset should also include demographic factors and all the relevant covariates for each individual patient. A description of each data item should be provided in a Define.pdf file.

Thank you.

Regards,  
Diane

CDR Diane Hanner  
Senior Program Management Officer  
FDA/CDER/OODP/DDOP  
10903 New Hampshire Avenue  
Bldg. 22/Room 2119  
Silver Spring, Maryland 20993  
(301) 796-2330  
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/s/  
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DIANE C HANNER  
06/01/2011



**FOOD AND DRUG ADMINISTRATION**

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**Meeting Date and Time:** May 24, 2010 2:00 p.m.  
**Meeting Type:** Teleconference  
**Meeting Category:** Guidance – Regarding the Concordance study IUO/LDT  
**Meeting Location:** Bldg. 62, Room 3100  
**Application Number:** NDA 202570 & P110012  
**Product Name:** Crizotinib/ PF-02341066 and Vysis ALK Break Apart FISH Probe Kit  
**Received Briefing Package** N/A  
**Sponsor Name:** Abbott and Pfizer  
**Meeting Requestor:** Pamela Swatkowski and Karen S. Long, Abbott Molecular  
**Meeting Chair:** Virginia Ellen Maher, M.D., Medical Team Leader, DDOP  
Karen E. Bijwaard, MS., OIVD/DIHD  
**Meeting Recorder:** Karen E. Bijwaard, MS., OIVD/DIHD  
**Meeting Attendees:**

Attendees from Abbott and Pfizer	
Dr. Erling Donnelly	Associate Director, Global Regulatory Lead, Pfizer
Ms. Paulina (Nina) Selaru	Director, Statistics Lead, Pfizer
Victoria Cohan	Pfizer
Dr. Keith Wilner	Senior Director, Lead Clinician for A8081001 and A8081005, Pfizer
Mr. Ron Domingo	Manager, US Regulatory Lead, Pfizer
Karen S. Long	DVP, Medical, Regulatory and Clinical Affairs, Abbott Molecular
Karen Sachs, PhD	Director, Biostatistics and Data Management, Abbott Molecular
Steve Dailey	Project Manager, Abbott Molecular
Fred Siebert, BS	Clinical Affairs Project Manager, Abbott Molecular
Pamela Swatkowski	Director, Regulatory Affairs, Abbott Molecular

FDA Attendees	
Virginia Ellen Maher, M.D.,	Medical Team Leader, DDOP
Shakun Malik, M.D.,	Medical Officer, DDOP
Reena, Philip, Ph.D.	Deputy Div. Director, DIHD, OIVD

<b>FDA Attendees</b>	
Abraham Tzou, M.D.	Medical Officer, OIVD/DIHD
Maria M. Chan, Ph.D.	Division Director for DIHD
Karen E. Bijwaard, MS.	Scientific Reviewer, OIVD
Arkendra De, Ph.D.	Mathematical Statistician, DRH/OSB/DBS/DDB

## **BACKGROUND**

Abbott Molecular requested a meeting regarding the repeat concordance study between the assay used in study 1001 and the to-be-marketed assay. In light of the NDA 202570 (Crizotinib) 60 day update scheduled for receipt on May 31st which pertains to the 1005 study, Abbott deemed it necessary to request a teleconference with Pfizer and FDA. This meeting was held on Tuesday, May 24, 2011, and the meeting objective was to ensure that all entities involved have a complete understanding regarding the data that Pfizer plans on submitting.

## **DISCUSSION**

Pfizer noted that the RR in study 1001 was 61% and the RR in study 1005 was 51% and that study 1005 was conducted with the to-be-marketed assay. Pfizer and Abbott questioned the need for a repeat concordance study and will send additional information on 10 patients who were re-examined by MGH.

Pfizer stated that the 1001 and 1005 studies formed the basis for the NDA Accelerated Approval submission.

### **1001 study –**

Patients were selected by the various LDTs. 81% of the 119 patients (116 evaluable) were retested by MGH. The ORR was 61%.

### **1005 study –**

At the time of the NDA submission 76 subjects were evaluable and the ORR was 30%. The update will be sent in to FDA on Thurs (5/26/11). At the time of the update, 133 subjects were response evaluable with an ORR 51%.

The mean duration of treatment for 1005 is 22 wks compared to 32 for 1001. Since submission the follow-up with treatment had increased 21%.

68% are still ongoing in 1005. Only a few of the subjects have progressed so far so the 51% is likely an underestimation.

### **Concordance study – Abbott Molecular**

The concordance study used patient specimens from 1005 and tested at them MGH using the MGH LDT protocol. They stated that FDA expressed concern about MGH following their protocol. Abbott stated that MGH did follow their protocol and that questions about the pathologist's assessment are outside the scope of the assay. They requested that MGH reassess

the 30 discordant specimens plus 10 others which were concordant. MGH changed their assessment on nine (9) of the 30 discordants. On further investigation, eight (8) of the nine (9) had response data. The reassessment changed the positive percent agreement to 95% which was consistent with the acceptance criteria agreed upon with OIVD.

FDA (OIVD) stated that their concern regarding MGH following the protocol was the result of being told by Abbot that MGH didn't follow their protocol.

Abbott stated that MGH may not have done the pathological assessment in the same way but that is outside the performance of the assay.

OIVD disagreed and stated that the pathological assessment is a component of the assay and FDA is interested in the whole process, including the interpretation of the results. OIVD also stated that it hasn't accepted the re-evaluation of the discrepant samples as being appropriate and that the 86.4% agreement was the result of the concordance study.

Abbott stated that when designing a concordance study it is necessary to have truth. Truth is the outcome of those patients.

OIVD stated that concordance is the agreed upon outcome. OIVD stated that the purpose for the concordance study was to tie the IUO results to 1001, if 1001 was used to support the NDA. OIVD repeated that it was worried about the results from the concordance study since the discrepancies were also very different (i.e., very negative vs. very positive and vice versa).

Pfizer agreed to provide a comparison for the data of the two studies.

OIVD asked Pfizer for more information surrounding the monitoring visit that was conducted at MGH where deviations and corrections were mentioned in the NDA. Pfizer asked OIVD to clarify more on this and they would get back to FDA.

It was noted that time was running short, and OIVD asked about whether information on the ALK negatives would be included in the update. Pfizer indicated that this would be the case and these were tested using the IUO test. A clarification was requested if the 25 ALK neg. were in addition to the five already included or a total of 25 in all. Pfizer stated the number was 25 total. They clarified further that the ALK negative were included for safety and not efficacy, but that would follow later in June.

Abbott indicated they would send minutes of the meeting to FDA and thanked FDA for listening.

The FDA stated that they would discuss the need for a repeat concordance study internally and get back to Abbott, but warned Abbott that the timeline was short and that a repeat concordance study would take considerable time.

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/s/  
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DIANE C HANNER  
06/02/2011

VIRGINIA E MAHER  
06/02/2011



**FOOD AND DRUG ADMINISTRATION**

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**Meeting Date and Time:** May 19, 2011 10:30 a.m.  
**Meeting Type:** Teleconference  
**Meeting Category:** Guidance  
**Meeting Location:** Bldg. 22, Room 4201  
**Application Number:** NDA 202570  
**Product Name:** Crizotinib/ PF-02341066  
**Received Briefing Package** N/A  
**Sponsor Name:** Pfizer  
**Meeting Requestor:** Ron Domingo, MS., RAC  
**Meeting Chair:** Virginia Ellen Maher, M.D., Medical Team Leader, DDOP  
**Meeting Recorder:** Diane Hanner, Senior Program Management Officer, DDOP  
**Meeting Attendees:**

<b>Attendees from Pfizer</b>	
Akintunde Bello, Ph.D.	Senior Director, Clinical Pharmacology
Darrel Cohen, M.D., Ph.D.	Senior Director, Global Clinical Lead
Ron Domingo, M.S.	Manager, US Regulatory Lead
Erling Donnelly, Ph.D.	Associate Director, Global Regulatory Lead
Jonathan French, Sc.D.	Director, Pharmacometrics
Dongwoo Kang, Ph.D.	Associate Director, Pharmacometrics
Paulina (Nina) Selaru, M.S., M.S.P.H.	Director, Statistics Lead
WeiWei Tan, Ph.D.	Associate Director, Clinical Pharmacology Lead
Yiyun Tang, Ph.D.	Manager, Statistics
Keith Wilner, Ph.D.	Senior Director, Lead Clinician for Studies A8081001 and A8081005

<b>FDA Attendees</b>	
Virginia Ellen Maher, M.D.,	Medical Team Leader, DDOP
Shakun Malik, M.D.,	Medical Officer (by phone)
Pengfei Song, Ph.D.,	Clinical Pharmacology Reviewer, DCP5
Qi Liu, Ph.D.,	Clinical Pharmacology Team Leader, DCP5
Anshu Marathe, Ph.D.,	Pharmacometrics Reviewer, OCP

<b>FDA Attendees</b>	
Christine Garnett, Pharm.D.,	Team Leader Pharmacometrics, OCP
Reena, Phillip, Ph.D.,	Deputy Div. Director, DIHD, OIVD
Elizabeth Mansfield, Ph.D.,	Director Personalized Medicine, OIVD
Maria M. Chan, Ph.D.,	Division Director for DIHD, OIVD
Karen E. Bijwaard, M.S.,	Scientific Reviewer, OIVD
Arkendra De, Ph.D.	Mathematical Statistician, DRH/OSB/DBS/DDB (by phone)
Diane Hanner, M.P.H., M.S.W.,	Senior Program Management Officer, DDOP

## **BACKGROUND**

Pfizer requested this meeting on Tuesday, May 17, 2011, in order to gain FDA concurrence regarding their high-level analysis plan for Crizotinib (PF-02341066). This study (NDA 202570) is being conducted in patients with advanced NSCLC patients who have had no previous therapy in the metastatic setting and who have tumors positive for an ALK fusion.

## **DISCUSSION**

FDA conveyed these key points to the sponsor.

1. Apart from the covariates that were mentioned in the analysis plan, the sponsor should also test for prior treatment regimens as a covariate.
2. Besides ECOG, the sponsor should test other measures of tumor burden/disease severity as a covariate.
3. FDA agreed that sponsor's proposed PK measure (i.e., individual steady state  $C_{avg}$ ) would account for dose reductions, dose interruptions, discontinuations as stated by the sponsor. However, FDA expressed concerns about the POP PK model that would be used for determining individual clearance for  $C_{avg}$  calculation. Sponsor's final POP PK model has parameters that were estimated with low precision. Thus, the secondary measure of exposure (i.e., geometric mean of the observed trough values) would be preferred.
4. Overall, the sponsor's analysis plan seems reasonable.

Pfizer discussed the following proposal:

### **1 Exposure-Response Analysis Plan for Efficacy and Safety Endpoints from Crizotinib Studies A8081001 and A8081005**

#### **1.1 Objectives**

- Exposure-response (ER) analysis of objective response (OR) and progression-free survival (PFS)
- ER analysis of key safety endpoints

The ER analyses of efficacy and safety endpoints will be used to evaluate the proposal for dosing strategy to maximize benefit-risk relationship.

## ***1.2 Analysis Populations***

Separate analysis will be conducted for studies A8081001 and A8081005.

For A8081001 (exclusively including ALK-positive NSCLC subjects from Recommended Phase 2 Dose Cohorts): Safety analysis set and response-evaluable population (as defined in the Statistical Analysis Plan (SAP)) will include the data as of cut-off date November 1<sup>st</sup> 2010. PK analysis set (as defined in the SAP) will include the data as of cut-off date September 13, 2010. These are the same datasets as in the original submission package.

For A8081005: Safety analysis set and response-evaluable population (as defined in the Statistical Analysis Plan (SAP)) will include the data as of cut-off date February 1<sup>st</sup> 2011. These are the updated datasets as for the 60-day update. PK analysis set (as defined in the SAP) will include the updated data as of cut-off date May 04, 2011.

For each study, two analysis sets will be used for the efficacy and two analysis sets will be used for the safety analyses. For both safety and efficacy analyses, the primary analysis set will be the Population-PK Analysis Set. Secondary analyses will be conducted using an Observed Subjects Analysis Set. The four analysis sets are defined below.

*Population-PK analysis population (Efficacy):* Patients in both the Response-evaluable population and the PK analysis set. These patients will have efficacy data and sufficient dosing information and concentration data to derive Population PK-based estimates of CL/F..

*Population-PK analysis population (Safety):* Patients in both the Safety Population and the PK analysis set. These patients will have safety data and sufficient dosing information and concentration data to derive Population PK-based estimates of CL/F.

*Observed-subjects analysis population (efficacy):* Response-evaluable population with at least one observed trough concentrations on or after Cycle 1, Day 15 who are also in the PK Analysis Population (as defined in the SAPs).

*Observed-subjects analysis population (safety)*: Safety Population with at least one observed trough concentrations on or after Cycle 1, Day 15 who are also in the PK Analysis Population (as defined in the SAPs).

### **1.3 Endpoints for Analysis**

#### **1.3.1 Efficacy Analyses**

Efficacy analyses will focus on two endpoints:

- Objective response (OR) and
- Progression-free survival (PFS).

Definitions of these endpoints can be found in the SAPs for the two studies.

#### **1.3.2 Safety Analyses**

Safety analyses will focus on the incidence of the following five adverse events:

- Pneumonitis
- Hepatic ALT elevation (Grades derived from the lab value)
- Neutropenia (Grades derived directly from the lab value)
- Fatigue

Specific definitions of these endpoints were included in the Summary of Clinical Safety.

#### **1.3.3 Measures of Exposure**

Two measures of exposure will be explored in this analysis. The primary measure of exposure will be the average steady-state concentration ( $C_{avg_{SS}}$ ) over the time on study. Specifically,

$$C_{avg_{SS,i}} = \frac{\text{Average Daily Dose}_i}{12 \times CL_{SS,i}},$$

where the Average Daily Dose is the average daily dose over the time on study (or until data cut-off for subjects who were on-study at the time of data cut-off) and  $CL_{SS,i}$  is the model-predicted steady-state CL/F for each subject from the previously submitted population pharmacokinetic (Pop PK) model (PMAR-00192). We note that this measure of exposure will directly account for dose-reductions, dose interruptions, dose discontinuations and, to the extent that it can be captured, non-compliance.

As a secondary measure of exposure, we will also explore the ER relationships using the geometric mean of the observed trough values for each patient.

## 1.4 Statistical Analysis Methods

### 1.4.1 Statistical Models

Logistic regression models will be used for OR and each of the safety endpoints. Since exposure is not randomized, we will use a modeling approach to balance to control for potential confounders and we will also explore potential effect modifiers (i.e., interactions between covariates and exposure).

Cox regression models will be used for PFS. Potential confounders of the ER relationship will be included in the Cox model as main effects. We will also explore potential effect modifiers (i.e., interactions between covariates and exposure) where possible.

Potential confounders to be included in each of the ER models are

- Asian vs. non-Asian
- Baseline ECOG status (coded as three categories: 0, 1, 2 and above; C1D1 as baseline; if not available, screening ECOG)
- Baseline body weight (C1D1 as baseline, if not available, screening WT)
- Gender
- Age
- Baseline ALT normality (yes /no)
- Concomitant use of a CYP3A inhibitor/Inducer (yes/no)
- Concomitant use of a proton pump inhibitor and/or a H2-receptor antagonist (yes/no)

Potential effect modifiers to be explored in the ER models include:

- Baseline ECOG status (coded as three categories: 0, 1, and 2 and above, same as above)
- Asian vs. non-Asian
- Concomitant use of a CYP3A inhibitor/Inducer (yes/no)
- Concomitant use of a proton pump inhibitor and/or a H2-receptor antagonist (yes/no)

To adjust for any potential imbalance of prognostic factors, all potential confounders will be included in each of the logistic regression and Cox regression models. Specifically, logistic regression models will add potential confounders in the following manner:

$$\begin{aligned} \text{logit}(p_i) = & \theta_1 + \theta_2 \times \text{Asian}_i + \theta_3 \times I[\text{ECOG}_i = 1] + \theta_4 \times I[\text{ECOG}_i \geq 2] + \\ & \theta_5 \times \text{Female}_i + \theta_6 \times (\text{BWT}_i - 70) + \theta_7 \times (\text{Age}_i - 55) + \theta_8 \times I[\text{bsl ALT}_i \text{ not normal}] + \\ & \theta_9 \times \text{CYP3A4}_i + \theta_{10} \times \text{PPI}_i \end{aligned}$$

where  $p_i$  is the probability of having an event (e.g., an objective response) for the  $i^{\text{th}}$  subject,  $I[X]$  is an indicator function taking the value of 1 if X is true and 0 otherwise.

Cox regression models will incorporate effects on the baseline hazard in the following manner

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

Where  $h_0(t)$  is the hazard for the reference group (female, non-Asian patients with baseline ECOG=0, baseline weight of 70 kg, baseline age of 55 years, normal baseline ALT and no concomitant CYP3A4 or proton pump inhibitors/H2-receptor antagonists).

The functional form for the exposure-response relationship will be determined by the data. Specifically, exposure (e.g., Cav<sub>gss</sub>) will be entered into the model linearly as either untransformed or log-transformed. For example, a logistic regression model with log-transformed Cav<sub>gss</sub> will have the form

$$\text{logit}(p_i) = \theta_1 + \theta_2 \times Asian_i + \theta_3 \times I[ECOG_i = 1] + \theta_4 \times I[ECOG_i \geq 2] + \theta_5 \times Female_i + \theta_6 \times (BWT_i - 70) + \theta_7 \times (Age_i - 55) + \theta_8 \times I[bslALT_i \text{ not normal}] + \theta_9 \times CYP3A4_i + \theta_{10} \times PPI_i + \theta_{11} \times \ln(\text{exposure}_i)$$

The exposure metric that yields a better fitting model (e.g., based on the lower deviance, also known as the objective function value or  $-2 \times \log$  likelihood) will be selected as the final model. If neither exposure metric is clearly preferred, then the log-transformed exposure will be selected.

Effect modifiers will be explored by including interactions between the potential effect modifiers and the final exposure metric. For example, in the logistic regression model potential effect modification by race will be coded as

$$\text{logit}(p_i) = \theta_1 + \theta_2 \times Asian_i + \theta_3 \times I[ECOG_i = 1] + \theta_4 \times I[ECOG_i \geq 2] + \theta_5 \times Female_i + \theta_6 \times (BWT_i - 70) + \theta_7 \times (Age_i - 55) + \theta_8 \times I[bslALT_i \text{ not normal}] + \theta_9 \times CYP3A4_i + \theta_{10} \times PPI_i + \theta_{11} \times \ln(\text{exposure}_i) + \theta_{12} \times Asian_i \times \ln(\text{exposure}_i)$$

The four potential effect modifiers will be evaluated individually. No detailed model building for interactions will be pursued.

Pfizer plans on updating the analysis plan based upon the teleconference discussion.

Pfizer will create a stand-alone document flagging the new or updated SAEs reported since the original regulatory submission.

Pfizer also stated that they will provide FDA with the Study A8081001 data analyses by June 7 followed by Study A8081005 data analyses by June 15.

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/s/  
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DIANE C HANNER  
05/26/2011

VIRGINIA E MAHER  
05/27/2011

**Hanner, Diane**

**From:** Hanner, Diane  
**Sent:** Monday, May 16, 2011 12:47 PM  
**To:** 'Domingo, Ron'  
**Subject:** RE: NDA 202570 (Crizotinib) Information Request  
**Importance:** High

Hi Ron,

I have been instructed send you the following information request regarding NDA 202570 (Crizotinib):

1. Please state the response rates in both arms of study “A8081007: Phase 3, Randomized, Open-Label Study of the Efficacy and Safety of Crizotinib Versus 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.” Please state when you expect to reach the pre-specified number of PFS events for Study 1007. Please reply to both requests by July 11.

Please reply to the remainder of these questions by May 23.

2. The payment for patient participation expenses are usually paid to the participating institution. Please explain the reason for the personal payments to the following PI’s and sub-PI’s.

	(b) (6)	\$155,200.00
		\$56,913.00
		\$52,000.00
		\$57,500.00
		\$42,750.00

3. Please provide a breakdown of the number of patients entered prior to each protocol amendment in Studies 1001 and 1005. Please also identify these patients by patient number or by a flag in your dataset.
4. Please provide pill counts, by patient and visit as well as summary information, for studies 1001 and 1005.
5. In the RP2D “Other cohort” 14 patients had non-small cell lung cancer. Please state whether the patients who do not have a result in dataset MRKTST were tested for the presence of the ALK mutation and their results, if any.

6. Protocol: A8081001 Subject ID: 10021061. A 41 yrs old male started study drug on May 17<sup>th</sup> 2009 with a PS 1. On 29 May2009 at a clinic visit was found to be hypoxic and a CT chest was performed. Patient died on (b) (6) IRC did not have any scans at the time of event May 29<sup>th</sup> scan for review and stated that the final assessment as pending. Please provide with the hospital records and CT scan reports for the time of event. The patient's death is reported to be PD. Please provide the rationale.
7. Protocol: A8081001: Subject ID: 10021080. 29 yr female started study drug 19Nov2009. On (b) (6) pt developed seizures and fever. MRI brain reveled no edema, bleed or increase in brain mets, The CT chest performed is narrated to suggest pneumonia. Patient died on (b) (6). CT chest (22Feb2010) and (26Apr2010) showed significant improvement. IRC noticed that the evaluation was inconclusive and suggested that CT chest from 18Jun2010 was to be provided before a definitive evaluation can be made. Please provide with the CT chest report of June 18<sup>th</sup> 2010 for the patient.
8. Protocol: A8081001Subject ID: 10051015. 71 yr male started study drug on 24Feb2010. On (b) (6) was hospitalization for Grade 3 dyspnea and died on (b) (6). IRC stated that the Assessment remains pending due to the unavailability of baseline scans. Please provide with the all CT chest report including one prior to the time of study enrollment of the patient.
9. Protocol: A8081001 Subject ID: 10061082. Patient started study drug on 18Mar2010, on (b) (6) was hospitalization and intubation with diagnosis of septic shock and ARDS and the patient died on (b) (6). IRC concluded that cause of death is probably pneumonia but bronchoscope and culture results would be helpful. Please provide a copy of bronchoscope report and cultures.
10. Protocol: A8081001Subject ID: 10061107. Patient started study drug 20May2010. On 27Jun2010 patient developed dyspnea and hypoxia and was diagnosed with Pneumonia, pneumothorax and ARDS. On (b) (6) Patient died. Autopsy was performed CT Chest Image Review by IRC (b) (6) was not consistent with tumor progression. Cultures were -ive. Please provide with a full autopsy report of the patient
11. Please confirm that you plan to submit data on additional ALK -ive patients as was indicated at the orientation meeting.

Regards,

Diane

CDR Diane Hanner  
Senior Program Management Officer  
FDA/CDER/OODP/DDOP  
10903 New Hampshire Avenue

Bldg. 22/Room 2119  
Silver Spring, Maryland 20993  
(301) 796-2330  
FAX (301) 796-9845  
E-mail: [diane.hanner@fda.hhs.gov](mailto:diane.hanner@fda.hhs.gov)

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/s/  
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DIANE C HANNER  
05/16/2011



NDA 202570

**FILING COMMUNICATION**

Pfizer Inc.  
Attention: Ron C. Domingo, M.S., RAC  
Manager  
Worldwide Regulatory Strategy  
10646 Science Center Drive  
San Diego, CA 92121

Dear Mr. Domingo:

Please refer to your New Drug Application (NDA) dated March 30, 2011, received March 30, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for crizotinib, 200 mg and 250 mg Capsules.

We also refer to your submissions dated January 4, 2011; February 22, 2011; February 24, 2011; March 31, 2011; April 13, 2011; April 15, 2011; April 26, 2011; and May 3, 2011.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is September 30, 2011.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by September 9, 2011.

We will review this application under the provisions of 21 CFR 314 Subpart H – *Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses*. Unless we otherwise inform you, as required by 21 CFR 314.550, you must submit during the preapproval review period copies of all promotional materials, including promotional labeling and advertisements, intended for dissemination or publication within 120 days following marketing approval (i.e., your launch

campaign). We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and proposed package insert (PI)/Medication Guide/patient PI (as applicable). Send each submission directly to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications (DDMAC)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

If you have any questions, call DDMAC at 301-796-1200.

**REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because the drug for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, call Diane Hanner, Regulatory Project Manager, at (301) 796-4058.

Sincerely,

*{See appended electronic signature page}*

Robert L. Justice, M.D., M.S.  
Director  
Division of Drug Oncology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research

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/s/  
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ANTHONY J MURGO

05/16/2011

Anthony J. Murgo, M.D., M.S. signing for:  
Robert L. Justice, M.D., M.S.

**Hanner, Diane**

---

**From:** Hanner, Diane  
**Sent:** Thursday, May 12, 2011 1:33 PM  
**To:** 'Domingo, Ron'  
**Subject:** Crizotinib ~ NDA 202570 Clin Pharm comments & Analysis

Hi Ron,

Please confirm that you received this e-mail. Thanks!

Please address the following Clinical Pharmacology comments regarding NDA 202570 (Crizotinib):

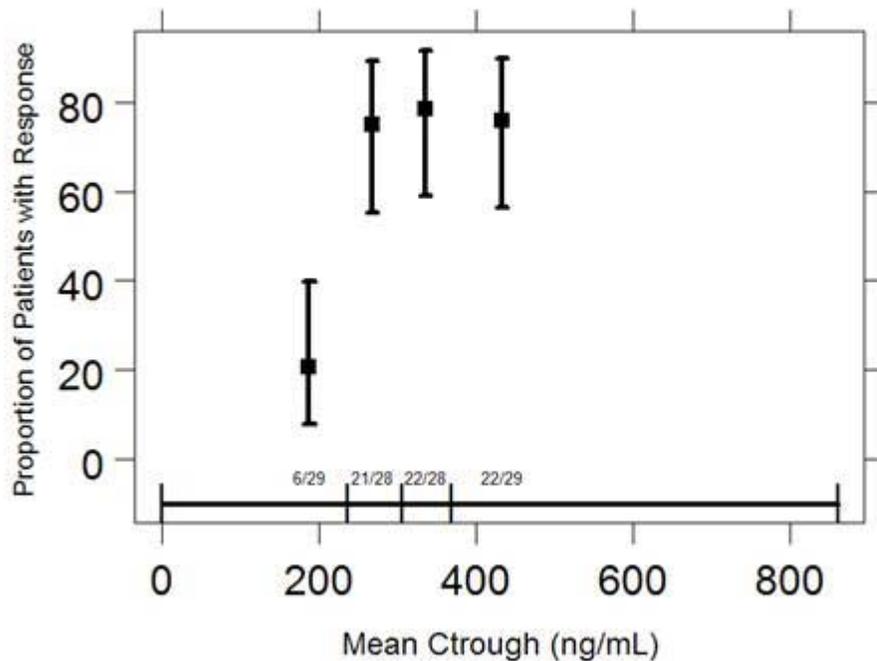
**1. Comments**

1. You should conduct exposure-response relationship analyses for ORR and PFS endpoints in Trial A8081001, as well as Trial A8081005. The analysis should include all possible covariates that are likely to influence response. Since pharmacokinetic samples were collected in these trials, we would prefer you to use observed crizotinib concentrations. Apply a case-control method to balance all possible risk factors to determine the difference in response rate and median PFS between patients with low exposures (<220 ng/mg) versus high exposures ( $\geq 220$  ng/ml).
2. Your analysis should identify factors that are responsible for low drug concentrations (< 220 ng/ml as shown in Figure 1 in Reviewer's Analysis). This should not only focus on patient demographics but also on dose interruptions, dose reductions, discontinuations, patient's non-compliance, co-medications (eg. CYP3A inducers, proton pump inhibitors) or any other factor that is likely to reduce crizotinib concentrations.
3. You should also conduct an exposure-response analysis for safety endpoints such as pneumonitis and liver-related toxicities.
4. Based on your findings, please provide a proposal for dosing strategies that would maximize the efficacy in all patients.
5. We request that you submit the results of these analyses by May 31, 2011. If needed, you can request a teleconference with the Agency to discuss our results or your analysis plan.

**2. Analysis**

An exposure-response analysis was conducted for objective response rate in study A8081001. Patients with pharmacokinetic samples (N=114) were divided into quartiles based on their steady state trough concentrations of the drug and the proportion of patients with response were determined for each quartile (Figure 1). Significantly lower response was observed in patients with lowest average steady-state trough concentrations. The response rate was 21% in the lowest quartile, while the response rate was 75% or greater in the upper three quartiles. However, the difference in response rate is not only due to concentrations but is also likely due

to other confounding factors that are not balanced between the lower and upper quartiles. The distribution of certain covariates in the lowest quartile versus higher quartiles is shown in Table 1. A stepwise logistic regression model also identified  $C_{\text{trough}}$  (log-transformed) as a significant predictor of response. The parameters of the model are shown in Table 2. The model tested for exposure, race, interaction between exposure and race, weight, age, ecog status, gender and prior treatment regimens as covariates. A preliminary analysis utilizing the case-control analysis to match the risk factors (ethnicity, ECOG status) in a subgroup of patients in the upper three quartiles also showed a significantly higher response of 71% compared to 21% in the lowest quartile.



**Figure 1: The proportion of patients with response (CR+PR) versus mean steady state trough concentrations of Crizotinib in study A8081001. Solid black symbols represent the observed percentage of patients responding to treatment in each  $C_{\text{trough}}$  quartile. The vertical black bars represent the 95% binomial confidence interval. The exposure range in each  $C_{\text{trough}}$  quartile is denoted by the horizontal black line. Mean  $C_{\text{trough}}$  represents the average of the observed  $C_{\text{trough}}$  in various cycles after steady state was reached.**

**Table 1: Summary of Covariates in Low Exposure Patients vs. High Exposure Patients**

Covariate	1 <sup>st</sup> Quartile	Combined 2 <sup>nd</sup> -4 <sup>th</sup> Quartile

	(N=29)	(N=85)
ECOG	0: 48.3 % 1: 44.8 % 2: 3.4 % 3: 3.4 %	0: 29.4 % 1: 55.3 % 2: 15.3 % 3: 0 %
Race	Asian: 10.3 % Non-Asian: 89.7%	Asian: 36.5% Non-Asian: 63.5%
Median body weight (Kg)	81.4	67.6

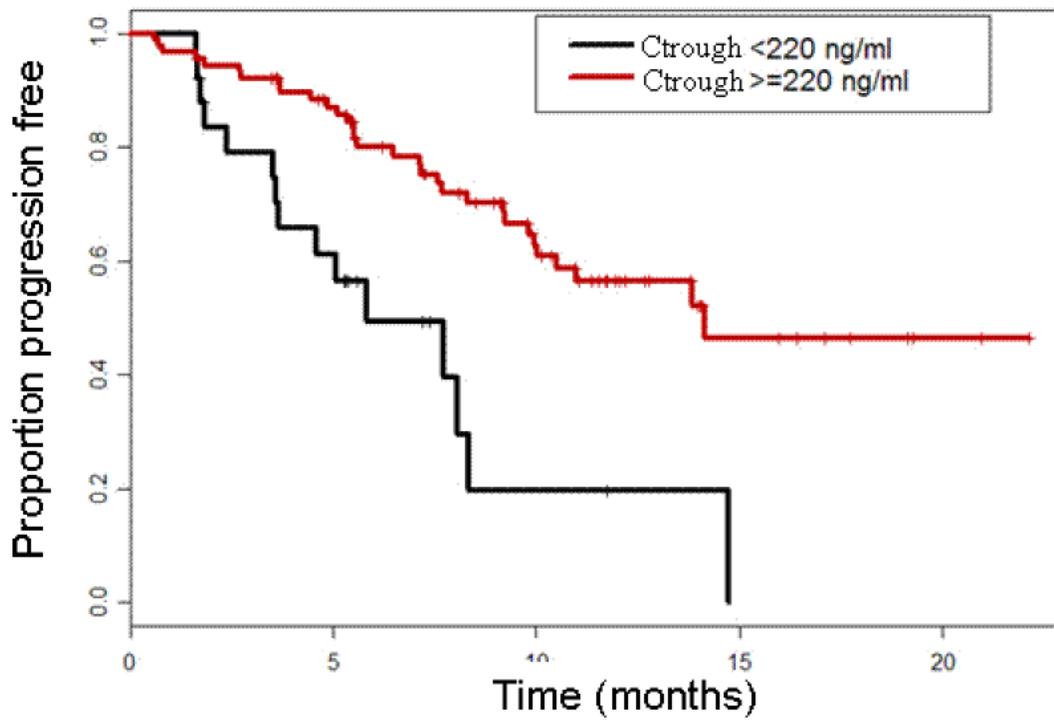
**Table 2: Logistic Regression Analysis Parameters**

Parameter	Estimate	Standard Error	Pr > ChiSq
Intercept	-11.7	3.53	0.001
Log(C <sub>trough</sub> )	2.16	0.63	0.0006

Additionally a classification and regression tree (CART) analysis showed that the steady state trough concentration of 220 ng/ml resulted in maximum separation of response. Patients with drug concentration < 220 ng/ml had lower response rate of 16% compared to 75% observed in patients with drug concentrations ≥ 220 ng/ml (Table 1). Furthermore, a clear separation in progression free survival (PFS) was observed in the Kaplan-Meier plots between these groups (Figure 2). The median PFS was 5.8 months in patients with drug concentration < 220 ng/ml and 14.2 months in patients with drug concentrations ≥ 220 ng/ml. The difference in PFS is not only due to concentration, but also likely due to other confounding factors. This analysis included 15 events in <220 ng/ml group and 31 in ≥ 220 ng/ml group.

**Table 3: Response Rate of Patients with Steady State Trough Concentration <220 and ≥ 220 ng/ml**

Concentration cut-off (ng/ml)	Number of subjects	Response rate (95% CI)
< 220	25	16 (4.5-36)
≥ 220	89	75 (65-83.8)



**Figure 2: Kaplan-Meier plots for progression free survival for patients with mean steady state trough concentrations <220 (black) and ≥220 ng/ml (red).**

Thank you.

Regards

Diane

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/s/  
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DIANE C HANNER  
05/12/2011

# REQUEST FOR CONSULTATION

TO (Division/Office):

**CDER OSE CONSULTS-(Safety Issue)**

-Attn: John Senior

FROM: HFD-150/Diane Hanner

RPM-DDOP

(301) 796-4058

DATE  
4-26-11

IND NO.  
073544

NDA NO.  
202570

TYPE OF DOCUMENT  
Electronic link dated  
3/30/11  
\\CDSESUB1\EVSPROD  
\NDA202570\202570.enx

DATE OF DOCUMENT  
3-30-11

NAME OF DRUG  
Crizotinib

PRIORITY CONSIDERATION  
High Priority (Pending  
final decision at filing  
meeting)

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE  
TBD at the filing meeting

NAME OF FIRM: Pfizer Inc., 10646 Science Center Drive, San Diego, CA 92121

## REASON FOR REQUEST

### I. GENERAL

- |  |   |  |
|--|---|--|
| <input type="checkbox"/> NEW PROTOCOL                  | <input type="checkbox"/> PRE--NDA MEETING           | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT               | <input type="checkbox"/> END OF PHASE II MEETING    | <input type="checkbox"/> FINAL PRINTED LABELING        |
| <input type="checkbox"/> NEW CORRESPONDENCE            | <input type="checkbox"/> RESUBMISSION               | <input type="checkbox"/> LABELING REVISION             |
| <input type="checkbox"/> DRUG ADVERTISING              | <input checked="" type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE   |
| <input type="checkbox"/> ADVERSE REACTION REPORT       | <input type="checkbox"/> PAPER NDA                  | <input type="checkbox"/> FORMULATIVE REVIEW            |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT         | <input type="checkbox"/> OTHER (SPECIFY BELOW):        |
| <input type="checkbox"/> MEETING PLANNED BY            |   |  |

### II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- TYPE A OR B NDA REVIEW  
 END OF PHASE II MEETING  
 CONTROLLED STUDIES  
 PROTOCOL REVIEW  
 OTHER (SPECIFY BELOW):

- CHEMISTRY REVIEW  
 PHARMACOLOGY  
 BIOPHARMACEUTICS  
 OTHER (SPECIFY BELOW):

### III. BIOPHARMACEUTICS

- |  |   |
|--|---|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS  |
| <input type="checkbox"/> PHASE IV STUDIES        | <input type="checkbox"/> IN-VIVO WAIVER REQUEST     |

### IV. DRUG EXPERIENCE

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL             | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)         | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP       |  |

### V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS. This is a new NME application that has been submitted, and DDOP is requesting that a review be done regarding the liver toxicity of this drug.

EDR Location: \\CDSESUB1\EVSPROD\NDA202570\202570.enx

356H Form: \\CDSESUB1\EVSPROD\NDA202570\0002\m1\us\356h.pdf

Cover Letter: \\CDSESUB1\EVSPROD\NDA202570\0002\m1\us\cover.pdf

\*Filing meeting & timeline discussion 5-3-11@4:00-5:00p.m.WO22room 2205

\*Midcycle before the office. 5-13-11@1:00-2:30 pm. WO22 room 2205

**PDUFA DATE: TBD**

**ATTACHMENTS**

**HFD-150/RPM Diane Hanner**

HFD- /Reviewers and Team Leaders **Medical Officers: Shakun Malik and Virginia E. Maher (T.L)**

NAME AND PHONE NUMBER OF REQUESTER

**Diane Hanner 301-796-4058**

METHOD OF DELIVERY (Check one)

DFS ONLY

MAIL

HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

5/28/05

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/s/  
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DIANE C HANNER  
04/26/2011

# REQUEST FOR CONSULTATION

TO (Division/Office):

**CDER OSE CONSULTS-(DMEPA)**

FROM: HFD-150/Diane Hanner  
RPM-DDOP  
(301) 796-4058

DATE  
4-26-11

IND NO.  
073544

NDA NO.  
202570

TYPE OF DOCUMENT  
Electronic link dated  
3/30/11  
\\CDSESUB1\EVSPROD  
\NDA202570\202570.enx

DATE OF DOCUMENT  
3-30-11

NAME OF DRUG  
Crizotinib

PRIORITY CONSIDERATION  
High Priority (Pending  
final decision at filing  
meeting)

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE  
TBD at the filing meeting

NAME OF FIRM: Pfizer Inc., 10646 Science Center Drive, San Diego, CA 92121

## REASON FOR REQUEST

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|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                  | <input type="checkbox"/> PRE--NDA MEETING        | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT               | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING        |
| <input type="checkbox"/> NEW CORRESPONDENCE            | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> LABELING REVISION             |
| <input type="checkbox"/> DRUG ADVERTISING              | <input type="checkbox"/> SAFETY/EFFICACY         | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE   |
| <input type="checkbox"/> ADVERSE REACTION REPORT       | <input type="checkbox"/> PAPER NDA               | <input type="checkbox"/> FORMULATIVE REVIEW            |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT      | <input type="checkbox"/> OTHER (SPECIFY BELOW):        |
| <input type="checkbox"/> MEETING PLANNED BY            |  |  |

### II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- |  |   |
|--|---|
| <input type="checkbox"/> TYPE A OR B NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES      | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW         | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW):  |   |

### III. BIOPHARMACEUTICS

- |  |   |
|--|---|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS  |
| <input type="checkbox"/> PHASE IV STUDIES        | <input type="checkbox"/> IN-VIVO WAIVER REQUEST     |

### IV. DRUG EXPERIENCE

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL             | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)         | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP       |  |

### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> PRECLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS/SPECIAL INSTRUCTIONS. This is a new NME the sponsor has submitted a proprietary name request on 3/31/11 but OODP is also requesting that DMEPA please also review labeling and carton and container labels.

EDR Location: \\CDSESUB1\EVSPROD\NDA202570\202570.enx

356H Form: \\CDSESUB1\EVSPROD\NDA202570\0002\m1\us\356h.pdf

Cover Letter: \\CDSESUB1\EVSPROD\NDA202570\0002\m1\us\cover.pdf

\*Filing meeting & timeline discussion 5-3-11@4:00-5:00p.m.WO22room 2205

\*Midcycle before the office. 5-13-11@1:00-2:30 pm. WO22 room 2205

EDUEA DATE: TBD  
Reference ID: 2937821

**ATTACHMENTS**

HFD-150/RPM Diane Hanner

HFD- /Reviewers and Team Leaders **Medical Officers: Shakun Malik and Virginia E. Maher (T.L)**

NAME AND PHONE NUMBER OF REQUESTER

Diane Hanner 301-796-4058

METHOD OF DELIVERY (Check one)

 DFS ONLY MAIL HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

5/28/05

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/s/  
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DIANE C HANNER  
04/25/2011

**Hanner, Diane**

---

**From:** Hanner, Diane  
**Sent:** Monday, April 18, 2011 10:25 AM  
**To:** 'Domingo, Ron'  
**Subject:** FW: QT Consult Request - NDA 202570 / Reports - Not a TQT study  
**Importance:** High

Hi,  
I have been instructed to request the following:

Please submit all related ECGs to the [REDACTED] <sup>(b) (4)</sup> for both studies (A8081001 & A8081005).

Thank you.  
Regards,  
Diane

CDR Diane Hanner  
Senior Program Management Officer  
FDA/CDER/OODP/DDOP  
10903 New Hampshire Avenue  
Bldg. 22/Room 2119  
Silver Spring, Maryland 20993  
(301) 796-2330  
FAX (301) 796-9845  
E-mail: [diane.hanner@fda.hhs.gov](mailto:diane.hanner@fda.hhs.gov)

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/s/  
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DIANE C HANNER  
04/18/2011



NDA 202570

**NDA ACKNOWLEDGMENT**

Pfizer Inc.  
Attention: Ron C. Domingo, M.S., RAC  
Manager  
Worldwide Regulatory Strategy  
10646 Science Center Drive  
San Diego, CA 92121

Dear Mr. Domingo:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: (Crizotinib 200 mg and 250 mg Capsules)

Date of Application: March 30, 2011

Date of Receipt: March 30, 2011

Our Reference Number: NDA 202570

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on May 30, 2011, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Oncology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have questions, call me, at (301) 796-4058.

Sincerely,

*{See appended electronic signature page}*

CDR Diane Hanner  
Senior Program Management Officer  
Division of Drug Oncology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research

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/s/  
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DIANE C HANNER  
04/15/2011

## Hanner, Diane

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**From:** Hanner, Diane  
**Sent:** Wednesday, April 13, 2011 10:29 AM  
**To:** 'Domingo, Ron'  
**Subject:** NDA 202570 Crizotinib (Information Request 4-13-11)

Hi,  
I have been instructed to request that you please provide us with the (NDA 202570) list of investigators that are involved with the two phase 3 studies that are currently enrolling patients.

Thank you.

Regards,  
Diane

CDR Diane Hanner  
Senior Program Management Officer  
FDA/CDER/OODP/DDOP  
10903 New Hampshire Avenue  
Bldg. 22/Room 2119  
Silver Spring, Maryland 20993  
(301) 796-2330  
FAX (301) 796-9845  
E-mail: [diane.hanner@fda.hhs.gov](mailto:diane.hanner@fda.hhs.gov)

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/s/  
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DIANE C HANNER  
04/13/2011

## Hanner, Diane

---

**From:** Hanner, Diane  
**Sent:** Friday, April 08, 2011 1:59 PM  
**To:** 'Domingo, Ron'  
**Subject:** FW: NDA 202570 Information Request 4-8-11

Hi Ron,  
I have been instructed to send you the following information request regarding NDA 202570:

- 1) Please provide information about the data you are including in the planned submission on 31<sup>st</sup>, May 2011.
- 2) On page 35 of the Clinical Overview, Section 1.5.1.4, it talks about the review of 46 pts with  $\geq$  gr 3 respiratory adverse events by an independent review committee. Please identify the study subjects # whose data was reviewed and the report from the independent review committee.

Thank you,  
Regards,  
Diane

CDR Diane Hanner  
Senior Program Management Officer  
FDA/CDER/OODP/DDOP  
10903 New Hampshire Avenue  
Bldg. 22/Room 2119  
Silver Spring, Maryland 20993  
(301) 796-2330  
FAX (301) 796-9845  
E-mail: [diane.hanner@fda.hhs.gov](mailto:diane.hanner@fda.hhs.gov)

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/s/  
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DIANE C HANNER  
04/08/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR DDMAC LABELING REVIEW CONSULTATION **Please send immediately following the Filing/Planning meeting**	
TO: <b>CDER-DDMAC-RPM</b>		FROM: (Name/Title, Office/Division/Phone number of requestor) HFD-150/Diane Hanner RPM-DDOP (301) 796-4058	
REQUEST DATE 3-31-11	IND NO. 73544	NDA/BLA NO. 202570	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW) Electronic link <a href="\\CDSESUB1\EVSPROD\NDA202570\202570.enx">\\CDSESUB1\EVSPROD\NDA202570\202570.enx</a>
NAME OF DRUG Crizotinib	PRIORITY CONSIDERATION <b>High Priority</b> (Pending final decision at filing meeting)	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE TBD at the time of filing
NAME OF FIRM: Pfizer Inc. 10646 Science Center Drive San Diego, CA 92121		PDUFA Date: TBD at the time of filing	
TYPE OF LABEL TO REVIEW			
TYPE OF LABELING: (Check all that apply) <input checked="" type="checkbox"/> PACKAGE INSERT (PI) <input type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input checked="" type="checkbox"/> CARTON/CONTAINER LABELING <input type="checkbox"/> MEDICATION GUIDE <input type="checkbox"/> INSTRUCTIONS FOR USE(IFU)		TYPE OF APPLICATION/SUBMISSION <input checked="" type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> IND <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> PLR CONVERSION	
REASON FOR LABELING CONSULT <input checked="" type="checkbox"/> INITIAL PROPOSED LABELING <input type="checkbox"/> LABELING REVISION			
<b>EDR link to submission:</b> EDR Location: <a href="\\CDSESUB1\EVSPROD\NDA202570\202570.enx">\\CDSESUB1\EVSPROD\NDA202570\202570.enx</a> 356H Form: <a href="\\CDSESUB1\EVSPROD\NDA202570\0002\m1\us\356h.pdf">\\CDSESUB1\EVSPROD\NDA202570\0002\m1\us\356h.pdf</a> Cover Letter: <a href="\\CDSESUB1\EVSPROD\NDA202570\0002\m1\us\cover.pdf">\\CDSESUB1\EVSPROD\NDA202570\0002\m1\us\cover.pdf</a>			
Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. The DDMAC reviewer will contact you at a later date to obtain the substantially complete labeling for review.			
COMMENTS/SPECIAL INSTRUCTIONS: *Sponsor Orientation mtg. 4-21-11 @10:30-12:00 p.m. WO22 room 1417 *Sponsor Data Set Discussion mtg. 4-21-11 @ 1:00 p.m. WO22 room 1415 *Filing meeting & timeline discussion 5-3-11@4:00-5:00p.m.WO22room 2205 *Midcycle before the office. 5-13-11@1:00-2:30 pm. WO22 room 2205			
SIGNATURE OF REQUESTER Diane Hanner-RPM			
SIGNATURE OF RECEIVER		METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> eMAIL <input type="checkbox"/> HAND	

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/s/  
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DIANE C HANNER  
03/31/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR CONSULTATION</b>			
TO (Division/Office): Devi Kozeli, Project Manager, OND/DCRP WO-22 Room 4183, 301-796-1128			FROM: Diane Hanner, Project Manager, OND/DDOP WO-22 Room 2119, 301-796-4058		
DATE: 3-31-11	IND NO.: 073544	NDA NO.: 202570	TYPE OF DOCUMENT: QT study	DATE OF DOCUMENT: 3-30-11	
NAME OF DRUG: Crizotinib		PRIORITY CONSIDERATION: <b>High Priority</b> (Pending final decision at filing meeting)	CLASSIFICATION OF DRUG:	DESIRED COMPLETION DATE: TBD at the time of filing Due 6 mo.: Due 10 mo.:	
NAME OF FIRM: Pfizer Inc., 10646 Science Center Drive, San Diego, CA 92121					
<b>REASON FOR REQUEST</b>					
<b>I. GENERAL</b>					
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY		<input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input checked="" type="checkbox"/> Electronic NDA <input type="checkbox"/> CONTROL SUPPLEMENT		<input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW OTHER (SPECIFY BELOW): <div style="text-align: right;"><b>New NDA</b></div>	
<b>II. BIOMETRICS</b>					
STATISTICAL EVALUATION BRANCH			STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER:			<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER:		
<b>III. BIOPHARMACEUTICS</b>					
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY/PK STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST			
<b>IV. DRUG EXPERIENCE</b>					
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP			<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
<b>V. SCIENTIFIC INVESTIGATIONS</b>					
<input type="checkbox"/> CLINICAL			<input type="checkbox"/> PRECLINICAL		
<b>COMMENTS/SPECIAL INSTRUCTIONS:</b> This consult requests a review of the protocol in the new NDA submission EDR Location: <a href="#">\CDSESUB1\EVSPROD\NDA202570\202570.enx</a> 356H Form: <a href="#">\CDSESUB1\EVSPROD\NDA202570\0002\m1\us\356h.pdf</a>  Cover Letter: <a href="#">\CDSESUB1\EVSPROD\NDA202570\0002\m1\us\cover.pdf</a>					
PDUFA Goal date: TBD at the time of filing					
SIGNATURE OF REQUESTER: Diane Hanner <i>{See appended electronic signature page}</i>			METHOD OF DELIVERY (Check one): <input checked="" type="checkbox"/> DFS/DARRTS <input type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER:			SIGNATURE OF DELIVERER:		

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/s/  
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DIANE C HANNER  
03/31/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR CONSULTATION</b>			
TO (Division/Office): <b>Mail: OSE-DRISK consult</b>			FROM: HFD-150/Diane Hanner RPM-DDOP (301) 796-4058		
DATE 3-31-11	IND NO. 073544	NDA NO. 202570	TYPE OF DOCUMENT Electronic link  <a href="#">\\CDSESUB1\EVSPROD\NDA202570\202570.enx</a>	DATE OF DOCUMENT: 3-30-11	
NAME OF DRUG: Crizotinib		PRIORITY CONSIDERATION <b>High Priority</b> (Pending final decision at filing meeting)	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE TBD at the time of filing	
NAME OF FIRM: Pfizer Inc. 10646 Science Center Drive, San Diego, CA 92121					
<b>REASON FOR REQUEST</b>					
<b>I. GENERAL</b>					
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY		<input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input checked="" type="checkbox"/> NDA <input type="checkbox"/> CONTROL SUPPLEMENT		<input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):  <b>NEW NDA</b>	
<b>II. BIOMETRICS</b>					
STATISTICAL EVALUATION BRANCH			STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):			<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
<b>III. BIOPHARMACEUTICS</b>					
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES			<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
<b>IV. DRUG EXPERIENCE</b>					
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP			<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
<b>V. SCIENTIFIC INVESTIGATIONS</b>					
<input type="checkbox"/> CLINICAL			<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: EDR Location: <a href="#">\\CDSESUB1\EVSPROD\NDA202570\202570.enx</a> 356H Form: <a href="#">\\CDSESUB1\EVSPROD\NDA202570\0002\m1\us\356h.pdf</a> Cover Letter: <a href="#">\\CDSESUB1\EVSPROD\NDA202570\0002\m1\us\cover.pdf</a>					
SIGNATURE OF REQUESTER Diane Hanner, RPM			METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> MAIL <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER			SIGNATURE OF DELIVERER		

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/s/  
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DIANE C HANNER  
03/31/2011

# REQUEST FOR CONSULTATION

TO (Office/Division): Yi Tsong, OTS/OB/DBVI

FROM (Name, Office/Division, and Phone Number of Requestor): Don Henry  
Project Manager, ONDQA, 301-796-4227

DATE  
March 30, 2011

IND NO.

NDA NO.  
202570

TYPE OF DOCUMENT  
original submission

DATE OF DOCUMENT  
March 30, 2011

NAME OF DRUG  
crizotinib

PRIORITY CONSIDERATION  
Prior Approval

CLASSIFICATION OF DRUG  
DDOP

DESIRED COMPLETION DATE  
May 30, 2011

NAME OF FIRM: Pfizer

## REASON FOR REQUEST

### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER     |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING            |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION                 |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE       |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW                |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

### II. BIOMETRICS

- |   |   |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |   |

### III. BIOPHARMACEUTICS

- |  |  |
|--|--|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES         | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

### IV. DRUG SAFETY

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |  |

### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: perform an statistical evaluation of the proposed design space for the manufacturing process.

SIGNATURE OF REQUESTOR  
{See appended electronic signature page}

METHOD OF DELIVERY (Check one)  
 DFS     EMAIL     MAIL     HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/  
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DON L HENRY  
04/05/2011

## Hanner, Diane

---

**From:** Hanner, Diane  
**Sent:** Monday, February 28, 2011 3:42 PM  
**To:** 'Domingo, Ron'  
**Subject:** FW: NDA 202570:crizotinib - DSI materials-IR regarding IND 73544

Hi,

I have been instructed to request the following regarding NDA 202570:

1. Copies of the protocols for the two clinical trials - A8081001 and A8081005.
2. A copy of the proposed package insert - marked DRAFT and dated.
3. Copies of the synopsis only of the full clinical report for each of the two clinical trials - marked Draft and dated.

would N.B. - provision of the above in electronic format, e.g. word processing files be appreciated.

Thanks.  
Regards,  
Diane

CDR Diane Hanner  
Senior Program Management Officer  
FDA/CDER/OODP/DDOP  
10903 New Hampshire Avenue  
Bldg. 22/Room 2119  
Silver Spring, Maryland 20993  
(301) 796-2330  
FAX (301) 796-9845  
E-mail: [diane.hanner@fda.hhs.gov](mailto:diane.hanner@fda.hhs.gov)

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/s/  
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DIANE C HANNER  
02/28/2011



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

IND 73,544

MEETING MINUTES

Pfizer, Inc.  
Attention: Ron Domingo, MS, RAC  
Manager, Worldwide Regulatory Strategy  
10646 Science Center Drive  
San Diego, CA 92121

Dear Mr. Domingo:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for crizotinib (PF-02341066).

We also refer to the meeting between representatives of your firm and the FDA on October 29, 2010. The purpose of the meeting was to obtain agreement with the Agency on CMC development plans and aspects of the Quality by Design approach in preparation of the NDA.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-4227.

Sincerely,

{See appended electronic signature page}

Don L. Henry  
Regulatory Project Manager  
Division of New Drug Quality Assessment I  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

Enclosure – meeting minutes

Reference ID: 2860990

Reference ID: 3016610

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FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
OFFICE OF NEW DRUG QUALITY ASSESSMENT

<b>Sponsor Name:</b>	Pfizer Inc.
<b>Application Number:</b>	IND 073544
<b>Product Name:</b>	Crizotinib (PF-02341066)
<b>Meeting Type:</b>	Type B
<b>Meeting Category:</b>	Chemistry, Manufacturing and Controls, Pre-NDA/Quality by Design
<b>Meeting Date and Time:</b>	Friday, October 29, 2010, 9:30 – 11:00 ET
<b>Meeting Location:</b>	Food and Drug Administration, White Oak Campus, Silver Spring, MD
<b>Received Briefing Package</b>	September 24, 2010

**FDA ATTENDEES:**

ONDQA

Sue Ching Lin, M.S., R.Ph., Review Chemist  
Haripada Sarker, Ph.D., CMC Lead  
Christine Moore, PhD, Deputy Director  
Richard T. Lostritto, Ph.D., Division Director  
Angelica Dorantes, Ph.D., Biopharmaceutics Team Leader  
John Duan, Ph.D., Biopharmaceutics Reviewer  
Don Henry, Regulatory Health Project Manager

OFFICE OF COMPLIANCE

Zi Qiang Gu, Compliance Officer, DMPQ

**PFIZER ATTENDEES:**

Gemma Cansell, Senior Principal Scientist, Chemical R&D  
Stephen T. Colgan, Associate Research Fellow, Global CMC  
Ron Domingo, Manager, Regulatory Strategy  
Erling Donnelly, Associate Director, Regulatory Strategy  
Craig Donnelly, Principal Scientist, Development Analytical R&D  
Richard Hutchins, Research Fellow, Development Portfolio Mgmt  
Megan E. McMahon, Principal Scientist, Global CMC

Reference ID: 2860990

## 1.0 BACKGROUND

Crizotinib is being developed by Pfizer for treatment of patients with anaplastic lymphoma kinase (ALK) positive advanced non-small cell lung cancer. Pfizer submitted a request for a CMC Pre-NDA meeting to obtain agreement with the Agency on CMC development plans and aspects of the Quality by Design approach in preparation of the NDA. The request was submitted and received on July 16, 2010. A Type B meeting was granted on August 17, 2010, for a face-to-face meeting to be held on October 29, 2010. The meeting briefing package was submitted and received September 24, 2010. The purpose of this document is to provide preliminary responses to the questions contained in the meeting briefing package. These responses are being archived and shared with Pfizer to promote an efficient discussion at the meeting scheduled for October 29, 2010.

## 2.0 SPONSOR QUESTIONS AND FDA PRELIMINARY RESPONSES

### 2.1 PROPOSED REGULATORY STARTING MATERIALS AND CONTROL STRATEGY

***Question 1:*** Part of the overall control strategy for crizotinib (PF-02341066) drug substance is the proper selection and control of the drug substance starting materials. Given the quality knowledge gathered to date and proposed analytical controls for (b) (4) [redacted] does the Agency agree that these are acceptable drug substance starting materials?

#### ***FDA Response to Question 1:***

Based on the information provided in your meeting package, your designation of the (b) (4) starting materials is acceptable. Clarify what constitutes "significant new impurities in the starting material" (Appendix 2, pg. 36). A full evaluation of adequacy of the proposed specifications would be done at the time of review. Include adequate data in your NDA submission to support the designation of starting materials; e.g., detailed information regarding the (b) (4) [redacted]

[redacted] proposed starting materials.

#### ***Pfizer Response:***

A significant new impurity in the starting material would be a new impurity present (b) (4) acceptance criterion for an unspecified impurity.

Adequate information and supporting data will be provided in the NDA to support the designation of the selected starting materials. (b) (4) [redacted]

**Pfizer Response:**



**2.4 FDA ADDITIONAL COMMENTS**

1. It is recommended that you evaluate the manufacturing method of the drug substance to determine the potential for formation of (b) (4) which are potentially genotoxic. Provide data to show that (b) (4) have consistently been controlled below threshold of toxicological concern (TTC) in the final drug substance.

**Pfizer Response:**

We agree. Pfizer is completing an evaluation for genotoxic impurities and is developing a robust control strategy. The relevant data will be provided in the NDA.

**Meeting Discussion:**

The Agency noted that (b) (4) which is used in capsule (b) (4) may need to be evaluated.

2. If dissolution is used in the development of a design space, it is advised that you contact the agency for early evaluation of the dissolution methodology and acceptance criteria. The drug substance has low solubility and low permeability and therefore dissolution may play an important role in its in vivo performance. The selection of dissolution methodology and acceptance criteria is an important factor to consider when a QbD approach is used.

**Pfizer Response:**

A discussion and justification of the dissolution methodology will be included in the briefing package that will be submitted in early December, 2010.

**Meeting Discussion:**

Since the dissolution method is used to develop the design space, the Agency recommended Pfizer to submit the dissolution development report as part of the amendment expected in early December. The information should include:

- a. Dissolution conditions used (e.g. apparatus, rotation speed, pH, media, volume and temperature, etc.)
- b. Justification for condition selected and why it is optimum
- c. Consider the in-vivo relevance of the conditions since the product has low solubility
- d. Include complete dissolution profiles
- e. Include raw data
- f. Consider multiple point dissolution during stability

**3.0 ISSUES REQUIRING FURTHER DISCUSSION**

There are no additional issues requiring further discussion at this time.

**4.0 ACTION ITEMS:**

There were no additional action items identified during the meeting

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## **5.0 CONCURRENCE:**

*{See appended electronic signature page}*

**Don L. Henry**  
Regulatory Health Project Manager for Quality  
Division of New Drug Quality Assessment I  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

*{See appended electronic signature page}*

**Richard T. Lostritto, Ph.D.**  
Division Director  
Division of New Drug Quality Assessment I  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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/s/  
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DON L HENRY  
11/05/2010

RICHARD T LOSTRITTO  
11/12/2010

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Office of Orphan Products Development  
Food and Drug Administration  
Building 32, Room 5271  
10905 New Hampshire Avenue  
Silver Spring, MD 20993

SEP 13 2010

Pfizer Inc.  
LaJolla Laboratories  
10646 Science Center Drive  
San Diego, California 92121

Attention: Ron Domingo, M.S., RAC  
Manager, World Wide Regulatory Strategy

Re: Designation Request # 10-3106

Dear Mr. Domingo:

Reference is made to your request for orphan-drug designation dated June 11, 2010, of crizotinib (also known as: PF-02341066) for "treatment of ALK-positive locally advanced or metastatic non-small cell lung cancer." Please also refer to our letter dated June 15, 2010.

Pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bb), your request for orphan-drug designation of crizotinib (also known as: PF-02341066) is granted for *treatment of ALK-positive non-small cell lung cancer*. Please be advised that it is the active moiety of the drug and not the formulation of the drug that is designated.

Please note that if the above drug receives marketing approval for an indication broader than what is designated, it may not be entitled to exclusive marketing rights under section 527 (21 U.S.C. 360cc). Therefore, prior to final marketing approval, we request that you compare the drug's designated orphan indication with the proposed marketing indication, and submit additional information to amend the orphan-drug designation if warranted.

Please submit to the Office of Orphan Products Development a brief progress report of drug development within 14 months after this date and annually thereafter until marketing approval (*see* 21 C.F.R. 316.30). Finally, please notify this Office within 30 days of a marketing application submission for the drug's designated use.

If you have questions regarding the development of your designated product, please feel free to contact J. Lloyd Johnson, Pharm.D. at (301) 796-8683. Please refer to this letter as official notification. Congratulations on obtaining your orphan-drug designation.

Sincerely yours,

A handwritten signature in black ink, appearing to read 'Timothy R. Coté', with a large, sweeping flourish above the name.

Timothy R. Coté, M.D., M.P.H.  
Director, Office of Orphan Products Development

OP File # 10-3106  
Chron  
LJohnson  
JD 9/5/10  
DESIGNATION GRANTED

**MEMORANDUM OF MEETING**

Date: June 24, 2010

From: Karen Bijwaard, MS, Scientific Reviewer  
CDRH/OIVD/DIHD

Subject: Official meeting minutes for Sponsor meeting regarding: G090233  
Abbott Molecular Vysis ALK Break Apart (BAP) FFPE FISH Kit and  
Pfizer drug crizotinib (IND 73,544) for ALK+ NSCLC

Meeting: Date: May 11, 2010  
Time: 4:00 – 5:00 pm  
Type: Face-to-face  
Leader: Karen Bijwaard  
Recorder: Tremel Faison

To: The Record – Official Meeting minutes

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**Attendees:**

Industry: Abbott Molecular  
Pamela Swatowski, Director Regulatory Affairs  
Lynda Hague, Director Clinical Affairs  
Karen Sachs, Director Bio-Statistics  
Fred Siebert, Clinical Affairs Project Manager  
Stephen Dailey, Project Manager R & D  
Ekaterina Pestova, PhD, Manager of Research and Development  
Pfizer  
Hakan Sakul, M.S., Ph.D., Senior Director and Global Head of  
Diagnostics  
Sreesh Srinivasa, Ph.D., Associate Director, Molecular Medicine  
Keith Wilner, Ph.D., Senior Director Clinical Lead  
Richard Buller, M.D., Ph.D., Vice President, Translational Oncology  
Paulina Selaru, M.S., M.S.P.H., Assoc. Director, Statistics Asset Lead  
Ramzi Dagher, M.D., Vice President, Regulatory  
Jamey Skillings, M.D., M.S.C., M.B.A., Senior Director, Global  
Clinical Lead  
Mace Rothenberg, MD, Senior Vice President, Clinical Development  
and Medical Affairs  
Lixin Han, PhD, Associate Director of Biostatistics  
Ron Domingo, M.S., RAC, Manager Regulatory Affairs

FDA: Karen Bijwaard, MS, Scientific Review/Lead Reviewer, DIHD

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Tremel Faison, MS, Scientific Reviewer, DIHD  
Robert Becker, MD, PhD, Chief Medical Officer, OIVD  
Maria Chan, PhD, Division Director, DIHD  
Reena Philip, PhD, Assoc. Director, DIHD  
Gene Pennello, PhD, Statistician, CDRH/OSB/DBS  
Ian Waxman, Md, Medical Officer, CDER/OND/OODP/DDOP  
Anthony Murgo, MD, Acting Deputy Director, CDER/OND/OODP

**Background:**

The sponsor has submitted an IND application (IND 73,544) for the drug crizotinib with the Vysis assay as a companion diagnostic to detect rearrangements involving the ALK gene via fluorescence *in situ* hybridization (FISH) in non-small cell lung cancer tissue specimens. An investigational device exemption for the diagnostic assay was approved on December 11, 2009. (G090233).

The sponsor requested this meeting to respond to questions from the Agency regarding Pfizer's request for accelerated approval of PF-02341066 (crizotinib), discuss the potential for expedited review status and approval of the Vysis ALK BAP kit, and clarify the previously discussed concordance study in view of the proposed accelerated drug approval pathway.

**Discussion:**

The meeting began with the sponsor giving an update on and overview of the clinical studies.

Sponsor: There are three trials:

- 1001 - single arm trial to establish efficacy, patients are selected independent of the number of previous chemotherapies, may have had 2 or 3 pretreatments
- 1007 – randomized vs. standard of care, basis of Phase III
- 1005 – single arm trial, chemotherapy arm of 1007, more than one pretreatment

Trials 1001 and 1005 form the basis for the submission. In 1001, there were 5 laboratory developed tests (LDTs), including an MGH LDT (referred to as the “reference LDT”). No information is available on the other four LDTs. A total of 80% of all samples were confirmed by MGH LDT and no discordances were seen between the LDT<sub>1-4</sub> and the reference LDT from Massachusetts General Hospital (LDT<sub>MGH</sub>).

Currently for 1005 and for 1007, all patients are enrolled using the IUO device. More than 100 of the specimens tested with the LDT(s) will have been also tested with the IUO

Assay concordance (see sponsor presentation slide 5): The Sponsor proposes to send 60 ALK+ and 60 ALK- tested by the IUO for testing by LDT<sub>MGH</sub>. Demonstrate positive and negative agreement.

Abbott Molecular Vysis ALK BAP FFPE FISH Probe/Pfizer drug crizotinib (IND 73,544)  
5/11/2010 Meeting minutes

Since the specimens would consist of specimens from 1005 and some are from 1007, FDA asked the Sponsor why they couldn't all be tested. The Sponsor stated that 27 ALK+ were from 1005 and 17 ALK+ were from 1007. Not all of the cases have enough tissue and they couldn't get enough tissue-only about 50%. FDA asked sponsor to provide a comparison of prognostic variables for the ones for which samples are depleted to the ones for which samples are not depleted.

Pfizer discussed the proposed Clinical Concordance (Slide 7) Study 1001, current response rate in 82 patients is 50%. Study 1005, tested 40 patients with the IUO, lower limit of the CI is 34% with a response rate of 50%. They also indicated that they would like to perform some studies postmarket.

FDA indicated concern with additional knowledge of the 4 LDTs due to the variety of testing asked how many were checked against the reference.

Pfizer indicated that to date ~80% of the results from the 105 patients have been confirmed with the LDT<sub>MGH</sub>, however all that have been tested have been confirmed positive by the LDT<sub>MGH</sub>. Two were found to be invalid due to technical reasons and Pfizer is attempting to locate 10-11 specimens from Memorial Sloan Kettering. In 1005, a few were prescreened with LDTs and 36/37 samples have been confirmed with the Abbott Investigational Use Only (IUO) device. Moving forward all patients will be tested with the IUO.

FDA inquired about whether there was concordance on negative calls, and Pfizer indicated that all the LDTs used the Vysis FISH probes and similar protocols.

FDA asked about the distribution of raw results (range of actual counts). For example, how far from the cut-point are typical positive and negative results were? Were they very, very negative or positive? Or close to the cut-point?

Pfizer responded that the LDTs used the same cut-off of 15%. They stated that the maximum signal they had observed in surrounding normal tissue (ALK-) was 11% and the lower level of ALK+ seen has been 25% and above. FDA asked sponsor to provide the limits of detection of all these LDT 1-4 assays.

FDA stated that it would need to look at the robustness of the discrimination between positive and negative samples. Since many weren't identified as negative by the LDTs and subsequently retested with the IUO or LDT<sub>MGH</sub>, there could have a negative by LDT that is positive by other methods.

Pfizer stated that is why the planned to test 60+ and 60- in the assay concordance.

FDA commented however that that didn't reach back to all LDTs and asked about the representativeness of all the positive samples selected? For example, the way you selected, the LDT may be *very* positive and not representative. Hypothetically, you may have exhausted the borderline samples by retesting.

Pfizer stated that they did have some data on the distribution of percentages of the positives.

FDA indicated that it was encouraging at the ranges they described, but that didn't nail it completely.

Pfizer indicated that only 3 ALK negatives have been treated to date (slide 9) but they have modified the protocol for patients with more than one treatment. These can be selected for the ALK- cohort.

FDA asked if Pfizer would be looking at ALK- in the context of the Phase III trial and what the outcome was of the 3 ALK- patients identified.

Pfizer stated that they would not be looking at ALK- in Phase III and those from 1001, were last ditch patients. The ALK- have shown no response. Two were CMet+ but they still needed to confirm they are ALK negative with the IUO.

FDA stated that they wanted to make sure that Pfizer had stepped through all the options.

Pfizer stated that they were trying to get some patients with only one previous treatment from 1001.

The discussion then moved to the sponsor's questions (*FDA responses are in italics*):

1. Does the Agency concur that expedited review status is an option for the AM Vysis ALK Break Apart (BAP) FFPE FISH Probe Kit (companion diagnostic) to align with the accelerated approval strategy for the drug crizotinib?

*FDA can not say definitely. FDA can not predict if there will be review issues. Regarding timelines for pre-submission; coordination with CDER is needed. A pre-meeting could also be productive.*

2. Is the proposed path forward for an expedited PMA review status submission for the companion device acceptable to FDA?

*FDA can not give a response at this meeting. We will need to coordinate and discuss with CDER.*

***[Post-meeting FDA note: CDRH does not have a method for conditional approval of the device, such as CDER's Accelerated Approval option and as such we will need to discuss with CDER whether or not there are potential concerns and timelines.]***

3. Would an alternative concordance study design be acceptable that parallels the accelerated approval of the drug?

*The team will need to look at the alternative concordance study in comparison to what was discussed before.*

The meeting closed at 4:00 pm.

Action Items:

FDA:

1. Provide sponsor with response regarding acceptability of concordance studies.

Sponsor:

1. Provide FDA with recently published information about ALK fusion prevalence in primary vs. metastatic tumors
2. Provide FDA with distribution of results, specimen % ranges, limits, etc.
3. Describe the representativeness of the population for concordant samples
4. Confirm IOU results in ALK negative patients (Study 1001)
5. Amend protocol to include multiple lines of treatment.

 6/24/10  
\_\_\_\_\_  
Karen Bijwaard                      Date



FOOD AND DRUG ADMINISTRATION

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**Meeting Date and Time:** July 29, 2010, 1:00 p.m.  
**Meeting Type:** Type B (teleconference)  
**Meeting Category:** End of Phase 3  
**Meeting Location:** Bldg. 22, Room 1309  
**Application Number:** IND 073544  
**Product Name:** PF-02341066 (Crizotinib)  
**Received Briefing Package** June 21, 2010  
**Sponsor Name:** Pfizer, Inc.  
**Meeting Requestor:** Ron Domingo, MS., RAC  
**Meeting Chair:** Virginia Ellen Maher, M.D., Medical Team Leader, DDOP  
**Meeting Recorder:** Diane Hanner, Senior Program Management Officer, DDOP

**Meeting Attendees:**

- Hakan Sakul, M.S., Ph.D., Senior Director and Global Head of Diagnostics
- Paulina (Nina) Selaru, M.S., M.S.P.H., Assoc. Director, Statistics Asset Lead
- Jamey Skillings, M.D., M.S.C., M.B.A., Senior Director, Global Clinical Lead
- Keith Wilner, Ph.D., Senior Director, Clinical Lead
- Tatiana Olifir, M.D., Director, Safety and Risk Management
- Diane Matsumoto, Ph.D., Associate Research Fellow
- Weiwei Tan, Ph.D., Associate Director, Clin Pharm lead
- Ron Domingo, M.S., R.A.C., Manager, Regulatory Affairs

**Attendee from Abbott Molecular**

- Pamela Swatkowski, B.S., Director, Regulatory Affairs

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### **FDA Attendees**

- Robert Justice, M.D., M.S., Director DDOP
- Anthony Murgo, M.D., Acting Deputy Director, DDOP
- Virginia Ellen Maher, M.D., Medical Team Leader, DDOP
- Ian Waxman, M.D., Medical Officer
- Shakun Malik, M.D., Medical Officer
- Pengfei Song, Ph.D., Clinical Pharmacology Reviewer, DCP5
- Qi Liu, Ph.D., Acting Clinical Pharmacology Team Leader, DCP5
- Hao Zhu, Ph.D., Senior Staff Fellow, OTS, OCP
- Timothy Pohlhaus, Ph.D., Senior Staff Fellow, DCRP
- Lijun Zhang, Ph.D., Biostatistics Reviewer, DBV
- Shenghui Tang, Ph.D., Acting Biostatistics Team Leader, DBV
- Brenda Gehrke, Ph.D., Pharmacology Toxicology Reviewer, DDOP
- Whitney Helms, Ph.D., Pharmacology Toxicology Reviewer, DDOP
- Reena, Phillip, Ph.D., Scientific Reviewer, DIHD, OIVD
- Gene Pennello, Ph.D., Biostatistics Reviewer, DDB
- Robert Becker, M.D., Director OIVD
- Karen E. Bijwaard, Ph.D., Regulatory Review, OIVD
- Justin Earp, Ph.D., Office of Combination Products
- Diane Hanner, M.P.H., M.S.W., Senior Program Management Officer, DDOP

### **BACKGROUND**

Pfizer requested this meeting in order to gain FDA concurrence regarding their registration strategy for PF-02341066, Crizotinib for the treatment of advanced NSCLC patients with tumors positive for the EMLA4-ALK fusion gene.

### **Discussion:**

**Question 1:** Does the Agency agree that the safety and efficacy data for Studies A8081001 and A8081005 will not be pooled for presentation in the submission and will only be presented individually by study?

**FDA Response:** We agree that efficacy data should not be pooled. Safety data from A8081001 and A8081005 may be presented separately, but an integrated summary of safety (ISS) included a pooled safety data analysis for the ALK+ NSCLC cohort from A8081001 and patients from A8081005 should also be provided. The ISS dataset should include all patients exposed to crizotinib, and should contain flags to identify ALK+ NSCLC patients and patients who received 250 mg po bid dosing.

**Sponsor Response:** Pfizer agrees to pool safety data from A8081001 and A8081005 and present combined safety data from these studies independent of CTC version. Pfizer proposes no mapping for grading or adverse event term (CTCAE 3.0 to 4.0) since we would expect no major impact on the more frequent adverse events or to the medical safety reporting conclusions in the ISS. In addition Pfizer proposes that separate adverse reaction tables for each of these studies will be presented in the US package insert. Is this acceptable to the Agency?

**Meeting Discussion:** It is acceptable to not map the CTCAE version 3 terms to version 4.

**Question 2:** The Sponsor proposes to provide updated data only from Studies A8081001 and A8081005 in the 120-day safety update. Does the Agency concur?

**FDA Response:** Please provide the projected status of your ongoing and planned trials, A8081007, A8081013, and A8081014, at the time of data cutoff for the Safety Update. FDA should have all available safety data from all completed and on-going trials at the time of submission of the original NDA and Safety Update.

**Sponsor Response:** At the time of the data cutoff for the Safety Update A8081007, A8081013, and A8081014 are all expected to be ongoing. In the NDA submission and safety update, Pfizer will submit a list of SAEs for all ongoing studies of single agent crizotinib. This list will be an aggregate for both study arms for ongoing Phase 3 studies to maintain data integrity. Does the Agency concur with this plan?

**Meeting Discussion:** The sponsor will provide data sets containing the SAEs on the crizotinib arm for these studies. FDA may ask for narratives for a select number of these SAEs.

**Question 3:** Does the Agency concur with the Sponsor's proposal to submit radiographic images from the independent third-party review as described?

**FDA Response:** It is unlikely that it will be necessary to submit these independently reviewed films. Please state the percentage of images you have been able to collect from A8081001.

Study A8081005 will use RECIST 1.1. Please state whether all responses on A8081005 will be confirmed.

**Sponsor Response:** The collection of images from A8081001 has just begun. It is the intention of Pfizer to require response confirmation as A8081005 is a Phase 2 study.

**Meeting Discussion:** It is unlikely that direct review of these films will be necessary.

**However, we cannot provide a definitive answer until we have reviewed the data.**

**Question 4:** Pfizer plans to follow the “Guidance for Industry Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document” dated April 2009, for the SCE and the SCS to meet the requirements of the Integrated Summary of Efficacy and the Integrated Summary of Safety. Does the Agency concur?

**FDA Response:** Please include in your submission (a) SAS programs that produced all efficacy results, (b) all raw as well as derived variables in .xpt format, and (c) SAS programs by which the derived variables were produced from the raw variables.

**Sponsor Response:** Pfizer agrees to provide the raw and derived variables as described in (b) above. Pfizer also agrees to provide output from the SAS programs for efficacy. However the actual programs to generate the derived variables and outputs as described in (a) and (c) above will not be provided as there are many interdependencies in the standard coding and these programs cannot be run in isolation.

Please see our response to Question 1 concerning the pooling of data.

**Meeting Discussion: The sponsor agreed to provide all programs and program definitions.**

**Question 5:** Does the Agency agree with the criteria for providing the patient narratives as described and that these may be prepared in the CIOMS format?

**FDA Response:** Please provide patient narratives and CRFs for all patients who:

- Died within 30 days of last treatment
- Discontinued study drug due to any adverse event
- Experienced any SAEs

The narratives and CRFs should be indexed and grouped according to category (e.g., died, discontinued, etc.), with hyperlinks.

**Sponsor Response:** We agree to this request with the clarification that we would include narratives for patients who died within 28 days of last treatment to be consistent with protocol language. However, we will provide a narrative on any treatment-related death regardless of time of occurrence. The narratives for patients discontinued for a non-serious adverse event will not be provided in CIOMS form.

**Meeting Discussion: This is acceptable.**

**Question 6:** Does the Agency agree with the criteria for inclusion of Case Report Forms.

**FDA Response:** You will need to submit all CRFs to OIVD. Please also include all CRFs with your NDA submission.

**Sponsor Response:** Pfizer agrees to submit in the NDA pdf casebooks (CRFs) for all patients in the database at the time of the cutoff for submission. The submission to OIVD will be done by Abbott Molecular.

**Question 7:** Does the Agency concur that the proposed nonclinical safety package is sufficient to support accelerated approval of crizotinib in the proposed indication?

**FDA Response:** Final reports of the studies described in the proposed nonclinical safety package would appear to be sufficient to support the submission of the crizotinib application; however, the final decision regarding the adequacy of the nonclinical studies to support accelerated approval will be a review issue.

**Question 8:** The Abbott Molecular Vysis ALK Break Apart FFPE FISH Probe Kit is a companion diagnostic to crizotinib. Pfizer plans to include in the NDA the diagnostic data used to select patients with ALK-positive NSCLC and cross reference detailed diagnostic data included in the CDRH submission. Is this acceptable to the Agency?

**FDA Response:** Yes.

**Question 9:** Does the Agency agree that the proposed contents of the NDA are adequate to support accelerated approval of crizotinib for the following indication? “Crizotinib is indicated for ALK-positive advanced non-small cell lung cancer.”

**FDA Response:** This will be a review issue.

**Question 10:** Does the Agency concur with the QTc evaluation from A8081001 study to support accelerated approval of crizotinib and the QTc evaluation from A8081007 sub-ECG study to be provided as a post-marketing commitment?

**FDA Response:** Yes. You may use the QTc evaluation from Study A8081001 to support accelerated approval of crizotinib. Please include central tendency analysis and categorical analysis in addition to concentration-QT analysis in your study report. We recommend you submit the report from the sub-ECG study of Study A8081007 once the results are available.

1. When you submit your QT study report, please include the following items:
  - a. Copies of the study report(s) for any other clinical studies of the effect of product administration on the QT interval that have been performed
  - b. Electronic copy of the study report
  - c. Electronic or hard copy of the clinical protocol
  - d. Electronic or hard copy of the Investigator’s Brochure
  - e. Annotated CRF
  - f. A data definition file which describes the contents of the electronic data sets
  - g. Electronic data sets as SAS.xpt transport files (in CDISC SDTM format – if possible) and all the SAS codes used for the primary statistical and exposure-response analyses

- h. Please make sure that the ECG raw data set includes at least the following: subject ID, treatment, period, ECG date, ECG time (up to second), nominal day, nominal time, replicate number, heart rate HR, intervals QT, RR, PR, QRS and QTc (any corrected QT as points in your report, e.g. QTcB, QTcF, QTcI, etc., if there is a specifically calculated adjusting/slope factor, please also include the adjusting/slope factor for QTcI, QTcN, etc.), Lead, and ECG ID (link to waveform files if applicable)
  - i. Data set whose QT/QTc values are the average of the above replicates at each nominal time point
  - j. Narrative summaries and case report forms for any
    - i. Deaths
    - ii. Serious adverse events
    - iii. Episodes of ventricular tachycardia or fibrillation
    - iv. Episodes of syncope
    - v. Episodes of seizure
    - vi. Adverse events resulting in the subject discontinuing from the study
  - k. ECG waveforms to the ECG warehouse ([www.ecgwarehouse.com](http://www.ecgwarehouse.com))
  - l. A updated Highlights of Clinical Pharmacology Table
2. We are also interested in the effects of crizotinib on other ECG intervals and changes in waveform morphology. Please submit PR and QRS interval data with the study report and descriptive waveform morphology changes.
3. We recommend that you incorporate the following elements into your assessment of the ECGs recorded during this study:
- a. Use of a central ECG laboratory employing a limited number of skilled readers, to control variability in interpretation
  - b. Blinding of ECG readers to treatment, time, and day (i.e., Day -1; Day 1) identifiers
  - c. Review of ECGs from a particular subject should be performed by a single reader
  - d. Pre-specify the lead for interval measurements
  - e. Baseline and on-treatment ECGs should be based on the same lead.

**Sponsor Response:** The Sponsor acknowledges the Agency's response. Please confirm that the listed items (No. 1-3) apply only to the ECG sub-study of Study A8081007 and its report.

**Meeting Discussion:** The sponsor agreed to provide all information as available from studies A8081001 and A8081005. The sponsor may also submit the ECG substudy from Study A8081007 with the 120 day safety update if the data is available at that time.

**The sponsor will submit information on the ECG intervals and will also try to submit hard copies of the triplicate ECGs in PDF with the study reports of A8081001 and A8081005.**

**Question 11:** Does the Agency agree that Crizotinib is classified as a moderate cytochrome P450 3A4 inhibitor based on the results from a drug interaction sub-study of A8081001 with midazolam in cancer patients?

**FDA Response:** This will be a review issue.

**Sponsor Response:** The Sponsor acknowledges the Agency's response.

**Question 12:** Does the Agency concur with the proposed biopharmaceutics and clinical pharmacology studies to support accelerated approval of crizotinib?

**FDA Response:** Your proposal may be acceptable, although we suggest that you initiate and complete the organ dysfunction studies as early as possible. Please submit your proposed study protocols in patients with renal or hepatic impairment for the Agency's review before initiating these studies. In addition, please also submit the following study reports:

- Bioanalytical methods validation reports for crizotinib and any active metabolites
- Non-clinical study reports addressing the drug-drug interaction potential of crizotinib

**Sponsor Response:** The Sponsor acknowledges the Agency's response.

The information to support adequate study designs for the hepatic impairment and renal impairment studies is being collected. Pfizer agrees to submit the study protocols to the Agency before the studies are initiated in mid 2011. Pfizer will submit the final study reports when completed.

As part of the NDA submission for accelerated approval, Pfizer will submit the appropriate bioanalytical method validation reports and non-clinical reports addressing the drug-drug interaction potential of crizotinib.

**Meeting Discussion:** This may be acceptable.

**Question 13:** Does the Agency concur with the proposed population pharmacokinetic analysis plan including data from Study A8081001 and A8081005 but not including data from healthy volunteer studies?

**FDA Response:** If there are clear differences in the PK between healthy subjects and cancer patients that are not easily explainable by covariates, it is reasonable to exclude data from healthy volunteers in your population PK analysis. You will need to provide a justification for excluding data from healthy volunteers.

This justification should include comparisons of both PK parameters and time courses of crizotinib concentrations for both healthy subject and patients.

We recommended that you conduct exposure-response analyses, where possible, to support the effectiveness and safety of crizotinib.

In your NDA submission, please submit the pharmacokinetic datasets including individual concentration vs. time and corresponding pharmacokinetic parameters by patient as SAS transport files. The following are the general expectations for submitting pharmacometric data and models:

- All datasets used for model development and validation should be submitted as a SAS transport files (\*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
- Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with \*.txt extension (e.g.: myfile\_ctl.txt, myfile\_out.txt).
- A model development decision tree and/or table which gives an overview of modeling steps.

For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual predication line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.

**Sponsor Response:** Due to the timing of the PK data availability from completed and ongoing studies, POPPK analysis and PK/PD modeling will be performed in 2 stages:

Stage 1: In the submission for accelerated approval, POPPK analysis will be conducted and reported using data (up to the time of data cutoff for the submission) in cancer patients from Study A8081001 and A8081005. Demographic factors, as well as measures of renal and hepatic status which may affect the disposition of crizotinib will be explored. Based on the timing of patient and healthy volunteer studies, Pfizer could include two patient studies (A8081001 and A8081005) containing ~ 230 patients and two single dose healthy volunteer studies (A8081008 and A8081009) containing 30 patients for POPPK analysis at Stage 1. Because the patient study A8081001 includes dense PK sampling in ~150 patients and the number of subjects in the two healthy volunteer studies is small relative to the two patient studies, inclusion of the healthy volunteer data should not meaningfully alter the results obtained by modeling the patient data alone. Therefore, Pfizer does not plan to include the PK data from these two healthy volunteer studies in the POPPK analysis in the submission for accelerated approval.

Stage 2: In the submission for full approval, updated POPPK analysis will be conducted and reported using pooled data from patient studies including but not limited to A8081001, A8081005, A8081007 (phase 3) and completed healthy volunteer studies.

The full POPPK data analysis plan entitled "Population Pharmacokinetics of Crizotinib in Subjects Included in Clinical Pharmacology Evaluations" will be provided upon the completion of the Stage 1 analysis. In addition, a population PK-PD analysis will be conducted to assess the correlation of crizotinib plasma exposure with selected efficacy and safety/tolerability endpoints from studies in patients with ALK (+) NSCLC.

Pfizer agrees to submit the dataset and population analysis reports according to the Agency's requirements listed in the FDA response as described above.

Does the Agency concur with this plan?

**Meeting Discussion: This is acceptable.**

**Question 14:** Does the Agency agree that the proposed NDA package and the overall strategy for biopharmaceutics and clinical pharmacology are adequate to support accelerated approval of crizotinib?

**FDA Response:** Please see Responses to Questions 10-13.

#### **Additional Comments**

1. In light of the criteria for accelerated approval, please state whether you have collected data, from patients enrolled in A8081001, concerning the patient's prior chemotherapy.

**Sponsor Response:** Yes, this data is being collected.

2. Please provide an analysis of all patients experiencing ocular toxicities. Please provide information regarding the severity and reversibility of the toxicity and the extent and conclusion of the work-up for each patient.

**Sponsor Response:** Several analyses will be performed to understand ocular toxicity. All available information will be provided by Pfizer.

3. Your response waterfall plot includes patients with a reported best response of stable disease and a decrease in tumor size of >30%. Please explain how these response designations were determined.

**Sponsor Response:** At the time that this waterfall plot was produced there were several patients who had not yet had confirmation of response or progressed/discontinued before response could be confirmed.

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-73544	GI-1	PFIZER INC	PF-02341066

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FOOD AND DRUG ADMINISTRATION

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**Meeting Date and Time:** April 14, 2010 4:00 p.m.  
**Meeting Type:** Type B  
**Meeting Category:** End of Phase 3  
**Meeting Location:** Bldg. 22, Room 1313  
**Application Number:** IND 073544  
**Product Name:** PF-02341066  
**Received Briefing Package** March 15, 2010  
**Sponsor Name:** Pfizer, Inc.  
**Meeting Requestor:** Ron Domingo, MS., RAC  
**Meeting Chair:** Virginia Ellen Maher, M.D., Medical Team Leader, DDOP  
**Meeting Recorder:** Diane Hanner, Senior Program Management Officer, DDOP

**Meeting Attendees:**

- Silvia Chioato, Ph.D., Director, Worldwide Regulatory Strategy Oncology
- Victoria Cohan, Ph.D., Senior Director, Asset Team Leader
- Mace Rothenberg, M.D., Senior Vice President, Clinical Development and Medical Affairs
- Hakan Sakul, M.S., Ph.D., Senior Director and Global Head of Diagnostics
- Paulina (Nina) Selaru, M.S., M.S.P.H., Assoc. Director, Statistics Asset Lead
- Jamey Skillings, M.D., M.S.C., M.B.A., Senior Director, Global Clinical Lead
- Maurizio Voi, M.D., Vice President, Thoracic Tumor Strategy Team Leader, Oncology
- Keith Wilner, Ph.D., Senior Director, Clinical Lead
- Ron Domingo, M.S., R.A.C., Manager, Regulatory Affairs

**Attendee from Abbott Molecular**

- Pamela Swatkowski, B.S., Director, Regulatory Affairs

**Consultant**

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### **FDA Attendees**

- Richard Pazdur, M.D., Director, OODP
- Robert Justice, M.D., M.S., Director DDOP
- Anthony Murgo, M.D., Acting Deputy Director, DDOP
- Virginia Ellen Maher, M.D., Medical Team Leader, DDOP
- Ian Waxman, M.D., Medical Officer
- Jennie Chang, Ph.D., Medical Officer
- Gideon Blumenthal, M.D., Medical Officer
- Shakun Malik, M.D., Medical Officer
- Qin Ryan, M.D., Medical Officer, DDOP
- Joseph Grillo, Ph.D., Clinical Pharmacology Reviewer, DCP5
- Qi Liu, Ph.D., Acting Clinical Pharmacology Team Leader, DCP5
- Christine Garnett, Ph.D., Senior Staff Fellow, DCRP
- Huanyu Chen Ph.D., Biostatistics Reviewer, DBV
- Kun He, Ph.D., Acting Biostatistics Team Leader, DBV
- Robeena Aziz, Ph.D., Pharmacology Toxicology Reviewer, DDOP
- Reena, Phillip, Ph.D., Scientific Reviewer, DIHD, OIVD
- Elizabeth Mansfield, M.D., Director Personalized Medicine
- Maria M. Chan, Ph.D., Division Director for DIHD
- Karen E. Bijwaard, Ph.D., Regulatory Review, OIVD
- Nitin Mehrotra, Ph.D., Office of Combination Products
- Christine, Garnett, Ph.D., Office of Combination Products
- Diane Hanner, M.P.H., M.S.W., Senior Program Management Officer, DDOP

### **BACKGROUND**

Pfizer requested this meeting in order to gain FDA concurrence regarding their registration strategy and registrational study design for PF-02341066. This study will be conducted in patients with advanced NSCLC patients who have had no previous therapy in the metastatic setting and who have tumors positive for an ALK fusion.

## DISCUSSION

### Pfizer Response:

In this meeting we would like to discuss

- accelerated approval with conversion to full approval based on the ongoing A8081007 trial (Phase 3 in previously treated patients).
- the A8081014 trial supporting the first line indication.

### Question 1a:

If the safety profile remains acceptable, and the observed results for ORR are maintained after at least 100 patients are evaluated in Studies A8081001 and A8081005, would it be acceptable to submit these data as the basis for accelerated approval under Subpart H, providing there is an Agency agreed upon mechanism for the Sponsor to provide ALK testing after approval?

**FDA Response: Yes. It would be acceptable to submit such data as the basis for accelerated approval. However, whether such response rate data would support accelerated approval is a review issue and will depend on the final response rate, durations of response, and the risk:benefit ratio. Please comment on the size of your safety database at the time of submission. We remind you that your confirmatory studies should be on-going at the time of approval.**

### Pfizer Response:

The safety database at submission for accelerated approval would include 200-250 patients (predominately US) from all non-randomized studies. Details will be discussed at a pre-NDA meeting, which will be requested later this year.

**Meeting Discussion: The safety database may be acceptable. However, this will be a review issue.**

### Question 1b:

Does the Agency agree with the diagnostic plan to support accelerated approval and the mechanism to provide ALK testing until the PMA is granted?

**FDA Response: CDRH requires further information about LDT prior to making this determination.**

### Pfizer Response:

We have initiated the scheduling of a meeting with CDRH/OIVD to discuss FDA's expectations for a diagnostic in conjunction with accelerated approval. We request that members from CDER attend the meeting (in person).

Could the Agency clarify whether making the IUO available through reference labs at the time of launch will be acceptable?

Could the Agency provide in writing what additional information is needed regarding the LDT?

**Meeting Discussion: CDRH expects that the test that will be used to determine eligibility for treatment under accelerated approval is substantially similar in performance to the test used to enroll patients in the trial. In addition, in order for the investigational test to be considered, analytical validation data should be provided to OIVD.**

**Question 2:**

Given the small number of NSCLC patients with a fusion event involving the ALK gene locus, does the Agency agree that one adequate and well-conducted pivotal phase 3 study (A8081014) meeting the primary efficacy assumptions with an acceptable safety profile is sufficient to submit an sNDA for full approval for patients previously untreated in the metastatic setting?

**FDA Response: For a single randomized trial to support an NDA, the trial must be well-designed, well-executed, internally consistent and provide statistically persuasive efficacy findings so that a second trial would be ethically or practically impossible to perform.**

**We recommend that you use overall survival as your primary endpoint in the first-line treatment of patients with Stage IIIB/IV NSCLC who have a translocation or inversion event involving the ALK gene. Whether the use of PFS will be able to support full approval of crizotinib will be a review issue and will likely be discussed at ODAC. Please note that the magnitude of improvement in PFS will be a review issue. We would expect your drug to have a greater effect on PFS (e.g., six month improvement in medians) than what you have postulated.**

**Pfizer Response:**

We believe that progression free survival should be the primary endpoint and overall survival a secondary endpoint given the expected subsequent treatment with crizotinib and other investigational ALK inhibitors, which will be in clinical trials and would likely confound the assessment of survival. In the previous meeting with FDA in April 2009 there was agreement that PFS is an acceptable endpoint for a targeted therapy such as crizotinib for full approval given a large effect size and an acceptable risk to benefit ratio.

Is it the Agency's opinion that survival is the only acceptable primary endpoint in a first-line setting for this patient population (ALK-positive)?

In what circumstance could PFS be used as a primary endpoint?

**Meeting Discussion: FDA emphasized that it will be necessary to demonstrate clinical benefit and that a first line trial should be powered for OS. A large difference in PFS combined with an acceptable safety profile may be acceptable. However, this will be a review issue.**

**Question 3a:**

Does the Agency agree that PFS is an acceptable primary endpoint for full approval for the proposed indication?

**FDA Response: OS is the preferred primary endpoint, and the trial should be adequately powered to detect an improvement in OS.**

**See response to Question 2.**

**Question 3b:**

Does the Agency agree that a minimum improvement of 50% in the median PFS (e.g. 6 months for chemotherapy to 9 months for crizotinib) with an acceptable safety profile may be regarded as clinically significant and would support the approval for the proposed indication?

**FDA Response: See responses to Questions 2 and 3a..**

**Question 3c:**

Does the Agency agree with the proposed secondary efficacy endpoints: ORR, overall survival (OS; including 6-month and 1-year survival probabilities), duration of response (DR) and patient reported outcomes (PRO; including health-related quality of life, lung cancer disease/treatment-related symptoms, and general health status) for full approval of the proposed indication? The Sponsor is not planning to seek a label claim with the PRO results.

**FDA Response: See response to Question 3a.**

**Question 4a:**

Does the Agency agree that the assumptions used for sample size calculation, as specified in the draft protocol, are adequate for evaluating the primary endpoint of PFS?

**FDA Response:** See response to Question 3a.

**Question 4b:**

The sample size of 320 patients includes 40 patients to account for PFS events being censored due to potential discordance between the investigator and independent radiology review of tumor assessment. Based on the Agency's recent experience with PFS as an endpoint in solid tumor studies, does the Agency agree that this is adequate.

**FDA Response:** See response to Question 3a.

**Question 5:**

Does the Agency agree that the proposed interim analyses (the first based on ORR after 100 randomized patients have been followed for at least 12 weeks and the second based on PFS after 70% of PFS events have been documented by independent radiology review) are adequate to assess safety, futility, and efficacy?

**FDA Response:** We *strongly* discourage an interim PFS analysis for the efficacy claim because an interim analysis of PFS may not represent an accurate or reproducible estimate of the treatment effect size due to inadequate follow-up, missing assessments, disagreements between radiological reviewers and/or disagreements between investigator and independent assessments. Stopping a trial based on interim PFS results which may not be verifiable after adjudication can be problematic and the trial results, in particular, may not be interpretable if the treatment in the control group was changed based on the interim results.

**Pfizer Response:**

Assuming we have reached agreement on using PFS as the primary endpoint for the study we would like to discuss the use of interim analysis data for approval. We understand the FDA's comments and to mitigate these concerns our proposal is for this interim analysis to be based on events determined by the independent radiology review including adjudication as appropriate. We would like to note that we expect greater than 90% of patients to be enrolled at the time of interim analysis. The independent radiology review uses a 72 hour turnaround period if progression is suspected by the investigator. In addition:

- the data used for interim analysis will be cleaned to satisfy submission quality requirements

- we will minimize the time between the data used for analysis and DMC review
- the DMC will be provided with sensitivity analyses to ensure robustness of efficacy results

It should also be noted that Pfizer submitted an amendment to A8081007 (amendment 2) (Phase 3 trial in previously treated patients) changing the interim analysis from ORR (agreed to with FDA at the April 2009 meeting) to an event driven PFS analysis and provided stopping rules for the study in the Statistical Analysis Plan. Does this remain an acceptable approach to convert from accelerated approval to full approval?

**Meeting Discussion: FDA recommends that the study be powered for OS at the final analysis.**

**Question 6:**

Does the Agency agree that if the primary PFS endpoint meets statistical significance at the pre-planned second interim analysis, these results could be submitted as the basis for full approval?

**FDA Response: No. See response to Question 5.**

**Question 7:**

Does the Agency agree with the proposed eligibility criteria provided in the draft protocol?

**FDA Response: The inclusion criteria should clearly state that eligible patients must have ALK gene locus translocation or inversion events that have been tested with the IUO ALK break-apart FISH assay at the designated central laboratory.**

**It is recommended that patients not be prescreened with a local or a secondary lab test to prevent introduction of bias to your population.**

**The inclusion criteria have been changed to include patients with brain metastases. If there is intent to test brain metastases specimens as well, additional analytical studies will be necessary as this tissue type was not originally indicated.**

**Question 8a:**

Does the Agency agree with the proposed stratification factors (ECOG performance status, prior adjuvant chemotherapy, presence of brain metastases)?

**FDA Response: Yes.**

**Question 8b:**

Does the Agency agree that region is not included as a stratification factor?

**FDA Response: Yes. However, you should ensure that patients entering this trial are representative of those in the US with NSCLC containing ALK rearrangement.**

**Pfizer Response:**

In the event that Pfizer chooses to stratify by region, how would FDA recommend that region be categorized?

**Meeting Discussion: This is your decision.**

**Question 9:**

Does the Agency concur with the investigator's choice of comparator (up to six cycles of pemetrexed/cisplatin or pemetrexed/carboplatin) without subsequent maintenance treatment?

**FDA Response: Please clarify whether patients on the crizotinib arm who have not progressed will continue to receive study drug after 6 cycles. If you are planning to allow crizotinib arm patients to continue treatment until progression regardless of the number of cycles received:**

- **You should give pemetrexed maintenance therapy after 6 cycles of comparator arm therapy, as pemetrexed maintenance has demonstrated a survival advantage over therapy without maintenance in the first-line setting in patients with non-squamous NSCLC; and**
- **You should consider a second randomization of crizotinib arm patients who have not progressed after 6 cycles to continuation of crizotinib vs. observation until progression.**

**Additionally, as bevacizumab has also demonstrated a survival advantage in the first-line setting in patients with non-squamous NSCLC, please comment on why you have chosen not to administer this medication in the comparator arm. Failure to administer appropriate US accepted therapies such as pemetrexed maintenance or bevacizumab may call into question the generalizability and applicability of your trial results.**

**Please comment on your decision to include patients with ECOG PS 2.**

**Please comment on your decision to administer 6 rather than 4 cycles of chemotherapy to patients who do not experience an earlier progression.**

**Pfizer Response:**

We selected pemetrexed with platinum as the active comparator for this trial as this is the recently approved active combination in non-squamous NSCLC, increasingly used as the standard of care world wide and to have a homogeneous comparator to answer the question of crizotinib superiority. In addition, maintenance pemetrexed had not been studied after pemetrexed platinum combination. The chemotherapy will be administered for up to 6 cycles which is an accepted current clinical use of platinum regimens in this setting (in keeping with current ASCO guidelines). Crizotinib will be continued until disease progression is demonstrated at the independent radiology review or as long as clinical benefit is observed by the investigator.

Does the agency agree that this is an adequate comparator?

PS 2 patients are included in the study in view of responses we have seen in preliminary crizotinib data. Pemetrexed/carboplatin is sufficiently well tolerated to be considered a treatment option in PS 2 patients. Given the infrequent occurrence of ALK fusion events we do not want to restrict the population more than necessary.

**Meeting Discussion: This will be a review issue.**

**Question 10:**

Does the Agency concur that it is acceptable to allow patients to cross from the chemotherapy arm to the crizotinib arm upon disease progression determined by independent radiology review?

**FDA Response: Since overall survival is the preferred primary endpoint, cross-over may confound the analysis of this endpoint.**

**Our understanding is that patients who cross over to crizotinib therapy must have centrally determined progressive disease. Is this correct? If so, how will you assure that this review occurs in real time?**

**Pfizer Response:**

Yes, crossover will only occur after progressive disease is centrally determined and the turnaround is 72 hours as described in our response to question 5.

**Question 11:**

Does the Agency agree with the safety assessments and monitoring frequency to assure patient safety as outlined in the draft protocol?

**FDA Response: Please require that at least a limited number of patients who develop visual symptoms be seen by an ophthalmologist and make the results of such exams accessible to FDA.**

**Question 12:**

Would the Agency agree to such retrospective use of these clinical specimens for potential follow-on PMA applications for additional diagnostic tests?

**FDA Response: Retrospective use of clinical specimens could be feasible if test results can be ascertained on a high percentage of trial patients and if the number of samples is sufficiently large for precise estimation of concordance.**

However, please note that an evaluation of concordance only on patients prescreened for ALK positive events is insufficient. Concordance between the current test and a future additional test is evaluated not only on patients who are ALK positive on the current test (positive percent agreement or PPA) but also on patients who are ALK negative on the current test (negative percent agreement or NPA). To evaluate NPA, a subset of samples of patients who are ALK negative on the current test is needed. For the future test to be considered equivalent to the current test, both PPA and NPA should be very high, e.g., significantly greater than 95%. The numbers of ALK negative and ALK positive samples should be large enough to power the study accordingly and we believe that this will require no fewer, or possibly more, than 100 ALK negative samples. Please note that any discordance between a future test and the current test leads to uncertainty in the treatment effect among patients who are ALK positive on the future test. This uncertainty in the treatment effect should be addressed when evaluating the concordance results. Additionally, accrual ALK negative samples for future testing will also likely require revision to the current Informed Consent document (A8081007, Version 4 Effective 06/MAY/2009).

Since there may also be additional issues regarding specimens and technology, CDRH strongly recommends that you submit a preIDE describing your future plans regarding next generation tests which include draft protocols for review and comment.

**Additional FDA Comments:**

1. Please provide a comprehensive list of CYP3A4 inhibitors and inducers and substrates in an Appendix.
2. Although not clearly mentioned in the protocol, we assume that you will make an effort to collect PK data from most of patients in the pivotal trial. The data from the relevant studies then must be combined to develop exposure-response for safety and effectiveness endpoints. The goals of these analyses are:
  - To provide supportive evidence of effectiveness
  - To support the dosing recommendations

**Pfizer Response:**

The appendix requested will be provided.

Population PK collection and analysis is an integral part of our studies.

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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IND-73544

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PFIZER INC

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PF-02341066

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**FOOD AND DRUG ADMINISTRATION**

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**Meeting Date and Time:** April 23, 2009 2:00 p.m.  
**Meeting Type:** Type B  
**Meeting Category:** End of Phase 2  
**Meeting Location:** Bldg. 22, Room 1309  
**Application Number:** IND 73,544  
**Product Name:** PF-02341066  
**Received Briefing Package:** March 27, 2009  
**Sponsor Name:** Pfizer, Inc.  
**Meeting Requestor:** Ron Domingo, MS., RAC  
**Meeting Chair:** Virginia Ellen Maher, M.D., Medical Team Leader, DDOP  
**Meeting Recorder:** Diane Hanner, RPM

**Meeting Attendees:**

- Mace Rothenberg, M.D., Senior Vice President, Clinical Development and Medical Affairs
- Keith Wilner, Ph.D., Senior Director, Clinical
- Diane Matsumoto, Ph.D., Associate Research Fellow, Toxicology
- James Christensen, Ph.D., Director, Translational Research
- Weiwei Tan, Ph.D., Associate Director, Clinical Pharmacology
- Greg Wei, Ph.D., Director, Statistics
- Hakan Sakul, Ph.D., Senior Director, Molecular Medicine
- David Readett, B.Med.Sci., B.M., B.S., MRCP, Senior Director, Oncology
- [REDACTED]
- Laurie Strawn, Ph.D., Senior Director, Regulatory Affairs
- Ron Domingo, M.S., Manager, Regulatory Affairs

**Teleconference Attendees:**

- Zuleima Aguilar, Ph.D., Team Leader
- Victoria Cohan, Ph.D., Team Leader
- Sophia Randolph, M.D., PhD, Director Translational Medicine
- Natalie Limmer, M.B.A., Director, Operations
- Martin Shreeve, M.D., PhD, Associate Director, Clinical Lead
- Shreesh Srinivasa, Ph.D., Associate Director, Molecular Medicine

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**FDA Attendees**

- Richard Pazdur, M.D., Director, OODP
- Anthony Murgo, M.D., Acting Deputy Director, DDOP
- Virginia Ellen Maher, M.D., Medical Team Leader, DDOP
- Qin Ryan, M.D., Medical Officer, DDOP
- Joseph Grillo, Ph.D., Clinical Pharmacology Reviewer, DCP5
- Qi Liu, Ph.D., Acting Clinical Pharmacology Teamleader, DCP5
- Christine Garnett, Ph.D., Senior Staff Fellow, DCRP
- Huanyu Chen Ph.D., Biostatistics Reviewer, DBV
- Kun He, Ph.D., Acting Biostatistics Teamleader, DBV
- Robeena Aziz, Ph.D., Pharmacology Toxicology Reviewer, DDOP
- Reena, Phillip, Ph.D., Scientific Reviewer, DIHD, OIVD
- Diane Hanner, M.P.H., M.S.W., Senior Program Management Officer, DDOP

**DISCUSSION**

**SPONSOR QUESTIONS:**

**Question 1:** Based on our estimation of 6,000 patients/year in the US and up to 40,000 patients/year worldwide with tumors harboring an EML4-ALK fusion event, Pfizer plans to submit a request for orphan drug designation. Does the Agency concur that this molecularly-defined subpopulation of NSCLC patients meets the disease condition of less than 200,000 people in the United States for which the drug is intended?

**FDA Response:** Your orphan drug application should be submitted to the orphan drug office for their review.

**Meeting Discussion:** None

**Question 2:** Does the Agency concur that advanced NSCLC patients with tumors harboring an EML4-ALK fusion represent an appropriately defined population with an unmet medical need qualifying under 21 CFR 312, Subpart E and 21 CFR 314, Subpart H?

**FDA Response:** The sponsor must show convincing evidence that patients with tumors harboring an EML4-ALK fusion do not respond or benefit from currently approved drugs for the treatment of advanced NSCLC. Your current submission does not provide this support.

**Pfizer Response:** Subsequent to submitting the briefing package for this meeting, the Sponsor completed collection of prior treatment data for patients with tumors harboring EML4-ALK fusions who enrolled in Study A8081001. Table 1 shows the previous treatments and responses for these patients. The previous systemic therapies are shown in chronological order for each patient.

Of the 14 patients who have had at least one on-treatment scan (i.e. evaluable patients), only 2 experienced partial responses on prior treatment, despite the fact that most of the patients received multiple lines of treatment. These data support those provided by Dr. Shaw and her colleagues (A. Shaw et al, in Appendix x of the briefing package submitted 26 March 2009, SN0029). This recent retrospective analysis demonstrated that patients with tumors harboring EML4-ALK fusions do not generally also have EGFR mutations and therefore, do not respond to EGFR inhibitors. There was some benefit to first-line chemotherapy similar to what is observed in the general advanced NSCLC population, although the number of patients analyzed was small. However, the patients on Study A8081001 did not generally appear to experience objective responses in the first-line or subsequent lines of therapy.

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**Table 1: Previous Systemic Treatment of NSCLC in Patients Enrolled in Protocol A8081001**

Patient ID	Treatments	BR	Duration	BR on PF-02341066
<b>Evaluable Patients in A8081001</b>				
10081001	Erlotinib	PD	N/A	PR (6 mo +)*
	Erlotinib/Paclitaxel/Carbo	PR	4 mo.	
10021038	Docetaxel/Cis	SD	2 mo.	PR (4 mo +)
	Erlotinib	SD	2 mo.	
10071016	Vinorelbine/Cis	PD	N/A	PR (2 mo +)
	Paclitaxel/Cis/Carbo	PD	N/A	
	Gem/Cis	PD	N/A	
10021039	Navelbine//Cis	PD	N/A	PR (3 mo +)
10021043	Gem/Carboplatin	PD	N/A	PR (2 mo +)
	Pemetrexed	SD	8 mo.	
10071019	Gem/Cis	PD	N/A	PR (unconfirmed)
	Docetaxel	SD	4 mo.	
	Gefitinib	PD	N/A	
	Vinorelbine/Itofamide/Mesna	SD	5 mo.	
	Paclitaxel/Carbo	SD	4 mo.	
	Pemetrexed	SD	9 mo.	
	Irinotecan	PD	N/A	
10021042	Pemetrexel/Cis	SD	5 mo.	PR
10021045	Paclitaxel/Carbo/Bevacizumab	SD	4 mo.	SD (3 mo +)
10021014	Gem/Cis	SD	3 mo.	SD (5 mo)

	Erlotinib	PD	N/A	
10021040	Erlotinib	PD	N/A	SD (4 mo)
10021026	Pem/Cis	SD	4 mo.	SD (10 mo)
	Erlotinib	PD	N/A	
	Pemetrexed	PD	N/A	
10021051	Cetaximab/Navelbine/Cis	PD	N/A	PD
10051003	Erlotinib	PD	N/A	PD
	Paclitaxel/Carbo/Bevacizumab	PR	4 mo.	
	Bevacizumab	PR	11 mo.	
	Pemetrexed	SD	7 mo.	
	Gemcitabine	SD	2 mo.	
10071021	Paclitaxel/Cis/Carbo	SD	2 mo.	PD
	Gem/Cis/Carbo	SD	4 mo.	
	Erlotinib	SD	1 mo.	

BR: best response; pem: pemetrexed; cis: cisplatin; carbo: carboplatin

\*Number in parentheses indicate duration of PR or duration of stable disease; a "+" indicates that a patient is still receiving treatment on study

Patients not yet evaluable indicate that there has not yet been an on-drug scan

**Question A:** Based on this additional information on limited responses to prior treatment for the patients enrolled in Study A8081001 and the lack of treatments available for refractory NSCLC patients, does the Agency agree that this patient population has an unmet medical need and qualifies for consideration under Subpart H? See also the Sponsor response to Question 3 for additional justification for a single-arm study.

**Meeting Discussion:** FDA expressed concern about the size of the database. FDA believes that the most expeditious way to develop this drug is to conduct a randomized trial against conventional therapy (Docetaxel or Pemetrexed).

The use of an interim analysis of response rate for accelerated approval, with a final analysis of progression free survival was discussed. The increase in PFS will be discussed outside this meeting.

**Question 3:** Does the Agency agree with the use of single-agent, targeted therapeutic, PF-02341066, in this molecularly-defined patient population for the pivotal, single-arm trial in previously-treated patients?

**FDA Response:** A single arm trial must define a population that would not benefit from available therapy. In addition, the response rate that you achieve must be reasonably likely to predict a clinical benefit (i.e., a survival improvement). We suggest that if you pursue accelerated approval that you entertain a randomized study with an interim analysis of a surrogate end point in a larger population.

**Pfizer Response:** The ORR in the current protocol of 50% (7/14 patients) in patients who generally did not respond to chemotherapy is much higher than that observed of approximately 10% with second-line chemotherapy currently available, and is also higher than the ORR for first-line treatments. These preliminary results are consistent with PF-02341066 directly targeting the molecular aberration that drives the growth of these oncogene-addicted tumors. This mechanism is also supported by both in vitro data (cell line studies) and in vivo data (mouse model). In addition, the responding patients in the current trial showed symptom improvement typically after just 1-2 cycles of treatment.

For second-line treatment in unselected patient populations, a randomized trial comparing the new drug to an established standard of care is completely reasonable. In the situation with PF-02341066 treatment of patients with EML4-ALK fusions though, there are several potential issues with a randomized study. First, the Sponsor is concerned that investigators may be reluctant to enroll patients on a study where they may be randomized to a more toxic, non-targeted therapy, such as pemetrexed or docetaxel, that does not directly target the molecular defect driving their tumors. The possibility of crossover upon disease progression may be expected, but would lead to confounding of the final survival data. Also, a randomized trial in this very rare patient population would be expected to take longer than a single-arm study, thereby delaying the availability of this potentially effective treatment to patients. Based on the results from the current Phase 1 trial, the retrospective analyses from Dr. Shaw and her colleagues, and the feasibility of completing a randomized trial with chemotherapy as a treatment alternative, we propose that a single arm trial in the second/third-line setting would be the more appropriate study design in this patient population for accelerated approval.

We do plan to conduct a randomized, two-arm study in the first-line treatment setting for clinical benefit confirmation. We acknowledge the caveats to the Agency's agreement to PFS as the primary endpoint provided in the response to Question 11b.

**Meeting Discussion:** See discussion for question 2.

**Question 4:** Does the Agency concur with the proposed indication for accelerated approval, “PF-02341066 is indicated for the treatment of locally advanced or metastatic non-small cell lung cancer after failure of at least one prior systemic treatment regimen in patients with tumors harboring a translocation or inversion event involving the ALK gene locus” for PF-0231006 treatment of this patient population?

**FDA Response:** This is a review issue. See questions 2 & 3 above.

**Pfizer Response:** Addressed in reply to the Agency’s responses to Questions 2 and 3 above.

**Meeting Discussion:** See discussion from question 2.

**Question 5:** Given the small number of NSCLC patients with an EML4-ALK fusion, does the Agency agree that one adequate pivotal single-arm study enrolling 80 patients and achieving the primary endpoint of ORR with an acceptable safety profile is sufficient for accelerated approval?

**FDA Response:** See questions 2 & 3 above.

**Pfizer Response:** Addressed in reply to the Agency’s responses to Questions 2 and 3 above.

**Meeting Discussion:** See discussion from question 2.

**Question 6:** Does the Agency agree with the proposed eligibility criteria provided in the protocol synopsis for Study A8081005 and summarized in Section 6.2.4?

**FDA Response:** See questions 2 & 3 above.

For accelerated approval based on a single arm study in this indication, you should define a population that would not benefit or respond to available therapy.

The third bullet in Key Eligibility Criteria (section 6.3.5) specifies "Positive for translocation or inversion events involving the ALK gene locus (e.g., EML4-ALK fusion)." A means for detecting ALK inversions is not clearly described in your briefing package. Please describe whether/how you intend to detect such inversions exclusively.

Please describe whether your eligibility criteria include patients with any translocation involving ALK (as written in the criterion), or only patients with an EML4-ALK fusion (as implied by your assay description in section 7.5). If you intend to include all ALK-translocation patients, describe why patients with translocations other than EML4-ALK are appropriate for inclusion in your trial. If you intend to include only patients with EML4-ALK fusions, describe whether/how the FISH test is specific for EML4-ALK fusions. The cytogenetic (FISH) detection of translocations and/or inversions (present separately or together) is only vaguely described in the materials received.

**Pfizer Response:** Based on the FDA response, we propose that the eligibility criteria (Section 6.3.5 of Protocol A8081005) will be modified as follows: “Positive for translocation or inversion events involving the ALK gene locus (e.g. resulting in EML4-ALK fusion) as determined by an ALK break apart FISH assay and defined by an increase in the proximity of 5’ and 3’ ALK probes or the loss of the 5’ probe.”

ALK and EML4 reside adjacent to each other in opposite orientation on chromosome 2p. The ALK break apart FISH assay is based on a dual color probe which is designed to distinguish the 5’ region of the ALK gene locus (green) from the 3’ region of the ALK gene locus (orange). The EML4-ALK fusion event (resulting from the inversion of the EML4 gene locus including 5’ end of ALK gene) can be detected by the spatial separation of the 5’ and 3’ ALK probes. According to current published reports, EML4 is the predominant fusion partner in NSCLC. The ALK break apart FISH assay is the primary screening assay for A8081001 and the majority of patients enrolled have exhibited a spatial separation of the 5’ and 3’ ALK probes. Additional analyses of enrolled patients and evaluation of archived lung adenocarcinoma samples have determined that a spatial separation of the 5’ and 3’ ALK probes is associated with the detection of an EML4-ALK fusion product by a PCR based assay. In addition, the loss of 5’ ALK probe (which is predicted to be due to translocation of yet unknown genes) leading to the expression of ALK fusion protein is predicted to respond to PF-02341066 based on nonclinical data generated in tumor cell lines (e.g., anaplastic large cell lymphoma). At least two such patients have been enrolled in our Phase 1 study A8081001. Therefore, we propose that the ALK break apart FISH assay will be utilized as the primary screening assay and that patients exhibiting either a spatial separation of 5’ and 3’ probes or loss of detection of the 5’ probe which would reflect presence of EML4-ALK or other ALK fusion partners will be utilized to define patient eligibility for the proposed trial.

**Meeting Discussion:** This should be discussed in a separate meeting with CDRH. FDA stressed the point that the test used for the study should be the same as that for registration and marketing.

**Question 6a:** We plan to also include patients who received only erlotinib as prior treatment. Is this acceptable?

**FDA Response:** See questions 2 & 3 above.

**Pfizer Response:** The Sponsor would like to discuss this further along with the responses to Questions 2 and 3.

**Meeting Discussion:** Prior exposure to erlotinib as first line treatment is acceptable in a randomized trial.

**Question 7:** The Sponsor plans to use RECIST version 1.0 for Study A8081005. Does the Agency concur?

**FDA Response:** Yes.

**Meeting Discussion:** None

**Question 8:** We plan to assess ORR as the primary endpoint and DR, DCR, PFS, OS, and PRO as secondary endpoints. The Sponsor is not planning on seeking a label claim for the PRO endpoints. Does the Agency agree with the choice of ORR as primary endpoint and DR, DCR, PFS and OS as secondary endpoints for accelerated approval for the proposed indication?

**FDA Response:** No. Please see questions 2 & 3 above. Time to event endpoints, such as PFS, OS in a single arm study can only be considered as exploratory.

**Pfizer Response:** Addressed in reply to the Agency's responses to Questions 2 and 3 above.

**Meeting Discussion:** See discussion to question 2.

**Question 8a:** If ORR is an acceptable primary endpoint, is an ORR of 40% acceptable for accelerated approval?

**FDA Response:** The magnitude of the ORR and the duration of response (along with the safety profile) that is reasonably likely to demonstrate clinical benefit will be a review issue. We note that the hypothesis testing proposed in your protocol will test  $H_0: ORR \leq 10\%$  vs.  $H_A: ORR > 40\%$ . This is problematic since responses in this range have not correlated with an improvement in overall survival.

**Pfizer Response:** With the historic ORR elevated from 10% to 20% in  $H_0$ , 80 patients will provide 98% power to detect a 20% (20% vs 40%) improvement in the proposed single arm study, using a one-sided test with a significance level at 2.5%.

**Meeting Discussion:** The sponsor proposed a single arm study enrolling patients who progressed from the chemotherapy control arm of the PF-02341066 randomized trial. This study will also allow patients who are not eligible for the randomized study to have access to the PF-02341066. The end point will be objective response rate in this study.

FDA stated that the single arm study data will only be considered as supplemental to the randomized trial. The single arm study alone will not be considered for registration.

**Questions 9:** Does the Agency agree with the safety assessments and monitoring frequency to assure patient safety, as outlined in the protocol synopsis (Attachment 1)?

**FDA Response:**

The information provided is insufficient for us to determine the adequacy of your safety monitoring plan. Please provide additional information concerning the related monoclonal antibody that has been associated with ocular toxicity (pg 24). Please provide additional information concerning the visual disturbances seen in the patients treated to date (e.g., visual acuity, visual fields, evoked potentials, etc.). Please present a plan to monitor patients for visual disturbances and to obtain ophthalmologic input in patients with such disturbances.

Please present a plan to monitor the effect of study drug on heart rate, QT interval, and left ventricular function.

**Pfizer Response:** The c-Met/HGFR monoclonal antibody for which an ocular safety finding was identified was CE-355,621, a monoclonal antibody intended to block ligand binding at the c-Met/HGFR receptor. In in vitro evaluations with CE-355,621, transient agonist activity was exhibited as a 3-fold increase in c-Met/HGFR receptor phosphorylation. This partial agonist property of CE-355,621 is thought to be responsible for the observation of melanocyte hyperplasia of the choroid and ciliary body in a 29-day cynomolgus monkey study following a single intravenous injection. In this study, the ocular changes were observed in all animals that had monoclonal antibody levels at predicted clinically relevant exposure throughout the 29 days.

A number of reports are supportive for the hypothesis that c-Met activation leads to melanocyte proliferation. Activation of the c-Met/HGFR receptor on melanocytes was shown to increase proliferation and further differentiation of melanoblasts by Hirobe, et al. (2004).

Additional reports in transgenic mice with overexpression of HGF also provided evidence of increased melanocyte proliferation. These animals exhibited hyperpigmentation in the skin of the extremities (Takayama et al 1997) and a number of tumors including mammary carcinomas, liver adenomas and sarcomas, as well as melanomas in skin (Otsuka et al 1998). There was also one animal that exhibited an extraorbital melanoma.

While CE-355,621 binds to the extracellular domain of the c-Met/HGFR receptor and demonstrated dual receptor agonist and antagonist properties, PF-02341066 binds in the active site of the receptor, inhibiting the catalytic activity of this kinase and has only demonstrated antagonist properties.

As part of a de-risking strategy, an exploratory study in cynomolgus monkeys was conducted to determine the potential for PF-02341066 to cause the ocular lesions observed with CE-355,621. In this non-GLP study, PF-02341066 was administered by oral gavage to cynomolgus monkeys (2/sex) for up to 28 consecutive days at a dose that provided systemic (AUC) exposure approximately 16.3 times the clinical exposure in humans at the recommended dose of 250 mg BID. One female was euthanized moribund on Day 21, but all other animals survived until scheduled euthanasia. The eyes and optic nerves of all monkeys were normal, suggesting that PF-02341066 and CE-355,621 exhibit distinctly different properties based on their modes of interaction with the receptor.

As indicated in Table 1 of the study synopsis provided in Appendix 1 of the briefing package, a baseline ophthalmologic exam will be conducted and additional exams will be conducted if clinically indicated.

In the upcoming PF-02341066 clinical trials, triplicate ECGs, along with time-matched PF-02341066 concentrations, will be collected for each patient at pre-dose and around  $T_{max}$  of PF-02341066 for 3 treatment cycles. Additionally, ECGs will be performed as clinically indicated. The HR interval and QT interval will be assessed as parameters from the ECG recordings. In addition, pulse rate will be monitored with the vitals signs collected throughout the study. No changes in LVF have been observed pre-clinically and there have not been any clinical signs of left ventricular dysfunction in the ongoing Phase 1 trial. Thus, at this time we do not plan to monitor LVF in the proposed trials.

**Question B:** Given that toxicology and clinical data to date have not indicated LV dysfunction, please clarify why LVF monitoring is being requested.

**Meeting Discussion:** The Agency recommends LVF monitoring of subset of patients in the randomized trial. The FDA recommends that the sponsor develop a plan for ophthalmological monitoring for all patients.

**Question 10:** Given the toxicities and limited efficacy of approved drugs for NSCLC, does the Agency agree with the use of single-agent, targeted therapeutic, PF-02341066, in this molecularly-defined patient population for the randomized trial in treatment-naive patients?

**FDA Response:** You have provided us with limited efficacy data concerning your drug and it is premature to answer this question without further clinical data regarding the activity of your drug.

**Meeting Discussion:** None

**Question 11:** Does the Agency agree that one adequate well-controlled randomized study enrolling 309 patients with the primary endpoint of PFS is sufficient for clinical benefit confirmation and full approval?

**FDA Response:** This will be a review issue.

**Meeting Discussion:** None

**Question 11a:** Does the Agency concur with the choice of gemcitabine/cisplatin or paclitaxel/carboplatin as the comparator arm in this trial?

**FDA Response:** Gemcitabine/cisplatin or paclitaxel/carboplatin are acceptable comparators in a first line setting.

**Meeting Discussion:** None

**Question 11b:** If PFS is an acceptable primary endpoint, is an increase in PFS of 50% above the comparator arm acceptable for full approval?

**FDA Response:** The calculated sample size using PFS as the primary endpoint appears acceptable. Since power calculations for a log-rank test are based on the number of events, we recommend pre-specifying the number of events for the timing of the analysis. Whether an improvement in PFS represents a direct clinical benefit of PF-02341066 depends on the magnitude of the effect and the risk-benefit of treatment with PF-02341066 compared to available therapies and will be a review issue.

**Meeting Discussion:** None

**Question 11c:** Does the Agency agree with the choice of OS, ORR, DR and DCR as secondary endpoints?

**FDA Response:** They appear to be acceptable but please see response to question 11.

**Meeting Discussion:** None

**Question 12:** The Sponsor plans to use RECIST version 1.0 for Study A8081007. Does the Agency concur?

**FDA Response:** It is acceptable.

**Meeting Discussion:** None

### 7.3. Safety and Data Monitoring

**Question 13:** Does the Agency concur with this approach to safety data monitoring on these studies as outlined in Sections 6.2.6 and 6.3.7?

**FDA Response:** Please see question 9.

**Pfizer Response:** Addressed in reply to the Agency's responses to Questions 2 and 3 above.

**Meeting Discussion:** See the discussion from question 2.

### 7.4. QT Interval Assessment Plan

The PK/PD modeling analysis of concentration-QTc relationship is being conducted using the time-matched ECG and PK data from the ongoing Phase 1 study (A8081001). The analysis will be extended to the proposed trials and will be detailed in the protocol. A dedicated QTc study with a positive control is not planned in the proposed registration strategy.

**Question 14:** Does the Agency concur with the proposed plan for QT assessment?

**FDA Response:** No, we do not agree. With the following recommendations incorporated, your QT assessment will be acceptable to detect large effects on the QTc interval. In the absence of both positive and negative controls, your QT assessment will not be able to detect small QTc effects (< 10 ms).

We recommend that you incorporate the following comments into your QT assessment plan:

1. In addition to characterizing the concentration-QTc relationship, your analysis plan should include:
  - a. Measures of central tendency: mean change from baseline for QTc, RR, PR and QRS intervals for each time point, including the 2-sided 90% CI.
  - b. Categorical analysis: number and percentage of individuals with:
    - i. Absolute QT/QTc values > 450 ms, >480 ms, and >500 ms; as well as the number and percentage of individuals with change from baseline > 30 ms and > 60 ms.
    - ii. PR changes from baseline  $\geq 50\%$  if absolute baseline value was < 200 ms and  $\geq 25\%$  if absolute baseline value was > 200 ms.
    - iii. QRS changes from baseline  $\geq 50\%$  if absolute baseline value was < 100 ms and  $\geq 25\%$  if absolute baseline value was > 100 ms.
  - c. Number and percentage of individuals with abnormal ECG findings.
  - d. Number and percentage of individuals with AEs that could be associated with prolongation of cardiac repolarization or proarrhythmia, e.g., palpitations, dizziness, syncope, cardiac arrhythmias, and sudden death.
2. For your concentration-QTc analysis, we encourage the exploration of the adequacy of the model fit to the assumption of linearity; therefore, diagnostic evaluation is expected as part of your evaluation. Additional exploratory analyses (via graphical displays and/or model fitting) include accounting for a delayed effect and the justification for the choice of pharmacodynamic model (linear versus nonlinear).
3. The following elements should be included into your assessment of ECGs:
  - a. Use of a central ECG laboratory employing a limited number of skilled readers, to control variability in interpretation
  - b. Blinding of ECG readers to treatment, time, and day identifiers
  - c. Review of all ECGs from a particular subject by a single reader on one day
  - d. Pre-specify the lead for interval measurements
  - e. Baseline and on-treatment ECGs should be based on the same lead

For drugs that affect heart rate, it is important that sufficient drug-free ECG data over a large range of heart rates are collect in individual subjects to allow for the computation of individual-specific heart rate correction factor (QTcI). The use of universal correction formula (e.g., Fridericia, Bazett) and QTcI computed from QT-RR relationship over a narrow range of heart rates may bias your results. If PF-02341066 causes significant heart rate changes, you might consider collecting a full day of baseline ECGs.

**Pfizer Response:** The sponsor agrees and will submit the QT/QTc data from A8081001 along with the overall plan for assessment of QT/QTc prolongation for QT-IRT review.

#### 7.5. Co-Development of ALK Diagnostic Test

The presence of an EML4-ALK fusion event in NSCLC patients will be required for eligibility into the pivotal study, and these patients are also the target population for the label indication. Thus, a diagnostic test for identification of EML4-ALK fusion will be developed in parallel to the drug development.

Enrollment in the ongoing Phase 1 trial is based upon a research use only (RUO) Fluorescence In Situ Hybridization (FISH) assay. The assay utilizes ALK break-apart probes to evaluate the EML4-ALK fusion event through a fluorescence proximity assessment assay (conducted by Dr. <sup>(b) (4)</sup>). <sup>(b) (4)</sup>. EML4-ALK fusion event is detected by greater than normal distance between the two probes directed against the ALK gene on chromosome 2. Although Immunohistochemistry (IHC) and Reverse Transcriptase PCR (RT-PCR) have been used to detect ALK fusions, FISH methodology appears to be the most robust technology currently available.

Therefore, we will engage a diagnostics company with a CLIA-certified laboratory for the development of a FISH-based RUO diagnostic assay, with the intent to convert this into an IUO test for patient enrollment in our upcoming trials.

**Question 15:** Does the Agency agree that an RUO assay developed by a CLIA-certified laboratory facility would be sufficient for enrollment in the pivotal trial?

**FDA Response:** Sponsor should bring the assay to an IUO (Investigational Use only) status, including the design controls, in time for use in the pivotal trial.

**Meeting Discussion:** None

### 7.5.1. Timelines for Assay Development

Pfizer intends to immediately start the development of a FISH-based RUO assay with a diagnostic partner for use in the pivotal trial.

Concurrent with the development of the RUO assay, we and our diagnostic partner in collaboration with the agency expect to convert the RUO to an IUO assay following the pre-IDE and IDE pathway. We will in parallel, explore the potential for IHC and RT-PCR as alternative diagnostic tests.

**Question 16:** Will an IUO assay be sufficient for the accelerated approval of PF-02341066?

**FDA Response:** We do not believe that an IUO assay is sufficient for accelerated approval of the drug. The sponsor would need approval of the marketable test in concert with approval of the drug. The test could be configured for use either in a single laboratory or as a kit sold to many labs.

**Meeting Discussion:** Claims for the test, using a marker-positive pivotal study, would likely be very limited. Sponsor should explore means of establishing a predictive claim for the test.

**Question 17:** Does the Agency recommend an additional meeting to further discuss the diagnostic aspects of this program?

**FDA Response:** Yes, a meeting with OIVD/CDRH (through CDER) is desirable.

**Meeting Discussion:** None

**Question 18:** Does the Agency concur that the proposed non-clinical safety package is adequate to support the proposed registration strategy?

**FDA Response:** The nonclinical studies conducted and/or planned appear adequate to support the proposed phase 2 trial. However, a final decision regarding the adequacy of the study will be made after review of studies submitted with your IND package.

**Meeting Discussion:** None

**Additional Comments:**

The following should be addressed during development:

1. We recommend that you validate the analytical method(s) used to measure the parent drug and any active metabolites according to the principles described in the Guidance for Industry entitled "Bioanalytical Method Validation".

**Pfizer Response:** The sponsor agrees. The analytical method currently used in Study A8081001 for determination of PF-02341066 concentrations has been fully validated according to the FDA Guidance entitled "Bioanalytical Method Validation". New analytical methods may be developed for measurement of metabolite(s) if any active metabolite(s) is identified in humans. All analytical methods used for clinical trials will be fully validated according to the FDA Guidance.

2. We recommend that you conduct a mass balance study to evaluate the disposition of PF-02341066 and its routes of elimination in humans. Based on the results of your ADME study, you may also need to consider studies of the effect of organ impairment on PF-02341066 exposure.

**Pfizer Response:** The Sponsor agrees and a human mass balance study using a single radio-labeled dose is in our plan for PF-02341066 development. We will consider studies of organ impairment depending on the results of human ADME study.

3. We recommend that you assess the activity of the metabolites of PF-02341066. Depending on the activity of the metabolite(s), we recommend that you characterize the pharmacokinetics of the metabolite(s) in your study.

**Pfizer Response:** Any metabolite qualifying for further study based on relative abundance will be synthesized and evaluated in a cell based assay designed to determine its potency for the inhibition of phosphorylated c-Met or ALK as well as evaluation of its potency across a panel of >100 kinases to determine selectivity for c-Met and ALK compared with other potential kinase targets. Based on the relative activity and abundance of the metabolite(s), we will consider characterizing the pharmacokinetics of the metabolite(s).

4. A formal food effect study needs to be conducted per the FDA guidance "Food-Effect Bioavailability and Fed Bioequivalence Studies". This study should be conducted with your final-market-image formulation.

**Pfizer Response:** The Sponsor agrees and a formal food effect study for the final-market-image formulation is planned.

5. You should determine either the absolute or relative bioavailability of your drug in humans.

**Pfizer Response:** Currently the sponsor does not plan to conduct a study of absolute bioavailability during PF-02341066 development. The Sponsor acknowledges the comment regarding relative bioavailability. Studies of relative bioavailability and/or bioequivalence may be conducted to support the development of new formulations.

6. We recommend that you assess whether PF-02341066 is a substrate, inhibitor of P-glycoprotein. These studies may help determine the potential for in vivo drug-drug interactions and the need for in vivo drug-drug interaction studies.

These should be conducted according to the principles described in the Guidance for Industry entitled “Drug Interaction Studies--Study Design, Data Analysis, and Implications for Dosing and Labeling”

**Pfizer Response:** The Sponsor acknowledges the comment. We have determined in Caco-2 and MDCK-MDR1 cell models with addition of potent P-gp inhibitors that PF-02341066 is a P-gp substrate. We will be evaluating whether any further in vivo clinical studies is needed. Regarding the P-gp inhibition, we intend to conduct a definitive in vitro study to evaluate the ability of PF-2341066 to inhibit P-gp and evaluate the need for further clinical studies according to the FDA Guidance.

**Meeting Discussion:** The Sponsor will submit absolute or relative bioavailability data to satisfy the CFR.

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Linked Applications

Sponsor Name

Drug Name / Subject

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IND 73544

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PFIZER INC

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PF-02341066

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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VIRGINIA E MAHER

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