

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202324Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 202324

SUPPL #

HFD # 150

Trade Name Inlyta®

Generic Name axitinib

Applicant Name Pfizer Pharmaceuticals, Inc.

Approval Date, If Known January 27, 2012

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?

Five years of marketing exclusivity for Inlyta

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 similar investigation was relied on:

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: Lisa Skarupa, RN, MSN
Title: Regulatory Project Manager
Date:

Name of Office/Division Director signing form: Amna Ibrahim, MD
Title: Deputy Division Director

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

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

/s/

LISA M SKARUPA
01/31/2012

AMNA IBRAHIM
01/31/2012

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.

Wisan Russell

Signature of Company Representative

03/10/11

Date

090177e181d86455\Final\Final On: 11-Mar-2 17:35

PFIZER CONFIDENTIAL

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 202324 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Inlyta® Established/Proper Name: axitinib Dosage Form: Tablets, 1 mg and 5 mg		Applicant: Pfizer Inc Agent for Applicant (if applicable):
RPM: Lisa Skarupa		Division: DOP1
<p>NDA: 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>505(b)(2) Original NDAs and 505(b)(2) NDA supplements: 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><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></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>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.</p>
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>February 14, 2012 (Actual Action Date January 27, 2012)</u> • Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<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 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____</p>		<input type="checkbox"/> Received

¹ 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.

❖ Application Characteristics ²	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only):</p> <p><input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies</p> <p><input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request</p> <p>BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies</p> <p>REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input type="checkbox"/> REMS not required</p> <p>Comments:</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)	<input type="checkbox"/> Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Press Office notified of action (by OEP)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information dissemination are anticipated	<input type="checkbox"/> None <input checked="" type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other ASCO Burst

² 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"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> 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> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires:
<ul style="list-style-type: none"> (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> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (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> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (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> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> 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> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> 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. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> 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. 	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"> [505(b)(2) applications] If the application includes a paragraph III 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). 	<input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV 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> 	<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

❖ Copy of this Action Package Checklist ³	Yes
Officer/Employee List	
❖ 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>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) January 27, 2012
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	January 26, 2012
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	April 13, 2011
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	NA

³ Fill in blanks with dates of reviews, letters, etc.

❖ 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 checked="" type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	January 26, 2012
<ul style="list-style-type: none"> Original applicant-proposed labeling 	April 13, 2011
<ul style="list-style-type: none"> Example of class labeling, if applicable 	NA
❖ Labels (full color 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"> Most-recent draft labeling 	January 26, 2012
❖ Proprietary Name	
<ul style="list-style-type: none"> Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) Review(s) (<i>indicate date(s)</i>) 	July 7, 2011 July 11, 2011 and January 19, 2012
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	<input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEPA <input checked="" type="checkbox"/> DRISK <input checked="" type="checkbox"/> DDMAC <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	June 21, 2011
❖ 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>)	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> If yes, Center Director's Exception for Review memo (<i>indicate date</i>) If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<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"> Date reviewed by PeRC <u>November 16, 2011</u> If PeRC review not necessary, explain: _____ Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" 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
❖ Outgoing communications (<i>letters (except action letters), emails, faxes, telecons</i>)	(Jan 25, 23, 20, 17, 13, 6, 2012 and Dec 19, 07, 01, and Nov 30, 29,

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

	28, 01 and Oct 18, 2011
❖ Internal memoranda, telecons, etc.	None
❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg Feb 18, 2011, July 12, 2010, Jan 27, 2010, February 3, 2009
• EOP2 meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg CMC EOP2 June 19, 2008, EOP2 May 17, 2007
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	NA
❖ Advisory Committee Meeting(s)	<input type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	December 7, 2011
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	Summary Minutes Dec 7, 2011
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input type="checkbox"/> None January 27, 2012
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None January 26, 2012
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None January 25, 2012
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None January 24, 2012
Clinical Information⁵	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	January 11, 2012
• Clinical review(s) (<i>indicate date for each review</i>)	January 10, 2012
• 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>)	January 10, 2012
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input type="checkbox"/> None IRT Review completed July 21, 2011
❖ 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>)	December 15, 2011
• 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>)	<input type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input type="checkbox"/> None requested December 20, 2011

⁵ Filing reviews should be filed with the discipline reviews.

Clinical Microbiology		<input checked="" type="checkbox"/> None
❖ Clinical Microbiology Team Leader Review(s) <i>(indicate date for each review)</i>		<input type="checkbox"/> None
Clinical Microbiology Review(s) <i>(indicate date for each review)</i>		<input type="checkbox"/> None
Biostatistics		<input type="checkbox"/> None
❖ Statistical Division Director Review(s) <i>(indicate date for each review)</i>		<input type="checkbox"/> None January 11, 2012
Statistical Team Leader Review(s) <i>(indicate date for each review)</i>		<input type="checkbox"/> None January 11, 2012
Statistical Review(s) <i>(indicate date for each review)</i>		<input type="checkbox"/> None January 11, 2012
Clinical Pharmacology		<input type="checkbox"/> None
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>		<input type="checkbox"/> None January 17, 2012
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>		<input type="checkbox"/> None January 17, 2012
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>		<input type="checkbox"/> None January 17, 2012
❖ DSI Clinical Pharmacology Inspection Review Summary <i>(include copies of DSI letters)</i>		<input checked="" type="checkbox"/> None
Nonclinical		<input type="checkbox"/> None
❖ Pharmacology/Toxicology Discipline Reviews		
• ADP/T Review(s) <i>(indicate date for each review)</i>		<input type="checkbox"/> None January 23, 2012
• Supervisory Review(s) <i>(indicate date for each review)</i>		<input type="checkbox"/> None January 6, 2012
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>		<input type="checkbox"/> None January 6, 2012
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>		<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>		<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting		<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary <i>(include copies of DSI letters)</i>		<input checked="" type="checkbox"/> None requested
Product Quality		<input type="checkbox"/> None
❖ Product Quality Discipline Reviews		
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>		<input type="checkbox"/> None January 25, 2012
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>		<input type="checkbox"/> None December 12, 2011
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>		<input type="checkbox"/> None December 12, 2011 x 3 and updated memos January 24 (2) and January 25, 2012
❖ Microbiology Reviews		<input type="checkbox"/> Not needed December 13, 2011
<input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>		
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>		
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>		<input type="checkbox"/> None Mathematical statistician-December 12, 2011

❖ Environmental Assessment (check one) (original and supplemental applications)		
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)		December 12, 2011
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)		NA
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)		NA
❖ Facilities Review/Inspection		
<input checked="" 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 sites⁶</i>)		Date completed: December 4, 2011 <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 type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)

⁶ I.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.

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

/s/

LISA M SKARUPA
01/31/2012

From: [Skarupa, Lisa](#)
To: ["Russell, Alison"](#)
Cc: [Strawn, Laurie](#)
Subject: RE: NDA 202324
Date: Wednesday, January 25, 2012 4:02:00 PM

Dear Alison,

It has been our practice to not share Press Releases with the Applicant. However, I was informed that your Press Office person (Kristen Neese) contacted our Press contact and they spoke this morning. She may be of help.

Lisa

From: Russell, Alison [mailto:Alison.Russell@pfizer.com]
Sent: Wednesday, January 25, 2012 3:04 PM
To: Skarupa, Lisa
Cc: Strawn, Laurie
Subject: NDA 202324

Lisa – I understand that the FDA Press Office will be issuing a press release over the news wire to share with media upon notification of approval. Is it possible for us to review this press release ahead of time?

Alison

Alison Russell
Axitinib Global Regulatory Lead
Pfizer Oncology
Tel: (858) 344-4473
Fax: (877) 481-0933
Assistant: Annette Scuderi (Tel: (858) 622-3031)

From: [Skarupa, Lisa](#)
To: ["Russell, Alison"](#)
Cc: [Strawn, Laurie](#)
Subject: RE: NDA 202324 Inlyta (axitinib) Package Insert and Patient Information
Date: Wednesday, January 25, 2012 10:35:28 AM
Attachments: [FDAResponse_25Jan2012_INLYTA_USPI+PI_TRACKED.doc](#)

Hello Alison,
Please see attached label.

Please help with the formatting of the Highlights so that it fits in one page.

Please review to be sure we got the correct labels, there were a couple versions that Monday.

Sincerely,
Lisa

From: Russell, Alison [mailto:Alison.Russell@pfizer.com]
Sent: Monday, January 23, 2012 12:31 PM
To: Skarupa, Lisa
Cc: Henry, Don; Strawn, Laurie
Subject: RE: NDA 202324 Inlyta (axitinib) Labels and status update

Lisa –

- We did have some changes to the PI – these are shown in tracked changes in the “merged” tracked changes USPI +PI document I sent you earlier today (see re-attached; see pages 19, 22, and 23 for proposed changes)
- I just sent the 1 and 5 mg container labels in a separate email.

Alison

Alison Russell
Axitinib Global Regulatory Lead
Pfizer Oncology
Tel: (858) 344-4473
Fax: (877) 481-0933
Assistant: Annette Scuderi (Tel: (858) 622-3031)

From: Skarupa, Lisa [mailto:Lisa.Skarupa@fda.hhs.gov]
Sent: Monday, January 23, 2012 9:18 AM
To: Russell, Alison
Cc: Henry, Don
Subject: RE: NDA 202324 Inlyta (axitinib) Labels and status update

Dear Alison,

1. We are reviewing the Package Insert.
2. Were all the language in the Patient Information section accepted by Pfizer?
3. Regarding container label, and our comment:
January 20, 2012 FDA Comment: We noted that ‘axitinib’ does not have the same prominence as the proprietary name (Inlyta) and the dosage form (tablets). Please

make 'axitinib' such that it has the same size font and thickness as 'Inlyta' and 'tablets'. Essentially there is no difference in font between all three.

January 23rd FDA response:

To clarify my recommendation, the name, 'axitinib' is stated in thin black font whereas the dosage form, 'tablets' is stated in fatter (bolder) font. The statement 'axitinib' should look the same as 'tablets'. The proprietary name, 'Inlyta' is acceptable as presented.

Please forward your proposed revision by e-mail as soon as possible and we will quickly respond in turn.

Sincerely,
Lisa

From: Russell, Alison [mailto:Alison.Russell@pfizer.com]
Sent: Monday, January 23, 2012 10:31 AM
To: Skarupa, Lisa
Cc: Henry, Don
Subject: RE: NDA 202324 Inlyta (axitinib) Labels and status update

Thanks Lisa.

We are trying to re-do the artwork this morning to send something to FDA later today ...so anything you can do to get back to me ASAP would be appreciated.

I assume you got the USPI + PI documents?

Alison

Alison Russell
Axitinib Global Regulatory Lead
Pfizer Oncology
Tel: (858) 344-4473
Fax: (877) 481-0933
Assistant: Annette Scuderi (Tel: (858) 622-3031)

From: Skarupa, Lisa [mailto:Lisa.Skarupa@fda.hhs.gov]
Sent: Monday, January 23, 2012 7:28 AM
To: Russell, Alison
Cc: Henry, Don
Subject: RE: NDA 202324 Inlyta (axitinib) Labels and status update

Good morning Alison.
I will try to find out for you.

From: Russell, Alison [mailto:Alison.Russell@pfizer.com]
Sent: Monday, January 23, 2012 10:06 AM
To: Skarupa, Lisa
Cc: Henry, Don
Subject: RE: NDA 202324 Inlyta (axitinib) Labels and status update

Lisa – If it's possible for you to send me an actual example of a label with the type of text for generic and trade name that the FDA reviewer is asking for, that would be the most helpful thing for us....

Thanks, Alison

Alison Russell
Axitinib Global Regulatory Lead
Pfizer Oncology
Tel: (858) 344-4473
Fax: (877) 481-0933
Assistant: Annette Scuderi (Tel: (858) 622-3031)

From: Russell, Alison
Sent: Monday, January 23, 2012 6:32 AM
To: 'Skarupa, Lisa'; Henry, Don
Subject: RE: NDA 202324 Inlyta (axitinib) Labels and status update

Lisa/Don - Can someone call me this morning? We would like some clarification regarding the FDA comment on the following comment regarding the container label:

January 20, 2012 FDA Comment: We noted that 'axitinib' does not have the same prominence as the proprietary name (Inlyta) and the dosage form (tablets). Please make 'axitinib' such that it has the same size font and thickness as 'Inlyta' and 'tablets'. Essentially there is no difference in font between all three.

Thank-you,
Alison

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Pfizer Oncology
Tel: (858) 344-4473
Fax: (877) 481-0933
Assistant: Annette Scuderi (Tel: (858) 622-3031)

From: Skarupa, Lisa [mailto:Lisa.Skarupa@fda.hhs.gov]
Sent: Friday, January 20, 2012 8:07 AM
To: Russell, Alison; Strawn, Laurie
Cc: Henry, Don
Subject: NDA 202324 Inlyta (axitinib) Labels and status update

Good morning Alison,

NDA review updates:

1. See attached label and "FDA Response to Labels". This is in response to the Pfizer labels received January 18th.
2. We did receive the email regarding the Pfizer response to CMC deficiencies and understand that official submission will be later today.
3. Proprietary Name re-review concluded the proposed proprietary name Inlyta, did not identify any vulnerability that would result in medication errors.
Inlyta is acceptable.

Administrative:

We are requesting a return of the labels by Monday (January 23rd) so we can stay inline with the reviews to be completed before action date January 27th.

To include Package Insert with Patient Information, ^{(b) (4)} containers.

Official submission does not have to be Monday.

Please let me know if these are acceptable.

24 Page(s) of Draft Labeling has been Withheld in Full
as B4 (CCI/TS) immediately following this page

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

/s/

LISA M SKARUPA
01/31/2012

From: [Russell, Alison](#)
To: [Skarupa, Lisa](#)
Subject: RE: NDA 202324 Inlyta (axitinib) Labels and status update
Date: Monday, January 23, 2012 5:01:07 PM

No, we are only using the bottles. We won't be using the (b) (4).

Alison Russell
Axitinib Global Regulatory Lead
Pfizer Oncology
Tel: (858) 344-4473
Fax: (877) 481-0933
Assistant: Annette Scuderi (Tel: (858) 622-3031)

From: Skarupa, Lisa [mailto:Lisa.Skarupa@fda.hhs.gov]
Sent: Monday, January 23, 2012 1:58 PM
To: Russell, Alison
Subject: FW: NDA 202324 Inlyta (axitinib) Labels and status update

Dear Alison,

Can you tell me if you are still using the (b) (4) labels?

Lisa

From: Skarupa, Lisa
Sent: Monday, January 23, 2012 12:18 PM
To: 'Russell, Alison'
Cc: Henry, Don
Subject: RE: NDA 202324 Inlyta (axitinib) Labels and status update

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Please forward your proposed revision by e-mail as soon as possible and we will quickly respond in turn.

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Sent: Monday, January 23, 2012 10:06 AM
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Lisa – If it's possible for you to send me an actual example of a label with the type of text for generic and trade name that the FDA reviewer is asking for, that would be the most helpful thing for us....

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Sent: Friday, January 20, 2012 8:07 AM
To: Russell, Alison; Strawn, Laurie
Cc: Henry, Don
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Administrative:

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Please let me know if these are acceptable.

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/s/

LISA M SKARUPA
01/31/2012

From: Skarupa, Lisa
To: "Russell, Alison"; Strawn, Laurie
Cc: Pithavala, Yazdi
Subject: NDA 202324 Inlyta (axitinib) Figure 1
Date: Friday, January 20, 2012 4:06:12 PM
Attachments: FDAresponse INLYTA (axitinib) Figure1_20Jan_2012 (4pm).doc

Dear Alison,

The following is the label with the newly placed Figure 1.

Let me know if you have any questions.

Lisa

From: Russell, Alison [mailto:Alison.Russell@pfizer.com]
Sent: Friday, January 20, 2012 1:33 PM
To: Skarupa, Lisa
Cc: Pithavala, Yazdi
Subject: RE: NDA 202324 Inlyta (axitinib) Labels and status update

Lisa –

Regarding FDA comment on Section 12.3 Pharmacokinetics, Drug-Drug Interactions, Figure 1: January 20, 2012: FDA recommendations for Figure 1: "We agree to your proposed change (i.e. Rabeprazole 20 mg QD x 5 days). We request that you update the forest plot using the formatting and text we proposed in the current draft. However, we also request that the text in the first column (population description) and last (recommendation) column be left justified, if possible. Please submit the updated plot for FDA review in the next version of the label submitted for review."

Since the FDA generated this figure, it would be easier if the Agency could update Figure 1 as described above and send this to Pfizer. Alternatively, if this is not feasible/acceptable, we would respectfully request that FDA send us the code used by FDA to generate the figure (and Pfizer will make the revision).

Alison

Alison Russell
Axitinib Global Regulatory Lead
Pfizer Oncology
Tel: (858) 344-4473
Fax: (877) 481-0933
Assistant: Annette Scuderi (Tel: (858) 622-3031)

From: Russell, Alison

Sent: Friday, January 20, 2012 8:15 AM
To: 'Skarupa, Lisa'
Cc: Henry, Don; Strawn, Laurie; Lynch, Michael P; Potter, Lisa M
Subject: RE: NDA 202324 Inlyta (axitinib) Labels and status update

Lisa

I plan to review with the team and will aim to reply via email by Monday 23 January. Just to verify, the CMC responses were officially submitted to FDA today (NDA 202324 SN 0027).

Thank-you,

Alison

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Axitinib Global Regulatory Lead
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Tel: (858) 344-4473
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/s/

LISA M SKARUPA
01/20/2012

From: Russell, Alison [mailto:Alison.Russell@pfizer.com]
Sent: Friday, January 20, 2012 11:15 AM
To: Skarupa, Lisa
Cc: Henry, Don; Strawn, Laurie; Lynch, Michael P; Potter, Lisa M
Subject: RE: NDA 202324 Inlyta (axitinib) Labels and status update

Lisa

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Alison

Alison Russell
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Pfizer Oncology
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From: Skarupa, Lisa [mailto:Lisa.Skarupa@fda.hhs.gov]
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Please let me know if these are acceptable.

Section 6.1 Adverse Reactions

PRIOR Communications:

FDA Suggested Change: FDA made some changes to the frequencies of adverse reactions and laboratory abnormalities in Tables 1 and 2.

Pfizer Response: In Tables 1 and 2, it appears that the modified numbers provided by the FDA for several of the adverse reactions and laboratory abnormalities may include findings that were reported prior to administration of the first dose of axitinib or sorafenib and did not worsen in severity on treatment. If this is the case, the Sponsor requests to retain the original numbers, as the pre-existing adverse events and laboratory abnormalities are clearly not treatment-related or, more importantly, treatment-emergent.

Request for Clarification: If this is not the case, please clarify what the sources of the numbers are.

FDA response: This is acceptable.

In Table 1, the Sponsor would like to add a footnote to explain that frequencies are based on treatment-emergent, all-causality adverse reactions.

In Table 2, Pfizer has made corrections to the (b) (4) hypocalcemia laboratory values, based on the data that were submitted in [A4061032 Clinical Study Report Supplement 2](#) on 9 November 2011, in which calcium levels were corrected for albumin. As a result of the corrections, hypocalcemia moved higher in the table (b) (4)

FDA Response: This is acceptable.

January 20, 2012: FDA response to permanent discontinuations: These are the patients for whom we are counting permanent discontinuations due to an adverse reaction.

<u>Patient ID</u>	<u># of Events</u>
<u>10241009</u>	<u>1</u>
<u>10511001</u>	<u>1</u>
<u>10561002</u>	<u>1</u>
<u>10661004</u>	<u>1</u>
<u>10741001</u>	<u>1</u>
<u>10771006</u>	<u>1</u>
<u>10811001</u>	<u>1</u>

<u>10811002</u>	<u>1</u>
<u>10871007</u>	<u>1</u>
<u>10941003</u>	<u>1</u>
<u>10981013</u>	<u>1</u>
<u>10981019</u>	<u>1</u>
<u>10991007</u>	<u>1</u>
<u>11061020</u>	<u>1</u>
<u>11061025</u>	<u>2</u>
<u>11091005</u>	<u>1</u>
<u>11101004</u>	<u>1</u>
<u>11101011</u>	<u>1</u>
<u>11111001</u>	<u>1</u>
<u>11211002</u>	<u>1</u>
<u>11351001</u>	<u>1</u>
<u>11371005</u>	<u>1</u>
<u>11481007</u>	<u>1</u>
<u>11481010</u>	<u>1</u>
<u>11511002</u>	<u>2</u>
<u>11541004</u>	<u>1</u>
<u>11591001</u>	<u>1</u>
<u>11671002</u>	<u>1</u>
<u>11711001</u>	<u>1</u>
<u>11741007</u>	<u>1</u>
<u>11811003</u>	<u>1</u>
<u>11821003</u>	<u>1</u>
<u>11971005</u>	<u>1</u>
<u>12281004</u>	<u>1</u>

**Section 12.3 Pharmacokinetics, Drug-Drug Interactions, Figure 1:
January 20, 2012: FDA recommendations for Figure 1**

We agree to your proposed change (i.e. Rabeprazole 20 mg QD x 5 days). We request that you update the forest plot using the formatting and text we proposed in the current draft. However, we also request that the text in the first column (population description) and last (recommendation) column be left justified, if possible. Please submit the updated plot for FDA review in the next version of the label submitted for review.

On January 18, 2012, the Agency received the Inlyta (axitinib) container (b)(4) labels.

January 20, 2012 FDA Container label comments

Original FDA Comment B-1 (December 19, 2011): We acknowledge that the established name is at least half as large as the proprietary name, however, in accordance with 21 CFR 201.10(g)(2), the presentation of the established name

should also “. . . have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast and other printing features”. Therefore, we request you revise the established name accordingly.

Pfizer Response: Pfizer accepts this recommendation.

January 20, 2012 FDA Comment: We noted that ‘axitinib’ does not have the same prominence as the proprietary name (Inlyta) and the dosage form (tablets). Please make ‘axitinib’ such that it has the same size font and thickness as ‘Inlyta’ and ‘tablets’. Essentially there is no difference in font between all three.

January 20, 2012 FDA Question: Please clarify the reason for submitting the (b)(4) labels (b)(4)

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/s/

LISA M SKARUPA
01/20/2012

From: [Skarupa, Lisa](#)
To: ["Russell, Alison"; Strawn, Laurie](#)
Subject: NDA 202324 date of action
Date: Friday, January 20, 2012 9:09:32 AM

Dear Alison,

Our team would like to move the action date to next Friday Jan 27th. That is assuming the CMC response is submitted today, and it is all acceptable.

So I will be asking the label be turned around faster.

I will give you the labels shortly.

Lisa

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/s/

LISA M SKARUPA
01/31/2012



NDA 202324

INFORMATION REQUEST

Pfizer Inc.
Attention: Alison Russell, PhD., Associate Director
10646 Science Center Drive
San Diego, CA 92121

Dear Dr. Russell:

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

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. In the process description section 3.2.S.2.2, for (b) (4), provide the conditions for (b) (4). Provide a level of detail comparable to that provided for (b) (4).
2. Your proposed control method for the drug substance crystal form could allow (b) (4) other polymorphs. Provide data and information to demonstrate that this level of polymorph content does not affect bioavailability.

Drug Product:

3. We have reviewed the Stability Summary Table 3.2.P.8.1-1 for Drug Product Primary Batch Information. The table provides listing of stability data from one lot of the 1 mg of the proposed commercial shape (oval) along with 3 lots of (b) (4) tablets. The table also contains listing of 3 lots 5 mg tablets of the proposed commercial shape. You have submitted 24 months stability data for the 1 mg strength of the proposed commercial shape, and 36 months for the (b) (4) 1 and 5 mg tablets. The proposed commercial scale is (b) (4) of the stability batch size.

Based on the ICH requirement and the proposed (b) (4) during commercial manufacture include the following in your post approval stability commitment:

Commit to placing the first two commercial lots of 1 mg strength of the proposed commercial shape on stability under both long term and accelerated conditions. Also, revise

the sampling points for both long term and accelerated conditions to meet the requirements of ICH Q1A(R2).

Since you are proposing a (b)(4) during commercialization commit to placing one lot of the 5 mg strength on long term stability according to the SUPAC IR analogy.

We acknowledge your annual stability commitment.

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/

SARAH P MIKSINSKI
01/17/2012

From: [Skarupa, Lisa](#)
To: ["Russell, Alison"](#)
Cc: [Henry, Don](#)
Subject: FW: NDA 202324 CMC deficiencies
Date: Tuesday, January 17, 2012 3:52:05 PM
Attachments: [NDA 202324 IR #4.pdf](#)

Just an FYI.
The CMC Deficiencies was forwarded to Michael Lynch.

Lisa

From: Henry, Don
Sent: Tuesday, January 17, 2012 3:48 PM
To: 'Lynch, Michael P'
Cc: Skarupa, Lisa
Subject: NDA 202324 CMC deficiencies

Hello Michael

Please find the attached letter which identifies the remaining CMC deficiencies. We have scheduled a teleconference to discuss these deficiencies for Thursday, January 19, 2012 at 1pm. Also, Dr. Mace Rothenberg has been requested to be in attendance at this meeting. Please confirm availability of your team and Dr. Rothenberg.

Thank you
Don

Don L. Henry
Food and Drug Administration
CDER/Office of New Drug Quality Assessment
Phone: 301-796-4227
Don.Henry@fda.hhs.gov

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/s/

LISA M SKARUPA
01/31/2012

From: [Ibrahim, Amna](#)
To: ["Rothenberg, Mace"](#)
Cc: [Skarupa, Lisa](#)
Subject: RE: CMC deficiencies
Date: Tuesday, January 17, 2012 3:49:23 PM
Attachments: [NDA 202324_IR.pdf](#)

Mace, the CMC issues are attached as requested.
Amna

From: Rothenberg, Mace [mailto:Mace.Rothenberg@pfizer.com]
Sent: Tuesday, January 10, 2012 5:13 PM
To: Ibrahim, Amna
Cc: Nicholson, Garry A
Subject: RE: CMC deficiencies

I understand, Amna. If possible, please cc me on that communication when it is issued.

Thank you.

Mace

From: Ibrahim, Amna [mailto:Amna.Ibrahim@fda.hhs.gov]
Sent: Tuesday, January 10, 2012 5:08 PM
To: Rothenberg, Mace
Subject: RE: CMC deficiencies

Mace - thanks. ONDQA prefers to provide Pfizer the finalized deficiencies. That will take a little time
Amna

From: Rothenberg, Mace [mailto:Mace.Rothenberg@pfizer.com]
Sent: Tuesday, January 10, 2012 2:04 PM
To: Ibrahim, Amna
Cc: Nicholson, Garry A
Subject: Re: CMC deficiencies

Thank you, Amina. Would you be able to summarize the 3 issues Rick referred to during our call? I have already begun to mobilize Pfizer colleagues to respond to the Agency's request so the sooner we can identify the remaining issues, the sooner we will be able to respond. You have my personal commitment that we will do everything possible to resolve these CMC issues to the satisfaction of the Agency.

Thanks to you, Rick, and Bob for contacting me directly with this.

Best regards,
Mace

From: Ibrahim, Amna [mailto:Amna.Ibrahim@fda.hhs.gov]
Sent: Tuesday, January 10, 2012 01:54 PM
To: Rothenberg, Mace

Subject: CMC deficiencies

Dr Rothenberg, you had asked for the remaining deficiencies. We expect that the written FDA CMC deficiencies for axitinib will get to you in a couple of days.

Regards

Amna

*Amna Ibrahim MD
Deputy Division Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
CDER, FDA*

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/s/

LISA M SKARUPA
01/31/2012

From: [Skarupa, Lisa](#)
To: "Russell, Alison"; [Strawn, Laurie](#)
Subject: NDA 202324 Inlyta axitinib Labeling from FDA Jan 13 2012
Date: Friday, January 13, 2012 6:17:53 PM
Attachments: [PatientInformationSection_01_13_2012.doc](#)
[INLYTA \(axitinib\)PackageInsertJan132012.doc](#)
[FDA responses to Dec19Pfize \(b\) \(4\) Comments.doc](#)
[Axitinib FDAResponse to Label Jan132012.doc](#)

Dear Alison,

Here are the all parts of the Labeling: package insert, (b) (4) and containers, and the patient information section.

We also included some of our responses to your requests for clarifications on a separate document.

Please let me know if you have any questions.

Please let us know next week when you are able to send the labeling back (single package insert with patient information section,

(b) (4) and containers.

I apologize for sounding in a hurry, but can we get something [back by Wednesday January 18th 12noon E.S.T.?](#)

Please when you send back the package insert/patient information in one document, can you please accept the changes - if you agree with them.

It makes it easier to see where else we need to work on. When you return the package insert, please submit it with the actual highlights in the

final view (the double column, spacing, font size). Just so we know it still fits all in one page.

Thank you.

Sincerely,

Lisa

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On December 19, 2011, the Agency provided comments on the Inlyta (axitinib) container (b)(4) labels. A response to the FDA comments is provided below. We are seeking clarification on items B-3, B-5 and B-6.

FDA general comments

FDA Comment A-1: Revise the statement, (b)(4) on the label and labeling to read “Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15-30°C (59-86°F) [See USP Controlled Room Temperature].”

Pfizer Response:

Pfizer accepts this suggestion, however we have made some additional changes in blue text below to be consistent in format.

“Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature].”

FDA Container label comments

FDA Comment B-1: We acknowledge that the established name is at least half as large as the proprietary name, however, in accordance with 21 CFR 201.10(g)(2), the presentation of the established name should also “. . . have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast and other printing features”. Therefore, we request you revise the established name accordingly.

Pfizer Response: Pfizer accepts this recommendation.

FDA Comment B-2: The established name includes the active ingredient and the finished dosage form. We request you relocate the dosage form, ‘tablets’, to appear after axitinib.

Pfizer Response: Pfizer accepts this recommendation.

FDA Comment B-3: Relocate the logo, ‘Pfizer’ which appears above the proprietary name, to the lower third of the label/labeling. Additionally, remove the name from the color block.

Pfizer Response: Pfizer has not received this request previously for any product. Please provide the rationale, considering this is not required in 21 CFR.

January 10, 2012 FDA response:

The logo, ‘Pfizer’ is presented in the same color scheme as the statement of strength and is located just above the proprietary name. This presentation of the logo minimizes the prominence of the proprietary name (because of the logo’s location above the drug name) and minimizes the

prominence of the strength statement (because it is the same color). As such, our recommendation to relocate the logo and remove it from the color block is intended to improve the prominence of the information used to identify the drug product and is based upon our general post marketing experience. We accept the container labels as presented and will monitor for reports of confusion.

FDA Comment B-4: The proprietary name is presented in upper case letters (INLYTA). To increase its readability, revise the proprietary name so that it is presented in title case (Inlyta).

Pfizer Response: Pfizer accepts this recommendation.

FDA Comment B-5: Increase the prominence of the four middle numbers in the NDC number as this information is how the pharmacist identifies the correct strength for drug products. For example, NDC 0069-0151-11 should be revised to read 0069-**0151**-11 for the 5 mg strength.

Pfizer Response: Pfizer has not received this request previously for any product. Please provide the rationale, considering this is not required in 21 CFR.

January 10, 2012 FDA response:

We have had reports of confusion during the dispensing process where the NDC number has been stated erroneously. We acknowledge that this problem is not likely to occur with the numbers as stated for Inlyta 1 mg and 5 mg tablets. They are acceptable as presented.

FDA Comment B-6: The blue banner containing the manufacturer name and logo that appears vertically across both the 1 mg and 5 mg labels minimizes the impact of the color differentiation between the strengths. To avoid selection errors, remove this banner.

Pfizer Response: This is an anti-counterfeit feature that will appear on the label as a metallic bar. The technology (b) (4) will show the name and logo at different angles when the bottle is rotated.

January 10, 2012 FDA response:

In our review of the container label affixed to the Xalkori bottle, we acknowledge that the blue banner does not distract from nor minimize the visibility of important information used to identify the drug product and that it is presented similarly on the Inlyta container label. As such, our concerns regarding the inclusion of this banner on the Inlyta container label are minimized.

FDA Comment B-7: Relocate the 'Rx only' statement to the bottom of the principal display panel.

Pfizer Response: Pfizer accepts this recommendation.

FDA Comment B-8: Remove the (b) (4) statement. The "distributed by" statement fulfills the regulatory requirement (21 CFR 201.1).

Pfizer Response: Pfizer accepts this recommendation.

On 19 December 2011, FDA provided Pfizer with comments on the draft INLYTA United States Package Insert (USPI). This document contains a response to the label comments provided by FDA. Pfizer is providing a revised copy of the USPI incorporating Agency feedback received on 19 December 2011, as well as additional edits suggested by Pfizer. Comments and notes for FDA are provided in the attached USPI.

Section 1 – Indications and Usage

FDA Suggested Change: FDA suggested the following indication statement: INLYTA is indicated for the treatment of advanced renal cell carcinoma (RCC) after failure of one prior systemic therapy.

Pfizer Response: Pfizer proposes to [REDACTED] (b) (4)

[REDACTED]

[REDACTED] (b) (4)

FDA response: We disagree, as the primary evidence for efficacy was from A4061032, the pivotal, randomized trial in patients after one prior systemic therapy.

Section 2.2 – Dose Modification Guidelines

FDA Suggested Changes: Several changes were made to this section including (b) (4)

Pfizer Response:

CYP3A4/5 Inhibitors and Hepatic Impairment: Throughout the USPI, the FDA has removed the phrase (b) (4) in reference to modification of the starting dose when co-administration of a strong CYP3A4/5 inhibitor is required or for patients with hepatic impairment. (b) (4)

Therefore, the Sponsor recommends that the deleted text be retained, and the word “approximately” be used when referring to halving the dose in Section 2.2 and throughout the label.

Request for Clarification: The Sponsor would like to seek FDA clarification (b) (4)

FDA Response:

CYP3A4/5 Inhibitors and Hepatic Impairment: When recommending a 50% reduction in dose for dose modifications for moderate hepatic impairment or concomitant use with a strong CYP3A4 inhibitor, we agree to use the word ‘approximately’ half the dose. (b) (4)

Section 5 – Warnings and Precautions

FDA Suggested Changes: Throughout the Warnings and Precautions section, the FDA has made modifications to the numbers of patients who have experienced many of the adverse events and the total number of patients treated in single-agent clinical trials ((b) (4) 715).

Pfizer Response: The numbers of adverse events and total number of patients who received single-agent axitinib do not match the source documents ([A4061032 Clinical Study Report](#), [Summary of Clinical Safety](#), and [Risk Management Plan](#)) submitted in the original NDA. The annotated USPI submitted in the NDA indicates the source for each of the numbers provided in the draft USPI. The Sponsor believes that FDA may have included the 16 patients treated on the Phase 1 dose-escalation study ([A4060010](#)) who received single-agent axitinib at starting doses greater than 5 mg BID prior to the identification of this dose as the maximum tolerated dose (MTD) and recommended starting dose. (b) (4)

Request for Clarification: Please clarify what the sources of these numbers of adverse events and total patients are. If N = 715 includes patients who received starting doses greater than 5 mg BID, please consider using (b) (4)

FDA Response: We did include the 16 patients to whom you refer from the Phase 1 dose escalation study in our analysis of the integrated safety database. We do not agree (b) (4)

Additionally, there are multiple requests to identify the source for FDA’s modified numbers for adverse events. For Study A4061032, all numbers for adverse events were obtained from Section 5.3.5.1.25.3.1 Analysis Datasets in the original NDA submission from the adverse dataset. For the integrated safety database, all numbers for adverse events were obtained from Section 5.3.5.3.25.3.1 Analysis Datasets for Complete Single Agent studies, specifically from the adverse dataset.

Section 5.1 – Hypertension

FDA Suggested Change: FDA added hypertensive crisis to the title of Warning/Precaution 5.1, updated the incidences of patients with hypertension reported in this section, clarified the considerations for discontinuation [REDACTED] (b) (4)

Pfizer Response: Pfizer accepts most of these changes. However, the Sponsor would like to add more detail regarding the time of onset of hypertension to make it clear that blood pressure increases may be seen as soon as 4 days after initiation of dosing. The information to support this is included in the [Summary of Clinical Safety Section 2.7.4.2.1.5.1](#), which reads, “Based on rigorous 24-hour BP monitoring, there was an early increase in median [blood pressure] BP by Day 4, with little incremental increase by Day 15 of axitinib treatment. The median [diastolic blood pressure] dBP increase from baseline was approximately 8 mmHg by Day 4, and 11 mmHg by Day 15; the median [systolic blood pressure] sBP increase was approximately 10 mmHg by Day 4, and 13 mmHg by Day 15. These data indicate that near peak BP was achieved early in the first cycle of treatment.”

In addition, the Sponsor proposes to retain the statement, “If INLYTA is interrupted, patients receiving antihypertensive medications should be monitored for hypotension,” as it provides useful medical advice.

Request for Clarification: If the Agency does not agree with retaining this statement, please provide the rationale.

FDA Response: We have no objections to the additional text inserted regarding timing and monitoring for hypotension upon interruption.

Section [5.5] – [REDACTED] (b) (4)

FDA Suggested Change: FDA deleted this section as well as references to [REDACTED] (b) (4) the Highlights and Adverse Reactions sections of the label.

Pfizer Response: The Sponsor included this information in the draft label [REDACTED] (b) (4)

Request for Clarification: Please clarify why all references to [REDACTED] (b) (4) were deleted.

FDA Response: We deleted this section for W&P [REDACTED] (b) (4)

Section 5.5 – Arterial Thromboembolic Events

FDA Suggested Change: Information was added regarding [REDACTED] (b) (4) two deaths due to cerebrovascular accident.

Pfizer Response: [Summary of Clinical Safety Table 5.2.1](#) Summary of Events with a Fatal Clinical Outcome for completed single-agent studies includes two deaths due to cerebrovascular accident [REDACTED] (b) (4)

Request for Clarification: Please clarify what the source of the information on deaths is.

FDA Response: [REDACTED] (b) (4)

Section 5.6 Gastrointestinal perforation and fistula formation

FDA Response: The patients for whom GI perforation or fistula formation were reported are listed below:

AE	Protocol	SID
Anal fistula	A4061014	1003 10031009
Intestinal perforation	A4061015	1001 10011001
Intestinal perforation	A4061015	1003 10031001
Large intestine perforation	A4061023	1002 10021006
Gastrointestinal perforation	A4061023	1005 10051012
Fistula	A4061032	1051 10511002
Gastrointestinal perforation	A4061032	1057 10571008
Gastrointestinal perforation	A4061032	1057 10571008
Anal fistula	A4061032	1077 10771008
Anal fistula	A4061035	1018 10181002

Section 5.8 – RPLS

FDA Suggested Change: One additional report of RPLS in other clinical trials was added to this section.

Pfizer Response: We agree with the suggested change, but according to [Risk Management Plan Table 8.7.3](#), there were a total of 3 reports of all grades RPLS, two of which were Grade 3/4. Therefore, the Sponsors proposes stain that there were two additional reports of RPLS.

FDA Response: We agree. The label describes one event in the A40161032 trial and two additional reports in other trials, for a total of three events of RPLS.

Section 5.11 – Hepatic Impairment

FDA Suggested Change: FDA removed magnitude of exposure change data.

Pfizer Response: In Section 5.11 and throughout the USPI, FDA has removed references to the

(b) (4)

Request for Clarification: Please clarify why the [redacted] has been deleted throughout the label.

(b) (4)

FDA Response: According to the guidance to industry referenced below, to the extent possible, redundancies should be avoided in labeling, and cross-referencing should be used instead. Please refer to the complete guidance found at the following link for more information:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075096.pdf>

Section 6.1 Adverse Reactions

FDA Suggested Change: FDA made some changes to the frequencies of adverse reactions and laboratory abnormalities in Tables 1 and 2.

Pfizer Response: In Tables 1 and 2, it appears that the modified numbers provided by the FDA for several of the adverse reactions and laboratory abnormalities may include findings that were reported prior to administration of the first dose of axitinib or sorafenib and did not worsen in severity on treatment. If this is the case, the Sponsor requests to retain the original numbers, as the pre-existing adverse events and laboratory abnormalities are clearly not treatment-related or, more importantly, treatment-emergent.

Request for Clarification: If this is not the case, please clarify what the sources of the numbers are.

FDA response: This is acceptable.

In Table 1, the Sponsor would like to add a footnote to explain that frequencies are based on treatment-emergent, all-causality adverse reactions.

In Table 2, Pfizer has made corrections to the [redacted] hypocalcemia laboratory values, based on the data that were submitted in [A4061032 Clinical Study Report Supplement 2](#) on 9 November 2011, in which calcium levels were corrected for albumin. As a result of the

corrections, hypocalcemia moved higher in the table (b) (4)

FDA Response: This is acceptable.

Section 7.1 – CYP3A4/5 Inhibitors

FDA Suggested Change: FDA deleted the (b) (4)

Pfizer Response: (b) (4)

Request for Clarification: Please clarify why the (b) (4)
has been deleted throughout the label.

FDA Response: For reasons similar to our response to the comment for Section 5.11 above, to the extent possible, we are avoiding redundancies in labeling, and using cross-referencing.

Section 7.2 – CYP3A4/5 Inducers

FDA Suggested Change: FDA added a list of moderate CYP inducers that should be avoided during treatment with INLYTA.

Pfizer Response: No clinical data are currently available regarding the impact of moderate CYP3A4/5 inducers on axitinib pharmacokinetics. Also, CYP3A4/5 inducers would cause a reduction in axitinib plasma concentrations and hence, would not pose a safety risk.

Request for Clarification: Given this, the Sponsor would like to confirm that the Agency still wants to include this additional wording on moderate CYP3A4/5 inducers.

FDA Response: Due to the potential negative effect on efficacy, we would still like to include this additional wording on moderate CYP3A4/5 inducers. Pfizer may choose to conduct a DDI study with moderate CYP3A4/5 inducers and request labeling changes.

Section 8.4 – Pediatric Use

FDA Suggested Change: The information revised by FDA does not include a statement (b) (4) and does not include malocclusions in the list of abnormalities of the teeth.

Pfizer Response:

(b) (4)

FDA Response:

(b) (4)

with including malocclusions

(b) (4)

. FDA agrees

Section 12.1 – Mechanism of Action

FDA Suggested Change: Platelet-derived growth factor receptor (PDGFR) and stem cell factor receptor (KIT) were added as additional target receptors in this section.

Pfizer Response: The Sponsor proposes removing references to

(b) (4)

FDA Response: This is acceptable. FDA made additional edits for clarity.

Section 12.2 – Pharmacodynamics

FDA Suggested Change: FDA included (b) (4) in reference to the QTc analysis.

Pfizer Response:

(b) (4)

suggests deleting

(b) (4)

To avoid confusion, the Sponsor

FDA Response: This is acceptable.

Section 12.3 –Pharmacokinetics

Absorption and Distribution:

FDA Suggested Change: FDA included “Dosing of axitinib at 5 mg twice daily resulted in **approximately 1.4-fold accumulation...**”. In addition, the FDA added CV% for the geometric means.

Pfizer Response: The exact source for 1.4-fold is unclear. In [Module 2, Section 2.7.2.3.3](#), it is noted that the accumulations were 1.35-, 1.48-, and 1.37-fold in three separate studies.

Request for Clarification: The Sponsor would like to confirm that the “1-4 fold” value is an average of those numbers. If not, what is the source? Also, with regard to the CV%, would the Agency prefer 90% confidence intervals along with the geometric mean values here? Or arithmetic mean with CV%?

FDA Response: The “**approximately 1.4-fold**” accumulation value came from rounding 1.37 up to “**approximately 1.4**”.

Regarding the use of CV% vs. 90% CI with geometric mean values, we selected to present CV% to provide clear information regarding the large variability observed in the PK. However, we are agreeable if Pfizer chooses to present the 90% CI with geometric mean values.

Metabolism:

FDA Suggested Change: “Following oral administration of a 5 mg radioactive dose of axitinib, **approximately 41% of the radioactivity** was recovered in feces and approximately 23% was recovered in urine.”

Pfizer Response: The source of this information is unclear.

Request for Clarification: The Sponsor would like to confirm that the 41% was estimated by Agency as the median fecal recovery from the study excluding the 2 outlier subjects ([Module 2, Section 5.3.3.1, A4061003 Clinical Study Report, End of Study Table 10C](#)).

FDA Response: We confirm that the 41% was estimated as the median fecal recovery from the study excluding the 2 outlier subjects.

Drug-Drug Interactions:

FDA Suggested Change: The Agency moved Figure 1 to this section, but has not included the ^{(b) (4)} results in the Forest plot (data provided in [Clinical Pharmacology Information Request](#), dated 30 November 2011).

Request for Clarification: The Sponsor would like to confirm if this is intentional, or if the preference is to use the Forest plot that includes (b)(4) results.

FDA Response: Pfizer used the individual post-hoc parameter estimates from the population PK model for the calculation of Cmax and AUC. (b)(4)

Thus, we decided to keep the (b)(4) results separate from the forest plot.

Section 13.1 – Carcinogenesis, Mutagenesis, Impairment of Fertility

FDA Suggested Change: FDA added that axitinib was (b)(4) in the mouse bone marrow micronucleus assay.

Pfizer Response: Kinetochore staining results indicated that the increases in micronucleated polychromatic erythrocytes observed in the *in vivo* mouse bone marrow micronucleus assay were due to an aneugenic (b)(4) mechanism. As a threshold for response can be defined for an aneugen, the (b)(4) have been included in the revised USPI (“Axitinib was genotoxic in the *in vivo* mouse bone marrow micronucleus assay (b)(4)”).

FDA Response: The change from (b)(4) to “genotoxic” is acceptable. FDA does not agree that including a (b)(4) is appropriate.

FDA Suggested Change: FDA modified text on findings in the male reproductive tract (b)(4)

Pfizer Response: As illustrated in the table below and in the study report (historical data also included in Appendix 7 of the study report LIA00238), sperm count and sperm density at 5 mg/kg/dose were not statistically significantly different from the concurrent study control group. These mean study values at 5 mg/kg/dose were above the historical control study mean values indicating that they were well within the range of normal values for this type of study in this animal model. Therefore the axitinib-related effect on sperm count or motility at 5 mg/kg/dose should not be considered adverse.

The decreased sperm density at 15 mg/kg/dose is considered treatment-related based on the statistically significant difference from control, despite being higher than the historical control study data mean values and a lack of evidence of male reproductive organ toxicity in general toxicity studies at this dose.

Cauda Epididymis	Control	5 mg/kg/dose	15 mg/kg/dose	50 mg/kg/dose	Historical data study mean (min-max)
------------------	---------	--------------	---------------	---------------	--------------------------------------

Sperm count	80.0	78.0	72.1	67.9	74.5 (55.6 - 103.1)
Sperm density	2491	2196	2099*	1914**	2078 (1510 - 2859)

* $p \leq 0.05$, ** $p \leq 0.01$.

Min = Minimum; Max = Maximum

FDA Response: This is acceptable.

FDA Suggested Change: FDA deleted reference to dogs in regard to findings in the female reproductive tract.

Pfizer Response: Female reproductive tract findings (delayed sexual maturity, absence of corpora lutea) were also observed in dogs at doses ≥ 5 mg/kg/dose in the 28-day dog toxicity study.

FDA Response: This is acceptable.

FDA Suggested Change: In regard to the fertility study in mice, FDA stated (b) (4)

Pfizer Response: The sponsor modified the margin to 57 times the AUC in patients at the recommended starting dose, which was calculated based on the total AUC of 15200 ng·h/mL in mice associated with the 100 mg/kg/day dose and total AUC of 265 ng·h/mL in humans given the recommended starting dose of 5 mg BID.

FDA Response: This is acceptable.

Section 14 – Clinical Studies

FDA Suggested Change: In Table 3, the Overall Survival (OS) data provided by FDA for sorafenib is (b) (4) months (17.5, 21.6).

Pfizer Response: Per the OS analysis submit 30 November 2011 in response to FDA's request for final OS data, the OS for sorafenib was 19.2 months (17.5, 22.3) [RSI Table 1.4.2.1].

Request for Clarification: Please clarify how these numbers were calculated.

FDA Response: The Final OS dataset had two records for one patient. We re-analyzed the data with a single line per patient, which yielded the numbers we are now providing.

FDA Suggested Change: The (b) (4) were deleted from Table 3.

Pfizer Response: [REDACTED] (b) (4)

Request for Clarification: Please clarify why the [REDACTED] (b) (4) were deleted.

FDA Response: The [REDACTED] (b) (4) were deleted for the reasons you note [REDACTED] (b) (4)

Sections 15 – [REDACTED] (b) (4) and 16 – How Supplied/Storage and Handling

FDA Suggested Change: FDA suggested that [REDACTED] (b) (4)

Pfizer Response: INLYTA tablets are film coated, and therefore, are unlikely to cause a safety issue when handled. In addition, other labels for oncology drugs do not include these [REDACTED] (b) (4).

Request for Clarification: Please clarify what the rationale is for including these references.

FDA Response: Section 15 – [REDACTED] (b) (4) were removed.

Comments from Project Manager’s e-mail

FDA Suggested Change: In addition to the comments made by FDA in the USPI document, the FDA Project Manager made the following requests by e-mail.

1. Just a reminder, please keep the 2-column format as required for the HIGHLIGHTS and TABLE of CONTENTS, and in one page.
2. Please help with the various fonts and spacing.
3. Please do not use the terms "adverse event" throughout the label, use the term "adverse reactions" instead.

Pfizer Responses:

1. The 2-column format has been retained. When viewed in “Final” or with Changes accepted, the Highlights and Table of Contents are on one page.
2. The font has been changed to Times New Roman throughout, with 8 point font in the Highlights section and Table of Contents, 12 point font for text in Full Prescribing Information, and 11 point font in tables. Spacing has been adjusted to be consistent throughout the document.
3. In the revised USPI, the term “adverse event” is only used when

- a. [REDACTED] (b) (4)
- b. [REDACTED] (b) (4)
- c. In references to NCI CTCAE grading.

Request for Clarification: Are these references to “adverse events” acceptable?

FDA Response: Based on “*Guidance for Industry Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products – Content and Format*”, January 2006, the package insert should remain consistent in how we are addressing reactions. Adverse reactions are still used “that resulted in a significant rate of discontinuation or other clinical intervention (e.g., dosage adjustment, need for other therapy to treat an adverse reaction) in clinical trials.” So adverse reactions is still the preferred terminology. However, I have attached the guidance for you to let you re-state your case. In terms of the terms when discussing NCI CTCAE, that is acceptable.

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

/s/

LISA M SKARUPA
01/31/2012

From: [Skarupa, Lisa](#)
To: ["Russell, Alison"](#)
Cc: [Strawn, Laurie](#)
Subject: RE: NDA 202324 axitinib labeling container Jan 6
Date: Friday, January 06, 2012 12:46:13 PM

[my office address:](#)

Lisa Skarupa, R.N., M.S.N., A.O.C.N.
Regulatory Project Manager
Food and Drug Administration
OND/OODP
Division of Hematology and Oncology Products
10903 New Hampshire Avenue
WO-22 Room 2171
Silver Spring, Maryland 20993
(301) 796-2219

From: Russell, Alison [mailto:Alison.Russell@pfizer.com]
Sent: Friday, January 06, 2012 12:45 PM
To: Skarupa, Lisa
Cc: Strawn, Laurie
Subject: RE: NDA 202324 axitinib labeling container Jan 6

What address should I advise my colleagues to send the bottle to?

Alison Russell
Axitinib Global Regulatory Lead
Pfizer Oncology
Tel: (858) 344-4473
Fax: (877) 481-0933
Assistant: Annette Scuderi (Tel: (858) 622-3031)

From: Skarupa, Lisa [mailto:Lisa.Skarupa@fda.hhs.gov]
Sent: Friday, January 06, 2012 9:42 AM
To: Russell, Alison
Cc: Strawn, Laurie
Subject: RE: NDA 202324 axitinib labeling container Jan 6

Alison,
Since I do not have the answer from the requestor, I would ask that you just send it my way.
Is there a draft bottle label with the blue anti counterfeiting feature? The question was how is it placed and how much could it be hiding information.

Lisa

From: Russell, Alison [mailto:Alison.Russell@pfizer.com]
Sent: Friday, January 06, 2012 11:10 AM
To: Skarupa, Lisa
Cc: Strawn, Laurie
Subject: RE: NDA 202324 axitinib labeling container Jan 6

Lisa – I have been informed by our packaging team that the specific bottle labels for INLYTA have not yet been printed. However, we currently use this same anti counterfeiting feature on other products. We are attempting to obtain one of these as an example. Can you let me know if this will suffice for FDA's review?

Alison

Alison Russell
Axitinib Global Regulatory Lead
Pfizer Oncology
Tel: (858) 344-4473
Fax: (877) 481-0933
Assistant: Annette Scuderi (Tel: (858) 622-3031)

From: Russell, Alison
Sent: Friday, January 06, 2012 8:00 AM
To: 'Skarupa, Lisa'
Cc: Strawn, Laurie
Subject: RE: NDA 202324 axitinib labeling container Jan 6

Lisa – What mailing address would you like the bottle to be sent (by FedEx) to? Also, can you pls provide a telephone number for that same address.

Alison Russell
Axitinib Global Regulatory Lead
Pfizer Oncology
Tel: (858) 344-4473
Fax: (877) 481-0933
Assistant: Annette Scuderi (Tel: (858) 622-3031)

From: Skarupa, Lisa [mailto:Lisa.Skarupa@fda.hhs.gov]
Sent: Friday, January 06, 2012 7:05 AM
To: Strawn, Laurie
Cc: Russell, Alison
Subject: RE: NDA 202324 axitinib labeling container Jan 6

Laurie and Alison,
Our labeling team would like to see the actual bottle after reading that the blue banner is an anti-counterfeit feature. Could you mail be one bottle for us to determine how prominent the banner is (and how its presentation impacts the rest of the information on the bottle)?

Sincerely,
Lisa

From: Strawn, Laurie [mailto:laurie.strawn@pfizer.com]
Sent: Wednesday, January 04, 2012 2:54 PM
To: Skarupa, Lisa
Cc: Russell, Alison
Subject: RE: NDA 202324 axitinib labeling first negotiations
Importance: High

Dear Lisa,

Attached please find the revised INLYTA USPI, Track Changes and clean versions, based on FDA comments that were received on December 19, 2011. In addition, a response document is attached which includes requests for clarification and rationale for not accepting some of FDA's comments.

The Track Changes version shows the FDA comments that we accepted, as well as a few other proposed changes which are described in the response document. For the FDA proposed changes where we are seeking clarity, the changes have not been made in the revised USPI. These areas are marked with "balloon" comments.

Also attached is a response document to the comments on the (b) (4) label. We are requesting clarification on 3 of the comments.

The formal submission to the NDA will be sent tomorrow.

Let us know if you have any questions.

Laurie

From: Skarupa, Lisa [mailto:Lisa.Skarupa@fda.hhs.gov]

Sent: Monday, December 19, 2011 3:39 PM

To: Russell, Alison; Strawn, Laurie

Subject: NDA 202324 axitinib labeling first negotiations

Dear Laurie and Alison,

Please see the attached labeling (PI) and recommendations for the (b) (4) container. Please note that the Patient Information section will be sent to you soon after the holidays.

1. Just a reminder, please keep the 2-column format as required for the HIGHLIGHTS and TABLE of CONTENTS, and in one page.
2. Please help with the various fonts and spacing.
3. Please do not use the terms "adverse event" throughout the label, use the term "adverse reactions" instead.

If you have any questions, please do not hesitate to contact me. I will only be out of the office 23rd and Dec 30th and Jan 3rd.

Please respond by Jan 4th or 5th.

Sincerely,
Lisa

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/s/

LISA M SKARUPA
01/31/2012

From: [Skarupa, Lisa](#)
To: ["Russell, Alison"; Strawn, Laurie](#)
Subject: NDA 202324 axitinib labeling first negotiations
Date: Monday, December 19, 2011 6:38:00 PM
Attachments: [NDA202324_Dec16_FDInitialresponselabeling.doc](#)
[NDA202324_Dec16_FDAresponse](#) (b)(4) [Container.doc](#)

Dear Laurie and Alison,

Please see the attached labeling (PI) and recommendations for the (b)(4) container. Please note that the Patient Information section will be sent to you soon after the holidays.

1. Just a reminder, please keep the 2-column format as required for the HIGHLIGHTS and TABLE of CONTENTS, and in one page.
2. Please help with the various fonts and spacing.
3. Please do not use the terms "adverse event" throughout the label, use the term "adverse reactions" instead.

If you have any questions, please do not hesitate to contact me. I will only be out of the office 23rd and Dec 30th and Jan 3rd.

Please respond by Jan 4th or 5th.

Sincerely,
Lisa

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

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/s/

LISA M SKARUPA
01/06/2012

From: Skarupa, Lisa
Sent: Tuesday, December 06, 2011 12:04 PM
To: 'Russell, Alison'
Subject: RE: December 7th ODAC (axitinib)

Alison,
Yes, this (one slide, and then paper copies of the slides) seems sufficient for the ODAC panel members.

Just a reminder that our last correspondence advised that: **You should submit the final overall survival data and analyses to the NDA as soon as possible so that we may review it before the PDUFA action date.**

Sincerely,
Lisa

From: Russell, Alison [mailto:Alison.Russell@pfizer.com]
Sent: Monday, December 05, 2011 4:09 PM
To: Skarupa, Lisa
Subject: December 7th ODAC (axitinib)

Lisa – Pfizer plans to present mature overall survival (OS) data as part of our presentation (1 additional slide) to ODAC on 7 . This data was not included in the Sponsor's briefing document to ODAC. I understand that paper copies of the slides will be available to the ODAC panel members. Can you confirm that this will be sufficient for the ODAC panel members to be able to review the OS data?

Alison

From: Russell, Alison [mailto:Alison.Russell@pfizer.com]
Sent: Saturday, December 03, 2011 1:12 PM
To: Skarupa, Lisa
Subject: RE: FDa response to Pfizer ODAC questions Dec 2, 2011

Lisa – Just to let you know, we plan to follow FDA's recommendation i.e. present the final OS analyses a part of our presentation at the ODAC meeting and make it clear that the data have not yet been submitted for FDA review.

Alison

Alison Russell
Axitinib Global Regulatory Lead
Pfizer Oncology
Tel: (858) 344-4473
Fax: (877) 481-0933
Assistant: Annette Scuderi (Tel: (858) 622-3031)

From: Skarupa, Lisa [mailto:Lisa.Skarupa@fda.hhs.gov]
Sent: Friday, December 02, 2011 5:36 PM
To: Russell, Alison
Subject: RE: FDA response to Pfizer ODAC questions Dec 2, 2011

no problem. thanks for your patience

From: Russell, Alison [mailto:Alison.Russell@pfizer.com]
Sent: Friday, December 02, 2011 5:35 PM
To: Skarupa, Lisa
Subject: RE: FDA response to Pfizer ODAC questions Dec 2, 2011

Lisa – Thanks, much appreciated.
Alison

From: Skarupa, Lisa [mailto:Lisa.Skarupa@fda.hhs.gov]
Sent: Friday, December 02, 2011 4:37 PM
To: Russell, Alison
Subject: FDA response to Pfizer ODAC questions Dec 2, 2011

Dear Alison,

Please see the following FDA responses to your two questions:

1) Can you tell me whether FDA would object if we present the final OS data to the ODAC or show the committee the data if they ask about this data?

For this specific application, the FDA recommends that you present the final OS analyses at ODAC as long as you make it clear that the data have not yet been submitted for FDA review. If the data are submitted before ODAC, please state the date of the submission in your presentation. If you do not include the final OS analysis in your presentation, you should be prepared to show the data if the ODAC asks. You should submit the final overall survival data and analyses to the NDA as soon as possible so that we may review it before the PDUFA action date.

2) Would the FDA also share their position on how they plan to respond should an ODAC member ask about final OS data?

We will respond that we do not have the final OS data or that it was just submitted and we have not yet confirmed the analyses.

Sincerely,

Lisa

From: Russell, Alison [mailto:Alison.Russell@pfizer.com]
Sent: Thursday, December 01, 2011 6:21 PM
To: Skarupa, Lisa
Cc: Tilley, Amy
Subject: RE: ODAC questions

Lisa – Can you tell me whether FDA would object if we present the final OS data to the ODAC or show the committee the data if they ask about this data? Would the FDA also share their position on how they plan to respond should an ODAC member ask about final OS data?

Alison

Alison Russell
Axitinib Global Regulatory Lead
Pfizer Oncology
Tel: (858) 344-4473
Fax: (877) 481-0933
Assistant: Annette Scuderi (Tel: (858) 622-3031)

From: Russell, Alison
Sent: Thursday, December 01, 2011 5:16 PM
To: 'Skarupa, Lisa'
Cc: Tilley, Amy
Subject: RE: ODAC questions

Lisa – Thanks for letting me know.
Alison

Alison Russell
Axitinib Global Regulatory Lead
Pfizer Oncology
Tel: (858) 344-4473
Fax: (877) 481-0933
Assistant: Annette Scuderi (Tel: (858) 622-3031)

From: Skarupa, Lisa [mailto:Lisa.Skarupa@fda.hhs.gov]
Sent: Thursday, December 01, 2011 4:45 PM
To: Russell, Alison
Cc: Tilley, Amy
Subject: ODAC questions

Dear Alison, FDA is not planning to present any final OS data that you provided us in the past week.

Sincerely,
Lisa

From: Russell, Alison [mailto:Alison.Russell@pfizer.com]
Sent: Wednesday, November 30, 2011 9:37 AM
To: Kacuba, Alice
Cc: Skarupa, Lisa; Tilley, Amy
Subject: RE: A Follow-up Information Request (IR)

Alice

With regards the FDA's IR sent 29 November 2011, see attached Pfizer's email response (an official submission of this response is being sent to NDA 202324). Please note, we have some queries in our letter (also noted below) regarding the upcoming ODAC. I would appreciate hearing back from you regarding these queries as soon as possible.

ODAC:

The Sponsor did not have these data available at the time the ODAC briefing package was submitted to the ODAC secretary. Given the late timing, we were not planning to submit an addendum to the ODAC briefing package, and therefore, were not planning to present this updated information at the ODAC meeting. However, we would like to know:

- 1) if FDA plans to share these results during their presentation or in response to questions from ODAC
- 2) the Agency's opinion on whether the Sponsor should refer to these data in its presentation or in response to questions from ODAC

Many thanks,

Alison

Alison Russell
Axitinib Global Regulatory Lead
Pfizer Oncology
Tel: (858) 344-4473
Fax: (877) 481-0933
Assistant: Annette Scuderi (Tel: (858) 622-3031)

From: Kacuba, Alice [mailto:Alice.Kacuba@fda.hhs.gov]
Sent: Tuesday, November 29, 2011 9:07 AM
To: Russell, Alison
Cc: Skarupa, Lisa; Tilley, Amy
Subject: A Follow-up Information Request (IR)
Importance: High

Hi,

Please submit the current, incomplete, OS analyses for the final OS analysis ASAP.

Thank you.

Alice

Alice Kacuba, RN, MSN, RAC
Chief, Project Management Staff
Division of Oncology Products 1 (new name for DDOP)
Office of Hematology and Oncology Products
OND/CDER/FDA
301-796-1381
(f) 301-796-9845
alice.kacuba@fda.hhs.gov

*Consider setting your email font setting to at least 12 font.

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/s/

LISA M SKARUPA
12/06/2011



NDA 202324

INFORMATION REQUEST

Pfizer Inc.
Attention: Alison Russell, PhD., Associate Director
10646 Science Center Drive
San Diego, CA 92121

Dear Dr. Russell:

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

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. The ID test needs to be performed for all used reagents / materials. Provide ID testing for [REDACTED] (b) (4)
2. A complete description of the commercial scale drug substance manufacturing processes should be provided and should include all process parameters. Therefore, include a master batch record and/or a detailed manufacturing process description in section S.2.2 (drug substance) of the application. The Agency recognizes that changes to non-critical process parameters can usually be managed under the firm's quality system without the need for regulatory review and approval prior to implementation. However, notification of all changes including changes to process parameters should be provided in accordance with 21CFR 314.70.
3. Your proposed design space for the [REDACTED] (b) (4) is not acceptable. [REDACTED] (b) (4)
4. Your justification for the exclusion of the potentially genotoxic impurities [REDACTED] (b) (4) in the drug substance specification is not acceptable based on the batch data provided in your submission. Include acceptance criteria for [REDACTED] (b) (4) in drug substance specification.

5. The justification for not conducting tests for Assay and Crystal form on stability is not acceptable. As critical CQAs, both tests including Assay and Crystal form need to be tested through the stability protocol. All three registration batches use [REDACTED] (b) (4) [REDACTED].
6. The justifications for not making a post approval stability commitment are not acceptable. It is not clear from the stability Table 3.2.S.7.1-1 of amendment, dated 10/21/2011 that the batch size for the primary stability lots are the same as that of the proposed commercial lot. [REDACTED] (b) (4) [REDACTED]. Also, revise the sampling points for both long term and accelerated conditions to meet the requirements of ICH Q1(R2).

Drug product

7. As previously mentioned, notification of all changes including changes to process parameters are to be provided in accordance with 21CFR 314.70. Therefore the process description (section P.3.3) is to be provided in accordance with 21 CFR 314.50 which indicates that the applicant submits: *“The proposed or actual master production record, including a description of the equipment, to be used for the manufacture of a commercial lot of the drug product or a comparably detailed description of the production process for a representative batch of the drug product.”* Therefore, to meet these regulatory requirements, your options are as follows:
 - a. Provide a master batch record to any section of module 3, with a reference/link to the master batch record in the process description (section P.3.3)
 - b. Provide a process description to section P.3.3 that is comparably detailed to the master batch record.
8. The justification for not including coating weight upper limit is not acceptable. Based on the information provided in the NDA, the dissolution does not support a film coating specification [REDACTED] (b) (4) [REDACTED]. Adopt an upper limit for coating weight based on the provided dissolution data.
9. The rationale provided for not performing microbial limits testing is not adequate as there is insufficient manufacturing history on which to evaluate the process control over time and manufacturing environmental conditions.

Microbial limit specifications should be set for release and stability. Once a satisfactory product history has been established, a post-approval supplement may be submitted to the FDA request the waiver of microbial limits testing during release; however the testing should remain in the stability program.
10. The justification for not conducting assay on stability is not acceptable. Update your stability protocol to include assay testing.

11. It is not clear from the stability Table 3.2.P.8.1-1 of amendment, dated 10/28/2011 that the batch size for the primary stability lots are the same as that of the proposed commercial lot. Therefore, your justification for not making a post approval stability commitment is not acceptable. Also, revise the sampling points for both long term and accelerated conditions to meet the requirements of ICH Q1(R2).

Analytical Procedures

12. Your MODR for the drug substance is unacceptable because one of the verification conditions (condition #2) failed. You should [REDACTED] (b) (4) [REDACTED] revise your MODR, accordingly.

Biopharmaceutics

13. The following dissolution acceptance criterion is recommended: $Q =$ [REDACTED] (b) (4) at 30 minutes. This recommendation is based on the following information/data:
- the mean in-vitro dissolution profiles for the 1 mg and 5 mg strengths at release and under long term (36 months) stability studies; and
 - the results from BA/BE Study A4061033 which indicates that the axitinib product made with [REDACTED] (b) (4) API particle size may not be bioequivalent to your proposed axitinib product made with [REDACTED] (b) (4) API particle size.

Revise the dissolution acceptance criterion accordingly and submit an updated sheet of specifications for the drug product.

14. We consider the use of [REDACTED] (b) (4) testing to support the design space not acceptable for the following reasons:
- Your product does not meet the criteria delineated in the ICH Q6A guidance in terms of the use [REDACTED] (b) (4) testing. The criteria in the ICH Q6A guidance are as follows:

[REDACTED] (b) (4)

- In addition, in your response to FDA query 38 received on Oct 19, 2011, it is stated that

[REDACTED] (b) (4)

Therefore, we recommend performing dissolution profile comparisons with f2 testing for any movements outside the NOR and within your proposed design space.

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

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

/s/

SARAH P MIKSINSKI
12/02/2011

From: Tilley, Amy
Sent: Thursday, December 01, 2011 10:11 AM
To: Russell, Alison [Alison.Russell@pfizer.com]
Cc: Skarupa, Lisa
Subject: RE: *Time Sensitive* NDA 202324 Axitinib – Clin Pharm IR

Importance: High
Alison,

The Clinical Pharmacology Review Team has the following response to your request to submit the information by December 12, 2011.

Yes. However, if you are able to complete the analysis and submit the information earlier, that is preferred.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD
20993

☎ 301.796.3994 (phone) ● 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov



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From: Russell, Alison [mailto:Alison.Russell@pfizer.com]
Sent: Thursday, December 01, 2011 7:04 AM
To: Tilley, Amy
Cc: Skarupa, Lisa
Subject: RE: *Time Sensitive* NDA 202324 Axitinib - Clin Pharm IR

Amy – I would like to request a short time extension. We can submit the information by December 12th.
Is that acceptable?
Alison

Alison Russell
Axitinib Global Regulatory Lead
Pfizer Oncology
Tel: (858) 344-4473
Fax: (877) 481-0933
Assistant: Annette Scuderi (Tel: (858) 622-3031)

From: Tilley, Amy [mailto:AMY.TILLEY@fda.hhs.gov]
Sent: Wednesday, November 30, 2011 3:02 PM
To: Russell, Alison

Cc: Skarupa, Lisa

Subject: RE: *Time Sensitive* NDA 202324 Axitinib - Clin Pharm IR

Alison,

At this time, just submit the revised plot and associated data.

Amy

From: Russell, Alison [mailto:Alison.Russell@pfizer.com]

Sent: Wednesday, November 30, 2011 2:56 PM

To: Tilley, Amy

Subject: Re: *Time Sensitive* NDA 202324 Axitinib - Clin Pharm IR

Thanks – have forwarded the Information Request to the team. I assume you don't need a revised label as part of this submission but simply a revised plot and associated data. Is that correct?

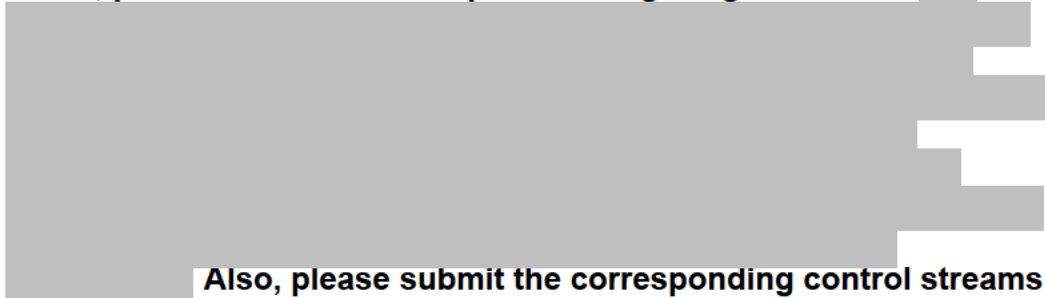
Sent from my iPhone

On Nov 30, 2011, at 11:05 AM, "Tilley, Amy" <AMY.TILLEY@fda.hhs.gov> wrote:

Alison,

I am covering for Lisa Skarupa today and have the following Clinical Pharmacology Information Request (IR).

Regarding the forest plot (Figure 1) in the proposed axitinib package insert, please include the rabeprazole drug-drug interaction ^{(b) (4)}



Also, please submit the corresponding control streams and dataset.

The Clinical Pharmacology Review Team respectfully requests your response to the above IR **no later than Noon on December 7, 2011.**

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology
Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver
Spring, MD 20993
☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov



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/s/

AMY R TILLEY
12/01/2011

Kacuba, Alice

From: Kacuba, Alice
Sent: Tuesday, November 29, 2011 12:07 PM
To: 'Alison.Russell@pfizer.com'
Cc: Skarupa, Lisa; Tilley, Amy
Subject: A Follow-up Information Request (IR)

Importance: High

Hi,

Please submit the current, incomplete, OS analyses for the final OS analysis ASAP.

Thank you.

Alice

Alice Kacuba, RN, MSN, RAC
Chief, Project Management Staff
Division of Oncology Products 1 (new name for DDOP)
Office of Hematology and Oncology Products
OND/CDER/FDA
301-796-1381
(f) 301-796-9845
alice.kacuba@fda.hhs.gov
*Consider setting your email font setting to at least 12 font.

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

/s/

ALICE KACUBA
11/29/2011

Kacuba, Alice

From: Kacuba, Alice
Sent: Monday, November 28, 2011 5:35 PM
To: 'alison.Russell@pfizer.com'
Cc: Skarupa, Lisa; Tilley, Amy
Subject: IR for NDA 202324 Axitinib

Importance: High

Hi,

In covering for Lisa Skarupa, I have the following Information Request (IR) from the clinical reviewer.

Please provide responses for the following two questions by 2 PM on Thursday, December 1.

1. What is the current number of total OS events in the AXIS trial?
2. Have you conducted any additional OS analyses other than the interim analysis submitted with the initial application?

Please submit a response by official channels amend the NDA as well as an email response so as to facilitate the review.

Thank you.

Alice

Alice Kacuba, RN, MSN, RAC
Chief, Project Management Staff
Division of Oncology Products 1 (new name for DDOP)
Office of Hematology and Oncology Products
OND/CDER/FDA
301-796-1381
(f) 301-796-9845
alice.kacuba@fda.hhs.gov
*Consider setting your email font setting to at least 12 font.

Tracking:	Recipient	Read
	'alison.Russell@pfizer.com'	
	Skarupa, Lisa	
	Tilley, Amy	
	McKee, Amy	Read: 11/29/2011 10:12 AM

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/s/

ALICE KACUBA
11/29/2011

From: Robertson, Kim
Sent: Tuesday, November 01, 2011 3:39 PM
To: 'Russell, Alison'
Cc: Skarupa, Lisa
Subject: RE: NDA 202324 November 1 2011 ClinPharm I.R.
[Hello Alison:](#)

The ClinPharm reviewer has informed me that you should also submit the code that was used to create the dataset and the figures as well.

Regards,
Kim

From: Russell, Alison [mailto:Alison.Russell@pfizer.com]
Sent: Tuesday, November 01, 2011 3:04 PM
To: Skarupa, Lisa
Cc: Robertson, Kim
Subject: RE: NDA 202324 November 1 2011 ClinPharm I.R.

Lisa - I received your email and am checking with the team regarding the timing of the response. Meantime, can you clarify whether the ClinPharm reviewers also need (in addition to the dataset used to create the figures) the code that was used to create the dataset and the figures?

Thanks, Alison

Alison Russell
Axitinib Global Regulatory Lead
Pfizer Oncology
Tel: (858) 344-4473
Fax: (877) 481-0933
Assistant: Annette Scuderi (Tel: (858) 622-3031)

From: Skarupa, Lisa [mailto:Lisa.Skarupa@fda.hhs.gov]
Sent: Tuesday, November 01, 2011 10:56 AM
To: Russell, Alison
Cc: Robertson, Kim
Subject: NDA 202324 November 1 2011 ClinPharm I.R.

Dear Alison,

Please see the following Clinical Pharmacology I.R. Please respond **by COB Thursday, Nov 3, 2011 (EST):**

Reference ID: 3037867

This is in reference to your study report **study-pmar-00079**. Please submit the datasets from which the Figure 23 and 24 (Page 74) for simulated Cmax were generated. The datasets should have the following columns (ID, Dose, Cmax and Tmax).

Sincerely,
Lisa

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/s/

KIM J ROBERTSON
11/01/2011

From: Russell, Alison [mailto:Alison.Russell@pfizer.com]
Sent: Tuesday, October 18, 2011 9:19 PM
To: Skarupa, Lisa
Subject: NDA 202324 (axitinib)

Lisa

By way of follow-up to the teleconference 14 October 2011, I wanted to let you know that we would like to go ahead with the December 7th ODAC as currently planned. The team intend to conduct a final analysis of overall survival (OS) in the near future and will submit this data to FDA when available.

Please let me know if you have any questions.

Alison

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/s/

LISA M SKARUPA
10/19/2011



NDA 202324

INFORMATION REQUEST

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Pfizer, Inc.
Attention: Alison Russell, Ph.D.
Associate Director
Worldwide Regulatory Strategy
10646 Science Center Drive
San Diego, CA 92121

Dear Dr. Russell:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Inlyta (axitinib) Tablets.

FDA investigators have identified significant violations to the bioavailability and bioequivalence requirements of Title 21, Code of Federal Regulation, Part 320 in bioanalytical studies conducted by (b)(4)¹. The pervasiveness and egregious nature of the violative practices by (b)(4) has led FDA to have significant concerns that the bioanalytical data generated at (b)(4) from April 1, 2005 to June 15, 2010, as part of studies submitted to FDA in New Drug Applications (NDA) and Supplemental New Drug Applications (sNDA) are unreliable. FDA has reached this conclusion for three reasons: (1) the widespread falsification of dates and times in laboratory records for subject sample extractions, (2) the apparent manipulation of equilibration or “prep” run samples to meet pre-determined acceptance criteria, and (3) lack of documentation regarding equilibration or “prep” runs that prevented (b)(4) and the Agency from determining the extent and impact of these violations.

Serious questions remain about the validity of any data generated in studies by (b)(4) (b)(4) this time period. In view of these findings, FDA is informing holders of approved and pending NDAs of these issues.

The impact of the data from these studies (which may include bioequivalence, bioavailability, drug-drug interaction, specific population, and others) cannot be assessed without knowing the details regarding the study and how the data in question were considered in the overall development and approval of your drug product. At this time, the Office of New Drugs is searching available documentation to determine which NDAs are impacted by the above findings.

¹ These violations include studies conducted by (b)(4) (b)(4) specific to the (b)(4) facility.

To further expedite this process, we ask that you inform us if you have submitted any studies conducted by [REDACTED] ^{(b) (4)} during the time period of concern (April 1, 2005 to June 15, 2010). Please submit information on each of the studies, including supplement number (if appropriate), study name/protocol number, and date of submission. With respect to those studies, you will need to do one of the following: (a) re-assay samples if available and supported by stability data, (b) repeat the studies, or (c) provide a rationale if you feel that no further action is warranted.

Please respond to this query within 30 days from the date of this letter.

This information should be submitted as correspondence to your NDA. In addition, please provide a desk copy to:

Office of New Drugs
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Room 6300
Silver Spring, MD 20993-0002

If you have any questions, call Alice Kacuba, Chief Project Manager Staff, at (301) 796-1381.

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/

ALICE KACUBA
09/29/2011
Signing for Dr. Justice.



NDA 202324

INFORMATION REQUEST

Pfizer Inc.
Attention: Alison Russell, PhD., Associate Director
10646 Science Center Drive
San Diego, CA 92121

Dear Dr. Russell:

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

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. Add an identification test to the specifications for the following:

(b) (4)



2. Provide additional detail for the following steps in Section 3.2.S.2.2, as requested below:

(b) (4)



3. In Section 3.2.S.2.6.5.4.3 (Design of Experiments for (b) (4) you state that a (b) (4)
(b) (4)
4. In Section 3.2.S.2.6.5.5.1 (b) (4), provide the data listing details for Experimental Conditions and Particle Size Results.
5. Your proposed plan in Section 3.2.S.2.6 to mitigate the risk associated with the change of supplier, manufacturing site and (b) (4) appears to be rational. Provide a statement that any such change will follow current guidance for changes to an approved application.
6. The potential mutagenic starting material (b) (4) and (b) (4) are introduced (b) (4). (b) (4) Include (b) (4) and (b) (4) in the drug substance specification or further justify your risk mitigation strategy.
7. Your proposal of not conducting assay on stability, post approval, is not acceptable. A specific stability indicating assay is required. Include all test attributes in the approved stability protocol to your post approval stability commitment.
8. In your stability protocol, the proposed annual testing frequency for long term storage conditions (25°C/60% RH, testing intervals from 0 to 24 months) does not conform with recommendations in ICH Q1A(R2). Revise the proposed stability protocol accordingly.

Drug product

9. Provide the submission dates containing the specific information you are cross referencing for the following DMFs: (b) (4)
10. Discuss if lot-to-lot variability in excipient properties (e.g. bulk density, particle size, surface area) would have any adverse impact on finished product quality. If there is an adverse impact, describe your control strategy.
11. In accordance with CFR 314.50, a complete description of the proposed 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

23. Conduct microbial limits testing during batch release and on stability according to USP<61>/<62> methodology or equivalent. The microbial limits specification should be consistent with USP <1111> recommendations for non-aqueous preparations for oral use. Once a satisfactory product history has been established, a post-approval supplement may be submitted to the FDA requesting the waiver of microbial limits testing during release.
24. Your justification to exclude ‘assay’ as one of the post-approval stability indicating attributes is not acceptable. We believe several potential post-approval changes (e.g, new lots of excipients, modified analytical methods) may introduce new impurities and degradation products. Include ‘assay’ in the post-approval stability protocol or further justify.
25. In the proposed post approval stability protocol for shelf life confirmation and annual lots, revise the sampling points for the first year to every three months, every six months for the second year, and every twelve months thereafter for the long term conditions, as recommended in the ICH guideline. For the accelerated conditions, include sampling points at 3 and 6 months.
26. Provide CFR citations for food contact for the (b) (4) bottle components. Provide results from USP <661> and <671>.
27. Clarify whether you are proposing to use a (b) (4) for commercial products. If so, include the mention of the (b) (4) in the “How Supplied” section, and include any pertinent information.
28. For the proposed Environmental assessment (EA), provide the calculation for EIC to show that the EIC is below 1 ppb.

Analytical Procedures

29. The Agency is still developing its regulatory standards for using QbD approaches to analytical methods. Therefore, the proposed ATP has not been assessed and no regulatory action will be taken.
30. The MODR for the drug substance is not acceptable for the following reasons:
 - The DoE study results were not assessed using either the ICH/USP acceptance criteria or the proposed ATP. Therefore, the DoE study in the drug substance section (b) (4) was not adequate to support the establishment of the initial MODR.
 - The choice of the experiment runs was not adequate to establish the final MODR for (b) (4) because only a limited number of experiment runs was carried out and they were not sufficient for the verification purpose.

31. Revise the following statement [REDACTED] (b) (4) as an example of non-regulatory change in Tables 3.2.S.4.3-12, Table 3.2.P.5.3-9 and 3.2.P.5.3-17. The liquid chromatography stationary phase particle size can be reduced by as much as 50%, but cannot be increased, as recommended by USP<621>.
32. Provide the equation used for calculation of % normalization results for each [REDACTED] (b) (4) in the Method [REDACTED] (b) (4).
33. The experiment design and study results were not sufficient to support the proposed MODRs in [REDACTED] (b) (4) [REDACTED] (b) (4). No modeling was performed to cover the entire MODR surfaces. However, it should be noted that the proposed ranges of the parameters involved in the MODRs are within the allowable ranges according to USP 621.

Biopharmaceutics

34. Provide complete dissolution profile data (raw data and mean values) from the clinical and primary stability batches supporting the selection of the dissolution acceptance criteria (i.e., specification-sampling time point and specification value).
35. Provide the complete dissolution profile data (*individual, mean, SD, profiles*) for the bioequivalent batches (1mg D0602467, 1 mg D0703783, 5 mg D0602468, 5 mg D0703784 from Figures Figure 3.2.P.2.2-17 and Figure 3.2.P.2.2-18) and batches with different particle size (formulations used in Figure 3.2.P.2.2-19).
36. Indicate if variation in % of film coat has any impact on dissolution with supporting data, if available.
37. Provide data demonstrating the adequate dissolution of axitinib with the proposed [REDACTED] (b) (4) [REDACTED]
38. Dissolution was deemed a key quality attribute; however, it was not studied in the drug product DOEs. Justify your rationale for not evaluating dissolution in the drug product DOEs.
39. To assure that the batches produced throughout the proposed design space have the same in vitro and in vivo performance, provide the f_2 values resulting from the comparison of the dissolution profiles obtained throughout the design space.

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/

SARAH P MIKSINSKI
09/26/2011



NDA 202324

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

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

ATTENTION: Alison Russell, PhD
Associate Director, Worldwide Regulatory Strategy

Dear Dr. Russell:

Please refer to your New Drug Application (NDA) dated April 14, 2011, received April 14, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Axitinib Tablets, 1 mg and 5 mg.

We also refer to your April 13, 2011, correspondence, received on April 14, 2011, requesting review of your proposed proprietary name, Inlyta. We have completed our review of the proposed proprietary name, Inlyta and have concluded that it is acceptable.

The proposed proprietary name, Inlyta, 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 April 14, 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, Lisa Skarupa at (301) 796-2219.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
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/

BRANTLEY H DORCH
07/11/2011

CAROL A HOLQUIST
07/11/2011



NDA 202324

FILING COMMUNICATION

Pfizer Inc
Attention: Alison Russell, Ph.D.
Associate Director
Worldwide Regulatory Strategy
10646 Science Center Drive
San Diego, CA 92121

Dear Dr. Russell:

Please refer to your New Drug Application (NDA) dated April 13, 2011, received April 14, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for axitinib tablet.

We also refer to your submissions dated May 13 and 27, June 9, and 10, 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 Standard. Therefore, the user fee goal date is February 14, 2012.

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 commitment requests by January 4, 2012.

We notified you on May 9, and May 23, 2011 of review issues identified by that time, and we received your responses on May 16, June 10, and 13, 2011. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

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(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call Lisa Skarupa, Regulatory Project Manager, at (301) 796-2219.

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/

AMNA IBRAHIM
06/23/2011
For Dr Robert Justice

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
May 17, 2011

IND NO.

NDA NO.
202324

TYPE OF DOCUMENT
original submission

DATE OF DOCUMENT
April 14, 2011

NAME OF DRUG
axitinb

PRIORITY CONSIDERATION
standard

CLASSIFICATION OF DRUG
DDOP

DESIRED COMPLETION DATE
September 14, 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 analytical methodology

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/

DON L HENRY
05/17/2011



NDA 202324

NDA ACKNOWLEDGMENT

Pfizer Inc.
Attention: Alison Russell, PhD
Associate Director, Worldwide Regulatory Strategy
10646 Science Center Drive
San Diego, CA 92121

Dear Dr. Russell:

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: axitinib
tablets for oral administration
1 mg and 5 mg

Date of Application: April 14, 2011

Date of Receipt: April 14, 2011

Our Reference Number: NDA 202324

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 June 13, 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 any questions, call Lisa Skarupa, Regulatory Project Manager, at (301) 796-2219.

Sincerely,

{See appended electronic signature page}

Lisa Skarupa, R.N., M.S.N., A.O.C.N.
Regulatory Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

LISA M SKARUPA
05/02/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): Mail: OSE		FROM: Lisa Skarupa, RPM, DDOP		
DATE April 25, 2011	IND NO.	NDA NO. 202324	TYPE OF DOCUMENT New NDA submission	DATE OF DOCUMENT April 14, 2011
NAME OF DRUG Axitinib		PRIORITY CONSIDERATION To be determined	CLASSIFICATION OF DRUG: New kinase inhibitor indicated to tx advanced renal ca.	DESIRED COMPLETION DATE Prior to September 9, 2011
NAME OF FIRM: Pfizer				
REASON FOR REQUEST				
I. GENERAL				
<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 type="checkbox"/> PAPER 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 checked="" type="checkbox"/> OTHER (SPECIFY BELOW): NEW NDA				
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 <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		
IV. DRUG EXPERIENCE				
<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		
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: EDR Location: \\CDSESUB1\EVSPROD\NDA202324\202324.enx Application Type/Number: nda202324 Incoming Document Category/Sub Category: Electronic_Gateway Supporting Document Number: 0 eCTD Sequence Number: 0000 Letter Date: 04/14/2011 Stamp Date: 4/14/2011 Applicant submitted "Risk Management Plan" which is more a routine pharmacovigilance activities.				
SIGNATURE OF REQUESTER Lisa Skarupa		METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> MAIL-(DARRTS) <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

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/s/

LISA M SKARUPA
04/25/2011

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: CDER-DDMAC-RPM		FROM: (Name/Title, Office/Division/Phone number of requestor) Lisa Skarupa, DDOP-RPM	
REQUEST DATE April 25, 2011	IND NO.	NDA/BLA NO. 202324	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
NAME OF DRUG Axitinib (proposed INLYTA)	PRIORITY CONSIDERATION To be determined	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
NAME OF FIRM: Pfizer		PDUFA Date: if priority = October 14, 2011	
TYPE OF LABEL TO REVIEW			
TYPE OF LABELING: (Check all that apply) <input checked="" type="checkbox"/> PACKAGE INSERT (PI) <input checked="" type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input checked="" type="checkbox"/> (b) (4)/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 type="checkbox"/> INITIAL PROPOSED LABELING <input type="checkbox"/> LABELING REVISION			
EDR link to submission: NDA202324 in DARRTS EDR Location: \\CDSESUB1\EVSPROD\NDA202324\202324.enx			
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. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to DDMAC. Once the substantially complete labeling is received, DDMAC will complete its review within 14 calendar days.			
COMMENTS/SPECIAL INSTRUCTIONS: Mid-Cycle Meeting: [Insert Date] Estimated July 14 Labeling Meetings: [Insert Dates] Estimated August to Sept Wrap-Up Meeting: [Insert Date] Estimated Sept 16			
SIGNATURE OF REQUESTER Lisa Skarupa			
SIGNATURE OF RECEIVER		METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> eMAIL (DARRTS) <input type="checkbox"/> HAND	

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/s/

LISA M SKARUPA
04/25/2011

REQUEST FOR CONSULTATION

TO (Office/Division): HFD-110
Devi Kozeli (IRT)

FROM (Name, Office/Division, and Phone Number of Requestor): HFD-150
Lisa Skarupa, DDOP

DATE
April 21, 2011

IND NO.

NDA NO.
202324

TYPE OF DOCUMENT
New NDA

DATE OF DOCUMENT
April 14, 2011

NAME OF DRUG
axitinib tablets

PRIORITY CONSIDERATION
to be determined

CLASSIFICATION OF DRUG
NME

DESIRED COMPLETION DATE
July 11, 2011

NAME OF FIRM:

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: We are requesting review of the QTc data obtained within trial A4061004 and the population PK/PD analyses of the data (reports pmar-00074 & pmar-00074s). These are the QTc data to support this NDA submission. Following your review of these reports, please provide labeling and PMC/PMR recommendations (if appropriate) to the review division. EDR Location: \\CDSESUB1\EVSPROD\NDA202324\202324.enx MO=Amy McKee; TL=John Johnson, ClinPharm Reviewer: Sarah Schrieber ClinPharm TL= Qi Liu Thank you. Checking this into DARRTS.

SIGNATURE OF REQUESTOR
Lisa Skarupa, DDOP

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/

LISA M SKARUPA
04/21/2011

1.0 BACKGROUND

The purpose of this meeting is to receive feedback from the Agency on whether the pivotal study proposed for inclusion in the original NDA submission may support an NDA submission and in particular an "advanced renal cell carcinoma (RCC)" indication.

2. DISCUSSION

1. Since the pivotal Phase 3 study in patients with advanced RCC (A4061032) met its primary endpoint, the Sponsor believes that the data support an NDA submission. Does the Agency agree?

FDA response to Question #1: The limited data that you provided, suggest that an NDA submission may be appropriate. However, the filing decision can be made only after the NDA is submitted.

2. Indirect and direct comparisons between axitinib and other drugs approved by the Food and Drug Administration (FDA) for advanced RCC have been made based on clinical data from the pivotal Phase 3 study A4061032 and published data. The observations are:
 - In similar patient populations, the median progression-free survival (PFS) associated with axitinib (12.1 months 95% confidence intervals [CI]: 10.1, 13.9) in cytokine-refractory patients with advanced RCC was numerically longer than that observed on treatment with sunitinib (8.8 months, 95% CI: 7.8, 13.5) and pazopanib (7.4 months 95% CI: not published). In a direct comparison within the pivotal study, axitinib treatment of cytokine-refractory patients resulted in statistically and clinically superior PFS compared to patients randomized to sorafenib (median PFS: 12.1 months vs. 6.6 months; hazard ratio [HR] 0.469; $p < 0.0001$).
 - In different patient populations, the median PFS associated with axitinib (12.1 months 95% CI: 10.1, 13.9) in cytokine-refractory patients with advanced RCC was similar to that observed in treatment-naïve patients for bevacizumab + interferon- α (IFN- α) (10.2 months; 95% CI: not published), comparable to that of pazopanib (11.1 months; 95% CI: not published) and sunitinib (11 months; 95% CI: 10.0, 12.0), and longer than that observed in treatment-naïve patients with poor prognosis for temsirolimus (5.5 months; 95% CI: 3.9, 7.0).

In light of this, the Sponsor considers that an indication of axitinib "for the treatment of patients with advanced RCC" is appropriate. Does the Agency agree?

FDA response to Question #2: This will be a review issue.

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/s/

LISA M SKARUPA
02/18/2011

Advanced Renal Cell Carcinoma

Revised List of Questions

1. To support the efficacy claim, the NDA will include efficacy data from the pivotal Phase 3 randomized metastatic RCC study in previously treated patients with metastatic RCC (A4061032) and also efficacy data from three supportive Phase 2 single arm studies in previously treated patients with mRCC (A4061012, A4061023 and A4061035). Per the Guidance for Industry entitled "Integrated Summaries of Effectiveness and Safety: Location within the Common Technical Document", the Sponsor understands that an Integrated Summary of Efficacy (ISE) is required in the NDA. The Sponsor proposes to split the text, listings, tables, figures, and datasets for the ISE between Modules 2 and 5. The text, listings, figures, and tables will be placed in Module 2 (Section 2.7.3) and datasets will be placed in individual clinical study reports in Module 5 (Section 5.3.5.3). This will allow identical versions of eCTD Module 2 to be used in regulatory submissions throughout several ICH regions. The Sponsor believes that this proposal is in accordance with the ICH Guidance M4E (adopted by the FDA as "Guidance for Industry. M4E: The CTD – Efficacy", issued August 2001). In the NDA, the Sponsor will explain where all the data are provided. In addition, the SCE documents will be sufficiently detailed so as to meet the Code of Federal Regulation (CFR) requirements for the text portion of the ISE.

Does the Agency concur with the Sponsor proposal to split the text, listings, tables, figures, and datasets of the Integrated Summary of Efficacy between Modules 2 and 5?

FDA Response: Yes

2. For the SCE:

The proposed Table of Contents (TOC) for the SCE is shown in Section 9 of Briefing Package Attachment 2. The proposed list of figures and tables for the SCE (cross-referenced from the final clinical study report for Phase 3 mRCC study A4061032) are shown in Section 10.1 and 10.2 of Briefing Package Attachment 2. The proposed data table shells for the SCE are shown in Section 10.3 of Briefing Package Attachment 2.

In the pivotal Phase 3 study in RCC patients (A4061032), as well as in several other clinical studies with axitinib, patients receive a starting oral dose of

Advanced Renal Cell Carcinoma
Revised List of Questions

5 mg BID with the possibility of dose titration (above 5 mg BID). Patients who tolerate axitinib with no adverse events related to axitinib above the Common Toxicity Criteria for Adverse Events (CTCAE) Grade 2 for ≥ 2 -week periods are allowed to have their dose increased by one dose level (i.e. up to 7 mg BID and subsequently up to a maximum of 10 mg BID) unless blood pressure (BP) is $>150/90$ mm Hg or the patient is receiving antihypertensive medication. For the Phase 3 mRCC study (A4061032), the majority of the data will be summarized by randomized treatment assignment (irrespective of what dose the patient subsequently received). In addition, a summary of PFS by treatment group will also be separately provided by maximum total daily dose level achieved (≤ 10 mg vs > 10 mg); no inferential statistics (such as hazard ratios and p-values) will be provided.

Does the Agency concur a) that the format and data presentations for the SCE are appropriate and b) with the Sponsor's proposal to present the majority of the data for the Phase 3 mRCC study (A4061032) according to randomized treatment assignment (irrespective of what dose the patient subsequently received)?

FDA Response: Yes

3. In the pivotal RCC study (A4061032), the following imaging data is being collected:

Imaging Data	Schedule	Assessments
Screening (Baseline Images)	Day -28 to Day 0	CT/MRI of the chest, abdomen, pelvis, and brain Bone scan
Follow-Up On-Treatment Exams	Every 6 calendar weeks for two timepoints then every 8 calendar weeks thereafter	CT/MRI of the chest, abdomen, and pelvis
	Every 6 calendar weeks for two timepoints then every 8 calendar weeks for bone disease for those subjects with bone lesions at baseline	Bone scan and correlative imaging
Confirmation	At least 4 weeks after CR or PR is	CT/MRI of the chest, abdomen,

Imaging Data	Schedule	Assessments
Timepoint	first noted by the investigator	and pelvis Bone scan and correlative imaging, as applicable
Withdrawal/ Discontinuation	At the time of withdrawal from the study or after study drug discontinuation and before starting any new treatment. No further imaging exams will be acquired after permanent discontinuation of study treatment.	CT/MRI scan of chest, abdomen, pelvis, and other applicable sites Bone scan and correlative imaging, as applicable
Unscheduled Exams	As clinically indicated	CT/MRI scan of chest, abdomen, pelvis, and other applicable sites, such as the brain Bone scan and correlative imaging

In the initial stages of the Phase 3 RCC study (prior to protocol A4061032 Amendment 3), pre-study scans were collected to document prior disease progression and confirm study eligibility. However, following a Type B meeting with FDA on 03 February 2009, an agreement was reached with FDA to discontinue collecting pre-study scans and instead to capture the method of documentation of prior disease progression in the case report form (see FDA Type B meeting minutes dated 03 February, 2009). In general, radiographic images obtained by the investigators will be collected and centrally archived by

(b) (4)

_____ to ensure that the images are of the same quality as those reviewed by the IRC.

Per the FDA Guidance for Industry: Cancer Drug and Biological Products Clinical Data in Marketing Applications (issued October 2001), the Sponsor understands that tumor images do not need be submitted with the NDA.

(b) (4)



(b) (4)

Does the Agency concur with the Sponsor's proposals regarding: a) timing of radiographic image submission, b) provision the radiographic images in (b) (4) format, c) provision of a (b) (4) to facilitate image retrieval, and d) radiographic image archiving?

FDA Response: No, we are unable to receive radiographic images unless they are in PDF format. We will ask for images in PDF format if required. (b) (4)

4. Per the Guidance for Industry entitled "Integrated Summaries of Effectiveness and Safety: Location within the Common Technical Document", the Sponsor understands that an Integrated Summary of Safety (ISS) is required to be included in the NDA. The Sponsor proposes to split the text, listings, tables, and datasets of the ISS between Modules 2 and 5. A textual summary of the clinical safety data (including in-text tables) will be included in Section 2.7.4. Pooled safety tables will be included in the appendix to Section 2.7.4. Safety data split by age, race, and gender will be included in Section 2.7.4. Safety data tables, Case Report Form tabulations, Case Report Forms for individual patients, individual patient narratives, and adverse event datasets will be part of individual clinical study reports in Module 5. Datasets for the SCS will be in Module 5. This allows identical versions of eCTD Module 2 to be used in regulatory submissions throughout several ICH regions. The Sponsor believes that this proposal is in accordance with the ICH Guidance M4E (adopted by the FDA as "Guidance for industry. M4E: The CTD – Efficacy", August 2001) and FDA's Guidance for Industry "Integrated Summaries of Effectiveness and Safety: Location Within the

Common Technical Document”, issued April 2009. In the NDA, the Sponsor plans to explain where all the data are provided. In addition, the SCS documents will be sufficiently detailed so as to meet the CFR requirements for the text portion of the ISS.

Does the Agency concur with the Sponsor proposal to split the text, listings, tables, and datasets of the Integrated Summary of Safety between Modules 2 and 5?

FDA Response: Yes.

5. An EOP2 meeting was held on 14 August 2006 between the Sponsor and FDA (*see FDA meeting minutes, dated 25 September 2006*). At this meeting, the Sponsor indicated that the results from the ketoconazole drug interaction healthy volunteer study A4061004, which included assessment of QTc under conditions of metabolic inhibition of axitinib and involved multiple, timed serial triplicate electrocardiogram (ECG) measurements and matched PK sample collections, would be included in the NDA as an “alternative thorough QT” study. Results from the PK-PD modeling of QTc versus axitinib plasma concentration and evaluation of study-specific QTc correction (QTcS) will be included in the A4061004 clinical study report. The analysis of non-linear mixed effects modeling of the correlation of QTc with plasma concentrations from the “alternative TQT study” (A4061004) will be described in Module 2, Section 2.7.2 (SCP).

In the Phase 3 mRCC study (A4061032), triplicate 12-lead ECGs are being collected to determine the mean QTc interval; the ECGs are being performed at Cycle 1 Day 1 pre-dose (baseline), approximately 1-2 hours following a dose of axitinib on Cycle 1 Day 15 for the first 50 patients randomized to the axitinib arm only. For all remaining patients (including the control arm), a single ECG measurement is being collected at Cycle 1 Day 1 pre-dose. If the mean QTc interval is prolonged (>500 msec), ECGs are re-read for confirmation. Additional ECGs are performed as clinically indicated. The results from this Phase 3 mRCC study will be summarized in the clinical study report. In addition, triplicate and single ECGs were collected pre- and post-dose in other studies in patients (triplicate: A4061010, A4061028, A4061035, and A4061044; single: A4061022

and A4061027). Single ECGs were also collected pre- and post-dose in other studies in healthy volunteers (A4061003, A4061007, A4061018, A4061021, A4061026, A4061033, A4061037, A4061047, and A4061050).

In Module 2, Section 2.7.4 (SCS), QTc data (presented using both Bazett's and Fridericia's correction factors) will be pooled for the following studies:

Single agent axitinib studies in patients in which triplicate ECG measurements were collected: A4061032 (pivotal Phase 3 RCC study; ECG data was collected from the first 50 axitinib-treated patients), A4061035 (Japanese study in cytokine-refractory patients; ECG data was collected from all [64] patients), and A4061044 (Phase 1 study in a various tumor types; ECG data was collected from all [6] patients).

Single agent axitinib studies in patients in which single ECG measurements were collected: A4061022 (12 patients) and A4061027 (50 patients).

Single agent axitinib studies in healthy volunteer studies in which single ECG measurements were collected: A4061003, A4061007, A4061018, A4061021, A4061026, A4061033, A4061037, A4061047, and A4061050.

In the SCS, QTc data (presented using both Bazett's and Fridericia's correction factors) will be presented separately for the following studies:

Axitinib + chemotherapy combination studies in patients in which triplicate ECG measurements were collected: A4061028 (Phase 3 non-registrational pancreatic cancer study of axitinib + gemcitabine; ECG data was collected from the first 100 patients [i.e. 50 patients in gemcitabine + axitinib arm and 50 patients in gemcitabine + placebo arm]) and A4061010 (Phase 2 breast cancer study of axitinib + docetaxel; ECG data was collected in all patients).

Single agent axitinib studies in healthy volunteer studies in which triplicate ECG measurements were collected: A4061004.

Per the FDA's Guidance for Industry: E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs (issued October 2005), categorical analysis will include presentation of absolute QTc interval prolongation (>450 milliseconds [msecs], >480 msecs, and >500 msecs) and change from baseline in QTc interval (> 30 msecs and > 60 msecs). In addition, non-categorical analysis will be included to present the mean QTc change on study.

Based on the currently known data, does the Agency concur with this proposal for QTc evaluation from individual and pooled studies and the proposed pharmacokinetic-pharmacodynamic analysis of QTc?

FDA Response:

QT-IRT Response: Your proposal is generally acceptable. However, we have the following comments for the dedicated QT evaluation in ketoconazole drug-drug interaction study (Study A4061004).

We encourage you to perform a pharmacokinetic-pharmacodynamic analysis in order to account for ketoconazole QTc effect in the combination group (ketoconazole + axitinib). We encourage the exploration of the adequacy of the model fit to the assumption of linearity (if a linear model is used) and the impact on quantifying the concentration response relationship. Therefore, diagnostic evaluation is expected as part of the application of the method recommended here. 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).

2. When you submit your QTc study report (study A4061004), 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)
- l. A completed Highlights of Clinical Pharmacology Table

3. In your study report, please indicate whether the following items were included.

- Use of a central ECG laboratory employing a limited number of skilled readers, to control variability in interpretation
- Blinding of ECG readers to treatment, time, and day (i.e., Day - 1; Day 1) identifiers
- Review of ECGs from a particular subject should be performed by a single reader
- Pre-specify the lead for interval measurements
- Baseline and on-treatment ECGs should be based on the same lead

7. The overall pooling strategy for reporting of safety data for axitinib is provided in Briefing Package Attachment 3 (see Section 2.4, Figure 1). In the SCS, the following safety data will be provided:

Comprehensive safety data will be presented for completed studies
Critical safety data (demographics, discontinuations, and serious adverse events [SAEs] including deaths occurring during the safety data collection period [estimated safety cutoff mid July 2010]) will be presented for ongoing Pfizer-sponsored studies, SAEs (including deaths) will be presented for ongoing Investigator-initiated research (IIR) studies

Once ongoing studies are finalized, complete safety data will be included in the final clinical study reports and these will be submitted to the IND.

Comprehensive safety data from the following completed studies will be pooled:

Axitinib single agent studies in mRCC and other solid tumors
Axitinib + chemotherapy studies in pancreatic cancer
Axitinib single agent studies in healthy volunteers

Comprehensive safety data from the following completed studies will be presented separately:

Axitinib single agent studies in mRCC (Phase 3 randomized pivotal study A4061032 and Phase 2 single-arm studies A4061012, A4061023, and A4061035)
Axitinib + chemotherapy studies
Hematological malignancy study (A4061013)
Hepatic-impairment study (A4061036)

Critical safety data from the following ongoing studies will be pooled:

Axitinib single agent studies in mRCC

Critical safety data from the following ongoing studies will be presented separately:

Axitinib + chemotherapy studies
Continued access study (A4061008)

SAEs including deaths from the following ongoing studies will be presented separately:

IIR studies

Advanced Renal Cell Carcinoma
Revised List of Questions

In Module 2, Section 2.7.4 (SCS), the Sponsor proposes to pool safety data according to a starting dose of 5 mg BID, and not according to whether the patient was dose titrated to >5 mg BID (>10 mg total daily dose) or reduced to <5 mg BID (<10 mg total daily dose). However, because of the flexibility with dose titration, some patients treated in the pivotal Phase 3 study in RCC (A4061032) who tolerated axitinib had their dose increased to >5 mg BID. Therefore, for the pivotal Phase 3 study (A4061032), additional select safety tables (Incidence and Grade of Treatment-Emergent Adverse Events [All Causalities and Treatment Related]) will be presented according to events observed in patients who received a total daily dose of >10 mg (at any point during the study) and those who did not.

Does the Agency concur with the Sponsor's proposed pooling strategy for the safety data to be included in the Summary of Clinical Safety in the NDA?

FDA Response: Yes

11. Annotated CRFs will be provided along with final CSRs in Module 5 of the eCTD for the Phase 3 mRCC study (A4061032) and all other completed studies, but will not be provided for ongoing studies. For healthy volunteer studies, annotated CRFs will be provided in the NDA for all studies that used a paper or electronic CRF to collect data (i.e. studies A4061003, A4061004, A4061006, A4061026, A4061036, and A4061050). For studies in which data was captured directly into the Sponsor's Phase 1 management system (PIMS), CRFs are not generated since data is directly downloaded into PIMS (i.e. studies A4061007, A4061018, A4061021, A4061033, A4061037, A4061047, A4061052, and A4061053); therefore, no annotated CRFs will be provided in the NDA for these studies. Completed CRFs (electronic hypertext-linked pdf versions) will be provided in the NDA, for the pivotal Phase 3 RCC study (A4061032) and other completed studies, for those patients who died during a clinical study, experienced a treatment-related SAE, or who did not complete a study due to an AE, per 21 CFR 314.50(f)(2). In all studies, the Sponsor collects AE and SAE information up to 28 days after the last administration of the investigational product. After 28 days of drug discontinuation, only SAEs that are suspected to have a causal relationship to axitinib are reported. The completed CRF will be provided in Module 5 of the eCTD. Patient profiles will not be provided for the submission. For healthy volunteer studies, completed CRFs (electronic hypertext-linked pdf

versions) will be provided in the NDA for those patients who died during a clinical study, experienced a treatment-related SAE, or who did not complete a study due to an AE from only those studies that used a paper or electronic CRF to collect data and will not be provided for those studies in which data was captured directly into the Sponsor's PIMS (studies listed previously).

Does the Agency concur with the Sponsor's proposals regarding annotated and completed CRFs?

FDA Response: Yes

15. The cutoff date for collection of safety data from the pivotal Phase 3 RCC study (A4061032) and ongoing clinical studies is currently estimated to be mid July 2010. The proposed NDA submission date is currently estimated to be February 2011. The Sponsor proposes to set a second safety cutoff date of February 2011 to collect safety data from ongoing and newly completed studies and will submit a Safety Update approximately 4 months after NDA submission. The Safety Update supporting the filing for axitinib will contain the following information submitted in the format of the SCS (as applicable):

Table of ongoing and completed studies

Complete safety data from any study completed after the NDA was submitted
Critical safety data (demographics, discontinuations, and SAEs including deaths) from all ongoing clinical studies (including Phase 3 mRCC study A4061032); these safety data will not be pooled. If the new data overall leads to a conclusion that is substantially different from conclusions in the initial submission, additional safety data will be provided.

Completed CRFs (electronic hypertext-linked pdf versions) and CIOMS not submitted in the original NDA submission for those patients who died during a clinical study, experienced an SAE, or who did not complete a study due to an AE; and

If necessary, additional relevant animal data and information on other pharmacologic properties may be included if it has bearing on the clinical safety; these data would be included in the nonclinical overview or Module 4.

For studies initiated 3 months before NDA submission or studies that have not yet enrolled any patients at the time of the initial safety cutoff data, critical safety data

(demographics, discontinuations, and SAEs including deaths) will be provided in the Safety Update.

The Safety Update will not contain CSRs (CSRs will be submitted to the IND upon completion and will be available upon request) or domain profiles and derived datasets (datasets will be available upon request).

Does the Agency concur with the proposed content and timing of the Safety Update?

FDA Response: Yes

20. Axitinib is metabolized primarily in the liver. Following oral administration of a 5 mg radioactive dose of axitinib, only 23% of the radioactivity was recovered in urine. The carboxylic acid and sulfoxide metabolites accounted for the majority of radioactivity in urine (axitinib parent drug was not detected in urine); these metabolites show approximately 400-fold and 8000-fold less in vitro potency, respectively, against VEGFR-2 compared to axitinib and, therefore, are considered to be “inactive”. Also, a preliminary population PK analysis (n= 486 subjects) showed no evidence for changes in axitinib clearance based on renal function (see Attachment 4, Section 5.3.2). Based on these findings, the Sponsor does not plan to conduct a study in renally-impaired patients to support the intended indication. In the NDA, the Sponsor proposes to present POPPK analyses regarding renal impairment that will provide guidance regarding use of axitinib in subjects with renal impairment. In the ‘Use in Specific Populations’ section (Section 8) of the draft label (see Attachment 9), the Sponsor proposes to include recommendations regarding the use of axitinib showing the use of axitinib in patients with hepatic and renal impairment, as shown below:

(b) (4)

(b) (4)

Based on currently known data, a) does the Agency generally think that the Sponsor's proposed recommendations regarding the use of axitinib in patients with hepatic and renal impairment appear to be appropriate and b) does the Agency concur with the Sponsor's proposal to present population pharmacokinetic (POPPK) analyses regarding renal impairment to support the recommendations for renally-impaired patients?

FDA Response: This will be a NDA review issue.

24.

(b) (4)

Does the Agency concur with the Sponsor's proposal [REDACTED] (b) (4).

!?

FDA Response: Please provide the rationale [REDACTED] (b) (4).
Also please provide us with the summary of the results of your Phase 3 trial.

28. Since the Agency previously designated the investigation of axitinib for mRCC following failure of one prior systemic first-line therapy as a Fast Track development program, the Sponsor proposes to submit the nonclinical sections of the eCTD (Modules 2.4, 2.6 and 4) for "rolling review" approximately 6 months prior to the targeted submission date for the other eCTD sections (i.e., estimated submission of nonclinical sections would be 3Q 2010).

Does the Agency concur with the Sponsor's proposal for rolling submission of the eCTD Modules?

FDA Response: Yes.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-63662	GI-1	PFIZER INC	AG013736

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/s/

LISA M SKARUPA
07/12/2010



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 063662

MEETING MINUTES

Pfizer Inc
Alison L Russell, Ph.D.
Associate Director
Worldwide Regulatory Strategy
10646 Science Center Drive
San Diego, CA 92121

Dear Dr. Russell:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for AG-013736 (axitinib).

We also refer to the meeting between representatives of your firm and the FDA on July 1, 2010. The purpose of the meeting was to receive feedback from the Agency on the revised statistical analysis plan (SAP) and amended study protocol proposed for the ongoing Phase 3 registrational study A4061051 in patients with metastatic renal cell carcinoma (mRCC).

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) 796-2219.

Sincerely,

{See appended electronic signature page}

Lisa Skarupa, R.N., M.S.N., A.O.C.N.
Regulatory Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type A Meeting (Teleconference)
Meeting Category: Guidance Meeting: revised Statistical Analysis Plan

Meeting Date and Time: June 11, 2010
Meeting Location: Teleconference

Application Number: IND 63662
Product Name: (AG-013736) Axitinib
Indication: treatment of patients with advanced RCC
Sponsor/Applicant Name: Pfizer Inc.

Meeting Chair: Shenghui Tang, Ph.D., Statistician Team Leader
Meeting Recorder: Lisa Skarupa, RN, MSN, Regulatory Project Manager

FDA ATTENDEES

Robert Justice, M.D., M.S., Director, DDOP
John Johnson, M.D., Clinical Team Leader, DDOP
Martin Cohen, M.D., Clinical Reviewer, DDOP
Shenghui Tang, Ph.D., Statistician Team Leader, OTS/OB/DBV
Somesh Chattopadhyay, Ph.D., Statistician Reviewer, OTS/OB/DBV

SPONSOR ATTENDEES

Isan Chen, M.D., (clinical), Pfizer, Inc.
Sinil Kim, M.D., (clinical), Pfizer, Inc.
Yong Ben, M.D., (clinical), Pfizer, Inc.
Paul Bycott, Ph.D., (statistics), Pfizer, Inc.
Jie Tang, M.S., (statistics), Pfizer, Inc.
Glen Andrews, M.S., (Team Leader), Pfizer, Inc.
Laurie Strawn, Ph.D., (regulatory), Pfizer, Inc.
Alison Russell, Ph.D., (regulatory), Pfizer, Inc.

BACKGROUND

Axitinib, a substituted indazole derivative, is a potent and selective inhibitor of vascular endothelial growth factor receptors (VEGFRs) 1, 2, and 3. This investigational new drug is currently being studied in Phase 1-3 clinical trials in patients with a range of solid tumor indications. The proposed indication for the current submission is "Axitinib is indicated for the treatment of patients with advanced RCC".

Axitinib is supplied as 1 mg and 5 mg film-coated tablets for oral administration. The drug product is stored at controlled room temperature (b) (4)

The oral dosing regimen in the ongoing clinical development program is a starting dose of 5 mg BID with dose titration to a maximum of 10 mg BID based on tolerability and blood pressure. Pfizer, Inc has previously:

- Met with FDA in an End of Phase 2 (EOP2) meeting, held May 17, 2007, to discuss the proposed clinical development of axitinib in patients with RCC.
- Submitted to FDA the Phase 3 protocol (A4061032) for review under a Special Protocol Assessment (SPA) and agreed that the "design and planned analysis of this study adequately address the objectives necessary to support a regulatory submission" (see FDA letter dated April 17, 2008).
- Met with FDA in a Type B meeting, held January 27, 2010, to discuss the proposed study (b) (4)

This meeting request provides for a draft version of protocol (b) (4) for review. The objective of this meeting is to receive feedback from the Agency (b) (4)

On June 10, 2010, the Sponsor responded to FDA's preliminary responses. For the teleconference, the Sponsor will focus the discussion on questions 1d and 1g.

DISCUSSION

(b) (4)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-63662	GI-1	PFIZER INC	AG013736

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/s/

SHENGHUI TANG
07/13/2010



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 063662

MEETING MINUTES

Pfizer Inc.
Alison L. Russell, Ph.D.
Associate Director
Worldwide Regulatory Strategy
10646 Science Center Drive
San Diego, CA 92121

Dear Dr. Russell,

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for AG-013736 (axitinib).

We also refer to the meeting between representatives of your firm and the FDA on January 27, 2010. The purpose of the meeting was to obtain FDA's feedback on a particular question

[REDACTED] (b) (4)

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 Lisa Skarupa at (301) 796-2219.

Sincerely,

{See appended electronic signature page}

Lisa Skarupa, RPM
Division of Drug Oncology
Office of New Drugs
Center for Drug Evaluation and Research

Minutes Attached



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: pre-NDA meeting

Meeting Date and Time: January 27, 2010
Meeting Location: White Oak Campus Building 22, Room 1419

Application Number: IND 063662
Product Name: AG-013736 (axitinib)
Indication: Proposed for the treatment of patients with advanced RCC
Sponsor/Applicant Name: Pfizer, Inc.

Meeting Chair: John Johnson, M.D., Medical Team Leader
Meeting Recorder: Lisa Skarupa, RPM

FDA ATTENDEES

Amna Ibrahim, M.D., Deputy Division Director, DDOP
John Johnson, M.D., Clinical Team Leader, DDOP
Martin Cohen, M.D., Clinical Reviewer, DDOP
Kun He, Ph.D., Statistical Team Leader, DDOP
Xiaoping Jiang, Ph.D., Statistical Reviewer, DDOP
Qi Liu, Ph.D., Clinical Pharmacology Team Leader, Division of Clinical Pharmacology 5
Sophia Abraham, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology 5
Nicole Gormley, M.D., CDER visiting Clinical Fellow

SPONSOR ATTENDEES

Sinil Kim, M.D., Clinical
Isan Chen, M.D., Clinical
Glen Andrews, M.Sc., Development Team Leader
Ramzi Dagher, M.D., Regulatory
Jie Tang, M.S., Biostatistics
Alison Russell, Ph.D., Regulatory
Laurie Strawn, Ph.D., Regulatory

BACKGROUND

On November 2, 2009, Pfizer Inc, submitted a Type B Meeting Request; corrected Meeting Request submitted on November 20, 2009. The briefing document was received December 15, 2009. FDA forwarded their preliminary comments January 23, 2010. Pfizer replied to FDA's preliminary comments, Pfizer wanted to reduce the Meeting agenda to cover Question 2(b). Pfizer concurred with FDA's responses to the other questions and will not be part of the meeting discussion.

The purpose of this meeting is to receive feedback from the Agency on whether the studies proposed for inclusion in the original NDA submission may support an "advanced renal cell carcinoma (RCC)" indication [REDACTED] (b) (4)

[REDACTED] This meeting reflects the discussion regarding FDA response to Question 2(b).

DISCUSSION

1. The proposed indication of "advanced RCC" for the original NDA will be supported by safety and efficacy data from the following completed studies, as follows:
 - Study A4061032 (N=650): Ongoing Phase 3, randomized, open-label, multi-center study comparing axitinib versus sorafenib in patients with mRCC whose disease has failed one prior systemic therapy including sunitinib, bevacizumab + interferon-alpha (IFN- α), temsirolimus, or cytokines;
 - Study A4061012 (N=52): Completed Phase 2, single-arm, open-label, multi-center study of axitinib in patients with mRCC whose disease had failed one prior cytokine based therapy;
 - Study A4061023 (N=62): Completed Phase 2, single-arm, open-label, multi-center study of axitinib in patients with mRCC whose disease had failed at least one prior treatment with sorafenib; most patients had additionally received prior treatment with sunitinib and/or other agents (i.e. multiple previous therapies);
 - Study A4061035 (n=64): Ongoing Phase 2, single-arm, open label, multi-center study of axitinib in patients with mRCC whose disease has failed one prior cytokine-based therapy; and
 - Safety data from Phase 1 and 2 studies of axitinib in various non-mRCC solid tumors.

[REDACTED] (b) (4)



OTHER ISSUES

- 1. Has the charter for the IRC for Phase 3 trial A4061032 been submitted?**

Sponsor response: Yes. All versions of the A4061032 IRC charter, including current version (Version 5.0 dated 16 June 2009), have been submitted to IND 63,662; the submission details are as follows:

- IRC Charter Version 1.0 (dated 13 December 2007) - IND 63,662 SN 0224 dated 18 December 2007 (First request for Special Protocol Assessment)*

- *IRC Charter Version 2.0 (dated 11 March 2008) - IND 63,662 SN 0238 dated 14 March 2008 (Second request for Special Protocol Assessment)*
 - *IRC Charter Version 3.0 (dated 23 February 2009) - IND 63,662 SN 0316 dated 03 March 2009 (Revised following agreements reached with FDA at meeting on 03 February 2009 regarding method of documentation of prior disease progression)*
 - *IRC Charter Version 4.0 (dated 01 May 2009) - IND 63,662 SN 0334 dated 22 June 2009 (Revision was designed to clarify that reviewers will not have access to pre-study images during efficacy review and to delete the requirement "if there are no other radiological exams available, new bone scan lesions that are not definitive will not be considered malignant". Revision 5.0 was designed to allow the reviewers to examine all available scans beyond progressive disease to capture all tumor measurements in the analysis database)*
 - *IRC Charter Version 5.0 (dated 16 June 2009) - IND 63,662 SN 0334 dated 22 June 2009 (Revision was designed to allow the reviewers to examine all available scans beyond progressive disease to capture all tumor measurements in the analysis database)*
2. If you plan to claim efficacy based on the selected secondary endpoints after the primary endpoint PFS analysis has demonstrated significant improvement in PFS, please pre-specify a statistical procedure/plan controlling overall family-wise type I error rate at one-sided 0.025 level for the selected secondary endpoints.

Sponsor response: No discussion required

ISSUES REQUIRING FURTHER DISCUSSION

None.

ACTION ITEMS

Sponsor will submit detailed revised Statistical Analysis Plan for study A4061051.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-63662	GI-1	PFIZER INC	AG013736

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/s/

LISA M SKARUPA
01/28/2010

JOHN R JOHNSON
01/28/2010

MEETING MINUTES

MEETING DATE: February 3, 2009 **TIME:** 3:00-4:00pm **LOCATION:** Teleconference

IND: 63662

Submission date: November 13, 2008

Briefing Document Submission Date: December 17, 2008

Drug: AG-013736 (Axitinib)

Sponsor: Pfizer Inc.

FDA Attendees:

Robert Justice, M.D., Director, DDOP

Patricia Cortazar, M.D., Clinical Team Leader, DDOP

Martin Cohen, M.D., Clinical Reviewer, DDOP

Kun He, Ph.D., Statistician, DDOP

Ian Waxman, M.D., IOTF fellow, DDOP

Ke Liu, M.D., Clinical Team Leader, DDOP

Sponsor Attendees:

Sinil Kim, M.D., Clinical Lead, Pfizer Inc.

Isan Chen, M.D., Clinical, Pfizer Inc.

Jamal Tarazi, M.D., Clinical, Pfizer Inc.

Brad Rosbrook, Ph.D., Statistics, Pfizer Inc.

Paul Bycott, Ph.D., Statistics, Pfizer Inc.

Alison Russell, Ph.D., Regulatory, Pfizer Inc.

Background:

On November 13, 2008, Pfizer Inc. submitted a meeting request to discuss AG-013736 (Axitinib).

Pfizer Inc. submitted the background package on December 17, 2008, and on January 26, 2009 FDA communicated their preliminary responses to the posed questions.

The following discussion was held on February 3, 2009 between Pfizer Inc. and FDA.

1. The ongoing Phase 3, open-label randomized study (A4061032) compares patients with mRCC receiving axitinib versus (vs) sorafenib after progression following one prior systemic first-line regimen containing one or more of the following agents: sunitinib, bevacizumab + interferon-alpha (IFN α), temsirolimus, or cytokine(s). During an End-of-Phase 2 (EOP2) meeting with FDA (*see FDA meeting minutes dated June 18, 2007*), the Sponsor informed the Agency that if a “prior therapy” fits into >1 stratum, patient data will be fitted into the strata in the following order of hierarchy: sunitinib/sunitinib-containing regimen > bevacizumab/ bevacizumab-containing regimen > mTOR inhibitor/ mTOR inhibitor-containing regimen > cytokines. This hierarchy was based on similarity of mechanism of action (MOA) of the prior therapy to that of axitinib. Following Special Protocol Assessment (SPA) review, FDA requested clarification regarding the inclusion criteria (*see FDA letter dated January 31, 2008*). Based on this feedback, the protocol was revised to stratify by Eastern Cooperative Oncology Group (ECOG) performance status (0 vs 1) and prior systemic first line regimen (i.e. sunitinib vs bevacizumab + IFN α vs temsirolimus vs cytokine[s]). However, due to these revisions, the Sponsor can no longer ensure that if a “prior therapy” fits into >1 stratum, patient data will be fitted into the order of hierarchy agreed upon during the EOP2 meeting (i.e. similarity of MOA of the prior therapy to that of axitinib). For example, patients previously treated (in first line) with bevacizumab in combination with temsirolimus will be randomized to the temsirolimus stratum or patients previously treated (in first line) with bevacizumab in combination with IL-2 will be randomized to the cytokine stratum. Therefore, in order to avoid this, the Sponsor proposes changing the stratification by prior systemic first line regimen to sunitinib-containing regimen vs bevacizumab-containing regimen vs temsirolimus-containing regimen vs cytokine-containing regimen in this order of hierarchy, respectively (see proposed protocol A4061032 amendment in **Attachment 1**). There will be no change in the previously agreed eligibility criteria regarding prior therapy in the proposed amendment. It should be noted that a few (< 10) patients have already been randomized according to the previous strata (i.e. order of hierarchy agreed upon following the SPA review). Does the Agency concur that this proposal is acceptable?

FDA response: Yes

2. In the ongoing Phase 3 study (A4061032), Section 4.1, Inclusion Criterion # 3 states that patients must have experienced disease progression on one prior systemic first-line regimen for mRCC. Inclusion Criterion # 3 also requires that *“disease progression will be defined by RECIST documented by 2 sets of CT/MRI (or sets of chest x-rays, bone scans, or x-rays of bone lesion) performed any time within period of 4 weeks prior to the first dose of prior therapy to 4 months after the last dose of prior treatment showing objective evidence of disease progression. These pre-study scans or x-rays documenting disease progression must be confirmed by the Principal Investigator prior to enrollment in the study (after patient enrollment, pre-study scans or x-rays must be submitted to independent third-party imaging core laboratory for retrospective review). Patients who*

discontinue first-line therapy without evidence of disease progression whilst on first-line therapy must subsequently have documented evidence (e.g., CT/MRI scan) of disease progression within 4 months after the last dose of their previous regimen.” In practice, key opinion leaders participating in this study have informed the Sponsor that it is difficult to obtain scans for some patients or that it is problematic to obtain scans in a timely manner. According to the same key opinion leaders, the limitation of the time period of 4 weeks prior to the first dose of prior therapy to 4 months after the last dose of prior treatment showing objective evidence of disease progression does not add clinical value to this study since patients with progressive disease require further therapy. In addition, since the scan confirmation is retrospective, it is not possible to remove those non-qualifying patients (i.e. those who are found not to have progressed by the independent third-party imaging core laboratory) from the study since these patients will already be included in the intent-to-treat (ITT) analysis. Therefore, the Sponsor proposes to amend the protocol to remove the requirement for collection of pre-study scans or x-rays documenting disease progression and to remove the limitation of the time period of 4 weeks prior to the first dose of prior therapy to 4 months after the last dose of prior treatment showing objective evidence of disease progression from Inclusion Criterion #3 (see proposed protocol A4061032 amendment in Attachment 1). Does the Agency concur with the Sponsor’s proposal to amend the protocol to remove the requirement for collection of pre-study scans or x-rays documenting disease progression and the limitation of the time period to document disease progression?

FDA response: An additional stratification variable should be added, i.e. documented disease progression by RECIST criteria, yes or no, to replace submission of radiographs documenting progression.

Meeting Discussion: Pfizer proposed revising eligibility criteria #3 to read as follows “Patient must have progressive disease by RECIST after one prior systemic first-line regimen for metastatic renal cell cancer.”

FDA stated that a stratification variable for prior disease progression would not be necessary but that the method of the documentation of prior disease progression should be captured in case report form.

The collection of scans to document prior disease progression is not necessary.

Linked Applications

Sponsor Name

Drug Name / Subject

IND 63662

PFIZER INC

AG013736

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/s/

PATRICIA CORTAZAR

02/09/2009

MEETING Minutes

Meeting Date: June 19, 2008 **Time:** 9:30am to 11:00am **Location:** FDA WO #1311

IND 63, 662

Type B CMC End-of-Phase 2 Meeting Submission Date: April 17, 2008

Briefing Document Submission Date: May 21, 2008

Drug: AG-013736 (axitinib)

Sponsor: Pfizer Inc.

FDA Attendees:

Ravi Harapanhalli, Ph.D., Branch Chief, ONDQA, DPAMS, Branch 5

Ravindra Kasliwal, Ph.D., Pharmaceutical Assessment Lead, ONDQA, DPAMS, Branch 5

Gene Williams, Ph.D., Clinical Pharmacology Team Leader, DCP5

Lisa Skarupa, M.S.N., Project Manager, DDOP

Pfizer Attendees:

Dr. Michael Lynch, Sr. Principal Scientist, Global Regulatory CMC

Dr. Tom Garcia, Research Fellow, Global Regulatory CMC

Dr. Robert Singer, Associate Research Fellow, Chemical R and D

Mr. Dan Gierer, Principal Scientist, Solids & PE Development

Dr. Keith Horspool, Senior Director, Materials Science

Mr. James Morgado, Scientist, Dev Analy & ICH Stability

Dr. Richard Hutchins, Associate Research Fellow, Development Portfolio Mgmt

Dr. Yazdi Pithavala, Director, Oncology

Dr. Alison Russell, Associate Director, Worldwide Regulatory Strategy

Meeting Background:

The purpose of the meeting is to obtain agreement with the Agency on several key development strategies and CMC plans that Pfizer intends to pursue during commercial development and preparation of the NDA. Pfizer submitted meeting request on April 17, 2008 and submitted the meeting briefing package on May 21, 2008. FDA sent their responses on June 16, 2008.

QUESTIONS FOR DISCUSSION

CMC

Question 1: Does FDA agree that [REDACTED] (b) (4) [REDACTED] are acceptable regulatory starting materials for the synthesis of AG-013736 (axitinib) and that their control strategies are appropriate?

FDA Response:

1. The compound [REDACTED] (b) (4) based on the justifications provided, appear to be acceptable regulatory starting materials.

Discussion: Pfizer agrees, no further discussion .

2. The compound (b) (4) may be acceptable provided impurities are appropriately controlled or data are provided concerning why is there no need to control impurities in this raw material.

Discussion: It was clarified that in justifying the (b) (4) starting materials Pfizer will demonstrate that impurities in these starting materials will not be carried over into the drug substance more than the qualification thresholds.

Additionally, if any of these impurities are shown to be genotoxic they would be limited to the TTC levels in the drug substance. Pfizer agrees to present the data to the NDA submission.

3. In the synthesis of (b) (4) preceding compounds appear to be potential mutagens. You will need to demonstrate that adequate controls exist to control the genotoxic impurities at the threshold for toxicological concerns (TTC) in the drug substance. If the impurities are specified and controlled (including the potential genotoxic impurities) at acceptable levels, (b) (4) may be considered as a regulatory starting material.

Discussion: Pfizer will provide in the NDA the spiking and purging data and impurity fate analysis to demonstrate the process capabilities and will propose adequate control strategies.

4. For each starting material, the level of each specified impurity should be justified based on spiking and purging studies. In general, a genotoxic impurity should be controlled so that its level in the drug substance will be no more than the TTC level. Other impurities should be controlled at a level so that a non-genotoxic impurity present in a starting material should be sufficiently purged (b) (4). If a genotoxic impurity is present, it should be reduced to below the TTC levels in the drug substance.

Discussion: See responses to Question #2 and #3.

5. Analytical methods for the starting materials should be shown to have sufficient resolution capability to detect and quantify all impurities. If need be, additional orthogonal methods may be employed to confirm the validity of a chosen analytical method. Similarly, the drug substance analytical method(s) should have adequate resolution capacity to detect and quantify process-related impurities as well as residual starting materials and the impurities in the starting materials.

Discussion: Pfizer agrees, no further discussion.

6. The "Management of Change" policy provided in Appendix 1 should also reflect that in addition to new impurities, if higher levels of specified impurities

are present, the purging experiments will be conducted to ensure purging in subsequent steps.

Discussion: Pfizer will conduct studies to demonstrate the process capabilities and purge of impurities to support their specifications for the ingoing raw materials.

Question 2: Pfizer plans to use the Quality by Design (QbD) risk based approach for establishing design space for AG-013736 (axitinib) drug substance manufacturing process. This includes the proposed control strategy for polymorphs, particle size and impurities. Does FDA concur with this approach?

FDA Response:

1. The Quality by Design (QbD) approach is encouraged.

Discussion: Pfizer agrees, no further discussion.

2. In addition to the development work and DOE experiments for polymorph control for (b) (4), justification for the presence of (b) (4) polymorph should also be provided based on kinetic and thermodynamic considerations and stability.

Discussion: Pfizer agrees to submit polymorph mining study data in the S26 section of the NDA (b) (4)

(b) (4) They will also justify a suitable control strategy for this polymorph (b) (4) by considering ICH Q6A decision tree number 4, and other considerations.

3. For drug substance impurities, impurity fate mapping to trace the impurities throughout the manufacturing process should be developed. This may be used to determine the attributes of the intermediates and starting materials that are linked to drug substance CQAs.

Discussion: Pfizer agrees, no further discussion.

4. In addition to other attributes, the drug substance attributes (e.g., crystal form, particle size, shape, etc.) that are critical to the drug product quality (e.g., dissolution, content uniformity, etc.) should be well understood and documented in the NDA.

Discussion: (b) (4)

(b) (4)

5. **An overall comprehensive control strategy should be developed based on the results of the statistical design of experiments and risk analysis.**

Question 3: Pfizer plans to use the QbD risk based approach for establishing design space for AG- 013736 (axitinib) drug product manufacturing process. Does FDA concur with this approach?

FDA Response:

1. **The Quality by Design (QbD) approach is encouraged.**
2. **You should develop a through understanding of relationships between material attributes, process parameters and the drug product CQA and document it in the NDA. Appropriate controls at input stage and during the process should be in place to assure that product of purported quality attributes is manufactured with high level of confidence at the commercial scale and on routine basis.**
3. **Models used should be appropriately validated. Parameters that affect should be well understood and incorporated in the model. Model should be periodically updated and verified.**
4. **The dissolution method needs to be sufficiently discriminatory. We recommend that the paddle speed be (b) (4). Provide the details of the dissolution method development in the NDA.**

Discussion: Pfizer will provide adequate data to justify the choice of the dissolution method in the NDA.

5. **We note that your commercial 1 mg and the 5 mg tablets will have red coatings. While the tablets may be slightly different size, they should also be of different color. Provide the color scheme that will be used to differentiate the two tablet strengths.**

Discussion: Pfizer indicated preferences the shape change rather than the color change because this does not involve formulation change. The (b) (4) shape would be proposed. Pfizer asked whether existing tablet (b) (4) can still be used for primary ICH studies. The Agency stated that this may be acceptable provided adequate CMC bridging is demonstrated between the two tablet shapes. This bridging could include manufacturing comparison,

product quality attributes, and comparative three months accelerated stability data of a 6 months study on a single batch of new tablet shape manufactured at comparative scale.

Alternative approach of using [REDACTED] (b) (4) was also proposed. Whether CMC bridging alone will suffice will depend on additional understanding of the formulation and the manufacturing process. If it is determined that the CMC bridging alone is sufficient this will include the above strategy and additional case C dissolution profile comparison in multiple media and multiple time-points with appropriate statistical analysis.

The agency will discuss internally whether distinction by tablet shape alone would be adequate under the clinical setting which this product will be used. Depending on FDA's feedback, Pfizer will discuss internally and will communicate to us their preferred option.

Question 4: Does FDA agree that submission with [REDACTED] (b) (4) drug product stability data is appropriate? The applicant will provide updated stability data i.e. [REDACTED] (b) (4) during the review period. The proposed shelf life will be as per ICH guidance.

FDA Response: If a stability update is submitted it should be accompanied by the statistical analysis of stability indicating quality attributes as indicated in ICH Q1E. Stability updates are expected by the mid cycle for a timely assessment, and they should conform to SAS transport or Excel spreadsheet format. Late submissions, if considered major, may not be reviewed or may result in the extension of clock. The expiration dating period will be evaluated as per the ICH Q1E guidance and accordingly granted. Please refer to this guidance for additional details.

Question 5: Does FDA concur with our plan to submit a comparability protocol for approval of [REDACTED] (b) (4) commercial expiry period based on ICH registration stability data via a notification supplement.

FDA Response: The proposed [REDACTED] (b) (4) expiration dating period is not appropriate for comparability protocol.

Discussion: It was clarified that during the NDA review there will be at least 12 months of real time data and 6 months of accelerated data for the ICH batches. There will be additional 6 months accelerated data in support of alternate tablet configuration for the lower strength. Pfizer proposes [REDACTED] (b) (4) [REDACTED] 36 months based on real time ICH stability data. This is with the understanding that commercial process and controls would be comparable to the process used to manufacture the ICH stability batches. At the time of the proposed [REDACTED] (b) (4) shelf life approximately 12 months of real time data would be available for the first three commercial batches. Pfizer will propose this in a comparability protocol in the NDA submission. This will be a reviewed appropriately in the NDA.

Clinical Pharmacology

Question 6: The Sponsor plans [REDACTED]

(b) (4)

[REDACTED], a bioequivalence (BE) study is planned in which healthy volunteers will be administered single 5-mg axitinib tablets of both formulations in the fasted state. This will be a single dose, two-sequence crossover study conducted in healthy volunteers in the fasted state.

Does the FDA agree with the proposed design of the BE study [REDACTED]

(b) (4)

FDA Response: Currently, the metric used to conclude bioequivalence during NDA review is average bioequivalence using observed C_{max} and trapezoidal AUC 0-last. While we do not want to discourage the planned replicate design, we do want to make you aware that our final analysis of the data is likely to be an analysis of average bioequivalence using observed C_{max} and trapezoidal AUC 0-last.

We recommend that you submit the full protocol for review.

Discussion: Pfizer agrees that the primary metric will be average bioequivalence and not population or individual bioequivalence. Pfizer will submit the final protocol for review.

Post Meeting note regarding Question #3, FDA response #5:

Agency prefers that the distinction by tablet colors is much more effective than that by tablet size. If the formulation is not amenable to different colors because of physico-chemical interactions that may impact the desired product performance, this should be clearly documented in the pharmaceutical development report.

Linked Applications

Sponsor Name

Drug Name

IND 63662

AGOURON
PHARMACEUTICALS
INC

AG013736

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/s/

RAVI S HARAPANHALLI
08/01/2008



IND 63,662

Pfizer Inc.
Attention: Alison L. Russell, Ph.D.
Associate Director, Worldwide Regulatory Strategy
10646 Science Center Drive
San Diego, CA 92121

Dear Dr. Russell:

We refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for AG-013736 (axitinib).

We also refer to your December 18, 2007, request, serial number 224, for a special clinical protocol assessment, received December 19, 2007. The protocol is entitled "A Randomized, Open-label Phase 3 Study of AG-013736 Versus Sorafenib in Patients with Metastatic Renal Cell Cancer Following Failure of One Prior Therapy".

We have completed our review and have determined that the design and planned analysis of your study do not adequately address the objectives necessary to support a regulatory submission. We have the following responses to your questions.

1. Patient Population

The Phase 3 randomized study will enroll subjects with metastatic RCC. The inclusion and exclusion criteria are outlined in the final draft Protocol A4061032 (see Attachment 1 of this briefing package).

- a. At the EOP2 meeting to discuss development of axitinib in 2nd line RCC, FDA considered it reasonable to include patients who have "disease progression on or intolerance to one prior systemic therapy, including sunitinib/sunitinib-containing regimens, bevacizumab/ bevacizumab-containing regimens, mTOR inhibitors/mTOR inhibitor-containing regimens, or cytokines (see FDA's EOP2 meeting minutes dated 18th June, 2007)." The Sponsor would like to simplify the wording to state that the prior regimen must have contained "one or more of the following agents: sunitinib, bevacizumab, mTOR inhibitors, or cytokines as first line treatment". The Sponsor would also like to clarify that 'prior regimens' may include approved therapies used in combinations which are under investigation for 1st line use (e.g. the combination of sunitinib + bevacizumab) and also may include non-approved mTOR inhibitors

(e.g. everolimus [RAD001]). Does the Agency concur with inclusion of non-approved combination regimens provided that at least one agent in the combination has been approved in the US or EU for the treatment of metastatic RCC and does the Agency concur with inclusion of non-approved mTOR inhibitors?

FDA Response:

Yes, we agree that 'prior regimens' may include approved therapies used in combinations which are under investigation for first line use. However, please clarify inclusion criterion #3 in the protocol to reflect this approach. The current wording suggests a prior regimen may include bevacizumab alone or an investigational mTOR inhibitor alone.

- b. At the EOP2 meeting to discuss development of axitinib in 2nd line RCC, the FDA concurred that disease progression on prior therapy be defined as: "Progressive disease documented by 2 sets of CT/MRI (or sets of chest x-rays, bone scans, or x-rays of bone lesion) performed any time within the time window beginning 4 weeks prior to the first dose of [the prior 1st line regimen] and ending at 4 weeks after the last dose of the first line therapy showing objective evidence of disease progression" was acceptable. The Sponsor would like to modify this definition of disease progression to: "Progressive disease by RECIST documented by 2 sets of CT/MRI (or sets of chest x-rays, bone scans, or x-rays of bone lesion) performed any time within a period of 4 weeks prior to the first dose of prior therapy to 4 months after the last dose of prior treatment showing objective evidence of disease progression." Does the Agency concur with this definition of disease progression?

FDA Response: Yes.

- c. At the EOP2 meeting to discuss development of axitinib in 2nd line RCC, the FDA concurred that the "pre-study scans or x-rays documenting disease progression must be received by the core imaging laboratory before the patient can be randomized" (see FDA's EOP2 meeting minutes dated 18th June, 2007). The Sponsor would like to clarify that pre-study scans or x-rays documenting disease progression will be confirmed by the Principal Investigator prior to enrollment in the study and retrospectively by the independent third-party core imaging laboratory. Does the Agency concur that conducting retrospective central confirmation of disease progression on previous therapy is adequate and acceptable?

FDA Response: Yes.

- d. At the EOP2 meeting to discuss development of axitinib in 2nd line RCC, the FDA concurred that intolerance to prior therapy be defined as: "Life threatening adverse events (i.e. Grade 4 toxicity according to NCI CTCAE Version 3.0)" (see FDA's EOP2 meeting minutes dated 18th June, 2007). The Sponsor would like to modify this definition of intolerance to prior therapy to: "Life-threatening adverse events (i.e., Grade 4 according to NCI CTCAE Version 3.0) during prior therapy, or unacceptable toxicity, specifically, grade 3 toxicity or grade 2 toxicity that is unacceptable to the patient (such as nausea) that persists despite standard countermeasures." Does the Agency concur with this definition of intolerance to prior therapy?

FDA Response:

Yes. However, we recommend that the group of patients intolerant to prior therapy be kept to a minimum (e.g., < 10%). In addition, please define a duration for persistence of grade 2 or 3 toxicity despite "standard countermeasures".

- e. At the EOP2 meeting to discuss development of axitinib in 2nd line RCC, the FDA recommended adding a criteria for life expectancy of ≥ 12 weeks (see FDA's EOP2 meeting minutes dated 18th June, 2007). Per FDA's recommendation, this has been added as part of the eligibility criteria. The Sponsor believes that the overall inclusion/exclusion criteria are appropriate for the proposed indication. Does the Agency concur with the overall inclusion/exclusion criteria for the patient population described in protocol A4061032?

FDA Response:

The overall inclusion/exclusion criteria appear acceptable except as discussed in response to #1a. The final determination of the acceptability of the indication will be made at the time of review of the results of the study in the NDA application.

2. Statistical Analysis Plan (SAP)

The final draft Statistical Analysis Plan for the proposed Phase 3 study (A4061032) is provided for FDA review (see Attachment 2 of this briefing package).

As agreed/recommended by FDA (see FDA's EOP2 meeting minutes dated 18th June, 2007):

- The Sponsor plans to conduct one interim analysis for futility and sample size re-estimation after approximately 50% of the PFS events. The criteria for re-estimating the sample size, and method of adjusting the test statistic have been included in the SAP.
- The final analysis of PFS will be used for approval purposes. The primary analysis will be conducted using a stratified log rank test. Interim analyses for OS will also occur at the time of the interim and final PFS analyses.

At the EOP2 meeting to discuss development of axitinib in 2nd line RCC, the FDA stated that the Agency “discourage claiming efficacy based on an interim PFS analysis” (see FDA’s EOP2 meeting minutes dated 18th June, 2007). The Sponsor would like to clarify that a stopping boundary for efficacy will be included in the study; although the Sponsor does not intend to stop the study early for efficacy such a boundary may be needed if the study shows ‘outstanding’ results at the interim analysis and the DMC considers it necessary to conduct a conversation with regulatory authorities around the appropriateness of continuing the trial.

- a. Does the Agency concur with the inclusion of a stopping boundary for efficacy with the caveat that the Sponsor does not (at this stage) intend to stop the study early?

FDA Response: Yes, if no efficacy claims are made based on the interim analysis.

- b. Does the Agency concur that the overall SAP is adequate and acceptable?

FDA Response:

You should be aware that PFS is subject to ascertainment bias. The results of the analysis may be influenced by any imbalance in assessment dates or missing data between treatment arms. Also note that a statistically significant difference in PFS may not necessarily demonstrate a clinically meaningful difference.

The third paragraph of Section 6.1.1 describes a proposal regarding situations where disease progression is recorded at a scheduled visit that is immediately preceded by a scheduled visit with missing tumor assessment data. FDA’s preferred approach for this situation is to use the date of the visit where disease progression is initially recorded as the date of progression rather than using the date of the preceding visit with missing data as an un-censored value for the date of progression (as is being proposed). Using the date from the preceding visit that has missing data could instead be used for a sensitivity analysis.

Section 3 provides an algorithm to be used for determining whether the sample size may be changed. We caution you that you will be able to detect a smaller effect which may not be clinically meaningful by increasing the sample size.

Secondary endpoint analyses are considered supportive only if the primary analysis is positive. Any claim based on PRO endpoints is unlikely to be considered in this open-label study. The FKSI and EQ-5D are not acceptable instruments for the proposed patient population. Please refer to the draft FDA Guidance for Industry “Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims”.

3. Efficacy Assessment by Independent Review Committee (IRC)

At the EOP2 meeting to discuss development of axitinib in 2nd line RCC, the FDA concurred that “an open-label study will be acceptable if you use a blinded independent committee to assess progression” (see FDA’s EOP2 meeting minutes dated 18th June, 2007). In accordance with this recommendation, the Sponsor plans to utilize an external Independent Review Committee (IRC) to review efficacy data for this Phase 3 study. The final draft IRC charter is included to facilitate review (see Attachment 3 of this briefing package). The final draft Core Imaging Laboratory Operations Manual (CIOM), Investigator Site Operations Manual (ISOM), and Image Acquisitions Guideline (IAG) are also included for FDA’s review (see Attachments 4, 5, and 6 of this briefing package).

Ongoing review of scans will be conducted by radiologists only (i.e. no review will be conducted by an oncologist). The radiologists will also review cytology reports (when available) to avoid non-malignant ascites and pleural effusion being considered as progressive disease; in the absence of a cytology report, new effusions will be considered progressive disease.

- a. Does the Agency concur with the Sponsor’s proposal to have ongoing review of scans and cytology reports (when available) be conducted by radiologists only?

FDA Response: Yes.

- b. Does the Agency concur that the remaining aspects of the IRC Charter are adequate and acceptable?

FDA Response: Yes.

- c. Does the Agency concur that the IRC-related documents (i.e. the CIOM, ISOM, and IAG) are adequate and acceptable?

FDA Response: Yes.

4. Pharmacogenomic Assessments

Protocol A4061032 includes a plan to explore the correlation between UGT1A1 genotyping, exposure to axitinib, and variables of safety and efficacy. Protocol A4061032 also includes an additional (optional) research component to investigate possible associations between genomic and metabonomic variations and response to axitinib. The final draft Molecular Profiling Supplement is included for FDA’s review (see Attachment 7 of this briefing package). At the EOP2 meeting, the FDA recommended the Sponsor to “explore the relationships between exposure to axitinib, inhibition of VEGFR activity, and safety/efficacy variables in your proposed Phase 3 study” (see FDA’s EOP2 meeting minutes dated 18th June, 2007). Although not included in the Phase 3 study for RCC, the Sponsor is conducting this exploration as part of the ongoing Phase 3 study for pancreas (Protocol A4061028; see IND 63,662 SN # 159, dated 21st December 2006). Does the Agency concur that the pharmacogenomic assessment plans included in Protocol A4061032 are adequate?

FDA Response: Yes.

5. Pharmacokinetic (PK) Sampling

For the Phase 3 2nd line RCC study (Protocol A4061032), no PK sampling is planned. Population PK (POPPK) samples have already been obtained from two previous Phase 2 studies in which patients with metastatic RCC were administered axitinib.

- In Phase 2 study A4061012, POPPK samples were collected on Day 1, Day 29, Day 57, and then every 8 weeks thereafter in 52 cytokine-refractory metastatic RCC patients who received single-agent axitinib.
- In Phase 2 study A4061023, POPPK samples have been collected on Day 1, Day 29, Day 57 and every 8 weeks thereafter in 62 sorafenib-refractory metastatic RCC patients who received single-agent axitinib.

The Sponsor consider that the pooled POPPK samples from these two Phase 2 studies will provide sufficient data to conduct appropriate correlations of axitinib PK with safety, dose-intensity, and efficacy endpoints in the RCC patient population. Does the Agency concur?

FDA Response:

We continue to recommend, although it is not a requirement, that you collect sparse plasma trough samples during your proposed Phase 3 Study A4061032. Data from this study may be pooled and the Phase 2 Studies A4061012 and A4061023 will provide sufficient data to obtain more adequate exposure-response relationships.

6. ECG Assessments

At the EOP2 meeting to discuss development of axitinib in 2nd line RCC, the FDA recommended collecting "ECGs at baseline and as clinically indicated" (see FDA's EOP2 meeting minutes dated 18th June, 2007). In the Phase 3 RCC study (Protocol A4061032), 8triplicate ECG measurements will be collected at screening, Cycle 1 Day 15 (C1D15) at Tmax, and as clinically indicated for the first 50 patients randomized to the axitinib arm. For all remaining patients (including those on the control arm), single ECG measurements will be collected at screening and as clinically indicated. Does the Agency concur that this is acceptable?

FDA Response: Yes, this is acceptable.

7. Safety Assessment by Data Monitoring Committee (DMC)

For the Phase 3 study, the Sponsor plans to utilize an external, independent DMC to review safety data to provide recommendations as to whether to stop for safety concerns or continue the study. The DMC will also evaluate interim efficacy data and make a recommendation about early termination due to observed results of the study. The final draft DMC charter is included to facilitate review (see Attachment 8 of this briefing package). Does the Agency concur that the DMC Charter is adequate and acceptable?

FDA Response:

When reviewing interim efficacy analyses, the DMC should consider any imbalances in baseline prognostic factors, missing data and internal consistency across study sites prior to making a recommendation.

All minutes or comments from the DMC should be submitted in the application to support regulatory action.

8. Case Report Form (CRF)

The unique pages from the final draft sample CRF for the Phase 3 study (Protocol A4061032) are included to facilitate review (see Attachment 9 of this briefing package). Does the Agency concur that the unique pages of the CRF book are adequate and acceptable?

FDA Response: The CRF should also include the following:

- Record documentation of progression after prior systemic therapy
- Include documentation of neurologic examination in physical examination.
- Include phosphate, lipase/amylase, and calcium in laboratory tests
- Document prior nephrectomy

It is not clear from the CRFs how a patient's prior therapy stratum would be determined. Add a field on the randomization CRF page where the prior therapy stratum would be recorded.

In addition, we have the following comments.

1. The acceptability of PFS as the primary endpoint for approval will depend upon the magnitude of the difference between the two treatment groups and the risk-benefit ratio. Final determination of acceptability of PFS to support approval will be made at the time of review of the results of the study in the NDA application.

2. Please include the following assessments in the protocol:
 - a. Blood pressure should be monitored weekly during the first 6 weeks of treatment to allow detection and management of patients who may experience hypertension.
 - b. Patients taking warfarin should have their INR monitored.
 - c. Dose interruption is recommended in patients undergoing major surgical procedures.
 - d. Caution should be used when sorafenib is administered with compounds metabolized/eliminated by UGT1A1 pathway.
 - e. Phosphates, lipase/amylase monitoring should be added to the schedule of activities. Abnormalities in these tests are associated with sorafenib use.
 - f. Please include a baseline test for calcium in chemistry testing.
 - g. Neurological testing should be specified and included with the physical examination.
3. The protocol should clarify that treatment will be continued until disease progression or unacceptable toxicity. We are concerned about your proposal to continue treatment in patients who have RECIST defined disease progression where there is “reasonable evidence of clinical benefit to justify continuation”. Please justify this approach.

If you wish to seek agreement with FDA via an SPA, you will need to submit a revised protocol that address all the issues itemized above. Your revised protocol should be submitted as a new request for special protocol assessment.

If you wish to discuss our responses, you may request a meeting. Such a meeting will be categorized as a Type A meeting (refer to our “Guidance for Industry; Formal Meetings With Sponsors and Applicants for PDUFA Products”). Copies of the guidance are available through the Center for Drug Evaluation and Research from the Drug Information Branch, Division of Communications Management (HFD-210), 5600 Fishers Lane, Rockville, MD 20857, (301) 827-4573, or from the internet at <http://www.fda.gov/cder/guidance/index.htm>. This meeting would be limited to discussion of this protocol. If a revised protocol for special protocol assessment is submitted, it will constitute a new request under this program.

If you have any questions, please contact Patricia Garvey, Senior Regulatory Project Manager, at 301-796-1356.

Sincerely,

{See appended electronic signature page}

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

Linked Applications

Sponsor Name

Drug Name

IND 63662

AGOURON
PHARMACEUTICALS
INC

AG013736

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/s/

ROBERT L JUSTICE
01/31/2008



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

IND 63,662

Pfizer Inc.
Attention: Alison L. Russell, Ph.D.
Associate Director, Worldwide Regulatory Strategy
10646 Science Center Drive
San Diego, CA 92121

Dear Dr. Russell:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AG-013736.

We also refer to the teleconference between you and the FDA on May 17, 2007, the purpose of this teleconference was to discuss your proposed development program in renal cell carcinoma.

The official minutes of that teleconference are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions me at (301)796-1356.

Sincerely,

{See appended electronic signature page}

Patricia N. Garvey, R.Ph.
Senior Regulatory Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure

TELECONFERENCE MINUTES

MEETING DATE: May 17, 2007 **TIME:** 10:10 am

IND 63,662

Meeting Request Submission Date: 3-2-07;sn172

Briefing Document Submission: 4-10-07; sn179

DRUG: AG-013736 (Axitinib)

SPONSOR/APPLICANT: Pfizer Inc.

TYPE OF MEETING:

1. End-of-Phase 2 (Type B meeting)
2. **Proposed Indication:**
AG-013736 is indicated for the treatment of advanced renal cell carcinoma

(b) (4)

FDA PARTICIPANTS:

Robert Justice, M.D.	-- Director, Division of Drug Oncology Products (DDOP)
Ramzi Dagher, M.D.	-- Medical Team Leader, DDOP (Chair)
Maitreyee Hazarika, M.D.	-- Medical Reviewer, DDOP
Kun He, Ph.D.	-- Statistical Reviewer, Division of Biometrics I (DBI)
Sophia Abraham, Ph.D.	-- Clinical Pharmacology and Biopharmaceutics Reviewer, Division of Clinical Pharmacology 5
Patty Garvey, R.Ph.	-- Senior Regulatory Project Manager, DDOP (Facilitator)

Pre-meeting:

Ann Farrell, M.D.	-- Acting Deputy Director, DDOP
Rajeshwari Sridhara, Ph.D.	-- Statistical Team Leader, DBI

INDUSTRY PARTICIPANTS:

Sinil Kim, M.D.	-- Clinical Lead
Isan Chen, M.D.	-- Clinical
James Tarazi, M.D.	-- Clinical
Paul Bycott, Ph.D.	-- Biostatistics
Yazdi Pithavala, Ph.D.	-- Clinical Pharmacology
Alison Russell, Ph.D.	-- Associate Director, Worldwide Regulatory Strategy

MEETING OBJECTIVE:

To gain FDA concurrence on the registration strategy for AG-013736 in the proposed indication above.

BACKGROUND:

AG-013736, a substituted indazole derivative, is a potent inhibitor of primarily VEGFRs with picomolar 50% inhibitory concentration (IC50) and also targeting PDGFRs and KIT with nanomolar IC50. This investigational new drug is currently being studied in Phase 1 and 2 clinical trials in patients with a range of solid tumor indications.

In the proposed two-arm, randomized, open-label, multi-center phase 3 study, protocol A4061032, the patient population will be mRCC after disease progression on or intolerance to one prior therapy of sunitinib/sunitinib-containing regimen, bevacizumab/bevacizumab-containing regimen (e.g. bevacizumab, bevacizumab + IF), mTOR inhibitor/mTOR inhibitor-containing regimen (e.g. temsirolimus), or cytokines (IL-2, IF, or IL-2 + IF) as first-line treatment. Patients will be randomized to receive AG-013736 (starting dose of 5 mg BID with food) or sorafenib tosylate (sorafenib 400 mg BID with food). The primary endpoint will be PFS and the secondary endpoints will be overall survival, objective response rate, safety and tolerability, duration response and patient reported outcomes (FKSI, EQ-5D).

The purpose of this end-of-phase 2 meeting was to discuss the sponsor proposed development program in renal cell carcinoma.

QUESTIONS for DISCUSSION with FDA RESPONSES and DECISIONS REACHED:

1. The proposed Phase 3, open-label randomized study will compare AG-013736 versus sorafenib in patients with advanced RCC after failure of one prior systemic therapy. Prior systemic therapy may include sunitinib/sunitinib-containing regimen, bevacizumab/bevacizumab-containing regimen (e.g. Avastin + IFN), mTOR inhibitor/mTOR inhibitor-containing regimen (e.g. temsirolimus [Torisel®]), or cytokines (e.g. IL-2, IFN, IL-2 + IFN). Cytokine-containing therapy has been routinely used in treatment-naïve advanced RCC patients. Recently, clinical data has been obtained demonstrating the clinical benefit of anti-vascular endothelial growth factor (VEGF) or VEGF receptor (VEGFR) therapies. The superior clinical benefit of sunitinib over interferon (IFN) was used as the basis for FDA's decision to grant full approval for sunitinib for the treatment of advanced RCC (and to enable an update of the US package insert). A randomized Phase 3 (AVOREN) trial of bevacizumab in combination with IFN versus IFN alone is ongoing to determine whether bevacizumab significantly improves progression-free survival (PFS) and overall survival (OS) in patients with mRCC. Clinical data has been obtained demonstrating the clinical benefit of inhibitors of the mammalian target of rapamycin (mTOR). The mTOR inhibitor temsirolimus has recently been shown to significantly improve OS compared to IFN for mRCC patients with poor-risk factors. RAD001, another mTOR inhibitor, and combinations of these new agents are also being studied clinically in 1st line mRCC. These new agents represent significant progress in the treatment of mRCC compared to cytokines. However, patients will inevitably progress after these new agents and the medical need of these patients in the 2nd line setting still needs to be addressed. Since it would be impractical to conduct several Phase 3 studies after failure to each of these individual new agents (or

combination of these agents) in the 2nd line setting, therefore a Phase 3 study after failure of one prior systemic therapy (including sunitinib/sunitinib-containing regimen, bevacizumab/ bevacizumab-containing regimen, mTOR inhibitors/ mTOR inhibitor-containing regimen, and cytokines) is a more practical option.

- a. Given the likely availability of several active agents for 1st line RCC in the near future, does the Agency concur that the patient population being suggested for this study (i.e. patients who have “disease progression on or intolerance to one prior systemic therapy” including sunitinib/sunitinib-containing regimens, bevacizumab/bevacizumab-containing regimens, mTOR inhibitors/mTOR inhibitor-containing regimens, or cytokines) is reasonable ?

FDA Response: Yes, it is reasonable.

Discussion: There was no further discussion needed.

- b. Based on the intended patient population, does the Agency concur that the proposed indication, “AG-013736 is indicated for the treatment of patients with advanced RCC [REDACTED]”, is reasonable? (b) (4)

FDA Response:

Final determination of the acceptability of the indication will be made at the time of review of the results of the study in the NDA application.

Discussion: There was no further discussion needed.

2. Clinical data exists in several compounds to justify the rationale for studying an anti-VEGFR compound (such as AG-013736 or sorafenib) following failure of prior antiangiogenic therapies. In an ongoing Phase 2 study (A4061023) in patients with sorafenib-refractory RCC, preliminary findings from analysis of all 62 evaluable patients indicate 9 PRs (14.5%); 8 PRs/48 sorafenib-refractory patients and 1 PR/14 patients following failure of both sorafenib and sunitinib treatment. With a median follow-up of 7.4 months, preliminary analysis indicates overall median PFS >7.7 months (see Section 4 of this briefing package for additional details). In addition, a Phase 2 study has also been conducted to evaluate the efficacy and safety of sunitinib in patients with metastatic RCC refractory to bevacizumab treatment (Rini BI *et al*, 2006). Patients with mRCC who demonstrated RECIST-defined disease progression within 3 months after bevacizumab-based therapy were treated with sunitinib (50 mg daily, 4 weeks out of a 6 week cycle). The primary endpoint of the study was ORR. The study accrued 60 patients. Out of 32 evaluable patients, 26 patients (81%) demonstrated some degree of tumor shrinkage, including 4 patients (13%) with an objective response. It was concluded that sunitinib has substantial antitumor activity in patients with metastatic RCC refractory to bevacizumab treatment. Does the Agency concur that there is sufficient clinical data in several

compounds to justify the rationale for studying an anti-VEGFR compound (such as AG-013736 or sorafenib) following failure of prior antiangiogenic therapies?

FDA Response: Yes.

Discussion: There was no further discussion needed.

3. In total, 114 subjects with advanced RCC have been enrolled and treated with single agent AG-013736 in protocols A4061012 (n=52 cytokine-refractory patients) and A4061023 (n=62 patients failed sorafenib; 14 of those patients failed sunitinib). The safety profile of AG-013736 in advanced RCC patients compares well to the safety observed with single agent AG-013736 in other solid tumor types. It was concluded that AG-013736 may be safely administered at a starting dose of 5 mg BID and dose titrated to a maximum of 10 mg BID in subjects with advanced RCC. Section 4 of this briefing package contains additional details regarding the safety of AG-013736 in patients with metastatic RCC in the 2nd line setting. Does the Agency concur that sufficient safety data exists to support the investigation of AG-013736 in the proposed patient population?

FDA Response: Yes.

Discussion: There was no further discussion needed.

4. The National Comprehensive Cancer Network (NCCN) recently (January 16th, 2007) published guidelines indicating that, although there is no uniform consensus regarding appropriate treatment, sorafenib is one potential treatment option for patients with advanced RCC following failure of available treatment options in the 1st line setting. In patients with advanced RCC who have received one prior systemic therapy (i.e. 2nd line), sorafenib has demonstrated superior clinical benefit over placebo; the median PFS for sorafenib in these advanced RCC patients is approximately 5 months (see Nexavar® package insert). Investigators from the Cleveland Clinic Foundation (CCF) conducted an institutional case analysis using patient data (generated from various studies at the CCF) to evaluate the efficacy of sorafenib (and sunitinib) in patients with metastatic RCC who failed prior treatment with antiangiogenic agents (Tamaskar I *et al*, 2006). Patients with mRCC receiving sorafenib (or sunitinib) on compassionate use trials and had received prior treatment with antiangiogenic agent were identified. The study identified 72 patients (39 sorafenib and 33 sunitinib). Out of 13 evaluable patients, 12 patients (92%) demonstrated tumor reduction, including 4 patients with objective PR. It was concluded that sorafenib (and sunitinib) have antitumor activity in patients who have received prior treatment with antiangiogenic agents. Does the Agency concur that sorafenib is an appropriate comparator in this patient population?

FDA Response: Yes.

Discussion: There was no further discussion needed.

5. Disease progression on, or intolerance to, one prior therapy of sunitinib/sunitinib-containing regimen, bevacizumab/bevacizumab-containing regimen (e.g. bevacizumab, bevacizumab + IFN), mTOR inhibitor /mTOR inhibitor-containing regimen (e.g. temsirolimus), or cytokines (IL-2, IFN, or IL-2 + IFN) as first-line treatment for metastatic renal cell cancer, will be defined as either one of the following:
- Progressive disease documented by submission of 2 sets of CT/MRI (or 2 sets of chest x-rays, bone scans, or x-rays of bone lesion) performed any time within the time window beginning 4 weeks prior to the first dose of sunitinib/sunitinib-containing regimen, bevacizumab/bevacizumab-containing regimen, mTOR inhibitor/mTOR inhibitor-containing regimen, or cytokines and ending at 4 weeks after the last dose of the first line therapy, showing objective evidence of disease progression. These pre-study scans or x-rays documenting disease progression must be received by the imaging core laboratory before the patient can be randomized.
 - Life-threatening adverse events (i.e., Grade 4 toxicity according to NCI CTCAE Version 3.0). The type, severity and duration of sunitinib/sunitinib-containing regimen, bevacizumab/bevacizumab-containing regimen, mTOR inhibitor /mTOR inhibitor-containing regimen, or cytokine intolerance must be documented. In the event both disease progression and drug intolerance are observed during treatment with sunitinib/sunitinib-containing regimen, bevacizumab/bevacizumab-containing regimen, mTOR inhibitor /mTOR inhibitor-containing regimen, or cytokines, then disease progression will be considered the entry criterion.

Does the Agency concur with the definition of disease progression on, or intolerance to, one prior therapy?

FDA Response: Yes.

Discussion: There was no further discussion needed.

6. The proposed Phase 3 study will be open-label. Based on a reported dermatology/skin adverse event incidence rate >90% (including a 66% incidence of rash/desquamation) for sorafenib (Ratain M *et al*, 2006), the Sponsor considers that blinding investigators to the treatment assignment is impractical. However the Sponsor will use a blinded independent review committee (IRC) to assess response and progression and these assessments will be the primary data for all analyses. Does the Agency concur with an open-label study design for the proposed Phase 3 study?

FDA Response:

An open-label study design will be acceptable if you use a blinded independent review committee to assess progression. Please also see response to question #7 regarding the primary endpoint.

Discussion: The sponsor agreed to use the blinded independent review.

7. The proposed Phase 3 study will include a primary endpoint of progression-free survival (PFS) and secondary endpoints of objective response rate (ORR), overall survival (OS), duration of response (DR), and patient-reported outcomes (PROs). The Sponsor considers that PFS is an appropriate primary endpoint for the proposed Phase 3 study. Does the Agency concur with the proposed primary endpoint?

FDA Response:

Given the limited lifespan of these patients and due to the heterogeneity of the population, we recommend that you consider overall survival (OS) as the primary endpoint.

In general, a substantial, robust improvement in PFS that is clinically meaningful and statistically persuasive, and has an acceptable risk-benefit profile may be considered for approval. Progression events should be confirmed by blinded independent review. Also note that a statistically significant difference in PFS may not necessarily demonstrate a clinically meaningful difference. Final determination of acceptability of PFS to support approval will be made at the time of review of the results of the study in the NDA application.

The results of secondary endpoints will be considered as supportive only if the primary analysis of the primary endpoint is positive. The secondary endpoints, of which you intend to make claims, if any, will need to be pre-specified in the protocol and agreed upon by the Agency.

Discussion:

FDA indicated PFS may be acceptable, however FDA reminded the sponsor of the above FDA comments in paragraph 2.

8. The proposed Phase 3 study will include patients who meet the inclusion and exclusion criteria described in the protocol (*the protocol synopsis for study A4061032 will be included in the EOP2 briefing package*). Does the Agency concur that the overall inclusion/exclusion criteria in the proposed Phase 3 study are appropriate?

FDA Response: Please include a criterion for life expectancy.

Discussion: The sponsor agreed with our comment.

9. The proposed Phase 3 study is designed to show a 40% improvement in median PFS from 5 months to 7 months in patients randomized (1:1) to receive AG-013736 assuming an accrual period of 18 months and a follow-up period of approximately 7 months. A total of 429 events and 540 patients are required for a log-rank test to have an overall 1-sided significance level of 0.025 and power of 0.90. This design will also have 80% power to detect an approximately 32% improvement in OS from 15 to 19.75 months. As stated previously, eligible patients will include patients with advanced RCC after failure of one prior systemic therapy. The median PFS is approximately 5.5 months for advanced RCC patients who have received one prior systemic therapy (including cytokine-containing therapy) and are subsequently treated with sorafenib (see Nexavar® package insert). However, the median PFS is unknown for advanced RCC patients who fail sunitinib/sunitinib-containing regimen, bevacizumab/bevacizumab-containing regimen, or mTOR inhibitor/mTOR inhibitor-containing regimen. Therefore, currently, for the purpose of calculating an initial sample size for the proposed Phase 3 study, the median PFS has been estimated as approximately 5 months. Two interim analyses will be performed after approximately 143 and 286 PFS events (about 33% and 67% of the total number of required events as assessed by the independent radiology review committee [IRC], respectively). One of the objectives of the second interim analysis will be to allow for sample size re-estimation (if necessary). The interim analyses will also be conducted to assess the safety of the study treatment and to stop the trial early due to futility or for positive efficacy (second interim analysis only).
- a. Does the Agency concur that a median PFS of 5 months (and OS of 15 months) is a reasonable initial estimate for patients who have failed one prior systemic therapy and are subsequently treated with sorafenib?

FDA Response:

We have insufficient information to judge whether your estimates are reasonable.

Discussion:

FDA has no further input on the sponsor sample size estimates at this time.

- b. Does the Agency concur that a 40% improvement in median PFS represents a clinically meaningful outcome for the patient population to be enrolled in the proposed Phase 3 study?

FDA Response:

Please see response to question # 7. This will be a review issue.

Discussion: The sponsor has no further comments.

- c. Does the Agency concur with the two proposed interim analyses and their objectives?

FDA Response:

We discourage claiming efficacy based on an interim PFS analysis.

Consideration of PFS as the primary endpoint for demonstration of efficacy for approval of drug products is based on the magnitude of the effect and the risk-benefit profile of the drug product. Because documentation of PFS assessments depends on the frequency, accuracy, reproducibility and completeness of tumor assessments, it is important that the observed magnitude of effect is robust. An interim PFS analysis may not provide an accurate or reproducible estimate of the treatment effect size due to inadequate follow-up, missing assessments, 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. Accrual should be completed before an interim analysis of PFS is performed.

We recommend you perform an interim analysis for OS at the time of PFS analysis.

Please specify the criteria of re-estimating the sample size, and method of adjusting the test statistic.

Discussion:

The sponsor proposed one interim analysis for futility and sample size re-estimation when 50% of PFS events have occurred. The final analysis for PFS will be used for approval purposes.

FDA indicated that the sponsor's proposal is acceptable.

10. The primary analysis will be based on the stratified log-rank test where the stratification factors are baseline ECOG performance status (0 vs 1) and prior therapy (sunitinib/sunitinib-containing regimen versus bevacizumab/bevacizumab-containing regimen versus mTOR inhibitor/mTOR inhibitor-containing regimen versus cytokines). Based on clinical data obtained in Phase 2 and 3 studies with sunitinib in cytokine-refractory RCC patients, baseline ECOG status was a strong independent predictor of efficacy (*see Section 5.1.3 of this briefing package*). Since the proposed Phase 3 study will include advanced RCC patients who have received a variety of different prior systemic therapies, and the efficacy of AG-013736 and sorafenib may depend on the previous treatment received, stratifying by prior therapy can help to minimize imbalance in the 2 study arms and reduce selection bias.

- a. Does the Agency concur that the primary analysis should be based on the stratified log-rank test?

FDA Response:

Yes. However, you may consider an unstratified log-rank test in case the number of events in some strata is too small.

Discussion:

FDA indicated that regardless of the method, the sponsor should pre-specify the analysis method in the protocol and statistical analysis plan.

- b. Does the Agency concur that the stratification factors for the proposed Phase 3 study are appropriate?

FDA Response:

You could consider the importance of prognostic factors by categorizing patients into three risk groups, favorable-, intermediate-, and poor-risk. Regardless of whether these groups are incorporated as a stratification factor, balance between the two arms with respect to risk category will be reviewed in the NDA submission.

Discussion:

The sponsor indicated that the risk categories for second line treatment are mainly based on a patient population receiving cytokines and not other therapies. Therefore, the sponsor does not plan to use risk category as a stratification factor.

FDA acknowledged this and stated that balance in certain risk variables will be assessed during review.

- c. If a "prior therapy" fits into > 1 strata, patient data will be "fitted" into the strata in the following order of hierarchy: sunitinib/sunitinib-containing regimen > bevacizumab/ bevacizumab-containing regimen > mTOR inhibitor/mTOR inhibitor-containing regimen > cytokines. Does the Agency concur that this is appropriate?

FDA Response: Please provide a rationale for your prioritization.

Discussion:

The sponsor indicated that prioritization was based on similarity of mechanism of action to AG-013736.

11. By the time of filing the Phase 3 study data in advanced RCC, the Sponsor estimates that approximately n=380 patients with advanced RCC will have been treated with single agent AG-013736 at the proposed dose and regimen (starting oral dose of 5 mg BID) i.e. n=270 patients in the proposed Phase 3 study (A4061032) in patients with advanced RCC after failure of one prior systemic therapy, n=52 patients in the Phase 2 study in patients with cytokine-refractory advanced RCC (Protocol A4061012), and n=62 patients in the Phase 2 study in patients with sorafenib-failure advanced RCC (A4061023). In addition, an estimated n=1100 patients with various other solid tumors will have been treated with an initial starting dose of 5 mg BID AG-013736 single agent (n=500 patients) and 5 mg BID AG-013736 in combination with cytotoxic chemotherapies (n=600 patients). Does the Agency concur that the estimated safety database is sufficient to support regular approval in the proposed indication?

FDA Response: The safety database should be adequate to support an application.

Discussion: There was no further discussion needed.

12. The Sponsor considers that the proposed Phase 3 study could be the basis to support a regular approval for AG-013736 in the proposed indication if the primary endpoint is achieved. The NDA filing will also include supportive safety and efficacy data from the completed Phase 2 study in cytokine-refractory advanced RCC patients (Protocol A4061012) and the ongoing Phase 2 study in sorafenib-failure advanced RCC patients (Protocol A4061023) as well as safety data from Phase 1 and 2 studies of AG-013736 in various other solid tumors. Does the Agency concur that the proposed Phase 3 study in 2nd line advanced RCC patients (A4061032), along with supportive safety and efficacy data from the two Phase 2 studies in advanced RCC patients (A4061012 and A4061023), as well as supportive safety data from Phase 1 and 2 studies of AG-013736 in various other solid tumors, will potentially support regular approval in the proposed indication?

FDA Response:

Possibly. For a single randomized trial to support an NDA, the trial should be well designed, well conducted, internally consistent and provide statistically persuasive efficacy findings so that a second trial would be ethically or practically impossible to perform. We strongly suggest that you conduct two adequate and well-controlled trials to support the proposed indication.

We refer you to the FDA guidance "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products" www.fda.gov/cder/guidance/1397fnl.pdf and to the evolving entries at website for Oncology Endpoints for clinical trials at <http://www.fda.gov/cder/guidance/6592dft.htm>

Please see response to question #7 regarding the primary endpoint.

Discussion: There was no further discussion needed.

12. At the End-of-Phase 2 (EOP2) meeting held between the Sponsor and FDA on 14th August 2006 (revised official minutes were issued by FDA on 25th September, 2006), the Sponsor described an 'alternative' TQT study that was conducted in healthy volunteers (study A4061004) and for which a PK/PD report was subsequently submitted (*see IND 63,662 SN # 0159, dated 21st December 2006*). In addition, the Sponsor also indicated that ECG information with timed PK samples would be collected in certain ongoing clinical studies in patients. As part of this commitment, in the Phase 3 pancreatic cancer study (A4061028), the Sponsor plans to collect 3 consecutive 12-lead electrocardiograms (ECGs) from the first 100 randomized patients. This was agreed to by FDA following Special Protocol Assessment of Protocol A4061028 (*see FDA letter dated 22nd November, 2006*). The ECGs tracings will be centrally-collected, but no independent central review is planned.

The Sponsor does not plan to perform ECG assessments and collect ECG readings as part of the proposed Phase 3 study in RCC patients (A4061032). Does the Agency concur that this is acceptable?

FDA Response:

The adequacy of the above QT evaluation will be a review issue. From a safety perspective, we recommend ECGs at baseline and as clinically indicated.

Discussion: The sponsor concurred with the FDA response.

ADDITIONAL FDA COMMENTS

1. We recommend that you explore the relationships between exposure to AG-013736, inhibition of VEGFR activity, and safety/efficacy variables in your proposed Phase 3 Study A4061032.

Discussion: The sponsor concurred with FDA recommendation.

2. Please submit the overall clinical pharmacology development plan for AG-013736. We recommend that it include a hepatic impairment study as the drug is primarily eliminated by metabolism.

Discussion:

The sponsor will submit the overall clinical pharmacology development plan. The sponsor remains fully committed to conducting a hepatic impairment study.

The FDA requested that the sponsor provide a rationale for the current plan for not including the severe group in a hepatic impairment study. A population PK analysis with correlation to liver function tests may not provide adequate justification for this exclusion.

The Sponsor noted that in a previous EOP2 discussion with FDA [REDACTED] (b) (4), the FDA meeting minutes indicated that the plan to assess the effect of hepatic impairment on PK in a population PK analysis and, in the absence of effect, conduct a study of patients with mild/moderate impairment only appeared acceptable to the Agency. The sponsor will submit to FDA a subsequent meeting request regarding the design of the hepatic impairment study.

Regulatory

1. Final Protocols

Please refer to the December 1999 DRAFT "Guidance for Industry - Special Protocol Assessment" (posted on the Internet 2/8/2000) and submit final protocol(s) to the IND for FDA review as a **REQUEST FOR SPECIAL PROTOCOL ASSESSMENT (SPA)** in bolded block letters at the top of your cover letter. Also, the cover letter should clearly state the type of protocol being submitted (i.e., clinical) and include a reference to this EOP2 meeting. A sample case report form (CRF) should be included. 10 desk copies of this SPA should be submitted directly to the project manager.

Since we may use an ODAC consultant for this protocol review, and their clearance takes several weeks, we would appreciate any lead-in time you could give us as to when the SPA will be submitted. You should also be aware that our using a consultant extends the due date on these SPAs till 45 days after we receive the consultant's written comments.

2. Submission of Clinical Trials to NIH Public Access Data Base

Section 113 of the Food and Drug Modernization Act (Modernization Act) amends 42 U.S.C. 282 and requires the establishment of a public resource for information on studies of drugs for serious or life-threatening diseases conducted under FDA's Investigational New Drug (IND) regulations (21 CFR part 312). The National Institutes of Health (NIH) through its National Library of Medicine (NLM), and with input from the FDA and others, developed the Clinical Trials Data Bank, as required by the Modernization Act. FDA has made available a final guidance to implement Section 113 of the Modernization Act. The guidance describes the type of information to submit and how to submit information to the Clinical Trials Data Bank. The guidance entitled "Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions" was made available on March 18, 2002. It is accessible through the Internet at <http://www.fda.gov/cder/guidance/4856fml.htm>

The clinical trial information for the Clinical Trials Data Bank should include the purpose of the trial, the patient eligibility criteria, the location of the trial sites and, a contact for patients wanting to enroll in the trial. The data fields and their definitions are available in the Protocol Registration System at <http://prsinfo.clinicaltrials.gov/>. Protocols listed in this system by will be made available to the public on the Internet at <http://clinicaltrials.gov>.

If you have any questions, contact Theresa Toigo at (301) 827-4460 or 113trials@oc.fda.gov.

3. Financial Disclosure Final Rule

We remind you of the requirement to collect the information on all studies that the FDA relies on to establish that the product is effective and any study in which a single investigator makes a significant contribution to demonstration of safety.

Please refer to the March 20, 2001 "*Guidance for Industry: Financial Disclosure By Clinical Investigators*" (posted on the Internet 3/27/2001) at <http://www.fda.gov/oc/guidance/financialdis.html>.

4. Pediatric Research Equity Act (PREA)

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We encourage you to submit a pediatric plan that describes development of your product in the pediatric population where it may be used. In any event, we hope you will decide to submit a pediatric plan and conduct the appropriate pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

5. Pediatric Exclusivity

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products. You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.

6. Demographics

In response to a final rule published 2-11-98, the regulations 21 CFR 314.50(d)(5)(v) and 314.50(d)(5)(vi)(a) were amended to require sponsors to present safety and effectiveness data "by gender, age, and racial subgroups" in an NDA. Therefore, as you are gathering your data and compiling your NDA, we request that you include this analysis. To assist you in this regard, the following table is a suggestion for presentation of the numeric patient demographic information. This data, as well as the pertinent analyses, should be provided in the NDA.

Please provide information for each category listed below from the primary safety database excluding PK studies.

CATE GORY	NUMBER EXPOSED TO STUDY DRUG	NUMBER EXPOSED TO STUDY DRUG	NUMBER EXPOSED TO STUDY DRUG
Gen- der	Males	All Females	Females >50
Age:	0-≤1 Mo.	>1 Mo.-≤ 2Year	>2-<12
	12-16	17-64	≥65
Race:	White	Black	Asian
	Other		

7. Chemistry

Prior to initiating pivotal clinical studies, we request a complete, updated submission of chemistry, manufacturing and controls (CMC). Please refer to the appropriate CDER guidelines for assistance in preparing this submission. At the time of this submission, we strongly urge you to request a meeting to discuss CMC issues, e.g., impurity profile, stability protocols, approaches to specifications, and attributes, packages, etc.

ACTION ITEMS:

1. The sponsor will submit the overall clinical development plan for AG-013736.
2. The sponsor will provide a rationale for not including the severe group in a hepatic impairment study.
3. The sponsor will submit a subsequent meeting request with the Division of Clinical Pharmacology V to discuss the design of the hepatic impairment study.

There were no unresolved issues. The meeting concluded at 11:15 am.

{See appended electronic signature page}

Patty Garvey, R.Ph.
Senior Regulatory Project Manager/Facilitator

Concurrence Chair:

{See appended electronic signature page}

Ramzi Dagher, M.D.
Medical Reviewer, DDOP

Attachment: Overall Development Plan

Overall Development Plan

Indication: AG-013736 is indicated for the treatment of patients with advanced RCC after failure of one prior systemic therapy.

Proposed pivotal trials: 1 Phase 3 randomized double-blind study (Protocol A4061032) entitled: “A Randomized, open-label Phase 3 Study of AG 013736 Versus Sorafenib in Patients with Metastatic Renal Cell Cancer after Disease Progression on or Intolerance to One Prior Therapy” is proposed to support regular approval.

Proposed supportive trials: Two Phase 2 open-label studies will be included in the filing as supportive for both safety and efficacy; these are Protocol A4061012 entitled: “Phase 2 Study of AG-013736 as Second-Line Treatment in Patients with Metastatic Renal Cell Cancer” and Protocol A4061023 entitled: “Phase 2 Study of the Antiangiogenesis Agent AG-013736 in Patients with Refractory Metastatic Renal Cell Cancer”. Several Phase 2 trials in various solid tumors in which AG-013736 is administered either as a single agent or in combination with chemotherapy will be included in the filing and will be supportive for safety.

Protocol Outline (Phase 3 Protocol A4061032)

Protocol number/title: A4061032 entitled “A Randomized, open-label Phase 3 Study of AG 013736 Versus Sorafenib in Patients with Metastatic Renal Cell Cancer after Disease Progression on or Intolerance to One Prior Therapy”

Objectives: Primary: Compare the PFS of patients administered AG-013736 versus sorafenib.

Secondary: Compare the OS, ORR, and estimate the DR of patients in both study arms, evaluate patient safety in each arm, and compare RCC-specific PROs.

Design: Phase 3, randomized (1:1), open-label, multi-center study comparing AG-013736 versus sorafenib. Randomization will be stratified by baseline ECOG performance status (0 vs 1) and prior therapy.

Patient population: Patients with patients with advanced RCC after disease progression on or intolerance to one prior systemic therapy locally.

Dosing plan/treatment plan/schema: Sorafenib: Administered orally at 400 mg BID (2 x 200 mg).

AG-013736: Administered continuously at a starting oral dose of 5 mg twice daily (BID). In the absence of a drug reaction greater than CTCAE Grade 2, AG-013736 doses will be escalated incrementally (5 mg BID to 7 mg BID to a maximum of 10 mg BID). It is anticipated that approximately 25% of patients will undergo such dose escalation. Patients experiencing drug reaction greater than CTCAE Grade 2, including hypertension, will undergo dose reductions.

Efficacy endpoints: Primary: PFS; **Secondary:** OS, ORR, DR, and PROs.

Definition of Endpoints: Primary: PFS: time from randomization to objective tumor progression or death (any cause), whichever comes first; **Secondary:** OS: time from randomization to date of death (any cause); ORR: proportion of patients with confirmed complete or partial response relative to all randomized patients. DR: time from initial objective tumor response that is subsequently confirmed to the first documentation of objective tumor progression or to death (any cause), whichever occurs first. PROs: measured by the FACT-Advanced Kidney Cancer Symptom Index (FKSI) questionnaire and general health status as measured by the EuroQol Group’s EQ-5D self-report questionnaire (EQ-5D).

Safety Monitoring: Independent Data Monitoring Committee will convene on a regular basis to review safety issues.

Statistical Plan:

Sample size/basis: 540 patients (1:1 randomization)/429 events (progressive disease or death) are required for a log-rank test with an overall 1-sided significance level of 0.025 to have power of 0.90. This assumes a 40% improvement in median PFS from 5 months to 7 months in patients randomized to receive AG-013736, an accrual period of approximately 18 months and follow-up period of approximately 7 months.

Analyses: Primary: PFS in each arm will be assessed using the Kaplan-Meier method and compared with a 1-sided stratified log-rank test at the $\alpha = 0.025$ significance level. As a secondary analysis, the unstratified log-rank test will also be evaluated. As additional sub analyses, a Cox proportional hazard model will be used to explore the potential influences of the baseline stratification factors and other patient characteristics on PFS. **Secondary:** OS: similar analyses will be done for OS as will be done for PFS. ORR: 2 treatment arms will be compared using the Pearson chi-square method for unstratified analyses and the Cochran-Mantel-Haenszel method for stratified analyses. DR: Estimates of the DR curves from the Kaplan-Meier method will be provided along with estimates of the median event time and a 2-sided 95% confidence interval for each treatment arm. PROs: At each assessment and for each treatment arm, descriptive statistics of the absolute scores and changes from baseline (Cycle 1 Day 1) will be obtained. Additionally, longitudinal mixed-effects models will be used to evaluate these data.

Interim analysis plan: Two interim analyses are planned after 143 and 286 PFS events (about 33% and 67% of the total number of required events as assessed by the IRC, respectively). One of the objectives of the second interim analysis will be to allow for sample size re-estimation (if necessary). The nominal level of significance for the final analysis of PFS will be adjusted for the interim analysis using the Lan DeMets procedure with an O'Brien-Fleming boundary. The trial will be also assessed for futility based on PFS using the Pampallona-Tsiatis Power boundary.

Estimated start and completion dates: 1Q08 – 1Q10 (last patient/last visit for PFS)

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/s/

Patricia Garvey
6/14/2007 02:22:25 PM

Ramzi Dagher
6/18/2007 09:27:40 AM