

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022405Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 022405

SUPPL #

HFD # 150

Trade Name not applicable

Generic Name vandetanib

Applicant Name AstraZeneca Pharmaceuticals LP, authorized US Agent for iPR Pharmaceuticals, Inc.

Approval Date, If Known April 6, 2011

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES NO

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

505(b)(1)

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

YES NO

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

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

d) Did the applicant request exclusivity?

YES NO

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

7 years

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

YES NO

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

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

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

YES NO

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES NO

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

NDA#

NDA#

NDA#

2. Combination product.

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

YES NO

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

NDA#

NDA#

NDA#

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

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

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

summary for that investigation.

YES NO

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

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

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

YES NO

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

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

YES NO

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

YES NO

If yes, explain:

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

YES NO

If yes, explain:

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

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

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

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

Investigation #1 YES NO

Investigation #2 YES NO

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

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

Investigation #1 YES NO

Investigation #2 YES NO

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

Explain:

! Explain:

Investigation #2

!

!

YES

! NO

Explain:

! Explain:

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

YES

NO

If yes, explain:

=====
Name of person completing form: Lisa Skarupa
Title: Regulatory Project Manager
Date: 4/05/2011

Name of Office/Division Director signing form: Robert L. Justice, M.D., M.S.
Title: 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
04/05/2011

ROBERT L JUSTICE
04/05/2011

1.3.3 DEBARMENT CERTIFICATION

Re: NDA 22-405

ZICTIFA™ (vandetanib) Tablets

Debarment Certification Statement

In response to the requirements of Section 306(k) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 335a (k)), as amended by the Generic Drug Enforcement Act of 1992 (GDEA), I hereby certify on behalf of AstraZeneca Pharmaceuticals LP (AstraZeneca), that we did not use and will not use in connection with this New Drug Application, the services of any person in any capacity debarred under section 306 (a) or (b).

Sincerely,



Cindy Lancaster, Executive Director and Regulatory
Portfolio Leader
Regulatory Affairs
AstraZeneca

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹

NDA # 022405 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: none at time of approval Established/Proper Name: vandetanib Dosage Form: 100 mg and 300 mg tablets		Applicant: AstraZeneca Pharmaceuticals LP, authorized US Agent for iPR Pharmaceuticals, Inc. Agent for Applicant (if applicable):
RPM: Lisa Skarupa		Division: DDOP
<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><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u> 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>
<p>❖ Actions</p> <ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>April 7, 2011</u> • Previous actions (<i>specify type and date for each action taken</i>) 		<p><input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR</p> <p><input checked="" type="checkbox"/> None</p>
<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>		<p><input type="checkbox"/> Received</p>

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	
Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority Chemical classification (new NDAs only): NME	
<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 checked="" type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC	
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	
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	
<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	
REMS: <input checked="" type="checkbox"/> MedGuide <input checked="" type="checkbox"/> Communication Plan <input checked="" type="checkbox"/> ETASU <input type="checkbox"/> REMS not required	
Comments:	
❖ 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>)	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Press Office notified of action (by OEP) 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> 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 type="checkbox"/> Other

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 BLA: 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"> NDA 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).

(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?

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 written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

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).

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.

CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist³

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 (*approvals only*)

Included

Documentation of consent/non-consent by officers/employees

Included

Action Letters

❖ Copies of all action letters (*including approval letter with final labeling*)

Action(s) and date(s) April 6, 2011

Labeling

❖ Package Insert (*write submission/communication date at upper right of first page of PI*)

- Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.
- Original applicant-proposed labeling
- Example of class labeling, if applicable

March 28, 2011

July 7, 2010

N/A

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 checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	3.23.2011
<ul style="list-style-type: none"> Original applicant-proposed labeling 	7.7.2010
<ul style="list-style-type: none"> Example of class labeling, if applicable 	N/A
❖ 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 	3.23.2011
❖ 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>) 	10.07.2010 10.22.2010
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	<input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEPA 10.22.10 <input checked="" type="checkbox"/> DRISK 2.25.11 <input checked="" type="checkbox"/> DDMAC 2.22.11; 2.15.11 <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>)	8.30.2010
❖ 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 checked="" 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 _____ If PeRC review not necessary, explain: <u>Not necessary as this is an orphan drug status</u> Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable
Outgoing communications (<i>letters (except action letters), emails, faxes, telecons</i>)	

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

Internal memoranda, telecons, etc.	
❖ 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 6.10.2010
• EOP2 meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg 6.9.2005 and 6.13.2005
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	
❖ Advisory Committee Meeting(s)	<input type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	12.2.2010
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	12.2.2010
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input type="checkbox"/> None 04.05.2011
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 04.01.2011
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 12.9.010
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None four
Clinical Information⁵	
Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	3.25.2011
• Clinical review(s) (<i>indicate date for each review</i>)	12.9.010
• 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>)	in Clinical Review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management <ul style="list-style-type: none"> • REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>) • 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>) 	REMS Documents 12.22.2010 <input type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input type="checkbox"/> None requested 11.22.2010

⁵ Filing reviews should be filed with the discipline reviews.

Clinical Microbiology <input checked="" type="checkbox"/> None	
Clinical Microbiology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (indicate date for each review)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None 12.16.2010
Statistical Review(s) (indicate date for each review)	<input type="checkbox"/> None 12.16.2010
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) (indicate date for each review)	<input type="checkbox"/> None 12.9.2010
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)	<input checked="" type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input type="checkbox"/> None 3.25.2011
• Supervisory Review(s) (indicate date for each review)	<input type="checkbox"/> None 3.25.2011
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	<input type="checkbox"/> None 12.10.2010
Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (include copies of DSI letters)	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Product quality review(s) including ONDQA biopharmaceutics reviews (indicate date for each review)	<input type="checkbox"/> None Premarketing Assessment 8.5.2010 Drug Substance 12.7.2010 Biopharmaceutics 12.8.2010
❖ Microbiology Reviews	<input checked="" type="checkbox"/> Not needed
<input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (indicate date of each review)	
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) (indicate date of each review)	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)	<input checked="" type="checkbox"/> None

<input checked="" type="checkbox"/> Environmental Assessment (check one) (original and supplemental applications)	
<input type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(all original applications and all efficacy supplements that could increase the patient population)	12/7/2010
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
<input checked="" type="checkbox"/> Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>) (<i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁶</i>)	Date completed: 12.8.2010 see CMC review dated 12.23.2010 <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
<input checked="" type="checkbox"/> NDAs: Methods Validation (<i>check box only, do not include documents</i>)	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input checked="" type="checkbox"/> Not yet requested <input 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 DRA.

Skarupa, Lisa

From: Skarupa, Lisa
Sent: Wednesday, March 23, 2011 10:02 AM
To: 'Doman, Natalie'; Shiozawa, Debi N
Cc: Maher, Virginia E.
Subject: NDA 22405 vandetanib label

Attachments: vandetaniblabelMarch23fromFDA.doc

Good morning Natalie,

Here is the vandetanib label, there are minor editorials.
Please also note to make the change below in Section 5.15 (blue letters).

Please call me if you have any questions. May I please have this label back, clean by 1pm today.

Sincerely,
Lisa



vandetaniblabelMar
ch23fromFDA....

5.15 Vandetanib REMS (Risk Evaluation and Mitigation Strategy) Program

Because of the risk of QT prolongation, Torsades de pointes, and sudden death, vandetanib is available only through a restricted distribution program called Vandetanib REMS Program. Only prescribers and pharmacies certified with the program are able to prescribe and dispense vandetanib.

An overview of the requirements for prescribers and pharmacies is included below.

- To be certified, prescribers must review the educational materials, agree to comply with the REMS requirements, and enroll in the program.
(The rest of this section IS FINE)

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

Skarupa, Lisa

From: Skarupa, Lisa
Sent: Friday, March 18, 2011 6:17 PM
To: 'Doman, Natalie'; Shiozawa, Debi N
Cc: Maher, Virginia E.
Subject: NDA 22393 vandetanib last revision to label March182011

Attachments: 31711 latest label.doc

Hello Natalie and Debi,

Here is our last revision of the label (PI with Med Guide).

Please make all the references consistent: italicized, parenthesis in the appropriate location. I have deferred correcting spacing to you; and to make all the fonts the same. Please return the clean label by COB Tuesday.

Sincerely,
Lisa



31711 latest
label.doc (410 KB...)

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

Skarupa, Lisa

From: Skarupa, Lisa
Sent: Friday, March 18, 2011 4:05 PM
To: 'Doman, Natalie'; Shiozawa, Debi N
Subject: RE: NDA 22405 vandetanib REMS documents

Natalie and Debi,
End of next week is not acceptable. If we target to meet the PDUFA, we have to the REMS documents by COB Tuesday.

Lisa

From: Doman, Natalie [mailto:Natalie.Doman@astrazeneca.com]
Sent: Friday, March 18, 2011 2:47 PM
To: Skarupa, Lisa; Shiozawa, Debi N
Subject: RE: NDA 22405 vandetanib REMS documents

Hi, Lisa:

I can't provide a specific day now, as our goal is to incorporate the interactive Healthcare Provider Knowledge Assessment and work on this is still ongoing. However, we are planning to submit towards the end of next week.

I hope this helps,
Natalie

Natalie Doman
Associate Director

AstraZeneca
Research & Development | Regulatory Affairs
C2B-705A, 1800 Concord Pike, PO Box 15437, Wilmington, DE, 19850-5437
T: +1 (302) 885 1441 F: +1 (302) 886 2822
natalie.doman@astrazeneca.com

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From: Skarupa, Lisa [mailto:Lisa.Skarupa@fda.hhs.gov]
Sent: Thursday, March 17, 2011 4:35 PM
To: Doman, Natalie; Shiozawa, Debi N
Subject: NDA 22405 vandetanib REMS documents

Hello Natalie and Debi
Do you know when you would be able to return the REMS documents after your revisions?

Lisa

Skarupa, Lisa

From: Skarupa, Lisa
Sent: Thursday, March 17, 2011 4:03 PM
To: 'Doman, Natalie'; Shiozawa, Debi N
Cc: Maher, Virginia E.
Subject: FW: NDA 22-405 vandetanib- Postmarketing Requirement - Finalizing Clinical PMR dates

Natalie and Debi,
Please see our responses in red letters.
The first reply is to your modifications to the language, which was acceptable, with our addition.
The last reply is about the every 6 months opth. exams.

Sincerely,
Lisa

From: Doman, Natalie [mailto:Natalie.Doman@astrazeneca.com]
Sent: Wednesday, March 16, 2011 6:01 PM
To: Skarupa, Lisa; Shiozawa, Debi N
Cc: Maher, Virginia E.
Subject: RE: NDA 22-405 vandetanib- Postmarketing Requirement - Finalizing Clinical PMR dates

Hi, Lisa:

Thank you for sending this and the correction to the REMS document comments.

We suggest the following modifications to the language:

(b) (4)



(b) (4)

You have accurately captured the dates. The official submission of a timetable for the Overall Survival analysis of Study 58 was made today, March 16, 2011 (Sequence No. 0057).

Thanks for your help,
Natalie

Natalie Doman
Associate Director

AstraZeneca
Research & Development | Regulatory Affairs
C2B-705A, 1800 Concord Pike, PO Box 15437, Wilmington, DE, 19850-5437
T: +1 (302) 885 1441 F: +1 (302) 886 2822
natalie.doman@astrazeneca.com

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From: Skarupa, Lisa [mailto:Lisa.Skarupa@fda.hhs.gov]
Sent: Wednesday, March 16, 2011 10:57 AM
To: Doman, Natalie; Shiozawa, Debi N
Cc: Maher, Virginia E.
Subject: NDA 22-405 vandetanib- Postmarketing Requirement - Finalizing Clinical PMR dates

Good morning Natalie and Debi,

The following are the accepted dates for the Clinical PMRs that will be used for the letter. Please see my inquiry (red letters below). Let me know if these dates were captured accurately.
Thank you. Lisa

(b) (4)

From: Doman, Natalie [mailto:Natalie.Doman@astrazeneca.com]
Sent: Thursday, February 24, 2011 7:46 AM
To: Skarupa, Lisa; Shiozawa, Debi N
Subject: NDA 22-405: Postmarketing Requirement - Proposal for Provision of Overall Survival Update for Pivotal Study D4200C00058

Good morning, Lisa:

Reference is made to teleconference held between FDA and AstraZeneca (AZ) on 10 December 2010, in which the Agency informed AZ that provision of the Overall Survival (OS) analysis from pivotal study D4200C00058 would be a postmarketing requirement (PMR) for this application.

The purpose of this e-mail is to propose fulfillment dates for the OS PMR for Study D4200C00058. The protocolled OS analysis will occur after 50% of the patients in the study have died. For the purposes of this PMR, the data cut-off for the OS analysis will be considered the study completion date. This date is currently estimated to be 31 December 2013, based on 26% of patients having died, but please note that the proposed date is event-driven and the confidence interval ranges from the end of January 2013 – beginning of January 2015. If necessary in the future, AZ would like to agree modification to the proposed fulfillment dates based on the actual data cut-off date.

Study completion: 31 December 2013

Submission of final report to FDA: 30 May 2014

AstraZeneca requests feedback from the Agency on the proposal above.

Thanks for your help,
Natalie

Natalie Doman
Associate Director

AstraZeneca
Research & Development | Regulatory Affairs
C2B-705A, 1800 Concord Pike, PO Box 15437, Wilmington, DE, 19850-5437
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natalie.doman@astrazeneca.com

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Skarupa, Lisa

From: Skarupa, Lisa
Sent: Wednesday, March 16, 2011 11:10 AM
To: 'Doman, Natalie'; Shiozawa, Debi N
Subject: NDA 22405 vandetanib REMS documents comments_CORRECTION

Good morning Natalie and Debi,

Please see the CORRECTIONS to the Knowledge Assessment section that I sent yesterday as they no longer pertain after our teleconference yesterday. Lisa

Knowledge Assessment Questions

1. Organize the questions into 6 categories as follows:

- Risk
- Appropriate patient selection
- Electrolyte monitoring
- ECG monitoring
- Drug drug interactions
- Dosage and administration

These categories are consistent with the 6 sections in the HCP Educational Pamphlet.

(b) (4)

3. Revise the prescriber knowledge assessment (or enrollment test) to include 6 questions (one from each

(b) (4)

6. In addition to accessing the knowledge assessment online, ensure you have a process in place to allow prescribers to complete the assessment on the phone.
7. Revise each question to reference the prescribing information or the HCP educational pamphlet. For example, "According to the Prescribing Information,"
8. When the REMS is approved, the knowledge assessment will be appended to the REMS. Because this information is publicly available, the final document that is attached to the REMS should *not* include the correct answers.

Skarupa, Lisa

From: Skarupa, Lisa
Sent: Wednesday, March 16, 2011 10:57 AM
To: 'Doman, Natalie'; Shiozawa, Debi N
Cc: Maher, Virginia E.
Subject: NDA 22-405 vandetanib- Postmarketing Requirement - Finalizing Clinical PMR dates

Good morning Natalie and Debi,

The following are the accepted dates for the Clinical PMRs that will be used for the letter. Please see my inquiry (red letters below). Let me know if these dates were captured accurately. Thank you. Lisa

Conduct a 2 arm randomized study comparing vandetanib 300 mg vs. 150 mg in patients with progressive, symptomatic medullary thyroid cancer. The primary endpoint should be overall response rate.

Final Protocol Submission: September (b) (4) 2011

Trial Completion Date: July (b) (4) 2014

Final Report Submission: December (b) (4) 2014

(b) (4)

Submit the results of the final analysis of overall survival data from the randomized clinical trial of vandetanib 300 mg vs. placebo in medullary thyroid cancer (study 58).

The timetable you submitted on XXXX (I do not see that this timetable was officially submitted, please submit or let me know where you submitted), states that you will conduct this trial according to the following timetable:

Final Protocol Submitted: February (b) (4) 2006

Reference ID: 2924356

3/28/2011

Trial Completion Date: December (b) (4) 2013

Final Report Submission: May (b) (4) 2014

From: Doman, Natalie [mailto:Natalie.Doman@astrazeneca.com]
Sent: Thursday, February 24, 2011 7:46 AM
To: Skarupa, Lisa; Shiozawa, Debi N
Subject: NDA 22-405: Postmarketing Requirement - Proposal for Provision of Overall Survival Update for Pivotal Study D4200C00058

Good morning, Lisa:

Reference is made to teleconference held between FDA and AstraZeneca (AZ) on 10 December 2010, in which the Agency informed AZ that provision of the Overall Survival (OS) analysis from pivotal study D4200C00058 would be a postmarketing requirement (PMR) for this application.

The purpose of this e-mail is to propose fulfillment dates for the OS PMR for Study D4200C00058. The protocolled OS analysis will occur after 50% of the patients in the study have died. For the purposes of this PMR, the data cut-off for the OS analysis will be considered the study completion date. This date is currently estimated to be (b) (4) December 2013, based on 26% of patients having died, but please note that the proposed date is event-driven and the confidence interval ranges from the end of January 2013 – beginning of January 2015. If necessary in the future, AZ would like to agree modification to the proposed fulfillment dates based on the actual data cut-off date.

Study completion: (b) (4) December 2013

Submission of final report to FDA: (b) (4) May 2014

AstraZeneca requests feedback from the Agency on the proposal above.

Thanks for your help,
Natalie

Natalie Doman
Associate Director

AstraZeneca
Research & Development | Regulatory Affairs
C2B-705A, 1800 Concord Pike, PO Box 15437, Wilmington, DE, 19850-5437
T: +1 (302) 885 1441 F: +1 (302) 886 2822
natalie.doman@astrazeneca.com

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Skarupa, Lisa

From: Skarupa, Lisa
Sent: Tuesday, March 15, 2011 3:53 PM
To: 'Doman, Natalie'; Shiozawa, Debi N
Cc: Maher, Virginia E.
Subject: NDA 22045 vandetanib REMS documents comments

Natalie and Debi,

Please be aware that these are preliminary comments. You will receive additional comments as your REMS undergoes further review.

REMS Document

1. See the attached revised REMS document.

(b) (4)



8. When the REMS is approved, the knowledge assessment will be appended to the REMS. Because this information is publicly available, the final document that is attached to the REMS should not include the correct answers.

Skarupa, Lisa

From: Skarupa, Lisa
Sent: Tuesday, March 15, 2011 10:34 AM
To: 'Doman, Natalie'; Shiozawa, Debi N
Subject: RE: NDA 22405 vandetanib Discussion on dose-finding study

Natalie and Debi
Your proposal is acceptable.

I will send another follow-up email so I can capture all the details.

From: Doman, Natalie [mailto:Natalie.Doman@astrazeneca.com]
Sent: Friday, March 11, 2011 1:14 PM
To: Skarupa, Lisa; Shiozawa, Debi N
Subject: RE: NDA 22405 vandetanib Discussion on dose-finding study

Hi, Lisa:

First, thanks for sending the three REMS documents and your response to our question regarding the Clinical Pharmacology section in the labeling.

Regarding the dosing study, we don't have specific questions but are keen to know whether our proposal is acceptable to the review team. I thought it might be helpful to earmark some time for discussion, in case the review team has any questions for us. What do you think?

Thanks again,
Natalie

Natalie Doman
Associate Director

AstraZeneca
Research & Development | Regulatory Affairs
C2B-705A, 1800 Concord Pike, PO Box 15437, Wilmington, DE, 19850-5437
T: +1 (302) 885 1441 F: +1 (302) 886 2822
natalie.doman@astrazeneca.com

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From: Skarupa, Lisa [mailto:Lisa.Skarupa@fda.hhs.gov]
Sent: Friday, March 11, 2011 9:49 AM
To: Doman, Natalie; Shiozawa, Debi N
Subject: NDA 22405 vandetanib Discussion on dose-finding study

Hello Natalie,

As follow-up to your request for a TCON for dose-finding study, would you have questions specific for this that I can frame my request to the team?

Lisa

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
03/28/2011

From: Skarupa, Lisa
Sent: Friday, March 11, 2011 11:05 AM
To: 'Doman, Natalie'; Shiozawa, Debi N
Subject: NDA 22405 vandetanib ClinPharm response to March3AZresponse

Dear Natalie and Debi,
I hope when I hit send, the Table 6 does not disappear. Here is a response (highlighted at the very bottom) from ClinPharm:

Clinical Pharmacology – 12.3 Pharmacokinetics - Special Populations – Ethnicity

- AZ was unable to verify the language added by FDA (below) on relative exposure in Japanese, Chinese Western patients.



Question 4 for FDA: Could FDA provide the data as a basis for this language?

FDA response (2/7/11): Please see the FDA's analysis as below:

The PK of vandetanib in the phase 1 dose escalation studies conducted in US and Australia (Study 01), Japanese (Study 43), and Chinese (Study 4) patients with solid tumors were evaluated using a non-compartmental analysis approach. Based on a cross-study comparison in a limited number of patients, Japanese and Chinese patients had on average exposures that were up to two-fold higher than other patients receiving the same dose, following single (Table 6) and multiple (Table 7) doses of vandetanib. In the pivotal trial, no conclusion could be reached on the effect of race on PK, as 95% of the patients were Caucasians.

Table 6. Single dose PK parameters following 300-mg dose of vandetanib in different studies.

	Study 1	Study 43	Study 4	Study 50
Study	Dose rising	Dose rising	Dose rising	PK/PD for permeability
Subjects	Malignant tumors	Malignant tumors	Malignant tumors	Colorectal cancer and liver metastases
Race	Caucasian 85.7% Black 6.5% Asian 2.6% Other 5.2%	Japanese	Chinese	Caucasian
Formulation	Phase I formulation	Phase I formulation	Commercial (100 mg X 3)	Commercial (300 mg x 1)
Sampling	dense	dense	dense	dense
Food intake	fast from midnight	feed (before breakfast)	no restriction	not shown
N	6-8	5-6	12	12
T _{max} (Median, (range)), h	7.5 (4-24)	5 (4-6)	8 (2-10)	4 (4 - 24)
C _{max} (Gmean) ng/mL (CV%)	213 (40.4)	392 (50.5)	330 (70.0)	269 (53.7)
T _{1/2}	109 ± 29.8 h	90.2 ± 13.7 h	—	—
AUC, ng-h/mL (CV%)	13929 ^a (98.84)	29400 ^b (40.1)	—	—
AUC _{0-24h} , ng-h/mL (CV%)	3019 (43.6)	5580 (44.4)	5643 (58.8)	4913 (55.5)

a: 50% of AUC was extrapolated; b: 40% of AUC was extrapolated; —: values are not reported

Table 7. Multiple dose PK parameters in patients following 300-mg dose of vandetanib in different studies

	Study 1	Study 43	Study 4	Study 50
Race	Caucasian 85.7% Black 6.5% Asian 2.6% Other 5.2%	Japanese	Chinese	Caucasian
N	9-10 (Day 29)	3 (Day 29)	7 (Day 43)	7 (Day 56)
T _{max} (Median, range), h	5 (0-24)	6	4 (0-24)	4 (4 - 24)
C _{max} (Gmean) ng/mL (CV%)	919.8 (60.70)	1580 (19.1)	2024 (39.1)	853 (38.5)
T _{1/2, day}	—	—	7.6 ± 1.76 ^a	—
AUC _{0-24h} , ng-h/mL (CV%)	17926 (58.35)	29900 (15.4)	38611 (38.4)	18260 (41.4)
Accumulation	5 (3-10)	5.3 (4.1-6.5)	8.1	4.5 (3.2-8.4)

^adata from population PK analysis; —: values are not reported

AZ response (3/3/11)

Following receipt of the FDA's data as basis for this language on 7 February 2011, AZ proposes it is more appropriate to revise the language in this section based on the following justification.

From:
Ethnicity

(b) (4)

Ethnicity

(b) (4)

Reason for alternative text

The data provided by FDA on 7 February 2011 to support their proposed label text on ethnicity is based on single and multiple doses PK exposure data from the 300 mg dose.

(b) (4)

(b) (4)

FDA response (3/9/11)

We agree that the number of patients used in our analysis is small. However, the observed trend (higher C_{max} and AUC in Asian) cannot be just neglected. We recommend new labeling language:

Ethnicity

“Based on a cross-study comparison in a limited number of patients, Japanese (N=3) and Chinese (N=7) patients had on average exposures that were higher than Caucasian (N=7) patients receiving the same dose.”

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
03/11/2011

From: Skarupa, Lisa
Sent: Monday, March 07, 2011 12:37 PM
To: 'Doman, Natalie'; Shiozawa, Debi N
Subject: NDA22405 vandetanib March7 Clinical I.R.

Dear Natalie,

Please see the following CLINICAL Information Request, please respond by COB Wednesday March 9th:

Please provide your precision estimates for overall response for the revised proposed clinical study.

Sincerely,
Lisa

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
03/07/2011

From: Doman, Natalie [mailto:Natalie.Doman@astrazeneca.com]
Sent: Wednesday, March 02, 2011 3:15 PM
To: Skarupa, Lisa; Shiozawa, Debi N
Subject: RE: NDA 22-405: Carcinogenicity PMR - FDA response

Hi, Lisa:

I'm writing to confirm receipt. Thanks to you and your team.

Regards,
Natalie

Natalie Doman
Associate Director

AstraZeneca
Research & Development | Regulatory Affairs
C2B-705A, 1800 Concord Pike, PO Box 15437, Wilmington, DE, 19850-5437
T: +1 (302) 885 1441 F: +1 (302) 886 2822
natalie.doman@astrazeneca.com

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From: Skarupa, Lisa [mailto:Lisa.Skarupa@fda.hhs.gov]
Sent: Wednesday, March 02, 2011 2:24 PM
To: Doman, Natalie; Shiozawa, Debi N
Subject: RE: NDA 22-405: Carcinogenicity PMR - FDA response

Dear Natalie and Debi,

FDA Response We have reviewed the revised proposal for the carcinogenicity PMRs sent on February 23, 2011 that includes the following timelines:

"For the 2-year carcinogenicity study in the rat, AstraZeneca agrees to have the CAC interaction by end of 2011. Following formal agreement with CAC, and assuming no delay in the start of the 2-year study (final protocol submission by (b) (4) March 2012), we would anticipate the study report to be submitted to FDA by (b) (4) December 2014."

"For the 6-month study in the mouse, AstraZeneca proposes to have the CAC interaction by the end of 1st quarter 2012. Following formal agreement with CAC, and assuming no delay to the start of the studies (final protocol submission by (b) (4) June 2012) we would anticipate the study report for the transgenic mouse study be submitted to FDA by (b) (4) December 2013."

The **revised timelines** for both the 2 year carcinogenicity study in the rat and the 6-month study in the transgenic (Tg.rasH2) mouse are acceptable. These dates will be used for the PMRs.

From: Doman, Natalie [mailto:Natalie.Doman@astrazeneca.com]
Sent: Wednesday, February 23, 2011 4:27 PM
To: Skarupa, Lisa; Shiozawa, Debi N
Subject: NDA 22-405: Carcinogenicity PMR - Revised Proposal

Hi, Lisa:

As promised, please find below a revised proposal for the carcinogenicity PMR.

Thank you for the clarification regarding your concern of the CAC timing for carcinogenicity PMR on 22 February 2011. With our agreement with you to conduct a 2-year carcinogenicity study in the rat and a 6-month study in the transgenic (Tg.rasH2) mouse, AstraZeneca proposes the following timings:

For the 2-year carcinogenicity study in the rat, AstraZeneca agrees to have the CAC interaction by end of 2011. Following formal agreement with CAC, and assuming no delay in the start of the 2-year study (final protocol submission by (b) (4) March 2012), we would anticipate the study report to be submitted to FDA by (b) (4) December 2014.

As previously indicated, the 6-month rat study was conducted in 2000 using Alderley Park Wistar strain rats which are no longer available. The 2-year carcinogenicity study will be conducted using the RCC Wistar strain rats. To account for potential differences between the 2 rat strains and to gain confidence in dose selection using data from the existing 6-month study, AstraZeneca will conduct a bridging 4-week toxicity/toxicokinetic study in the RCC Wistar rats, which will be initiated in the near future. Data from the 4-week in RCC Wistar rats and the 6-month study in Alderley Park Wistar rats will be used together to select doses for the 2-year carcinogenicity RCC Wistar rats.

For the 6-month study in the mouse, AstraZeneca proposes to have the CAC interaction by the end of 1st quarter 2012. Following formal agreement with CAC, and assuming no delay to the start of the studies (final protocol submission by (b) (4) June 2012) we would anticipate the study report for the transgenic mouse study be submitted to FDA by (b) (4) December 2013.

AstraZeneca would like to confirm these milestone dates at the time of each CAC, and if necessary agree modification to these dates based on the CAC outcome.

Please let us know if you agree with our proposal or whether further discussion is necessary.

Thanks,
Natalie

Natalie Doman
Associate Director

AstraZeneca
Research & Development | Regulatory Affairs

C2B-705A, 1800 Concord Pike, PO Box 15437, Wilmington, DE, 19850-5437
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/s/

LISA M SKARUPA
03/02/2011

From: Doman, Natalie [mailto:Natalie.Doman@astrazeneca.com]
Sent: Wednesday, March 02, 2011 4:22 PM
To: Skarupa, Lisa; Shiozawa, Debi N
Subject: RE: NDA 22405 Section 13 Labeling March_2

Thanks, Lisa.

Natalie

Natalie Doman
Associate Director

AstraZeneca
Research & Development | Regulatory Affairs
C2B-705A, 1800 Concord Pike, PO Box 15437, Wilmington, DE, 19850-5437
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From: Skarupa, Lisa [mailto:Lisa.Skarupa@fda.hhs.gov]
Sent: Wednesday, March 02, 2011 3:34 PM
To: Doman, Natalie; Shiozawa, Debi N
Cc: Maher, Virginia E.
Subject: NDA 22405 Section 13 Labeling March_2

DEAR NATALIE
PLEASE SEE THE CHANGES TO VANDETANIB LABELING SECTION 13.

13. NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with vandetanib.

(b) (4)

Vandetanib was not mutagenic *in vitro* in the bacterial reverse mutation (Ames) assay and was not clastogenic in both the *in vitro* cytogenetic assay using human lymphocytes or in the *in vivo* rat micronucleus assay.

Based on non-clinical findings, male and female fertility may be impaired by treatment with vandetanib. In a fertility study in male rats, vandetanib had no effect on copulation or fertility rate when undosed females were mated with males administered 1, 5, or ^{(b) (4)} 20 mg/kg/day of vandetanib (approximately 0.03, 0.22, or ^{(b) (4)} 0.40 times, respectively, the AUC in patients with cancer at the recommended human dose of 300 mg/day). There was a slight decrease in the number of live embryos at 20 mg/kg/day and an increase in preimplantation loss at ≥ 5 mg/kg/day. In a female fertility study, there was a trend towards increased estrus cycle irregularity, a slight reduction in pregnancy incidence and an increase in implantation loss. In a repeat-dose toxicity study in rats, there was a decrease in the number of corpora lutea in the ovaries of rats administered 75 mg/kg/day vandetanib (approximately 1.8 times the AUC in patients with cancer at the recommended human dose) for 1 month.

13.2 Animal Pharmacology and/or Toxicology

In an animal model of wound-healing, mice dosed with vandetanib had reduced skin-breaking strength compared with controls. This suggests that vandetanib slows but does not prevent wound healing. The appropriate interval between discontinuation of vandetanib and subsequent elective surgery required to avoid the risks of impaired wound healing has not been determined.

Nodular masses were observed in a 6-month toxicology study in rats during treatment with ≥ 5 mg/kg/day vandetanib (approximately 0.22 or 0.40 times, respectively, the AUC in patients with cancer at the recommended human dose of 300 mg/day). Masses were palpable during clinical assessments as early as week 13, were observed in multiple organs, and were associated with hemorrhagic or inflammatory findings.

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/s/

LISA M SKARUPA
03/02/2011

From: Doman, Natalie [mailto:Natalie.Doman@astrazeneca.com]
Sent: Wednesday, February 23, 2011 5:10 PM
To: Skarupa, Lisa; Shiozawa, Debi N
Cc: Maher, Virginia E.
Subject: RE: NDA 22-405: Proposed Indication

Hi, Lisa:

I'm writing to confirm that I received your e-mail. Thank you very much for the prompt response.

Regards,
Natalie

Natalie Doman
Associate Director

AstraZeneca
Research & Development | Regulatory Affairs
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From: Skarupa, Lisa [mailto:Lisa.Skarupa@fda.hhs.gov]
Sent: Wednesday, February 23, 2011 4:03 PM
To: Doman, Natalie; Shiozawa, Debi N
Cc: Maher, Virginia E.
Subject: RE: NDA 22-405: Proposed Indication

Natalie and Debi,

The Clinical team has reviewed your email and found your proposal (red letters) for the vandetanib's indication acceptable.
Please make the changes throughout the labeling where it is appropriate.

Lisa

From: Doman, Natalie [mailto:Natalie.Doman@astrazeneca.com]
Sent: Wednesday, February 23, 2011 11:56 AM
To: Skarupa, Lisa; Shiozawa, Debi N
Subject: NDA 22-405: Proposed Indication

Hi, Lisa:

Thank you for providing the FDA's proposed wording on the proposed vandetanib indication yesterday. We have the following comments for the Full Prescribing Information, Section 1 Indications and Usage.

It is AstraZeneca's position that the clinical data for vandetanib supports the indication AstraZeneca submitted on January 26, 2011 (Sequence 0046). That said, we accept FDA's position that the indication should include the modifiers "symptomatic or progressive" to further describe the patient population appropriate for vandetanib. However, we are concerned that the location of the words "symptomatic or progressive" in FDA's proposed version of the first sentence could be potentially confusing to prescribers. To make it clearer, we propose the following language: *Vandetanib is indicated for the treatment of symptomatic or progressive medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease.* The proposed rewording is intended simply to make it clear at what stage and in which patients vandetanib treatment is appropriate.

We believe the addition of "symptomatic or progressive" in the first sentence of the indication makes the second sentence, which was intended to clarify the indication and risks absent these terms, potentially confusing. To make it clearer that vandetanib should be used only with caution in patients who are asymptomatic or where the disease is indolent or slowly progressing, we propose revising that sentence to read: *Use of vandetanib in patients with indolent, asymptomatic or slowly progressing disease should be carefully considered because of the treatment related risks of vandetanib.*

Based on these changes, we propose the following as the full indication for vandetanib:

Vandetanib is indicated for the treatment of symptomatic or progressive medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease.

Use of vandetanib in patients with indolent, asymptomatic or slowly progressing disease should be carefully considered because of the treatment related risks of vandetanib.

AstraZeneca requests a teleconference with the Division as soon as possible.

Additionally, reference is made to the e-mail of February 18, 2011 where AstraZeneca sent questions for clarification on FDA's comments on labeling sections 2-16 (February 7, 2011). Feedback on these questions will enable us to finalize our comments and submit them for FDA review.

Regards,
Natalie

Natalie Doman
Associate Director
AstraZeneca
Research & Development | Regulatory Affairs
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T: +1 (302) 885 1441 F: +1 (302) 886 2822
natalie.doman@astrazeneca.com

From: Doman, Natalie [mailto:Natalie.Doman@astrazeneca.com]
Sent: Tuesday, February 22, 2011 2:32 PM
To: Skarupa, Lisa; Shiozawa, Debi N
Subject: RE: NDA 22405 Labeling Communications_Indications

Hi, Lisa:

Thanks for sending this. Would you please provide a list of FDA attendees from today's teleconference? I did not catch all of the names.

Thanks,
Natalie

Natalie Doman

Associate Director

AstraZeneca

Research & Development | Regulatory Affairs

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T: +1 (302) 885 1441 F: +1 (302) 886 2822

natalie.doman@astrazeneca.com

From: Skarupa, Lisa [mailto:Lisa.Skarupa@fda.hhs.gov]
Sent: Tuesday, February 22, 2011 1:13 PM
To: Shiozawa, Debi N
Cc: Doman, Natalie
Subject: RE: NDA 22405 Labeling Communications_Indications

Debi and Natalie,

I am thinking the indication was a word.doc problem as I attempted various ways of isolating just that section, and I believe it captured the original version somehow. So please disregard the prior email.

This is how the INDICATION on the labeling should be:

INDICATIONS AND USAGE-----

(b) (4)



Sincerely,
Lisa

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/s/

LISA M SKARUPA
02/23/2011

From: Shiozawa, Debi N [mailto:debi.shiozawa@astrazeneca.com]
Sent: Friday, February 18, 2011 12:57 PM
To: Skarupa, Lisa
Cc: Doman, Natalie
Subject: RE: NDA 22405 proposal for the carc PMR vandetanib

Lisa,

In response to FDA's comments on our proposal for the carcinogenicity PMR for vandetanib, please consider the following:

AstraZeneca appreciates the FDA's feedback on our carcinogenicity proposal and acknowledges the concern regarding the timing of the CAC interaction. Considering our recent experience regarding time requirements of TG sighting work from other projects, AstraZeneca now proposes that the vandetanib CAC interaction would occur by the end of 1st quarter 2012. Following formal agreement with CAC, and assuming no delay to the start of the studies (proposed final protocol submission by (b) (4) June 2012) we would anticipate the study report for the transgenic mouse study be submitted to FDA by (b) (4) December 2013, and the study report for the 2-year carcinogenicity study submitted to the FDA by (b) (4) (b) (4). AstraZeneca would like to confirm these milestone dates at the time of CAC, and if necessary agree modification to these date based on the CAC outcome.

We look forward to hearing your thoughts on this revised proposal.

Thank you,
Debi

Debra N. Shiozawa, Ph.D.

Regulatory Affairs Director
Office (302) 886-3137
debi.shiozawa@astrazeneca.com

From: Shiozawa, Debi N [mailto:debi.shiozawa@astrazeneca.com]
Sent: Friday, February 18, 2011 9:51 AM
To: Skarupa, Lisa
Cc: Doman, Natalie
Subject: RE: NDA 22-405: Agenda Items for Future Teleconferences

Lisa,

Thank you for providing the feedback on our carcinogenicity proposal.

I am currently discussing the FDA reviewer's concern on the timing of the CAC with our toxicologist and will respond as soon as possible after that.

Regards,
Debi

From: Skarupa, Lisa
Sent: Thursday, February 17, 2011 11:34 AM
To: 'Doman, Natalie'; Shiozawa, Debi N
Subject: NDA 22405 proposal for the carc PMR vandetanib

Hello Natalie and Debi,

Please see FDA response below regarding the proposal for the carcinogenicity PMR for vandetanib.

Your proposal to conduct a 2 year carcinogenicity study in the rat and a 6 month study in the transgenic (Tg.rasH2) mouse to fulfill the PMRs for carcinogenicity studies is acceptable. The proposed timeline for your submission of a carcinogenicity protocol for evaluation by the CAC, however, appears to be protracted. We request that your protocol be submitted for CAC evaluation by the end of 2011. Please adjust your proposed timeline to incorporate an earlier initiation of the studies or provide justification for the timeline proposed.

Lisa

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/s/

LISA M SKARUPA
02/22/2011



NDA 022405

**PROPRIETARY NAME REQUEST
WITHDRAWN**

iPR Pharmaceuticals, Inc
c/o: AstraZeneca Pharmaceuticals LP
1800 Concord Pike
PO Box 8355
Wilmington, Delaware 19803-8355

ATTENTION: Debra N. Shiozawa, Ph.D.
Director, Regulatory Affairs

Dear Dr. Shiozawa:

Please refer to your New Drug Application (NDA), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vandetanib Tablets, 100 mg and 300 mg.

We acknowledge receipt of your January 25, 2011, correspondence, on January 25, 2011, notifying us that you are withdrawing your request for a review of the proposed proprietary name (b) (4). This proposed proprietary name request is considered withdrawn as of January 25, 2011.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Sarah Simon, 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) 796-3994.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
02/09/2011

From: Skarupa, Lisa
Sent: Monday, February 07, 2011 9:06 PM
To: 'Doman, Natalie'; Shiozawa, Debi N; Lancaster, Cindy
Subject: FDA's proposed changes to labeling Feb 07 2011

Hello Natalie,
Please see attached sections (Section 2 through 16) on the labeling.

We will be discussing indication this week, so perhaps next week we will be ready for a TCON on indication.

If you have any questions, please do not hesitate to contact me.

Sincerely,
Lisa



NDA22405FDA'spro
posedchanges2....

{ATTACHMENT}

18 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
02/07/2011

From: Doman, Natalie [mailto:Natalie.Doman@astrazeneca.com]
Sent: Monday, February 07, 2011 12:07 PM
To: Skarupa, Lisa
Cc: Mesmer, Deborah; Lancaster, Cindy
Subject: RE: NDA 22405 vandetanib FDA responses to AstraZeneca's Questions

Hi, Lisa:

I'm writing to acknowledge that I received your response—thank you for sending it.

I would like to clarify our Question #3:

In places the Agency has used the term “safety database” and in other places the Agency has used the term “safety program overall”. Is there a difference in meaning between the two terms; if so, what is the difference? For example:

In section 6.1, page 10, first paragraph, last sentence (marked up version of the labeling provided 26 January), the Agency's statement reads,

- [REDACTED] (b) (4)

In section 6.1, page 10, second paragraph, last sentence (marked up version of the labeling provided 26 January), the Agency's statement reads,

- [REDACTED] (b) (4)

Second, I noted the statement in the “Additional Comments” section:

- “We will discuss your indication statement next week.”

Just to clarify, will you want to discuss the indication statement at a teleconference **this week** (week of February 7-11) or **next week** (week of February 14-18)?

Note that I have copied Cindy Lancaster on this e-mail, as she is covering for Debi Shiozawa this week.

Regards,
Natalie

Natalie Doman
Associate Director

AstraZeneca
Research & Development | Regulatory Affairs
C2B-705A, 1800 Concord Pike, PO Box 15437, Wilmington, DE, 19850-5437
T: +1 (302) 885 1441 F: +1 (302) 886 2822
natalie.doman@astrazeneca.com

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From: Skarupa, Lisa [mailto:Lisa.Skarupa@fda.hhs.gov]
Sent: Monday, February 07, 2011 10:03 AM
To: Doman, Natalie; Shiozawa, Debi N
Cc: Mesmer, Deborah
Subject: NDA 22405 vandetanib FDA responses to AstraZeneca's Questions

Hello Natalie,

Please see attached document which has FDA responses to your Questions you submitted in the January 26, 2011 cover letter.

Let me know if you have any questions.

Sincerely,
Lisa

[ATTACHMENT]

FDA response to question in 1-26-11 cover letter

Question 1 to FDA: Does the FDA agree that Bazett's correction is acceptable in the label?

FDA Comment: No. In referring to the FDA Guidance for Industry: E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs it is stated, "Bazett's correction is frequently used in clinical practice and in the medical literature. In general, however, Bazett's correction overcorrects at elevated heart rates and under corrects at heart rates below 60 beats per minute (bpm) and hence is not an ideal correction. Fridericia's correction is more accurate than Bazett's correction in subjects with such altered heart rates." In the FDA labeling changes to sections pertaining to QT prolongation, we utilized QTcF based on the above principles.

Question 2 to FDA: Please clarify if this statement is based on information submitted in the 4-month safety update?

FDA Response: Yes, this comment was based on the 2 patients who were reported to have died in the 4-month safety update. These patients were being treated in the open-label portion of the study as the deaths occurred after the original study cut-off. However, they were initially randomized to the vandetanib arm of the trial and died within 30 days of last dose. The two patients were E1101004 and E0011010.

Question 3 to FDA: Please clarify the differences, if any, between these safety databases.

FDA Response: We are unclear as to which section is being referred to in the above question.

Question 4 for FDA: Could FDA provide the data as a basis for this language?

FDA response: Please see the FDA's analysis as below:

The PK of vandetanib in the phase 1 dose escalation studies conducted in US and Australia (Study 01), Japanese (Study 43), and Chinese (Study 4) patients with solid tumors were evaluated using a non-compartmental analysis approach. Based on a cross-study comparison in a limited number of patients, Japanese and Chinese patients had on average exposures that were up to two-fold higher than other patients receiving the same dose, following single (Table 6) and multiple (Table 7) doses of vandetanib. In the pivotal trial, no conclusion could be reached on the effect of race on PK, as 95% of the patients were Caucasians.

Table 6. Single dose PK parameters following 300-mg dose of vandetanib in different studies.

	Study 1	Study 43	Study 4	Study 50
Study	Dose rising	Dose rising	Dose rising	PK/PD for permeability
Subjects	Malignant tumors	Malignant tumors	Malignant tumors	Colorectal cancer and liver metastases
Race	Caucasian 85.7% Black 6.5% Asian 2.6% Other 5.2%	Japanese	Chinese	Caucasian
Formulation	Phase I formulation	Phase I formulation	Commercial (100 mg X 3)	Commercial (300 mg x 1)
Sampling	dense	dense	dense	dense
Food intake	fast from midnight	feed (before breakfast)	no restriction	not shown
N	6-8	5-6	12	12
T _{max} (Median, (range)), h	7.5 (4-24)	5 (4-6)	8 (2-10)	4 (4 - 24)
C _{max} (Gmean) ng/mL (CV%)	213 (40.4)	392 (50.5)	330 (70.0)	269 (53.7)
T _{1/2} , h	109 ± 29.8 h	90.2 ± 13.7 h	—	—
AUC, ng·h/mL (CV%)	13929 ^a (98.84)	29400 ^b (40.1)	—	—
AUC _{0-24h} , ng·h/mL (CV%)	3019 (43.6)	5580 (44.4)	5643 (58.8)	4913 (55.5)

a: 50% of AUC was extrapolated; b: 40% of AUC was extrapolated;
—: values are not reported

Table 7. Multiple dose PK parameters in patients following 300-mg dose of vandetanib in different studies

	Study 1	Study 43	Study 4	Study 50
Race	Caucasian 85.7% Black 6.5% Asian 2.6% Other 5.2%	Japanese	Chinese	Caucasian
N	9-10 (Day 29)	3 (Day 29)	7 (Day 43)	7 (Day 56)
T _{max} (Median, range), h	5 (0-24)	6	4 (0-24)	4 (4 - 24)
C _{max} (Gmean), ng/mL (CV%)	919.8 (60.70)	1580 (19.1)	2024 (39.1)	853 (38.5)
T _{1/2} , day	—	—	7.6 ± 1.76 ^a	—
AUC _{0-24h} , ng·h/mL (CV%)	17926 (58.35)	29900 (15.4)	38611 (38.4)	18260 (41.4)
Accumulation	5 (3-10)	5.3 (4.1-6.5)	8.1	4.5 (3.2-8.4)

^adata from population PK analysis; —: values are not reported

Question 5 to FDA: In light of this clarification, does FDA still consider carcinogenicity studies as a required post-marketing requirement?

FDA Response: Yes. The post-marketing requirement for carcinogenicity studies is based on the indication and life expectancy of the patients that will be treated with vandetanib, not on the observation of masses/nodules observed in the 6-month rat toxicology study. Results of the clinical trial used to support marketing (Study 58) indicate that the median time of exposure to vandetanib was ~90 weeks suggesting that patients with medullary thyroid cancer will be exposed to the drug for relatively long periods of time. Additionally, the estimated time when 50% of the patients enrolled on the trial will have died is estimated to be over 5 years and signifies that at least 50% of the patients will be living 5 years after first being exposed to vandetanib. Carcinogenicity is a safety concern with chronic drug exposure, particularly for drugs in a pharmacologic class with previous demonstrations of carcinogenic potential. Vandetanib is a kinase inhibitor and other kinase inhibitors have demonstrated carcinogenicity in nonclinical carcinogenicity studies. Therefore, there is a concern that chronic exposure to vandetanib could cause additional cancers in patients with medullary thyroid cancer treated with the drug. To address this concern, a long-term

rodent carcinogenicity study in the rat and a rodent carcinogenicity study in the mouse are being required to assess the carcinogenic potential of vandetanib.

Question 6 to FDA: Please provide the number of patients at risk for the various time points for inclusion with the figure.

FDA Response: Objective response rate will be included in Section 14; however, as there was no pre-specified alpha spending, the p-value will not be included. (b) (4)

We have previously provided the PFS dataset from which the figure was obtained and the number of patients at risk for the various time points can be obtained from the dataset.

Question 7 to FDA: Please provide the dataset of this post-hoc subgroup analyses so that this plot can be accurately recreated for the label.

FDA Response: (b) (4)

A statement concerning PFS in the subgroup of symptomatic patients and those who progressed within 6 months prior to their enrollment will be included in labeling.

Additional Comments

Please focus your REMS on the risk of QT prolongation and sudden death. We will discuss your indication statement next week.

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/s/

LISA M SKARUPA
02/07/2011

MEMORANDUM

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

RESEARCH

MEETING DATE: January 21, 2011
TIME: 2:30 PM
LOCATION: WO 22 Room 4440
APPLICATION: NDA 022405
DRUG NAME: Vandetanib tablets 100 mg, 300 mg
TYPE OF MEETING: Proposed Primary Proprietary Name

MEETING CHAIR: Denise Baugh

MEETING RECORDER: Sarah Simon

FDA ATTENDEES:

Todd Bridges, R.Ph., Team Leader, DMEPA
Denise Baugh, PharmD, BCPS, Safety Evaluator, DMEPA
Colleen Brennan, R.Ph, Safety Evaluator, DMEPA
Sarah Simon, PharmD, Safety Regulatory Project Manager, OSE
Lisa Skarupa, RN, MSN, AOCN, Regulatory Project Manager, DDOP

EXTERNAL CONSTITUENT ATTENDEES:

Joseph Cordaro, PharmD, MBA: Executive Director, Development
Debi Shiozawa, Director, US Regulatory Affairs
Wendy White, Director, Global Regulatory Affairs
Jamie Blackport, Director, Global Marketing
Eric Vogel, Executive Director, Commercial
Sherry Rowell, Associate Director, Labeling, Regulatory Affairs

BACKGROUND:

FDA acknowledged a request for review of the proprietary name, (b) (4) which was submitted by AstraZeneca Pharmaceuticals (AZ) to the FDA on December 20, 2010.

MEETING OBJECTIVES:

The purpose of the call was to let AZ know that DMEPA has completed their review of the name, (b) (4) and finds it unacceptable because of this name's similarity to (b) (4).

DMEPA CONCERNS WITH THE PROPOSED NAME

DMEPA finds the name, [REDACTED]^{(b) (4)} unacceptable because of its orthographic or phonetic similarity to [REDACTED]^{(b) (4)} as well as overlapping product characteristics with all of the following products. The specific similarities are as follows:



Steps Forward

1. FDA explained the options for moving forward to AZ:
 - a. Wait for the official completed results of our review, with the OSE PDUFA due date of February 2, 2011, or
 - b. Withdraw the proprietary name, [REDACTED]^{(b) (4)} and resubmit a new proprietary name.

DISCUSSION

AZ confirmed that they will withdraw the proprietary name, (b) (4) within 1 week. They agreed to send an electronic copy directly to Sarah Simon and Lisa Skarupa as soon as possible and follow with a formal submission.

FDA explained that if AZ intends to have a proprietary name for this product, we recommend that the new request be submitted for a proposed proprietary name review as soon as possible. (See the draft Guidance for Industry, *Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm121568.htm> and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”).

DMEPA confirmed that no matter when the proprietary name is submitted, there will be a 90 day clock associated with the review. However, if AZ chooses to submit a name very soon, DMEPA will make every attempt to meet the OND PDUFA date of April 7, 2011.

DMEPA agreed to look at 2-3 proposed names prior to an official submission and give AZ initial feedback if the proposed names are submitted by AZ directly to Sarah Simon and Lisa Skarupa as soon as possible.

AZ inquired about the possibility of waiting to submit a new proposed proprietary name until after the OND PDUFA date of April 7th, 2011. Lisa Skarupa agreed to ask the appropriate parties within DDOP and OODP whether they would allow an action on the application without a proprietary name (ie- drug would go to market with established name only). Lisa confirmed that she could give AZ an answer by Monday, January 24th, 2011. AZ agreed to make a quick decision once they receive an answer from Lisa Skarupa regarding approval without an approved proprietary name.

Lisa Skarupa agreed to send DMEPA’s comment on the Package Insert to AZ on Monday, January 24th, 2011.

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/s/

SARAH J SIMON
01/24/2011

TODD D BRIDGES
01/24/2011



NDA 022405

PRE-APPROVAL REMS NOTIFICATION

iPR Pharmaceuticals, Inc,
c/o AstraZeneca Pharmaceuticals, LP
Attention: Debra N. Shiozawa, Ph.D.
Director, Regulatory Affairs
1800 Concord Pike, P.O. Box 8355
Wilmington, DE 19803-8355

Dear Dr. Shiozawa:

Please refer to your July 7, 2010, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for vandetanib tablets, 100 and 300 mg.

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)].

We acknowledge receipt of your proposed REMS, included in your submission dated December 22, 2010, which contains a Medication Guide, communication plan, and a timetable for submission of assessments of the REMS.

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for vandetanib to ensure the benefits of the drug outweigh the risks of QT prolongation and torsades de pointe.

Your revised proposed REMS must include the following:

Medication Guide: As one element of REMS, FDA may require the development of a Medication Guide, as provided for under 21 CFR 208. Pursuant to 21 CFR 208, FDA has determined that vandetanib poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of vandetanib. FDA has determined that vandetanib is a product for which patient labeling could help prevent serious adverse effects and that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use vandetanib, and that the drug is important to health and patient adherence to directions for use is crucial to the drug's effectiveness.

Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed vandetanib.

Communication Plan: We have determined that a communication plan targeted to healthcare providers who are likely to prescribe vandetanib will support implementation of the elements of your REMS for three years from the date of approval. The communication plan must provide for the dissemination of information about QT prolongation and torsades de pointes.

The communication plan must include, at minimum, the following:

1. A Dear Healthcare Provider Direct Mail communication that contains the FDA-approved labeling, and addresses the risks of QT prolongation and torsades de pointes. This should be sent within 60 days of approval of the REMS, or in conjunction with product launch, whichever is sooner, and annually for the next three years to all prescribers who are prescribing or likely to prescribe vandetanib.

(b) (4)

3. A plan for dissemination of the risk information and appropriate-use information in conjunction with professional societies and/or their associated medical journals to healthcare providers.

4. A description of the intended audience for the communication plan, stating specifically the types and specialties of healthcare providers to which the letters will be directed. This should be inclusive of prescribers who are likely to prescribe vandetanib.

5. All the above components of the communication plan as well as the professional labeling must be available via a REMS-specific link on the vandetanib website. The Medication Guide, the communication plan materials and the professional labeling must also be available via hardcopy from AstraZeneca sales specialists, through AstraZeneca's medical information department.

Elements to Assure Safe Use: We have determined that elements to assure safe use are necessary to mitigate serious risks listed in the labeling of the drug. In addition, we have determined that a Medication Guide and a Communication Plan are not sufficient to mitigate the serious risks. Your REMS must include tools to manage these risks, including at least the following:

- Healthcare providers who prescribe the drug are specially certified or trained [section 505-1(f)(3)(A)]
- Pharmacies, practitioners, or health care settings that dispense the drug are specially certified [section 505-1(f)(3)(B)]

Implementation System: The REMS must include an implementation system to monitor and evaluate the implementation of the elements to assure safe use (outlined above) that require pharmacies, practitioners, or health care settings that dispense the drug be

specially certified. Include an intervention plan to address any findings of non-compliance with the elements to assure safe use and to address any findings that suggest an increase in risk.

Timetable for Submission of Assessments: The proposed REMS must include a timetable for submission of assessments that shall be no less frequent than every six (6) months for the first year following the approval of vandetanib oral tablets, and annually thereafter. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

Your revised proposed REMS submission should include two parts: a “proposed REMS” and a “REMS supporting document.” Attached is a template for the proposed REMS that you should complete with concise, specific information pertinent to vandetanib (see Appendix A). Additionally, all relevant proposed REMS materials including: enrollment forms, educational, and communication materials should be appended to the proposed REMS. Once FDA finds the content acceptable and determines that the application can be approved, we will include these documents as an attachment to the approval letter that includes the REMS. The REMS, once approved, will create enforceable obligations.

The REMS supporting document should be a document explaining the rationale for each of the elements included in the proposed REMS (see Appendix B).

Before we can continue our evaluation of this NDA, you will need to submit the revised proposed REMS.

Under 21 CFR 208.24(d), you are responsible for ensuring that the label of each container or package includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and states how the Medication Guide is provided. You should submit marked up carton and container labels of all strengths and formulations with the required statement alerting the dispenser to provide the Medication Guide. We recommend one of the following statements, depending upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):

- “Dispense the enclosed Medication Guide to each patient.” or
- “Dispense the accompanying Medication Guide to each patient.”

For administrative purposes, designate all subsequent submissions related to the proposed REMS “**PROPOSED REMS-AMENDMENT for NDA022405.**” If you do not submit electronically, please send 5 copies of your REMS-related submissions.

NDA 022405

Page 4

If you have any questions, call Ms. Susan Jenney, Regulatory Project Manager, at (301) 796-0062.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURES:

REMS Appendices A and B

APPENDIX A

Application number **TRADE NAME (DRUG NAME)**

Class of Product as per label

Applicant name
Address
Contact Information

PROPOSED RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL(S):

List the goals and objectives of the REMS.

II. REMS ELEMENTS:

A. Medication Guide or PPI

A Medication Guide will be dispensed with each [drug name] prescription. [Describe in detail how you will comply with 21 CFR 208.24.]

B. Communication Plan

[Applicant] will implement a communication plan to healthcare providers to support implementation of this REMS.

List elements of communication plan. Append the printed material and web shots to the REMS Document.

C. Elements To Assure Safe Use

List elements to assure safe use included in this REMS. Elements to assure safe use may, to mitigate a specific serious risk listed in the labeling, require that:

A. Healthcare providers who prescribe [drug name] have particular training or experience, or are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS;

B. Pharmacies, practitioners, or healthcare settings that dispense [drug name] are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS ;

C. [Drug name] may be dispensed to patients only in certain healthcare settings (e.g., hospitals);

- D. [Drug name] may be dispensed to patients with documentation of safe-use conditions;
- E. Each patient using [drug name] is subject to certain monitoring. Append specified procedures to the REMS; or
- F. Each patient using [drug name] be enrolled in a registry. Append any enrollment forms and other related materials to the REMS Document.

D. Implementation System

Describe the implementation system to monitor and evaluate implementation for, and work to improve implementation of, Elements to Assure Safe Use (B),(C), and (D), listed above.

E. Timetable for Submission of Assessments

Specify the timetable for submission of assessments of the REMS. The timetable for submission of assessments at a minimum must include an assessment by 18 months, 3 years, and in the 7th year after the REMS is initially approved, with dates for additional assessments if more frequent assessments are necessary to ensure that the benefits of the drug continue to outweigh the risks.

APPENDIX B: SUPPORTING DOCUMENT

This REMS Supporting Document should include the following listed sections 1 through 6. If you are not proposing to include one of the listed elements, the REMS Supporting Document should simply state that the element is not necessary. Include in section 4 the reason you believe each of the potential elements you are proposing to include in the REMS is necessary to ensure that the benefits of the drug outweigh the risks.

1. Table of Contents
2. Background
3. Goals
4. Supporting Information on Proposed REMS Elements
 - a. Additional Potential Elements
 - i. Medication Guide
 - ii. Patient Package Insert
 - iii. Communication Plan
 - b. Elements to Assure Safe Use, including a statement of how the elements to assure safe use will mitigate the observed safety risk
 - c. Implementation System
 - d. Timetable for Submission of Assessments of the REMS (for products approved under and NDA or BLA)
5. REMS Assessment Plan (for products approved under a NDA or BLA)
6. Other Relevant Information

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/s/

ROBERT L JUSTICE
01/21/2011

From: Skarupa, Lisa
Sent: Monday, January 10, 2011 12:25 PM
To: 'Doman, Natalie'; Shiozawa, Debi N
Subject: NDA 22405 vandetanib DMEPA containers IR

Dear Natalie,

Regarding the question on whether you can send another proposed proprietary name before February 1, 2011 end of (b) (4) review, it will not be reviewed while (b) (4) is being reviewed. On the other hand, if you wish to no longer pursue the name (b) (4), you can submit a request to withdraw and then submit a different tradename for review. This will start another 90 day review clock.

It is noted that you submitted an "amendment to proprietary review name", however the contents were revisions to container labeling in response to ONDQA comments. Please see comments from DMEPA in response to your 21December 2010 dated letter.

A. General Comments

We note that carton labeling was not included in the submission. However, if you plan to market this product with carton labeling, then we request you submit this labeling as soon as possible.

B. Container Labels

1. The established name is presented (b) (4)

2. We note that the container labels for both strengths utilize the same color scheme (b) (4)

3. The 30 tablet bottle size is considered a 'unit-of-use' package. Since these can be dispensed directly to patients, please ensure these bottles have a child protective cap.

4. The dosage form (tablets) is not stated following the established name. Please add this information.

Sincerely,
Lisa

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/s/

LISA M SKARUPA
01/10/2011



NDA 022405

**REVIEW EXTENSION –
MAJOR AMENDMENT**

iPR Pharmaceuticals, Inc.
AstraZeneca Pharmaceuticals LP, Authorized US Agent
Attention: Debra N. Shiozawa, Ph.D.
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

Dear Dr. Shiozawa:

Please refer to your July 7, 2010 New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zictifa™ (vandetanib) Tablets, 100 mg and 300 mg.

On December 22, 2010, we received your December 22, 2010, submission of your REMS solicited major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is April 7, 2011.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with “PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012.” If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by March 10, 2011.

If you have any questions, call Amy Tilley, Regulatory Project Manager, at 301-796-3994.

Sincerely,

{See appended electronic signature page}

Amy R. Tilley
Regulatory Health Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

AMY R TILLEY
12/23/2010

NOV-DEC, 2010 INFORMATION REQUESTS
NDA 022405 vandetanib

Date of Information Request	AstraZeneca's response (DARRTS SDN)
December 2, 2010 Clinical	SDN 39 (December 7, 2010)
NOVEMBER 24 th Clinical	SDN 37 (November 30, 2010)
NOVEMBER 15 th Clinical	SDN 34 (November 17, 2010)
NOVEMBER 5 th Clinical	SDN 31 (November 10, 2010)
NOVEMBER 3rd Clinical	SDN 30 (November 10, 2010)
NOVEMBER 3rd Clinical	SDN 29 (November 9, 2010)

Skarupa, Lisa

From: Skarupa, Lisa
Date: Thursday, December 02, 2010 3:04 PM
To: Doman, Natalie; 'Shiozawa, Debi N'
Subject: NDA 22405 vandetanib 12/2/10 Clinical IR

Dear Natalie and Debi,

On 11-17-10, sequence 35, you sent a revised AE dataset for the vandetanib 300 mg monotherapy program, R_AEFDA2. Selecting ACTARM = gefitinib 250 mg/vandetanib 300 mg, placebo, vandetanib 300 mg, vandetanib 300 mg/gefitinib 250 mg, and vandetanib 300 mg, there are 1769 patients in the dataset. However, your reports state that 1839 patients have received 300 mg vandetanib. Please explain.

Thank you
Lisa

Skarupa, Lisa

From: Tilley, Amy
Sent: Wednesday, November 24, 2010 12:37 PM
To: 'Shiozawa, Debi N'
Cc: Skarupa, Lisa; Doman, Natalie
Subject: RE: NDA 22405 Vandetanib - Clinical Information Request

Thank you, we look forward to receiving your response by 12-1-10.

Have a nice Thanksgiving!

Amy

From: Shiozawa, Debi N [mailto:debi.shiozawa@astrazeneca.com]
Sent: Wednesday, November 24, 2010 12:34 PM
To: Tilley, Amy
Cc: Skarupa, Lisa; Doman, Natalie
Subject: RE: NDA 22405 Vandetanib - Clinical Information Request

Amy,

Thank you for the information request – I will be passing to the team for consideration.

Regards,
Debi

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From: Tilley, Amy [mailto:AMY.TILLEY@fda.hhs.gov]
Sent: Wednesday, November 24, 2010 12:30 PM
To: Doman, Natalie
Cc: Skarupa, Lisa
Subject: NDA 22405 Vandetanib - Clinical Information Request
Importance: High

Natalie,

Below is an Information Request from the Clinical Reviewer.

Please provide additional clinical information regarding the 2 patients in study 44 who developed grade 4 drug hypersensitivity: patient E5013001 and E5013002. Please

Reference ID: 2876310

12/12/2010

include written patient narratives if available.

The Clinical Reviewer requests your response no later than December 1, 2010.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Drug Oncology Products,
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



consider the environment before printing this e-mail

Skarupa, Lisa

From: Skarupa, Lisa
At: Monday, November 15, 2010 12:43 PM
To: 'Doman, Natalie'; Shiozawa, Debi N
Subject: NDA 22405 vandetanib Clinical IR November 15

Dear Natalie and Debi,

Here is a Clinical IR, please respond by tomorrow EDT noon.

The R_AEFDA dataset is not usable and was sent without adequate instructions.

1. We note that you have included several variables such as AEANFL, SAFETY, SAFETY2, SAFETY3, TRTP, and TRTP2. Are these variables to be used in selecting patients? From the define.pdf, it appears that only AEANFL should be used. We understood that this dataset would contain only patients who received vandetanib and that it would not be necessary to use such variables. For example, patients in study 3 were randomized to vandetanib followed by gefitinib or gefitinib followed by vandetanib. In the previous dataset, it was necessary to isolate the AEs which occurred while the pt was receiving vandetanib using data contained in another dataset. We understood that this dataset would contain only AEs which occurred while the pt was on vandetanib. Please clarify this point and provide instructions for the use of this dataset.

2. The R_AEFDA dataset does not contain complete coding for AESER (AE Serious Y/N), CTC (CTC Grade), and ACTARM (treatment arm). Please ensure that information is included for each AE. If you are unable to do so, please provide an explanation.

3. The R_AEFDA dataset does not provide results which are consistent with the tables provided in sequence 26, submitted 10-27-10. For example, the tables contained in sequence 26 state that in the vandetanib 300 mg monotherapy program there have been **79 deaths**, **553 patients with a SAE**, and **253 patients with an AE leading to discontinuation**.

Deaths

Using the R_AEFDA dataset and selecting ACTARM = Gefitinib 250 mg/Vandetanib 300 mg, Placebo, Vandetanib 300 mg, Vandetanib 300 mg/Gefitinib 250 mg, and Vandetanib 300 mg and then CTC = 5 without additional variables, there are **69 deaths**. If AEANFL = ANALYSIS is used, this number is **66**. If this is done without first selecting the vandetanib 300 mg monotherapy program (ACTARM = all), then there are **71 deaths**.

SAEs

Using the R_AEFDA dataset and selecting ACTARM = Gefitinib 250 mg/Vandetanib 300 mg, Placebo, Vandetanib 300 mg, Vandetanib 300 mg/Gefitinib 250 mg, and Vandetanib 300 mg and then AESET = Y without additional variables, there are **559 SAEs**. If AEANFL = ANALYSIS is used, this number is **551**. Using ACTARM = all, there are 628 SAEs. If AEANFL = ANALYSIS is used, this number is **615**.

Lisa

Skarupa, Lisa

From: Skarupa, Lisa
Sent: Friday, November 05, 2010 8:23 PM
To: 'Doman, Natalie'
Subject: RE: NDA 22405 Clinical IR Nov 5 2010

thank you

From: Doman, Natalie [mailto:Natalie.Doman@astrazeneca.com]
Sent: Friday, November 05, 2010 5:31 PM
To: Skarupa, Lisa
Subject: RE: NDA 22405 Clinical IR Nov 5 2010

Good afternoon, Lisa:

I confirm that I received this IR, and I have passed it along to the team for discussion. I'll be in touch regarding the requested time period early next week, after I speak with the team.

Have a great weekend,
Natalie

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From: Skarupa, Lisa [mailto:Lisa.Skarupa@fda.hhs.gov]
Sent: Friday, November 05, 2010 3:28 PM
To: Doman, Natalie; Shiozawa, Debi N
Subject: NDA 22405 Clinical IR Nov 5 2010

Good afternoon,

Please see the following Clinical I.R.:

We are concerned that the prolonged half-life of vandetanib may make the treatment of patients with marked prolongations in their QTc interval difficult. Please develop a plan to assess the ability to remove vandetanib, through hemodialysis, etc., from the patient's circulation. Please provide a timeline for development and completion of this plan (in vitro, in vivo, or patient testing, as needed) within 2 weeks.

Please verify you received this I.R. and agree to the requested time period.

Sincerely,
Lisa

Skarupa, Lisa

From: Skarupa, Lisa
Sent: Wednesday, November 03, 2010 4:32 PM
To: 'Doman, Natalie'
Cc: Shiozawa, Debi N
Subject: RE: NDA 22405 Clinical IR Nov 3

I will find out.

From: Doman, Natalie [mailto:Natalie.Doman@astrazeneca.com]
Sent: Wednesday, November 03, 2010 4:31 PM
To: Skarupa, Lisa
Cc: Shiozawa, Debi N
Subject: RE: NDA 22405 Clinical IR Nov 3

Hi, Lisa:

I have forwarded your request to my colleagues for resolution. My team has a clarifying question:

Please state the extent of incorrect dosing for patient 58/E2802012. This should include an explanation of why the incorrect product was administered.

Is this a typographical error? We don't see a patient E2802012 in study 58.

Thanks for your help,
 Natalie

Confidentiality Notice: This message is private and may contain confidential and proprietary information. If you have received this message in error, please notify us and remove it from your system and note that you must not copy, distribute or take any action in reliance on it. Any unauthorized use or disclosure of the contents of this message is not permitted and may be unlawful.

From: Skarupa, Lisa [mailto:Lisa.Skarupa@fda.hhs.gov]
Sent: Wednesday, November 03, 2010 1:23 PM
To: Doman, Natalie; Shiozawa, Debi N
Subject: NDA 22405 Clinical IR Nov 3

Dear Natalie and Debi,

An attachment is added with this I.R.

NDA 22-405
 Information Request 11-3-10

1. Despite your most recent communication, we are unable to work with the R-AE dataset contained in Module 5.3.5.3.25.3.1 of Amendment 0 (submitted 7-7-10). Please provide a revised dataset containing only the following information within 1 week of receipt of this information request.
 - a. Please include only adverse events which occurred while the patient was receiving vandetanib. For example, adverse events for Study 3 would include only the events which occurred while a patient was on vandetanib. That is, prior to the switch from vandetanib to gefitinib or after the switch from gefitinib to vandetanib.
 - b. If you wish, AEs which occurred prior to dosing may be included in this dataset. If so, please include a variable such as AESTFL or TEAE Y/N that would allow us to differentiate AEs on study and pre-dose.
 - c. Please include information on the dose of vandetanib administered to the patient as in the variable

Reference ID: 2876310

12/12/2010

ACTARM.

- d. Please include USUBJID, AEACN, AESER, AETERM, AEDECOD, AEBODSYS, AESTDY, AEOUT, AGEGRP, RACE, and SEX.
- e. Please also include the AE duration in the dataset, either as a derived variable or with the AE start and end date.
- f. Please include, as a separate row, each time the AE is reported and the AE grade reported.

2. Please provide, within 1 week, detailed instructions on how to use the R_LB datasets in Study 58.

Please provide a timeline by 11-4-10 for submission of your responses to the following additional items.

We noted that patient 58/E2005007 reported ongoing, grade 2 unilateral blindness. Please provide a narrative which includes information on the patient's degree of impairment and the suspected cause of their unilateral blindness.

Please clearly state whether a change in visual acuity was seen in patients with vortex keratopathy. If so, please state the degree of change.

Please state the extent of incorrect dosing for patient 58/E2802012. This should include an explanation of why the incorrect product was administered.

We have conducted an analysis of the primary endpoint using censoring criteria for:

- a. No measurable disease at baseline
- b. Radiation during randomized treatment
- c. Patients with premature discontinuation of randomized therapy based on investigator's assessment of progression.

With these criteria, we have calculated different PFS variables and censoring variables than what you have submitted on 10/26/10 which are highlighted in the enclosed XLS file. A summary of our analysis is as follows:

This primary analysis of progression free survival is shown in the table below. This analysis censors the following patients:

- 51 patients with investigator-determined, but without IRC-determined progression leading to early discontinuation of study drug. These patients were censored the last RECIST assessment prior to discontinuation of study drug;
- 6 patients who received radiation during the study period. These patients were censored at the last RECIST assessment prior to radiation therapy; and
- 32 patients who had no measurable disease by the IRC at baseline. These patients were censored at day 1.*

* - Patients who fit more than one category of censoring were censored at the earliest time point.

Progression Free Survival	Vandetanib N = 231	Placebo N = 100
Number of Events	59 (25.5%)	41 (41.0%)
Censored	172	59
Median PFS	NE	19.7 months (16.3, NE)
Hazard Ratio		0.35
p-value (logrank test)		0.0001

The following patients were flagged as having RECIST progression according to site-read but not central read (REPRTYPE = RECIST progression; REPRGDTC has a date), but they were not taken off of randomized therapy (RFEN1DTC has no date). Please confirm these findings and explain why randomized study drug was not discontinued and the patient was not switched to open label therapy.

E0008004
E1101004
E1701007
E1703012
E2102001
E2801001

E2801023

E2801031

E2802005

The following patients are reported to have died due to cardiopulmonary arrest; yet no adverse events are listed in the AE dataset. Please comment.

D4200C00036/E0052001

D4200C00036/E0091007

D4200C00036/E0091021

D4200C00036/E0091030

OCTOBER, 2010 INFORMATION REQUESTS
NDA 022405 vandetanib

Date of Information Request	AstraZeneca's response (DARRTS SDN)
October 25 th Clinical	SDN 26 (October 27, 2010)
October 19 Clinical & Stats	SDN 25 (October 22, 2010)
October 12 Clinical	SDN 23 (October 19, 2010)
October 5th Clinical & Stats	SDN 22 (October 18, 2010)
October 5th Clinical & Stats	SDN 20 (October 8, 2010)
October 5th Clinical & Stats	SDN 20 (October 8, 2010)

Skarupa, Lisa

From: Skarupa, Lisa
Sent: Tuesday, October 26, 2010 1:43 PM
To: 'Doman, Natalie'
Cc: Shiozawa, Debi N
Subject: RE: NDA 22-405: Response to Information Request 26 October 2010

Thank you everyone, it has been forwarded to the reviewers.

From: Doman, Natalie [mailto:Natalie.Doman@astrazeneca.com]
Sent: Tuesday, October 26, 2010 1:39 PM
To: Skarupa, Lisa
Cc: Shiozawa, Debi N
Subject: NDA 22-405: Response to Information Request 26 October 2010

Dear Lisa:

Please find attached the efficacy dataset information you requested during today's teleconference and via IR:

"Please provide a new dataset with the same variables that is included in the information request response on October 22 2010. In this dataset please include the PFS variable and Censoring variable used to calculate the FDA primary analysis results."

An updated transport file and define file are provided. Two new variables, PFS time variable and FDA censoring variable (pfs1 and pfs1cens1) have been added.

Regards,
Natalie

Natalie Doman
Associate Director

AstraZeneca Pharmaceuticals LP
Research and Development, Regulatory Affairs
C2B-705A, 1800 Concord Pike, PO Box 15437, Wilmington, DE, 19850-5437
Tel +1 302 885 1441 Fax +1 302 886 2822
natalie.doman@astrazeneca.com

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Skarupa, Lisa

From: Skarupa, Lisa
It: Monday, October 25, 2010 10:00 AM
to: 'Doman, Natalie'; Shiozawa, Debi N
Subject: NDA 22405 still clarifications on recreating dataset IR. October 25 2010

Good morning,
This is regarding Dr. Maher's recreating datasets:

I have used the following instructions to isolate the vandetanib 300 mg population.

There are 11 studies included in the safety pool (TVE1511, 1, 2, 3, 7a, 8, 39, 50, 44, 57, 58). Due to the design of 2 of the studies (3 and 58) they are programmed differently to the remaining 9 as explained below:

For studies (TVE1511, 1, 2, 7a, 8, 39, 50, 44, 57) apply the following subsetting:

safety='Y' and actarm ne ' ' and aeterm ne ' ' and upcase(aeanfl) eq 'ANALYSIS'

For study 3 patients were randomized to either Gefitinib or vandetanib in part A and on progression could switch over to the other treatment in part B. So patients who received vandetanib in either part of the study need to be included in the AE counts.

To do this

- select all AEs for patient who were randomized to Vandetanib in part A include all AEs irrespective of whether they switched to Gefitinib.
- For patients who were randomized to Gefitinib in part A and switched to Vandetanib in part B include only AEs from the time of switching.
- Then apply the following:

o safety='Y' and actarm ne ' ' and aeterm ne ' ' and upcase(aeanfl) eq 'ANALYSIS'

For study 58 this has a randomized and open label phase and all AE are included across the 2 treatment periods where a patient has taken at least one dose of vandetanib. Apply the following subsetting:

Safety3='Y' and actarm ne ' '

After making 3 datasets, I put these back together and selected AEEVNT5 = Y. When I do this I get 433 patients, all from studies 44, 57, and 58. It seemed unlikely that SAEs only occurred on these 3 studies. Table 2.7.4.2.1.3.2 in ISS Tables in Module 5.3.5.3.28 states that 453 pts had a SAE.

By COB, please either send an e-mail explaining how to do this analysis or set up a tcon to go over it step by step.

Skarupa, Lisa

From: Skarupa, Lisa
Sent: Friday, October 22, 2010 5:38 PM
To: 'Doman, Natalie'; Shiozawa, Debi N
Subject: RE: NDA 22405 ODAC to the morning

thank you.

From: Doman, Natalie [mailto:Natalie.Doman@astrazeneca.com]
Sent: Friday, October 22, 2010 5:35 PM
To: Skarupa, Lisa; Shiozawa, Debi N
Subject: RE: NDA 22405 ODAC to the morning

Hi, Lisa:

It's fine to move us to the morning session.

Thanks,
Natalie

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From: Skarupa, Lisa [mailto:Lisa.Skarupa@fda.hhs.gov]
Sent: Friday, October 22, 2010 3:44 PM
To: Doman, Natalie; Shiozawa, Debi N
Subject: NDA 22405 ODAC to the morning

Dear Natalie,

We would like to change the schedule for ODAC meeting Dec 2nd to the morning session (8am to 12noon) instead of the PM session.

We need a reply back ASAP (if you can reply today, please do so) - yes/no.

Sincerely,
Lisa

Skarupa, Lisa

From: Skarupa, Lisa
it: Thursday, October 21, 2010 1:11 PM
to: 'Doman, Natalie'; 'Shiozawa, Debi N'
Subject: RE: NDA 22405 Clinical IR Oct21 second IR today

Dear Natalie and Debi,

Please see our SECOND I.R. for today:

Please describe in detail the methods you used to determine the number of patients who experienced an AEs, SAEs, discontinuation of IP, or death in the R_AE database found in module 5.3.5.3.25.3.1. I have tried to use AEEVNT5 and AEEVNT1 and have been unable to reproduce your results.

Please again describe in detail the method you used to obtain the median duration of dose interruption in Study 58.

Please respond by COB 10-22-10.

From: Skarupa, Lisa
Sent: Thursday, October 21, 2010 9:46 AM
To: 'Doman, Natalie'; Shiozawa, Debi N
Subject: NDA 22405 Clinical IR Oct21

Good morning,

Here is another question from Dr. Maher to extend the discussion from yesterday's tcon:

In our 10-20-10 discussion of the R_AE dataset contained in module 5.3.5.3.25.3.1, it was noted that the number of patient deaths could be calculated from the variable AEEVNT10, but not from the variable CTCGMAX = 5. It was also noted that a lower number of deaths was obtained by using CTCGMAX = 5. Please explain this.

Thank you
Lisa

Skarupa, Lisa

From: Skarupa, Lisa
It: Thursday, October 21, 2010 9:46 AM
to: 'Doman, Natalie'; Shiozawa, Debi N
Subject: NDA 22405 Clinical IR Oct21

Good morning,

Here is another question from Dr. Maher to extend the discussion from yesterday's tcon:

In our 10-20-10 discussion of the R_AE dataset contained in module 5.3.5.3.25.3.1, it was noted that the number of patient deaths could be calculated from the variable AEEVNT10, but not from the variable CTCGMAX = 5. It was also noted that a lower number of deaths was obtained by using CTCGMAX = 5. Please explain this.

Thank you
Lisa

Skarupa, Lisa

From: Skarupa, Lisa
At: Tuesday, October 19, 2010 12:58 PM
To: 'Doman, Natalie'; Shiozawa, Debi N
Subject: NDA 22405 ClinicalStats IR Oct192010

Good afternoon,

**Based on the last two submissions to NDA 22405 as responses to our requests, we have this request below.
Sincerely, Lisa**

For the primary PFS analysis, we plan on censoring patients for the following:

- 1) Patients who had progression by site-read and had randomized treatment discontinued before documented progression by central read - patients will be censored at the last RECIST assessment prior to discontinuation.
- 2) Patients who had radiation treatment during randomized treatment - patients will be censored at the last RECIST assessment prior to radiation therapy.

We ask that you adjust your PFS dates based on the criteria above and perform PFS analysis accordingly.

For the secondary endpoint of overall response rate, we ask that you do not count responses which occurred while on open-label therapy.

Please create one single efficacy dataset with single record per patient. The dataset should include the following variables:

Subject ID
ARM
Age
Gender
Start date of therapy
End date of randomized therapy
Date of randomization
Date of Progression - by Central Review
Date of Progression - by Site Read
Date of Death
PFS Time
PFS Censoring Status
Prior Systemic therapy (Y/N) - should include chemotherapy/targeted therapy/and other investigational agents
Date of Diagnosis
Date of last documented progression
CTN doubling time
CEA doubling time
Hereditary v. Sporadic
Any Radiation Treatment during randomized treatment period
Date of radiation treatment during randomized treatment period
Hypointense lesions appearing in 1st 2 RECIST assessments
Calcification presence
PFS without hypointense adjustments (PGHPSTDY)
PFS Censoring status without hypointense adjustments (PGHPCENS)
PFS without calcification adjustments (PRGCSTDY)
PFS Censoring status without calcification adjustments (PRGCSTDY)
Patient went on to receive open label therapy (Y/N)
OS Time
OS Censoring status
Best response by central read
Duration of response

Skarupa, Lisa

From: Skarupa, Lisa
Sent: Monday, October 18, 2010 3:15 PM
To: 'Doman, Natalie'; Shiozawa, Debi N
Subject: RE: Request to meeting with clinical team and dataset team

The clinical team did not have specific questions, just the area of interest:

Calculating the median duration of exposure, including dose interruptions.

Using the AE dataset from the analyses of more than 1 study.

Just so not everyone is called, perhaps clinical and stats/dataset folks.

Lisa

From: Doman, Natalie [mailto:Natalie.Doman@astrazeneca.com]
Sent: Monday, October 18, 2010 3:08 PM
To: Skarupa, Lisa; Shiozawa, Debi N
Subject: RE: Request to meeting with clinical team and dataset team

Hi, Lisa:

I will contact my team. Has the review team given any indication of the types of questions they have, so we can have the appropriate attendees present (e.g., medical, safety, statistics, programming, others)?

Many thanks,
Natalie

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From: Skarupa, Lisa [mailto:Lisa.Skarupa@fda.hhs.gov]
Sent: Monday, October 18, 2010 2:40 PM
To: Doman, Natalie; Shiozawa, Debi N
Subject: Request to meeting with clinical team and dataset team

Good afternoon,

The clinical review team would like to have a teleconference to review dataset?
The only option I have is Oct 20th Wed 330pm to 4pm

Skarupa, Lisa

From: Skarupa, Lisa
Date: Tuesday, October 12, 2010 4:00 PM
To: Doman, Natalie
Cc: 'Shiozawa, Debi N'
Subject: Clinical IR Oct 12 2010

Good afternoon,

Please note a new Clinical Information Request:

Provide detailed information concerning the dataset and method you used to derive the median duration of actual exposure and the median duration of dose interruptions.

Sincerely,
Lisa

Skarupa, Lisa

From: Skarupa, Lisa
Sent: Thursday, October 14, 2010 3:17 PM
To: Doman, Natalie
Cc: 'Shiozawa, Debi N'
Subject: RE: NDA 22405 Information Request ClinStats Oct 5, 2010

Good afternoon,
Based on the telephone conversation today, the response to Question #1 will be by Oct 19th.
Just want to be sure if there is anyway it can be before Oct 19th, is that still a possibility?

Lisa

From: Doman, Natalie [mailto:Natalie.Doman@astrazeneca.com]
Sent: Friday, October 08, 2010 12:16 PM
To: Skarupa, Lisa; Shiozawa, Debi N
Subject: RE: NDA 22405 Information Request ClinStats Oct 5, 2010

Hi, Lisa:

Our response to Question 2 was submitted through the Gateway today. Response to Question 1 to follow, on or before 19 October.

Thanks,
Natalie

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From: Skarupa, Lisa [mailto:Lisa.Skarupa@fda.hhs.gov]
Sent: Tuesday, October 05, 2010 2:51 PM
To: Doman, Natalie; Shiozawa, Debi N
Subject: NDA 22405 Information Request ClinStats Oct 5, 2010

Dear Natalie and Debi,

We are considering a REM strategy to address the prolonged QT interval seen with vandetanib. We will have further guidance for you the week of October 18th or 25th.

At this time, I have an Information Request from our Clinical-Stats Review Team:

1. We are asking that you submit the following items for Study 58 as soon as possible but no later than October 19, 2010.

- a. More detailed description of each dataset. The description of a dataset should allow the reviewers

to understand its role. Avoid anything that is vague. For example, the present description of the dataset RECLANA as “RECLANA Reporting Dataset” is not informative at all. It does not allow one to understand how it is different from other reporting datasets.

- b. More detailed description of the variables than the mostly sketchy and vague descriptions provided in the define.pdf file. The description should allow the reviewers to distinguish between similar variables and understand their roles. Remember that the reviewers have not created the datasets and define.pdf is the only way to know what each variable means. For example, 4 variables (AEEVNT01, FULL, SAFETY, and TRTP) appear to identify the randomized population in the R_AE dataset, but actually identify different numbers of adverse events.
 - c. Some of the variable labels are misleading. For example PFS variables are labeled as progression variables, although PFS is not just progression, they include deaths as well. Please make sure that the description of the variable is stated correctly in the Comments column of the define.pdf file.
 - d. For each data file, indicate the primary and secondary keys.
 - e. For each table in the study report, a list of variables that were used to generate the table and the SAS program that generated the table.
 - f. There should be a navigational aid for the folder containing all SAS programs. A document should list each SAS program submitted and what it does.
2. We could not verify the hazard ratio reported by you for the primary analysis of the endpoint PFS. Provide the variable names and the program used to derive it.

For any future submission, make sure that the datasets are well-documented. In addition follow the following rules.

- a. Do not use hyphen (-) in any dataset names, rather use underscore (_).
- b. When you create the SAS transport files, use the same name for the dataset and the xpt file that contains the dataset.

If you have any further questions, please do not hesitate to contact me.

Sincerely,
Lisa

Skarupa, Lisa

From: Skarupa, Lisa
Sent: Friday, October 08, 2010 12:34 PM
To: 'Doman, Natalie'
Subject: RE: NDA 22405 Information Request ClinStats Oct 5, 2010

thank you, forwarded to reviewers

From: Doman, Natalie [mailto:Natalie.Doman@astrazeneca.com]
Sent: Friday, October 08, 2010 12:16 PM
To: Skarupa, Lisa; Shiozawa, Debi N
Subject: RE: NDA 22405 Information Request ClinStats Oct 5, 2010

Hi, Lisa:

Our response to Question 2 was submitted through the Gateway today. Response to Question 1 to follow, on or before 19 October.

Thanks,
Natalie

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From: Skarupa, Lisa [mailto:Lisa.Skarupa@fda.hhs.gov]
Sent: Tuesday, October 05, 2010 2:51 PM
To: Doman, Natalie; Shiozawa, Debi N
Subject: NDA 22405 Information Request ClinStats Oct 5, 2010

Dear Natalie and Debi,

We are considering a REM strategy to address the prolonged QT interval seen with vandetanib. We will have further guidance for you the week of October 18th or 25th.

At this time, I have an Information Request from our Clinical-Stats Review Team:

1. We are asking that you submit the following items for Study 58 as soon as possible but no later than October 19, 2010.

- a. More detailed description of each dataset. The description of a dataset should allow the reviewers to understand its role. Avoid anything that is vague. For example, the present description of the dataset RECLANA as "RECLANA Reporting Dataset" is not informative at all. It does not allow one to understand how it is different from other reporting datasets.
- b. More detailed description of the variables than the mostly sketchy and vague descriptions provided in the define.pdf file. The description should allow the reviewers to distinguish between similar variables and understand their roles. Remember that the reviewers have not created the

Reference ID: 2876310

12/12/2010

datasets and define.pdf is the only way to know what each variable means. For example, 4 variables (AEEVNT01, FULL, SAFETY, and TRTP) appear to identify the randomized population in the R_AE dataset, but actually identify different numbers of adverse events.

- c. Some of the variable labels are misleading. For example PFS variables are labeled as progression variables, although PFS is not just progression, they include deaths as well. Please make sure that the description of the variable is stated correctly in the Comments column of the define.pdf file.
 - d. For each data file, indicate the primary and secondary keys.
 - e. For each table in the study report, a list of variables that were used to generate the table and the SAS program that generated the table.
 - f. There should be a navigational aid for the folder containing all SAS programs. A document should list each SAS program submitted and what it does.
2. We could not verify the hazard ratio reported by you for the primary analysis of the endpoint PFS. Provide the variable names and the program used to derive it.

For any future submission, make sure that the datasets are well-documented. In addition follow the following rules.

- a. Do not use hyphen (-) in any dataset names, rather use underscore (_).
- b. When you create the SAS transport files, use the same name for the dataset and the xpt file that contains the dataset.

If you have any further questions, please do not hesitate to contact me.

Sincerely,
Lisa

SEPTEMBER, 2010 INFORMATION REQUESTS
NDA 022405 vandetanib

Date of Information Request	AstraZeneca's response (DARRTS SDN)
September 16 th Clinical	SDN 19 (September 29, 2010)
September 2nd Clinical	SDN 17 (September 17, 2010)
September 8th Clinical	SDN 16 (September 13, 2010)
September 3rd Clinical Pharm	SDN 15 (September 10, 2010)
September 8 th Clinical Pharm	SDN 14 (September 09, 2010)

Skarupa, Lisa

From: Skarupa, Lisa
nt: Thursday, September 16, 2010 4:37 PM
cc: 'Doman, Natalie'; Shiozawa, Debi N
Subject: Information Request Clinical Sept 16, 2010 NDA22405

Dear Natalie and Debi,

We will be meeting with you tomorrow, in an adjacent room after your presentation, with the clinical and stats team to assist us in navigating your datasets. Could you please see the following IR? It would help us tomorrow as we navigate the datasets with your presence. Lisa

We also request that you submit the following information:

1. To fully assess the adverse events included in patient labeling, it will be necessary to submit written patient narratives for the following events in your Safety Database. Please provide these narratives within 2 weeks.
 - a. In Section 2.1.2.11 of your ISS, you note that 3 patients on Study 57 and 10 patients in your 300 mg monotherapy program developed heart failure. Please provide written narratives and information on the patient's ejection fraction (if available) for the following patients.

D4200C00057/E1501010
D4200C00057/E1209008
D4200C00057/E3106015
D4200C00001/E0030065
D4200C00039/E6407009
D4200C00006/E0011002
D4200C00036/E0182002
 - b. Please provide a written narrative for patient D4200C00057/E1409002 who discontinued due to hypertensive crisis. Please clarify whether this was a grade 4 event, hypertensive crisis or a grade 3 event. Please provide information on the end organ systems affected by this event.
 - c. In Section 2.1.3.1 of your ISS, you noted that interstitial lung disease was reported in several patients in your non-small cell lung cancer studies and that pneumonitis has been reported in your study of medullary thyroid cancer. Please provide written narratives for the following patients.

D4200C00003/E0027006
D4200C00003/E0027006
D4200C00003/E0035001
D4200C00003/E0043002
D4200C00044/E1103010
D4200C00044/E3409009
D4200C00044/E5505013
D4200C00044/E5506005
D4200C00044/E5508003
D4200C00044/E5601001
D4200C00057/E2411001

D4200C00057/E2902009

D4200C00057/E3702006

- d. Please identify and provide written narratives for all patients with a concomitant elevation in ALT > 3xULN and bilirubin > 2xULN. In Section 3.2.1 of your ISS, it appears that 3 patients met these criteria. We were able to locate narratives for each of these patients, but will require additional information to fully assess this safety signal. For patient E3801030/Study 57, please state whether imaging studies were performed at the time of the patient's elevation in liver function tests (LFTs) and whether the patient had liver metastases. For patient E3703001/Study 44, please state whether the patient's pre-existing elevation in LFTs was due to metastatic disease and whether the LFTs improved following discontinuation of vandetanib.
- e. In Section 2.1.2.14 of your ISS, you note that 5 patients in the vandetanib arm in Study 44 developed a grade 4 increase in amylase. Please state whether these patients developed symptomatic pancreatitis and whether alternative explanations exist for this elevation in amylase.
- f. In Section 2.1.3.2 of your ISS, you note that 4 patients receiving vandetanib developed reversible posterior leukoencephalopathy. We have been unable to locate the narratives for 3 of the patients described; 2 patients on the sponsor-investigator study IRUSZACT0051 and 1 patient on the sponsor-investigator study IRUSZACT0070.
- g. In Section 2.1.2.1 of your ISS, you note that Stevens-Johnson syndrome was reported by 6 patients in the vandetanib 300 mg monotherapy program. We were able to identify the following patients and to locate e-narratives for these patients.

D4200C00007A/E0601505

D4200C00044/E5104001

D4200C00044/E5202003

D4200C00044/E5202010

D4200C00057/E1203007

D4200C00057/E3803017

However, we were unable to fully assess the details of their skin condition, need for admission to specialized units, degree of infection, skin areas involved and the dressing used, etc. Further, it appears that none of these patients discontinued due to Stevens-Johnson syndrome.

- h. In Section 2.1.2.5 of your Integrated Summary of Safety (ISS), you identify 2 patients who have developed torsades de pointes. Please provide a written narrative for the patient identified in Study 79.
2. To fully assess the adverse events associated with vandetanib, it will be necessary to submit written patient narratives for the following events in Study 58. Please provide these narratives within 2 weeks.
- a. Heart Failure: patient E1901004
 - b. Hypertensive Crisis: E2503001, E1401001, E1701017, E1703006, E3301007
 - c. Interstitial Lung Disease/Pneumonitis: E2501011, E2501015, and E2501019
 - d. Possible Intestinal Perforation : E1601004, E0003002, E0014001, E1702005
 - e. Other: E0002002 (convulsion), E2501028 (sensorimotor neuropathy), E2801024 (myopathy)
 - f. Skin Disorders: E2501017, E2501031

3. Please provide a discussion of the applicability of data obtained outside the U.S. to patients within the US. This should include a comparison of progression free survival and an assessment of adverse events in patients who received vandetanib outside the U.S. and within the U.S.

Skarupa, Lisa

From: Skarupa, Lisa
It: Wednesday, September 08, 2010 12:43 PM
to: 'Doman, Natalie'
Subject: Clinical I.R. Sept 8th

Dear Natalie,

Please see Clinical Information Request below:

Please account for the discrepancies between what is reported in the CSR and what is reported in the datasets in regard to those patients with no measurable disease. The CSR reports patients who have no measurable disease by investigator assessment; however, the independent radiological review found a substantially higher number of patients without baseline measurable disease. Is this correct? Have you performed sensitivity analyses which exclude these patients? Details are as follows:

In the clinical study report (section 6.2, table 7; table 11.1.4; and Appendix 12.2.2.1), you provide a total of 14 patients (9 on vandetanib and 5 on placebo) who had no measurable tumors at baseline.

They are:

Placebo:

- 1) E0006003
- 2) E1703009
- 3) E2001011
- 4) E3002001
- 5) E3301004

Vandetanib:

- 1) E0008004
- 2) E0009009
- 3) E0018001
- 4) E0021003
- 5) E1102010
- 6) E1901002
- 7) E2002010
- 8) E3003001
- 9) E3301001

However, In reviewing the REC_LANA and RECLANA1 raw data sets and the RECLANA and RECLANA1 reporting data sets, these 32 (placebo = 12, vandetanib = 20) patients had no measurable tumors on their screening V1 assessments:

Placebo:

- 1) E0013007
- 2) E1001010
- 3) E1501002
- 4) E1601003
- 5) E1701007
- 6) E1703003
- 7) E2001011
- 8) E2505015
- 9) E2803006
- 10) E3002001
- 11) E3301004
- 12) E3301010

Vandetanib:

- 1) E0002011
- 2) E0008004
- 3) E0009001
- 4) E0009009
- 5) E0015002
- 6) E1102010

- 7) E1205002
- 8) E1601005
- 9) E1701021
- 10) E1702005
- \ E1703007
- , E1703012
- 13) E1801006
- 14) E2501003
- 15) E2504005
- 16) E2505014
- 17) E2601005
- 18) E2701001
- 19) E2801018
- 20) E3301001

Skarupa, Lisa

From: Skarupa, Lisa
Sent: Wednesday, September 08, 2010 2:20 PM
To: 'Doman, Natalie'
Subject: RE: ClinPharm I.R. urgent Sept 8

yes Study 58

From: Doman, Natalie [mailto:Natalie.Doman@astrazeneca.com]
Sent: Wednesday, September 08, 2010 12:38 PM
To: Skarupa, Lisa
Subject: RE: ClinPharm I.R. urgent Sept 8

Dear Lisa:

Thank you—I have sent this to our team for resolution. This refers to the Study 58 clinical study report, correct? The page numbers match up, but just wanted to be sure.

Thanks,
Natalie

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From: Skarupa, Lisa [mailto:Lisa.Skarupa@fda.hhs.gov]
Sent: Wednesday, September 08, 2010 11:41 AM
To: Doman, Natalie
Subject: ClinPharm I.R. urgent Sept 8

Dear Natalie,

Please see the following ClinPharm Information Request to please send to us by tomorrow 5pm (Sept 9th).

Please refer to the "Efficacy Model" on Page 133 in the study report entitled "Population Pharmacokinetic (PK) and Pharmacokinetic-Pharmacodynamic (PK-PD) Analysis", which was included as Appendix 12.1.13 in your submission of NDA022405 (Sequence No. 0000) dated 09 July 2010.

Please submit the dataset "RESPONSE.CSV" as an *xpt file, with variable definitions in a PDF file.

Sincerely,
Lisa

Skarupa, Lisa

From: Skarupa, Lisa
Sent: Friday, September 03, 2010 2:58 PM
To: 'Doman, Natalie'
Cc: Shiozawa, Debi N
Subject: RE: Information Requests ClinPharm and Clinical Sept 2

Good afternoon,
We will get back to you next week.

Lisa

From: Doman, Natalie [mailto:Natalie.Doman@astrazeneca.com]
Sent: Friday, September 03, 2010 10:21 AM
To: Skarupa, Lisa
Cc: Shiozawa, Debi N
Subject: RE: Information Requests ClinPharm and Clinical Sept 2

Good morning, Lisa:

The AZ team discussed these information requests, and clarification of the following would be helpful. I have reproduced the original questions below, followed by our response.

Clinical question, bullet 1:

- Were there any deaths in Studies 1, 2, 3, 7A, 8, 9, 39, 50, and 43? If so, how would we identify those?
Response: We were not able to locate a study 9 in the submission. Would you please clarify?

Clinical question, bullet 2:

- In your pre-NDA briefing document (7-14-2008), you stated that you would provide safety data from studies 6, 32, 36, 38, 41, 46, 55, and 68. While separate datasets are provided for studies, 6, 32, 36, 38, 41, 55, and 68, we are unable to locate the datasets for Study 46. Further, we are concerned that each of these datasets will need to be examined separately. We understand that the studies which used vandetanib 300 mg as monotherapy and which are included in the ISS datasets are most relevant to this indication. However, we would like to examine patient deaths and uncommon adverse events in the other studies. Please state the location of the datasets for Study 46. Please state whether you will be able to readily and easily provide a single dataset which includes all of these studies. If such a dataset can be readily provided, particularly one which contains fewer variables, please submit this to your NDA.
Response: A pooled dataset already exists for studies 6, 32, 36, 41, 46, 55, and 68. The dataset for Phase I study 38 is not yet standardized and mapped so that it can be pooled with the others. Would it be acceptable to provide the existing pooled dataset, or should we proceed with preparing the single dataset, including study 38? Also, you prefer a single dataset that contains fewer variables. Would you please provide some guidance regarding what type of information you want the truncated dataset to contain, and what may be removed?

Thanks and Regards,
Natalie

Reference ID: 2876310

12/12/2010

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From: Doman, Natalie
Sent: Thursday, September 02, 2010 5:24 PM
To: 'Skarupa, Lisa'
Subject: RE: Information Requests ClinPharm and Clinical Sept 2

Hi, Lisa:

I confirm that I have received your request and have passed it along to my team for resolution.

Thanks,
Natalie

From: Skarupa, Lisa [mailto:Lisa.Skarupa@fda.hhs.gov]
Sent: Thursday, September 02, 2010 4:50 PM
To: Doman, Natalie
Subject: Information Requests ClinPharm and Clinical Sept 2

Dear Natalie,
Please see the following Information Requests from Clinical and ClinPharm:

Clinical

Refer to Amendment 0, Section 5.3.5.3, the ISS dataset R_AE

We would like to examine the number of deaths in the safety database. Using CTCMAX, we are able to identify 9 patients with a grade 5 AE. All are from Study 58. Using CTCGMAX, we are able to identify 100 patients with a grade 5 AE. All are from Studies 44, 57, or 58.

- Were there any deaths in Studies 1, 2, 3, 7A, 8, 9, 39, 50, and 43? If so, how would we identify those?
- In your pre-NDA briefing document (7-14-2008), you stated that you would provide safety data from studies 6, 32, 36, 38, 41, 46, 55, and 68. While separate datasets are provided for studies, 6, 32, 36, 38, 41, 55, and 68, we are unable to locate the datasets for Study 46. Further, we are concerned that each of these datasets will need to be examined separately. We understand that the studies which used vandetanib 300 mg as monotherapy and which are included in the ISS datasets are most relevant to this indication. However, we would like to examine patient deaths and uncommon adverse events in the other studies. Please state the location of the datasets for Study 46. Please state whether you will be able to readily and easily provide a single dataset which includes all of these studies. If such a dataset can be readily provided, particularly one which contains fewer variables, please submit this to your NDA.

ClinPharm

They should submit the information no later than COB of **September 10, 2010**.

1. Please submit a description of the composition and components of the oral solution formulation used in Study 30.
2. Please provide your justification for the use of tablet dispersion in water for patients who have difficulty in swallowing solids.
3. Please submit model codes and output listings that were used for calculation of GLS mean for C_{max} and AUC in Study 16 and Study 22.

Reference ID: 2876310

12/12/2010

Sincerely,
Lisa

AUGUST, 2010 INFORMATION REQUESTS
NDA 022405 vandetanib

Date of Information Request	AstraZeneca's response (DARRTS SDN)
August 18th Clinical Pharm	SDN 13 (August 25, 2010)
August 17 Clinical	SDN 11 (August 24, 2010)
August 5 Clinical	SDN 10 (August 20, 2010)
August 13 Clinical	SDN 9 (August 18, 2010)
August 4 TCON	SDN 8 (August 13, 2010)
August 6 email	SDN 7 (August 13, 2010)

Skarupa, Lisa

From: Skarupa, Lisa
Sent: Wednesday, August 25, 2010 3:44 PM
To: 'Doman, Natalie'
Subject: RE: Aug 18 ClinPharm I.R.

thank you

From: Doman, Natalie [mailto:Natalie.Doman@astrazeneca.com]
Sent: Wednesday, August 25, 2010 3:22 PM
To: Skarupa, Lisa
Subject: RE: Aug 18 ClinPharm I.R.

Hi, Lisa:

The response to this IR was submitted through the Gateway this afternoon.

Also, would you please supply a list of attendees from this morning's teleconference?

Thanks,
Natalie

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From: Skarupa, Lisa [mailto:Lisa.Skarupa@fda.hhs.gov]
Sent: Wednesday, August 18, 2010 9:53 AM
To: Doman, Natalie
Subject: Aug 18 ClinPharm I.R.

Dear Natalie,

The following is an Information Request from Clinical Pharmacology Review Team. The datasets and models must be submitted no later than COB of August 23, 2010.

Please refer to the section of 5.3.3.5 (regarding the population PK study reports) in your submission of NDA022405 (Sequence No. 0000) dated 09 July 2010. Submit the companion pharmacometric models and datasets including individual concentration vs. time and corresponding pharmacokinetic parameters by patient as SAS transport files. The following are the general expectations for submitting pharmacometric models and data:

- *All datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.*

Reference ID: 2876310

12/12/2010

- *Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).*
- *A model development decision tree and/or table which gives an overview of modeling steps.*

Sincerely,
Lisa

From: Doman, Natalie [mailto:Natalie.Doman@astrazeneca.com]
Sent: Tuesday, August 17, 2010 6:47 PM
To: Skarupa, Lisa
Cc: Shiozawa, Debi N
Subject: RE: Clinical I.R. August 17 NDA22405

Hi, Lisa:

I'm writing to confirm that I received your request and passed it along to the clinical team for evaluation and resolution. I will follow up with you regarding its status. Also, the narratives you requested will be submitted this week.

Have a good evening,
Natalie

Natalie Doman
Associate Director

AstraZeneca Pharmaceuticals LP
Research and Development, Regulatory Affairs
C2B-705A, 1800 Concord Pike, PO Box 15437, Wilmington, DE, 19850-5437
Tel +1 302 885 1441 Fax +1 302 886 2822
natalie.doman@astrazeneca.com

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From: Skarupa, Lisa [mailto:Lisa.Skarupa@fda.hhs.gov]
Sent: Tuesday, August 17, 2010 2:12 PM
To: Doman, Natalie
Cc: Shiozawa, Debi N
Subject: Clinical I.R. August 17 NDA22405

Good afternoon,

Please see the following clinical Information Request; we request that your response be received within one week. Please provide a timeline for this submission in your response.

CLINICAL Information Request

Please explain the following discrepancies.

If these apparent discrepancies cannot be explained, please ensure that the remainder of your CRFs match the information in your datasets and please provide the remainder of your CRFs.

Sites
0013

- Pt E0013008-It appears that the following AEs are not in the dataset: diarrhea (increasing), edema bilateral lower legs, hot flashes, palpitations, nausea (intermittent), depression (increased), insomnia, fatigue.

1201

- Pt E1201001-The following AEs do not appear to be in the dataset: worsening bone pain, intermittent vomiting.

1202

- Pt E1202002-The following AE does not appear to be in the dataset: infected urinary stent.

1701

- Pt 1701007-The following AE do not appear to be in the dataset: bilateral groin pain.
- Pt 1701014-In the SAE loss of consciousness, the comments state that 5 d after the event a prolonged QTc was seen. Should prolong QTc be in the dataset?
- Pt 1701017-Polyglobulia is mapped to polycythaemia. Is this correct?
- Pt 1701019-In the SAE bad physical condition, the comments state the pt had a BP 220/130. Hypertension was not captured as an AE at the time. Should this be in the dataset?

1702

- Pt E1702005-In the SAE hypertension, the patient's "collapse" is recorded in the comments, but is not in the dataset. Is this correct?

2005

- Pt E2005002-In the comments for the SAE gastroenteritis, respiratory failure is also mentioned. This is not in the dataset.
- Pt E2005007-The AE term visual field reduction is mapped to visual acuity reduced. Is the mapping correct? Also, blindness OS is recorded as a grade 2 event. Is this correct?

2302

- Pt E2302001-The following AEs do not appear to be in the dataset: lymphopenia, hypokalemia, hypocalcemia.

2501

- Pt 2502017-The following AEs do not appear to be in the dataset: dispnea, hepatic colic.

2601

- Pt 2601002-Abdominal pain is included in the dataset. In the comments for this SAE, hypoxia (apparently pO₂ of 50) is mentioned, but not in dataset.

- Pt 2601003-Gr 4 hypokalemia is recorded. In the comments for this SAE, QT prolongation is also mentioned. This is not in the dataset.

2801

- Pt 2801009-The following AEs do not appear to be in the dataset: lymphopenia, increased of hepatic enzymes, intermittent edema palpebra, interstitial nephropathy.
- Pt 2801004-Papillar excavation of right eye is mapped to conjunctival disorder. Is the mapping correct?
- Pt 2801012-Muscular hypotrophie is mapped to hypotonia. Is the mapping correct?
- Pt 2801038-In the comments for the SAE bradycardia, it states the pt had AV block. AV block is not in the database.

2803

- The CRFs for 2801018 is under this site rather than 2801.

Sincerely,
Lisa

From: Doman, Natalie [mailto:Natalie.Doman@astrazeneca.com]
Sent: Wednesday, August 18, 2010 5:14 PM
To: Skarupa, Lisa
Subject: RE: PharmTox Request NDA 22405

Good evening, Lisa:

I'm writing to confirm that all outstanding (formerly cross-referenced) Pharm/Tox reports were submitted through the Gateway this afternoon, as Sequence 0006. Also included in the submission are all of the previously cross-referenced Clinical Pharmacology study reports, with the exception of Study 21, which was submitted per your request on August 3, 2010, as Sequence 0003. All Module 2 summary documents were included in the original submission of NDA 22-405, Sequence 0000.

Given the size of the submission, I have attached the cover letter only, for your reference.

Regards,
Natalie

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From: Skarupa, Lisa [mailto:Lisa.Skarupa@fda.hhs.gov]
Sent: Friday, August 13, 2010 4:13 PM
To: Doman, Natalie
Cc: Shiozawa, Debi N
Subject: PharmTox Request NDA 22405

Good afternoon Natalie,

We have looked into the original comment that you stated "AstraZeneca can reference any prior submissions". It seems that comment was placed in the acknowledgement of the withdrawal for NDA (b) (4)

I believe the sentence was "You may reference information contained in this withdrawn application in any resubmission." I need to clarify that that sentence is specifically for any resubmission to NDA (b) (4)

This statement in that letter **does not** pertain to a NEW NDA, with a NEW indication which is NDA 22405.

So we ask that you submit the **ENTIRE PharmTox data** that you are referencing in the current NDA 22405 ZICTIFA. When you submit, please make sure you remove any titles (b) (4) since this submission will now be for NDA 22405. This submission is key since all the information will be in one NDA, especially as you consider future supplements (should this section be needed).

Since we are losing time for review, we ask that you submit this information electronically within the week. Please let me know if you need anything clarified.

Sincerely,
Lisa

Skarupa, Lisa

From: Skarupa, Lisa
Sent: Monday, August 09, 2010 3:28 PM
To: 'Doman, Natalie'
Subject: RE: Aug 6 I.R. full report missing

Hi Natalie,

Please see reply to you request for clarification:

On page 172 of the clinical study report, section 8.5.3 it says: "The consultant ophthalmologist concluded that the association of study drug to the occurrence of vortex keratopathy can be classified as certain by World Health Organization criteria. This conclusion is strengthened by the fact that the actual prevalence of vortex keratopathy is decidedly low in the general population. At present, even with partial analysis possible, it appears that at least 3 months of dosing is required for the first appearance of vortex keratopathy. No serious corneal AE has yet been associated with study drug. For this reason, the consultant ophthalmologist indicated that there is no need to stop dosing even in instances where vortex keratopathy develops. The full report of the consultant ophthalmologic is provided in **Appendix 12.2.10.**"

Sincerely,
Lisa

From: Doman, Natalie [mailto:Natalie.Doman@astrazeneca.com]
Sent: Friday, August 06, 2010 5:10 PM
To: Skarupa, Lisa
Subject: RE: Aug 6 I.R. full report missing

Hi, Lisa:

Please clarify—Appendix 12.2.10 of which document? Are you referring to a particular clinical study report?

Thanks,
Natalie

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From: Skarupa, Lisa [mailto:Lisa.Skarupa@fda.hhs.gov]
Sent: Friday, August 06, 2010 4:59 PM
To: Doman, Natalie
Subject: Aug 6 I.R. full report missing

Dear Natalie,

Please note that your submission references a full report of a consultant ophthalmologist provided in appendix 12.2.10. However, there is no report in this appendix. Please submit this report, and please provide a timeline for this submission of this report?.

Sincerely
Lisa

Reference ID: 2876310

12/12/2010

Skarupa, Lisa

From: Doman, Natalie [Natalie.Doman@astrazeneca.com]
Sent: Thursday, August 05, 2010 4:44 PM
To: Skarupa, Lisa
Subject: RE: Information Request Aug 5 Clinical Narratives
Follow Up Flag: Follow up
Flag Status: Red

Good afternoon, Lisa:

I confirm that I received your e-mail. I have passed your request along to our clinical team, who will advise me regarding response timing. I will follow up with you ASAP.

Regards,
 Natalie

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From: Skarupa, Lisa [mailto:Lisa.Skarupa@fda.hhs.gov]
Sent: Thursday, August 05, 2010 4:38 PM
To: Doman, Natalie
Subject: Information Request Aug 5 Clinical Narratives

Good afternoon Natalie,

Please provide written narrative for the following pts (see list below) who discontinued vandetanib. Please let me know that you received this email, and as to the timeline of your response (official submission).

Sincerely,
 Lisa

1. E0008002 Fatigue
2. E0013006 QTc prolongation
3. E0019002 Nausea/vomiting
4. E1001006 Rash
5. E1601004 Peritonitis
6. E1901002 Creatinine increased
7. E1901004 QTc prolongation/decreased EF
8. E2501007 Hypertension
9. E2501011 Neuropathy
10. E2501019 Pneumonitis
11. E2501030 Creatinine increased
12. E2501031 Rash/pruritus
13. E2701002 Fatigue

Reference ID: 2876310

12/12/2010

14. E2701004 Peripheral ischemia/dysphonia/hypertension
15. E2801003 Dysphagia
16. E2801005 Asthenia
17. E2801010 Asthenia
18. E2801012 Asthenia
19. E2801029 Diarrhea/Dyspnea/cough/fever/asthenia
20. E2801033 General deterioration
21. E2901002 Arthralgia/fever
22. E2901007 Chylothorax
23. E2901011 Pancreatitis
24. E3601002 Rash
25. E3601003 Eczema
26. E0007001 MI
27. E0008003 Dysgeusia/vision blurred
28. E001004 Depressed level of consciousness
29. E1203003 Myalgia/nausea
30. E2501028 Neuropathy

Skarupa, Lisa

From: Skarupa, Lisa
At: Thursday, August 05, 2010 4:38 PM
To: 'Doman, Natalie'
Subject: Information Request Aug 5 Clinical Narratives

Good afternoon Natalie,

Please provide written narrative for the following pts (see list below) who discontinued vandetanib.
Please let me know that you received this email, and as to the timeline of your response (official submission).

Sincerely,

Lisa

1. E0008002 Fatigue
2. E0013006 QTc prolongation
3. E0019002 Nausea/vomiting
4. E1001006 Rash
5. E1601004 Peritonitis
6. E1901002 Creatinine increased
7. E1901004 QTc prolongation/decreased EF
8. E2501007 Hypertension
9. E2501011 Neuropathy
10. E2501019 Pneumonitis
11. E2501030 Creatinine increased
12. E2501031 Rash/pruritus
13. E2701002 Fatigue
14. E2701004 Peripheral ischemia/dysphonia/hypertension
15. E2801003 Dysphagia
16. E2801005 Asthenia
17. E2801010 Asthenia
18. E2801012 Asthenia
19. E2801029 Diarrhea/Dyspnea/cough/fever/asthenia
20. E2801033 General deterioration
21. E2901002 Arthralgia/fever
22. E2901007 Chylothorax
23. E2901011 Pancreatitis
24. E3601002 Rash
25. E3601003 Eczema
26. E0007001 MI
27. E0008003 Dysgeusia/vision blurred
28. E001004 Depressed level of consciousness
29. E1203003 Myalgia/nausea
30. E2501028 Neuropathy

Skarupa, Lisa

From: Doman, Natalie [Natalie.Doman@astrazeneca.com]
Sent: Thursday, August 05, 2010 4:23 PM
To: Skarupa, Lisa
Subject: RE: Information Request Aug 5th clinical datasets

Hi, Lisa:

Thank you for sending this—I have passed it along to our clinical team for resolution.

Regards,
Natalie

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From: Skarupa, Lisa [mailto:Lisa.Skarupa@fda.hhs.gov]
Sent: Thursday, August 05, 2010 3:34 PM
To: Doman, Natalie
Subject: Information Request Aug 5th clinical datasets

Hello Natalie,

As agreed in yesterday's teleconference between AstraZeneca and our Clinical Team, here are our request for a clarification:

You have provided multiple adverse event datasets.

- In dataset AELOG, I found 241 SAEs.
- In dataset SAE, I found 208 events.
- In dataset AE, I found 232 events.
- In dataset R_AE, I found 160 events using the variable AEEVNT05 and 231 events using the variable AESER.

Please explain these differences and state which variable provides the correct number of SAEs.

Sincerely,
Lisa

JULY, 2010 INFORMATION REQUESTS
NDA 022405 vandetanib

Date of Information Request	AstraZeneca's response (DARRTS SDN)
July 28 Clinical	SDN 6 (August 4, 2010)
July 28 Clinical	SDN 4 (August 3, 2010)
July 16 Clinical	SDN 3 (July 27, 2010)

Skarupa, Lisa

From: Doman, Natalie [Natalie.Doman@astrazeneca.com]
Sent: Wednesday, July 28, 2010 4:59 PM
To: Skarupa, Lisa
Subject: RE: July 28th I.R. QT study

Hi, Lisa:

I'm confirming that I received your request and have forwarded it to my colleagues so they can begin to prepare a response. I do have one clarifying question: The Study 21 report and datasets were previously submitted to NDA (b) (4) and have been cross-referenced in the current submission, NDA 22-405. The location of this information was provided in Module 1.4.4, Cross Reference to Other Applications. Just to make sure I understand—do you want us to re-submit all of the information below as opposed to accessing it through NDA (b) (4)

Thanks for your help,
Natalie

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From: Skarupa, Lisa [mailto:Lisa.Skarupa@fda.hhs.gov]
Sent: Wednesday, July 28, 2010 4:25 PM
To: Doman, Natalie
Subject: July 28th I.R. QT study

Good afternoon Natalie,

1. Please submit to your NDA 22405 the study report to Study 21 and related datasets.
2. Please fill out the "Highlights of Clinical Pharmacology" table attached and submit with your submission for Study 21.

If you have any questions, please do not hesitate to contact me.
Please send submit the requested information in 7 days.

Sincerely,
Lisa

<<HighlightsofClinicalPharmacology.doc>>

Skarupa, Lisa

From: Skarupa, Lisa
Date: Wednesday, July 28, 2010 4:25 PM
To: 'Doman, Natalie'
Subject: July 28th I.R. QT study
Attachments: HighlightsofClinicalPharmacology.doc

Good afternoon Natalie,

1. Please submit to your NDA 22405 the study report to Study 21 and related datasets.
2. Please fill out the "Highlights of Clinical Pharmacology" table attached and submit with your submission for Study 21.

If you have any questions, please do not hesitate to contact me.
Please send submit the requested information in 7 days.

Sincerely,
Lisa



HighlightsofClinicalP
harmacolo...

Skarupa, Lisa

From: Skarupa, Lisa
Date: Friday, July 16, 2010 5:50 PM
To: 'Natale.Doman@astrazeneca.com'
Subject: New NDA

Dear Natale,

I would like to send cc this to Dr. Shiozawa, however, I could not find her email address in the documents, please forward to her.

I found your email address in the referenced IND.

The Clinical Team would like for Astra Zeneca to please add to the submitted DSI information you included in your NDA submission the following:
(I saw your DSI information, I know you had the site information, and number of patients) I could not find the matching A.E.s to that site, nor the response rates and number of protocol violations. Please send this information as soon as possible; please let me know if end of next week is possible. The clinical team wanted in a table format please, see below.

Site # Address Telephone No.	# Pts Enrolled	# Grade 3-4 AEs	Response Rate	# Protocol Violations

Sincerely,
Lisa
Regulatory Project Manager
796-2219

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
12/12/2010

MEMORANDUM OF MEETING MINUTES

MEETING DATE: Wednesday, November 24, 2010
TIME: 9:00 – 9:30 ET
LOCATION: Teleconference
APPLICATION: NDA 22-405
DRUG NAME: vandetanib tablets

FDA ATTENDEES: (Title and Office/Division)

Sarah Pope, Ph.D., Branch Chief II
Christine Moore, Ph.D., Deputy Director, Science and Policy
John Duan, Ph.D., Biopharmaceutics Reviewer
Debasis Ghosh, Ph.D., Chemistry Reviewer
Patrick Marroum, Ph.D., Biopharmaceutics Supervisor
Don Henry, Regulatory Project Manager

ASTRAZENECA ATTENDEES:

Paul Dickinson – Principal Scientist, Pharmaceutical Development
David Holt – Principal Scientist, Analytical Sciences
Mike Parker - Pharmaceutical Development Project Director
Gavin Reynolds – Associate Principal Scientist, Formulation Science
Robert Timko - Director Regulatory Affairs CMC
David White – Manager, Pharmaceutical Development

BACKGROUND:

After some internal discussions related to the use of a regression model as a surrogate for dissolution in NDA 22-405, the review team decided to arrange a teleconference with the applicant (AstraZeneca). The following information was provided to the applicant prior to the teleconference to facilitate the discussion:

1. We agree with your general approach for developing a regression model as a surrogate for dissolution. However, the current model is not acceptable based on the following points.

- a.



(b) (4)

2. We have the following considerations for rebuilding the model.



- e. We recognize your intent to scale-up your manufacturing process. Given that the proposed model was verified using data not representative of commercial scale, describe how your model maintenance will evaluate changes in batch size, including the statistically relevant number of batches that would be used to verify model prediction at commercial scale.

DISCUSSION POINTS AND ACTION ITEMS:

AZ agreed that rebuilding the model would provide better discriminating power. AZ agreed to rebuild the dissolution model and to consider all comments that were provided. The teleconference proceeded with further discussion/clarification of some of the comments:

Item 2b: The Agency clarified that if the analytical procedures for (b) (4) are based on pharmacopeia methods, the reference method should be provided in the application, and no additional information would be required.

Item 2c: AZ indicated that the model incorporates the variability and the supporting information will be provided

Item 2d: AZ indicated that (b) (4) is used to monitor the process and would be used to detect process shifts or variability.

Item 2e: AZ indicated that the model is (b) (4) and expect that scale-up will have little effect. However, as mentioned in item 2d, the use of (b) (4) would detect whether scale-up has any effect on the model. Any changes to the model would be handled under the Quality System.

Conclusion:

The Agency indicated that a submission of an amendment to update the dissolution model would be considered a major amendment and could trigger an extension of the review cycle. The Agency discussed that if AZ chose to submit an updated model as a post-approval change, that they would provide a timely review using the same review team. AZ decided that they would withdraw the dissolution model from the application with an expectation that an updated model would be submitted as a prior approval supplement.

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

/s/

DON L HENRY
12/05/2010

From: Tilley, Amy
Sent: Wednesday, November 24, 2010 12:30 PM
To: 'Natalie.Doman@astrazeneca.com'
Cc: Skarupa, Lisa
Subject: NDA 22405 Vandetanib - Clinical Information Request

Importance: High

Follow Up Flag: Follow up
Due By: Wednesday, December 01, 2010 12:00 AM
Flag Status: Flagged

Natalie,

Below is an Information Request from the Clinical Reviewer.

Please provide additional clinical information regarding the 2 patients in study 44 who developed grade 4 drug hypersensitivity: patient E5013001 and E5013002. Please include written patient narratives if available.

The Clinical Reviewer requests your response [no later than December 1, 2010.](#)

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Drug Oncology
Products, 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
11/24/2010



NDA 022405

MEETING MINUTES

iPR Pharmaceuticals, Inc.
c/o AstraZeneca Pharmaceuticals LP
1800 Concord Pike, PO Box 8355
Wilmington, DE 19803-8355

Attention: Debra N. Shiozawa, PhD
Director, Regulatory Affairs

Dear Dr. Shiozawa:

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

We also refer to the telecon between representatives of your firm and the FDA on November 22, 2010. The purpose of the meeting was to discuss outstanding items pertaining to the pending NDA review.

A copy of the official minutes of the telecon 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) 796-4256.

Sincerely,

{See appended electronic signature page}

Christy Cottrell
Regulatory Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

Meeting Type: N/A
Meeting Category: Guidance

Meeting Date and Time: November 22, 2010 at 10:00 am
Meeting Location: WO22, Room 1201

Application Number: NDA 022405
Product Name: Vandetanib
Indication: **Medullary thyroid cancer**
Sponsor/Applicant Name: AstraZeneca

Meeting Chair: V. Ellen Maher, MD
Meeting Recorder: Christy Cottrell

FDA ATTENDEES

Richard Pazdur, MD, Director, OODP
Robert Justice, MD, MS, Director, DDOP
Anthony Murgu, MD, Acting Deputy Director
V. Ellen Maher, MD, Clinical Team Leader
Katherine DeLorenzo, MD, Clinical Reviewer
Geoffrey Kim, MD, Clinical Reviewer
Shenghui Tang, PhD, Biometrics Team Leader
Somesh Chattopadhyay, PhD, Biometrics Reviewer
Leigh Verbois, PhD, Pharm/Tox Team Leader
Brenda Gehrke, PhD, Pharm/Tox Reviewer
Christy Cottrell, Regulatory Project Manager

SPONSOR ATTENDEES

Peter Langmuir, MD, Executive Director, Medical Science
Mark Steinberg, MD, Senior Safety Medical Director
Donna Francher, Vice President, vandetanib
Joe Cordaro, PharmD, MBA, Executive Director, Development
Natalie Doman, Associate Director, Regulatory Affairs
James Vasselli, MD, Director, Clinical Research
Richard Knight, PhD, Principal Scientist
Paul Martin, PhD, Clinical Pharmacology and DMPK Leader
Paul Elvin, PhD, Principal Scientist
Alan Webster, BSc, MSc, Global Product Statistician
Wendy White, BSc, (Hons), Director, Global Regulatory Affairs
Andrew Dickinson, Clinical Response Team Leader
Cindy Lancaster, MS, MBA, JD, Executive Director Regulatory Affairs

BACKGROUND

NDA 022405 for Vandetanib was submitted on July 7, 2010. The PDUFA due date for the application is January 7, 2010. Proposed indication is [REDACTED] ^{(b) (4)}. This telecon was held to discuss questions pertaining to ODAC, request for a REMS, and potential PMRs.

DISCUSSION

The sponsor began by asking when they can expect to receive the Division's questions for ODAC. Dr. Maher explained that the questions have not been written yet, but that the questions will center around restricting use to a symptomatic population or patients with rapidly progressing disease and the need for a PMR to evaluate a lower dose of Vandetanib to examine dose more closely. Dr. Pazdur asked the sponsor to begin thinking of different proposals to evaluate a lower dose or a dosing strategy. Dr. Pazdur further explained the Division's rationale for restricting use. He noted that newly diagnosed patients have a long natural history and that this needs to be considered when examining the risk-benefit profile of this drug.

Dr. Maher stated that the Division will be proposing a REMS for QT prolongation, interstitial lung disease and Stevens-Johnson Syndrome. The REMS would include a Medication Guide and a Physician Education Program, but no Elements to Assure Safe Use (ETASU). Dr. Maher noted that the Division is drafting a letter for the sponsor regarding the REMS and it will be sent out shortly.

Regarding the proposed PMRs, Dr. Maher reiterated that the Division will request a trial to evaluate a 300 mg dose and a lower dose of Vandetanib in a small population (not non-inferiority). The trial would examine risk, adverse reaction profile, QT prolongation, and patient outcome. The Division noted that the study would have to be conducted in patients with medullary thyroid cancer; data could not be extrapolated from follicular or papillary thyroid cancers. The Division noted that the sponsor should be prepared to discuss a plan for this study at ODAC. The Division stated that there would also be a non-clinical PMR to assess carcinogenicity in two species [a lifetime study in rat and a mouse study (design up for discussion)].

The sponsor had some additional questions for the Division. In Table 12 of the ODAC briefing document, Adverse Events Leading to Death, the sponsor noted that the Division had 6 vandetanib patients and 1 placebo patient, while the sponsor calculated 5 vandetanib patients and 2 placebo patients. The Division agreed to provide the patients numbers for these patients. The sponsor also asked about the mechanics of ODAC (i.e., how many presenters). The Division noted that there would be two FDA presenters (one presentation). The Division agreed to make the ODAC questions publically available prior to the meeting. The sponsor asked whether there was anything else they could do to assist in the review of the application. The Division responded that the applicant should be thinking about a revised indication to reflect the limited use that the Division recommends.

ISSUES REQUIRING FURTHER DISCUSSION

None

NDA 022405
November 22, 2010 telecon

ACTION ITEMS

The Division agreed to provide the patients numbers for these patients (Done).

ATTACHMENTS AND HANDOUTS

None

Christy Cottrell (for Lisa Skarupa)
Regulatory Project Manager

Concurrence: _____
V. Ellen Maher, MD
Clinical Team Leader

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/s/

CHRISTY L COTTRELL
11/29/2010

VIRGINIA E MAHER
12/09/2010



NDA 22-405

INFORMATION REQUEST

AstraZeneca Pharmaceuticals LP
Attention: Robert J. Timko, Ph.D.
Director, Regulatory Affairs, CMC
1800 Concord Pike
PO Box 8355
Wilmington DE 19803-8355

Dear Dr. Timko:

Please refer to your new drug application (NDA) originally submitted on July 7, 2010, under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, for vandetanib tablets.

We are reviewing the 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.

Overall:

1. A complete description of the commercial scale drug substance and 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 section S.2.2 (drug substance) and P.3.3 (drug product) 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.

Drug Substance:

Starting Materials:

2. Provide the risk assessment data pertaining to change of supplier, synthesis scheme and impurity profile of the starting materials. Since starting material attributes are part of the proposed design space, also provide risk assessment and control strategies to ensure the overall quality of the drug substance.

(b) (4)

Drug Product Manufacturing

5. Identify the K-value of the povidone used in the drug product. Provide a summary of the results obtained from the excipient compatibility studies outlined in P.2.1.2 Table 7.
6. Comment on how you will evaluate the impact of variability in excipient characteristics on drug product quality over the product life cycle, especially when the excipient variability exceeds your prior knowledge. Provide data (e.g. Response to IR Comment 2d Table 6) for the excipient variability studies that evaluated microcrystalline cellulose (MCC), povidone, and croscopvidone. For the MCC variability study, include data on the resulting blend uniformity and tablet content uniformity, if available.

(b) (4)

9. Provide the statistically derived p-values associated with the various parameters listed in your ANOVA analysis summaries included in P.2.3.2.3.2.2 – Table 8 and Table 9 along with P.2.3.2.4.1.3 – Table 14. Provide the p-values and % Variance determined for any additional parameters studied along with the main effects presented in these tables.
10. Provide a summary of the ANOVA analysis, including p-values, (b) (4) if available. Include any additional parameters studied along with the main effects.

11. Resolution III DoEs do not allow for assessment of interactions. You note that the Process Screening DoE was Resolution III. Identify the resolution for the other multivariate DoEs listed in Section P.2 Attachment B Table 3. For the Resolution III DoEs, provide justification that the assessment of the study factor interactions is not important for process understanding and control of product quality.
12. As final packaging is identified as part of your proposed design space and may occur at the iPR site, update Section P.3 of your submission to include the final packaging process step and any associated critical process parameters or in-process controls.

(b) (4)

14. We note your intent to evaluate any changes to your container closure systems through your change management process, which may or may not result in regulatory notification. However, notification of changes to your container closure system should comply with the requirements set forth in 21 CFR 314.70.
15. Provide the post-approval stability testing schedule for the drug product.
16. Provide certified, English-translated copies of the executed drug product batch records.

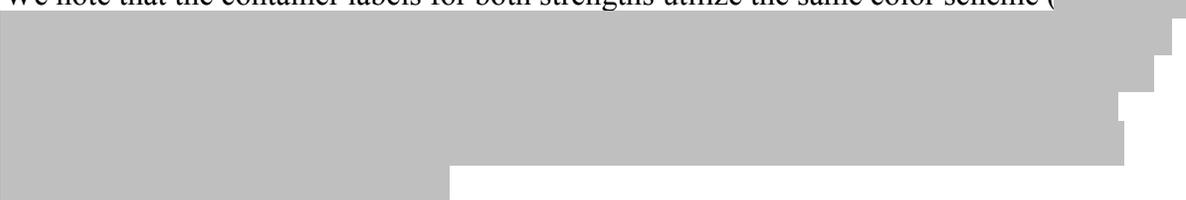
Packaging/Labeling

(b) (4)

18. Revise all USP controlled room temperature statements, in both the labels and labeling, to read as follows: “Store at 25°C (77°F); excursions permitted to 15°C – 30°C (59°F – 86°F) [see USP controlled room temperature].”
19. We note that carton labeling was not included in the submission. However, if you plan to market this product with carton labeling, then we request you submit this labeling as soon as possible.
20. The established name is presented in

(b) (4)

21. We note that the container labels for both strengths utilize the same color scheme ( (b) (4)



22. The dosage form (tablets) is not stated following the established name. Add this information.

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 I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

SARAH P MIKSINSKI
11/04/2010

MEMORANDUM OF MEETING MINUTES

MEETING DATE: Wednesday, October 27, 2010
TIME: 12:15 – 13:00 ET
LOCATION: Teleconference
APPLICATION: NDA 22-405
DRUG NAME: vandetanib tablets

FDA ATTENDEES: (Title and Office/Division)

Christine Moore, Ph.D., Deputy Director, Science and Policy, ONDQA
Sarah Pope Miksinski, Ph.D., Branch Chief, ONDQA
Haripada Sarker, Ph.D., CMC Lead, ONDQA
Wendy Wilson, Ph.D., Product Quality Reviewer, ONDQA
Tara Gooen, Team Leader, Office of Compliance (OC)
Vipul Dholakia, Compliance Officer, Office of Compliance
Don Henry, Regulatory Project Manager, ONDQA

ASTRAZENECA ATTENDEES:

Noel Baker – Senior Project Scientist, Global Operations
Ryan Gibb – Team Manager, Formulation science
David Holt – Principal Scientist, Analytical Sciences
Tony Lane – Principal Chemist, Process Development
Mike Parker, Pharmaceutical Development Project Director
Gavin Reynolds – Associate Principal Scientist, Formulation Science
John Smart – Associate Director, Product Development
Robert Timko - Director Regulatory Affairs CMC
David White – Manager, Pharmaceutical Development
Alan Watts – Manager, Process R&D

BACKGROUND:

As part of the original NDA submission, AstraZeneca included three comparability protocols (CP):

1. Change of Site for the Manufacture of Vandetanib
2. Change of Site for [REDACTED] ^{(b) (4)} of Vandetanib
3. Concurrent Validation for Vandetanib 300 Mg Film-Coated Tablet

Based on the review of the protocols, a teleconference was initiated to discuss the Agency's recommendations.

DISCUSSION POINTS AND ACTION ITEMS:

Regarding the CP for site changes (#1 & 2, above), OC indicated that a review of the site could be needed for inspectional purposes and CBE-0 supplement would not allow time for an appropriate review. AZ agreed to amend the CP to change the reporting category to CBE-30. Additionally OC requested to be copied on the supplements when they are submitted to help expedite the inspection process.

Regarding the concurrent validation protocol (#3), the Agency indicated that they do not approve process validation approaches, protocols, or specific batches used in the validation studies. The actual protocols, acceptance criteria and study outcomes would be evaluated during an inspection. It is the company's responsibility to conduct all studies necessary to assure the commercial manufacturing process is capable of consistently delivering high quality product. Orphan drug or unmet medical need status is recognized as a situation where, potentially, distribution of any given lot before completion of the initial process validation study may be justified for the greater public health benefit. A meeting request can be submitted to OC to discuss your validation proposal. The Agency also indicated that they do not typically see validation protocols within the application and that the application is not the appropriate location for such protocols. AZ decided to withdraw the CP for concurrent validation from the application.

Post meeting communication:

The following OC contact information was provided to AZ regarding the supplements for site changes: Project Manager Jaewon Hong (jaewon.hong@fda.hhs.gov) and one of the following people, depending on the location of the site: Team Leader Concepcion Cruz (concepcion.cruz@fda.hhs.gov) (US) or Compliance Officer Elizabeth Philpy (elizabeth.philpy@fda.hhs.gov) (ex-US).

The following OC contact information was provided to AZ regarding a meeting request to discuss any validation approaches: FDA/Office of Compliance/Division of Manufacturing and Product Quality/Division Director Rick Friedman, rick.friedman@fda.hhs.gov or OC/DMPQ/Manufacturing Assessment and Pre-Approval Compliance Branch/Branch Chief Barry Rothman, barry.rothman@fda.hhs.gov

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/s/

DON L HENRY
11/05/2010



NDA 022405

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

iPR Pharmaceuticals, Inc.
c/o AstraZeneca Pharmaceuticals LP
1800 Concord Pike
PO Box 8355
Wilmington, Delaware 19803-8355

ATTENTION: Debra N. Shiozawa, PhD
Director, Regulatory Affairs

Dear Dr. Shiozawa:

Please refer to your New Drug Application (NDA) dated July 7, 2010, received July 7, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vandetanib Tablets, 100 mg and 300 mg.

We also refer to your July 12, 2010, correspondence, received July 12, 2010, requesting review of your proposed proprietary name, Zictifa. We have completed our review of the proposed proprietary name, Zictifa, and have concluded that the name is unacceptable for the following reasons.

1.



(b) (4)

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”.

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 Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
10/07/2010



NDA 22405

NDA ACKNOWLEDGMENT

iPR Pharmaceuticals, Inc.
AstraZeneca Pharmaceuticals LP, Authorized US Agent
Attention: Debra N. Shiozawa, Ph.D.
Regulatory Affairs Director
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

Dear Dr. Shiozawa:

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: Zictifa™ (vandetanib, ZD6474) Tablets, 100 mg and 300 mg

Date of Application: July 7, 2010

Date of Receipt: July 7, 2010

Our Reference Number: NDA 022405

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 September 5, 2010 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.

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
09/21/2010

NDA 022405

FILING COMMUNICATION

iPR Pharmaceuticals, Inc.
AstraZeneca Pharmaceuticals LP, Authorized US Agent
Attention: Debra N. Shiozawa, Ph.D.
Regulatory Affairs Director
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

Dear Dr. Shiozawa:

Please refer to your new drug application (NDA) dated July 7, 2010, received July 7, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for ZICTIFA™ (vandetanib, ZD6474) Tablets, 100 mg and 300 mg.

We also refer to your submissions dated August 13, 18, 20, 24, 25, and September 9, 10, and 13, 2010.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is Priority. Therefore, the user fee goal date is January 7, 2011.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by December 17, 2010.

We also request that you submit the following information:

1. To fully assess the adverse events included in patient labeling, it will be necessary to submit written patient narratives for the following events in your Safety Database. Please provide these narratives within 2 weeks.
 - a. In Section 2.1.2.11 of your ISS, you note that 3 patients on Study 57 and 10 patients in your 300 mg monotherapy program developed heart failure. Please

provide written narratives and information on the patient's ejection fraction (if available) for the following patients.

D4200C00057/E1501010
D4200C00057/E1209008
D4200C00057/E3106015
D4200C00001/E0030065
D4200C00039/E6407009
D4200C00006/E0011002
D4200C00036/E0182002

- b. Please provide a written narrative for patient D4200C00057/E1409002 who discontinued due to hypertensive crisis. Please clarify whether this was a grade 4 event, hypertensive crisis or a grade 3 event. Please provide information on the end organ systems affected by this event.
- c. In Section 2.1.3.1 of your ISS, you noted that interstitial lung disease was reported in several patients in your non-small cell lung cancer studies and that pneumonitis has been reported in your study of medullary thyroid cancer. Please provide written narratives for the following patients.

D4200C00003/E0027006
D4200C00003/E0027006
D4200C00003/E0035001
D4200C00003/E0043002
D4200C00044/E1103010
D4200C00044/E3409009
D4200C00044/E5505013
D4200C00044/E5506005
D4200C00044/E5508003
D4200C00044/E5601001
D4200C00057/E2411001
D4200C00057/E2902009
D4200C00057/E3702006

- d. Please identify and provide written narratives for all patients with a concomitant elevation in ALT > 3xULN and bilirubin > 2xULN. In Section 3.2.1 of your ISS, it appears that 3 patients met these criteria. We were able to locate narratives for each of these patients, but will require additional information to fully assess this safety signal. For patient E3801030/Study 57, please state whether imaging studies were performed at the time of the patient's elevation in liver function tests (LFTs) and whether the patient had liver metastases. For patient E3703001/Study 44, please state whether the patient's pre-existing elevation in LFTs was due to metastatic disease and whether the LFTs improved following discontinuation of vandetanib.

- e. In Section 2.1.2.14 of your ISS, you note that 5 patients in the vandetanib arm in Study 44 developed a grade 4 increase in amylase. Please state whether these patients developed symptomatic pancreatitis and whether alternative explanations exist for this elevation in amylase.
- f. In Section 2.1.3.2 of your ISS, you note that 4 patients receiving vandetanib developed reversible posterior leukoencephalopathy. We have been unable to locate the narratives for 3 of the patients described; 2 patients on the sponsor-investigator study IRUSZACT0051 and 1 patient on the sponsor-investigator study IRUSZACT0070.
- g. In Section 2.1.2.1 of your ISS, you note that Stevens-Johnson syndrome was reported by 6 patients in the vandetanib 300 mg monotherapy program. We were able to identify the following patients and to locate e-narratives for these patients.

D4200C00007A/E0601505
D4200C00044/E5104001
D4200C00044/E5202003
D4200C00044/E5202010
D4200C00057/E1203007
D4200C00057/E3803017

However, we were unable to fully assess the details of their skin condition, need for admission to specialized units, degree of infection, skin areas involved and the dressing used, etc. Further, it appears that none of these patients discontinued due to Stevens-Johnson syndrome.

- h. In Section 2.1.2.5 of your Integrated Summary of Safety (ISS), you identify 2 patients who have developed torsades de pointes. Please provide a written narrative for the patient identified in Study 79.
2. To fully assess the adverse events associated with vandetanib, it will be necessary to submit written patient narratives for the following events in Study 58. Please provide these narratives within 2 weeks.
- a. Heart Failure: patient E1901004
 - b. Hypertensive Crisis: E2503001, E1401001, E1701017, E1703006, E3301007
 - c. Interstitial Lung Disease/Pneumonitis: E2501011, E2501015, and E2501019
 - d. Possible Intestinal Perforation : E1601004, E0003002, E0014001, E1702005
 - e. Other: E0002002 (convulsion), E2501028 (sensorimotor neuropathy), E2801024 (myopathy)
 - f. Skin Disorders: E2501017, E2501031
3. Please provide a discussion of the applicability of data obtained outside the U.S. to patients within the US. This should include a comparison of progression free survival and

an assessment of adverse events in patients who received vandetanib outside the U.S. and within the U.S.

If you have not already done so, you must 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>. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

REQUIRED PEDIATRIC ASSESSMENTS

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

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

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

Sincerely,

{See appended electronic signature page}

Alice Kacuba, RN, MSN, RAC
Chief, Project Management Staff
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

ALICE KACUBA
09/17/2010



NDA 22-405

INFORMATION REQUEST

AstraZeneca Pharmaceuticals LP
Attention: Debra N. Shiozawa, Ph.D.
Director, Regulatory Affairs
1800 Concord Pike
PO Box 8355
Wilmington DE 19803-8355

Dear Dr. Shiozawa:

Please refer to your new drug application (NDA) originally submitted on July 7, 2010, under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, for vandetanib tablets.

We are reviewing the 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. Provide further clarification for the proposed design space. It would facilitate the review if you could provide a summary of how the risk assessment was done and experimental data that supports the proposed design space.

Drug Product:

2. The ranges for excipients in the commercial formulation are not adequately supported by the provided data. Provide clarification and data, as needed, to support your rationale concerning the following:



(b) (4)

(b) (4)



d. Provide data describing how raw material properties impact on manufacturability.

(b) (4)



5. Based on the submitted information, your proposed dissolution method and specification are not acceptable, for the following reasons:

(b) (4)



We recommended that a new dissolution method be developed and validated using conditions where the [REDACTED] (b) (4)

[REDACTED] Provide the complete dissolution data (individual, mean-SD, and plots) generated during the development/validation of your dissolution test.

[REDACTED] (b) (4)

Provide the following information to support your proposed model:

- a. Summary of multivariate model (e.g. type of DOE and resolution, factors, responses, replicates, ANOVA tables with α and p-values, plots, residuals, and scale of manufacture), model verification data, and plans for model maintenance throughout the product life cycle.
 - b. Details outlining how the model would be used to ensure product quality (i.e. meeting acceptable dissolution specification) throughout the design space
 - c. Comparison of model prediction with measured dissolution
7. Your design space as in tables in Section 2.3 is not consistent with ICHQ8(R) definition of “The multidimensional combination and interaction of **input** variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality.” You propose a design space [REDACTED] (b) (4)

[REDACTED].
Propose a design space for drug product processing consistent with the ICH Q8(R) definition. Provide experimental data, including results from studies summarized in Section P.2 of your submission and their respective scale of manufacture that supports the proposed design space. Include a discussion about the interaction of input parameters, such as raw material attributes, and process parameters. Update section P.3 to include the design space.

8. Provide details regarding [REDACTED] (b) (4)
[REDACTED] used for ZICTIFA 100mg and 300 mg tablet
manufacture. Clarify if [REDACTED] (b) (4)
Provide a discussion, supported by data, [REDACTED] (b) (4)
[REDACTED]

9. Note that all tests listed on the specification sheet need to be performed to release all batches. The specification should include all in-process tests proposed in lieu of release tests with a notation describing that these tests are performed in-process. Identify which tests are performed on the tablet cores and which tests are performed on the final coated tablets. Identify all the methods on the specification sheet by their specific method number. Provide a revised drug product specification sheet.
10. In light of our comments concerning the dissolution method which is also used to support much of the formulation and manufacturing design space, provide a reassessment of validity of the proposed design space.
11. Provide statistical analysis of the stability data to support 36 month expiration dating period based on the 24-month data provided in your submission.

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 I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22405	ORIG-1	IPR PHARMACEUTICA LS INC	Zictifa (Vandetanib)

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/s/

SARAH P MIKSINSKI
09/15/2010

DATE: 25-AUG-2010
TO: NDA 22-405 [Zictifa™ {proposed} (vandetanib) tablets; 100 mg and 300 mg] Inspection Team
FROM: Wendy Wilson-Lee, Ph.D., Review Chemist [office: 301-796-1651; wendy.wilson@fda.hhs.gov]
THROUGH: Christine Moore, Ph.D., Deputy Director for Science and Policy, ONDQA
SUBJECT: Considerations for Inspection for NDA 22-405

iPR Pharmaceuticals, Inc. seeks approval of vandetanib film-coated tablets for the treatment of patients with unresectable, locally advanced, or metastatic medullary thyroid cancer under NDA 22-405. This memo provides:

- An overview of the drug product manufacturing process
- A summary of the QbD elements in the drug product development, manufacturing, and control strategy
- A summary of the reviewer's risk assessment
- A summary of the CMC perspective on areas of consideration during inspections

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/s/

WENDY I WILSON
10/13/2010

SARAH P MIKSINSKI
10/15/2010

From: Doman, Natalie [mailto:Natalie.Doman@astrazeneca.com]
Sent: Wednesday, August 25, 2010 3:23 PM
To: Skarupa, Lisa
Subject: RE: NDA 22405

Hi, Lisa:

I'm writing to confirm that I received your e-mail, and to thank you for letting us know of your plans.

Regards,
Natalie

Confidentiality Notice: This message is private and may contain confidential and proprietary information. If you have received this message in error, please notify us and remove it from your system and note that you must not copy, distribute or take any action in reliance on it. Any unauthorized use or disclosure of the contents of this message is not permitted and may be unlawful.

From: Skarupa, Lisa [mailto:Lisa.Skarupa@fda.hhs.gov]
Sent: Wednesday, August 25, 2010 1:52 PM
To: Doman, Natalie
Cc: Shiozawa, Debi N
Subject: NDA 22405

Dear Natalie and Debi,

This is to let you know that we plan to bring NDA 22405 to an Oncology Drug Advisory Committee in Dec 1, 2010.
The plan to bring you to an ODAC is NOT public yet and should not be disclosed until the FR publishes.

Please let me know if you have any questions.

Lisa

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22405

ORIG-1

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LS INC

Zictifa (Vandetanib)

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/s/

LISA M SKARUPA
08/25/2010

REQUEST FOR CONSULTATION

TO (*Division/Office*) Division of Anti-Infective and
Ophthalmology Products (DAIOP)
Frances LeSane and Maureen Dillon-Parker

FROM: HFD-150Lisa Skarupa

DATE
August 20, 2010

IND NO.

NDA NO.
22405

TYPE OF DOCUMENT
Amendment Sequence 0007
EDR

DATE OF DOCUMENT
08/13/2010

NAME OF DRUG: Vandetanib
"ZICTIFA"

PRIORITY
CONSIDERATION

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE
November 19, 2010

NAME OF SPONSOR: Astra Zeneca

REASON FOR REQUEST

I. GENERAL

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

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

TYPE A OR B NDA REVIEW
END OF PHASE II MEETING
CONTROLLED STUDIES
PROTOCOL REVIEW
OTHER

CHEMISTRY REVIEW
PHARMACOLOGY
BIOPHARMACEUTICS
OTHER

III. BIOPHARMACEUTICS

DISSOLUTION
BIOAVAILABILITY STUDIES
PHASE IV STUDIES

DEFICIENCY LETTER RESPONSE
PROTOCOL-BIOPHARMACEUTICS
IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
DRUG USE e.g. POPULATION EXPOSURE,
ASSOCIATED DIAGNOSES
CASE REPORTS OF SPECIFIC REACTIONS (*List below*)
COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP

REVIEW OF MARKETING EXPERIENCE, DRUG USE AND
SAFETY
SUMMARY OF ADVERSE EXPERIENCE
POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

9 CLINICAL

9 PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: There is an Astra-Zeneca ophthalmologist report that can be found by going to Amendment 7 submitted 8/13/2010 and clicking on the hyperlink in the cover letter, going directly to 5.3.5.1.23.

Questions:

In study 58, 83.6% of the patients treated with the study drug vandetanib had abnormalities in either eye as compared to 61.5% of the patients in the placebo arm.

- 1) Please comment on the nature of vortex keratopathy; specifically, the natural history and need for treatment of this condition.
- 2) Please comment on the consultant ophthalmologist's conclusion that there is no need to stop or adjust dosing in instances where vortex keratopathy develops.
- 3) Please comment on the clinical significance of the other abnormalities that were increased in the treatment arm compared to placebo as derived from Table 11.3.8.1.17. Specifically:
 - a. Stromal abnormalities (17.6% v. 2%)
 - b. Optic disc abnormalities (19% v. 3%)
- 4) Astra Zeneca's ophthalmology report states that "VK rarely, if ever, needs treatment stopped." What would be the conditions in which treatment should be stopped. The report also went on to say that once stopping therapy, "regression usually follows." If regression does not follow, what is the sequelae, and does the impairment continue to progress?

SIGNATURE OF REQUESTER Lisa Skarupa	METHOD OF DELIVERY (<i>Check one</i>) <input type="checkbox"/> FAX <input checked="" type="checkbox"/> EMAIL
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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

Application
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Zictifa (Vandetanib)

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/s/

LISA M SKARUPA
08/24/2010

From: Doman, Natalie [mailto:Natalie.Doman@astrazeneca.com]
Sent: Thursday, August 05, 2010 4:23 PM
To: Skarupa, Lisa
Subject: RE: Information Request Aug 5th clinical datasets

Hi, Lisa:

Thank you for sending this—I have passed it along to our clinical team for resolution.

Regards,
Natalie

Confidentiality Notice: This message is private and may contain confidential and proprietary information. If you have received this message in error, please notify us and remove it from your system and note that you must not copy, distribute or take any action in reliance on it. Any unauthorized use or disclosure of the contents of this message is not permitted and may be unlawful.

From: Skarupa, Lisa [mailto:Lisa.Skarupa@fda.hhs.gov]
Sent: Thursday, August 05, 2010 3:34 PM
To: Doman, Natalie
Subject: Information Request Aug 5th clinical datasets

Hello Natalie,

As agreed in yesterday's teleconference between AstraZeneca and our Clinical Team, here are our request for a clarification:

You have provided multiple adverse event datasets.

- In dataset AELOG, I found 241 SAEs.
- In dataset SAE, I found 208 events.
- In dataset AE, I found 232 events.
- In dataset R_AE, I found 160 events using the variable AEEVNT05 and 231 events using the variable AESER.

Please explain these differences and state which variable provides the correct number of SAEs.

Sincerely,
Lisa

Application
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Product Name

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/s/

LISA M SKARUPA
08/05/2010



[INTERNAL COMMUNICATION]

MEMORANDUM OF TELECON

DATE: August 4, 2010

TIME: from 3:15pm to 3:30pm

APPLICATION NUMBER: NDA 022405

BETWEEN: AstraZeneca

AND Division of Drug Oncology Products

SUBJECT: CLARIFICATION REQUEST FROM FDA TO ASTRAZENECA

FDA requested a teleconference with AstraZeneca to discuss their NDA submission. The discussion focused on their submitted clinical datasets; FDA to send the question regarding the clinical datasets and to schedule a follow-up tcon.

From AstraZeneca:

Donna Francher - Vice President, Vandetanib
Peter Langmuir, M.D. - Senior Director, Medical Science
Nigel Midford, Senior Statistical Programmer
Jessica Read – Statistician (at U.K.)
Debra Shiozawa, Ph.D - Director, US Regulatory Affairs
Mark Steinberg, M.D., Senior Safety Medical Director
James Vasselli, M.D. - Director, Clinical Research
Alan Webster, B.Sc., M.Sci. - Global Product Statistician (at U.K.)
Natalie Doman, Associate Director, Regulatory Affairs

From FDA:

Ellen Maher, M.D., Clinical Team Leader, CDTL, DDOP
Katherine Delorenzo, M.D., Clinical Reviewer, DDOP
Geoffrey Kim, M.D., Clinical Reviewer, DDOP

Application
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Type/Number

Submitter Name

Product Name

NDA-22405

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LS INC

Zictifa (Vandetanib)

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/s/

LISA M SKARUPA
08/05/2010

From: Skarupa, Lisa
Sent: Wednesday, July 28, 2010 5:05 PM
To: 'Doman, Natalie'
Subject: RE: July 28th I.R. QT study

Hi Natalie,

Yes, every NDA application has to be complete and have ALL the information we need to review that Application.

Lisa

From: Doman, Natalie [mailto:Natalie.Doman@astrazeneca.com]
Sent: Wednesday, July 28, 2010 4:59 PM
To: Skarupa, Lisa
Subject: RE: July 28th I.R. QT study

Hi, Lisa:

I'm confirming that I received your request and have forwarded it to my colleagues so they can begin to prepare a response. I do have one clarifying question: The Study 21 report and datasets were previously submitted to NDA (b) (4) and have been cross-referenced in the current submission, NDA 22-405. The location of this information was provided in Module 1.4.4, Cross Reference to Other Applications. Just to make sure I understand—do you want us to re-submit all of the information below as opposed to accessing it through NDA (b) (4)?

Thanks for your help,
Natalie

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From: Skarupa, Lisa [mailto:Lisa.Skarupa@fda.hhs.gov]
Sent: Wednesday, July 28, 2010 4:25 PM
To: Doman, Natalie
Subject: July 28th I.R. QT study

Good afternoon Natalie,

1. Please submit to your NDA 22405 the study report to Study 21 and related datasets.
2. Please fill out the "Highlights of Clinical Pharmacology" table attached and submit with your submission for Study 21.

If you have any questions, please do not hesitate to contact me.
Please send submit the requested information in 7 days.

Sincerely,
Lisa

<<HighlightsofClinicalPharmacology.doc>>

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22405

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Zictifa (Vandetanib)

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/s/

LISA M SKARUPA
07/28/2010

From: [Doman, Natalie](#)
To: [Skarupa, Lisa](#); [Shiozawa, Debi N](#);
Subject: RE: AstraZeneca - vandetanib NDA 22-405
Date: Tuesday, July 20, 2010 11:51:46 AM
Attachments: [NDA022405-study-titles.doc](#)

Good morning, Ms. Skarupa:

I'm following up to inform you that we are working towards the timelines you provided in your request for information below. If there are any unforeseen delays, I will let you know.

I would also like to let you know how I have handled FDA information requests for past submissions, to make sure it is acceptable to you. If you would prefer that I proceed differently for this application, please advise. I generally confirm that I have received your information request, and will follow up with a timeframe for response once it is known. After I receive notification that the response has been successfully processed through the Gateway, I will inform you. If some time will pass between completion of the response and processing through the Gateway, I may provide an advance copy to you via e-mail so the review team will have access to the response as soon as possible. Similarly, if you pose a question that can be quickly answered via e-mail, I will respond via e-mail. Do you wish for me to follow up with an official submission of an e-mail response?

Finally, I have attached a screen shot provided by the Office of Business Informatics. I think it will be helpful for you to have a visual representation in hand when we discuss the feedback AZ received from OBI.

Thanks and Regards,
Natalie

Natalie Doman

Associate Director

AstraZeneca Pharmaceuticals LP

Research and Development, Regulatory Affairs
C2B-705A, 1800 Concord Pike, PO Box 15437, Wilmington, DE, 19850-5437
Tel +1 302 885 1441 Fax +1 302 886 2822
natalie.doman@astrazeneca.com

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From: Skarupa, Lisa [<mailto:Lisa.Skarupa@fda.hhs.gov>]
Sent: Monday, July 19, 2010 10:16 AM
To: Shiozawa, Debi N
Cc: Doman, Natalie
Subject: RE: AstraZeneca - vandetanib NDA 22-405

Good morning,

The Clinical Team would like for Astra Zeneca to please add to the submitted DSI information you included in your NDA submission the following:

(I saw your DSI information, I know you had the site information, and number of patients) I could not find the matching A.E.s to that site, nor the response rates and number of protocol violations. Please send this information as soon as possible; please let me know if end of next week is possible. The clinical team wanted in a table format please, see below.

Site #				
Address	# Pts Enrolled	# Grade 3-4 AEs	Response Rate	# Protocol Violations
Telephone No.				

Sincerely,

Lisa

Regulatory Project Manager

301-796-2219

From: Shiozawa, Debi N [mailto:debi.shiozawa@astrazeneca.com]
Sent: Monday, July 19, 2010 8:59 AM
To: Skarupa, Lisa
Cc: Doman, Natalie
Subject: AstraZeneca - vandetanib NDA 22-405

Lisa,

Thank you for your phone message late last week.

We are excited about working with you and beginning the review of the vandetanib NDA 22-405.

Natalie Doman, Associate Director in Regulatory (email: Natalie.doman@astrazeneca.com Phone: (302) 885-1441) works with me on the vandetanib project. Natalie will be your day-to-day contact person for matters regarding this NDA. However, please include us both on any email correspondence so that we can ensure our team members are communicated the appropriate information as quickly as possible.

As you should be aware, Natalie placed a phone call to you last week regarding the NDA orientation meeting date and a matter raised by FDA's Office of Business Informatics (OBI). We would appreciate feedback so that we can determine a way forward.

Regards,
Debi Shiozawa

Debra N. Shiozawa, Ph.D.

Regulatory Affairs Director
Office (302) 886-3137
debi.shiozawa@astrazeneca.com

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not permitted and may be unlawful.

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/s/

LISA M SKARUPA
07/20/2010

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, HFD 150 301-796-2219		
REQUEST DATE July 16, 2010	IND NO.	NDA/BLA NO. 022405	TYPE OF DOCUMENTS (via Gateway/ eDR) (PLEASE CHECK OFF BELOW) \\cdsesub1\EVSPROD\NDA022405\0000	
NAME OF DRUG Vandetanib, ZD6474 ZICTIFA Tablets: 100; 300 mg		PRIORITY CONSIDERATION Applicant request priority review	CLASSIFICATION OF DRUG NME	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting) Primary Reviews Nov 29 th (tentative; PDUFA Jan 7, 2011)
NAME OF FIRM: AstraZeneca Pharmaceuticals LP		PDUFA Date: Jan 7, 2011		
TYPE OF LABEL TO REVIEW				
TYPE OF LABELING: (Check all that apply) <input type="checkbox"/> PACKAGE INSERT (PI) <input type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input type="checkbox"/> CARTON/CONTAINER LABELING <input type="checkbox"/> MEDICATION GUIDE <input type="checkbox"/> INSTRUCTIONS FOR USE(IFU)		TYPE OF APPLICATION/SUBMISSION <input checked="" type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> IND <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> PLR CONVERSION		REASON FOR LABELING CONSULT <input type="checkbox"/> INITIAL PROPOSED LABELING <input type="checkbox"/> LABELING REVISION
EDR link to submission: \\cdsesub1\EVSPROD\NDA022405\0000				
Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. The DDMAC reviewer will contact you at a later date to obtain the substantially complete labeling for review.				
COMMENTS/SPECIAL INSTRUCTIONS: NEW NDA. Assigned DDOP Clinical Team for this new NDA: CDTL=Ellen Maher; Geoffrey Kim/ Ellen Maher; Katie DeLorenzo/Amna Ibrahim. Indication: the treatment of patients with unresectable locally advanced or metastatic medullary thyroid cancer. The Applicant requested for a priority review. Filing Meeting Day 30 (Aug 6, 2010) Mid-Cycle Meeting: Oct 7, 2010 (actual meeting to be scheduled) Labeling Meetings: To be scheduled, Oct-November (possibly complete this NDA earlier than Jan 7 th) Wrap-Up Meeting: Usually the last Labeling Meeting.				
SIGNATURE OF REQUESTER Lisa Skarupa				
SIGNATURE OF RECEIVER		METHOD OF DELIVERY (Check one) <input type="checkbox"/> eMAIL <input type="checkbox"/> HAND		

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22405

ORIG-1

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LS INC

Zictifa (Vandetanib)

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/s/

LISA M SKARUPA
07/16/2010

REQUEST FOR CONSULTATION

TO (Office/Division): **SEALD for labeling review**

FROM (Name, Office/Division, and Phone Number of Requestor): **Lisa Skarupa, DDOP RPM**

DATE July 15, 2010	IND NO.	NDA NO. 022405	TYPE OF DOCUMENT eDR \\cdsesub1\EVSPROD\NDA022405\0000	DATE OF DOCUMENT July 7, 2010
NAME OF DRUG ZICTIFA (vandetanib, ZD6474)Tablets 100, 300mg		PRIORITY CONSIDERATION Applicant requested priority Review	CLASSIFICATION OF DRUG NME	DESIRED COMPLETION DATE November 29th 2010 PDUFA Jan7, 2011

NAME OF FIRM: **AstraZeneca Pharmaceuticals LP**

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 checked="" type="checkbox"/> PAPER NDA | <input 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"/> BIOAVAILABILTY 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 checked="" type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|--|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: Assigned DDOP Clinical Team for this new NDA: CDTL=Ellen Maher; Geoffrey Kim/ Ellen Maher; Katie DeLorenzo/Amna Ibrahim. Indication: the treatment of patients with unresectable locally advanced or metastatic medullary thyroid cancer. Applicant sent it via eDR, here is the link:
\\cdsesub1\EVSPROD\NDA022405\0000 Filing Meeting Day 30 Aug 6, 2010 (actual meeting to be scheduled)
Day 74 Sept 19, 2010 (actual meeting to be scheduled); Midcycle Oct 7, 2010 (actual meeting to be scheduled)

SIGNATURE OF REQUESTOR Lisa Skarupa, DDOP RPM sending via DARRTS	METHOD OF DELIVERY (Check one) <input type="checkbox"/> DFS <input type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
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PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER
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Application
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Submission
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Submitter Name

Product Name

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/s/

LISA M SKARUPA
07/15/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Office/Division): Devi Kozeli/QT-IRT		FROM (Name, Office/Division, and Phone Number of Requestor): Lisa Skarupa, DDOP RPM HFD 150 301-796-2219		
DATE July 15, 2010	IND NO.	NDA NO. 022405	TYPE OF DOCUMENT eDR \\cdsesub1\EVSPROD\NDA022405\0000	DATE OF DOCUMENT July 7, 2010
NAME OF DRUG Vandetanib, ZD6474 ZICTIFA Tablets: 100; 300 mg	PRIORITY CONSIDERATION Applicant request priority review	CLASSIFICATION OF DRUG NME	DESIRED COMPLETION DATE Primary Reviews Nov 29th, 2010. PDUFA Jan 7, 2011	
NAME OF FIRM: AstraZeneca Pharmaceuticals LP				
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 2a MEETING <input type="checkbox"/> END-OF-PHASE 2 MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY / EFFICACY <input checked="" 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 type="checkbox"/> OTHER (SPECIFY BELOW):				
II. BIOMETRICS				
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III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE 4 STUDIES <input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST				
IV. DRUG SAFETY				
<input type="checkbox"/> PHASE 4 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 checked="" type="checkbox"/> CLINICAL <input type="checkbox"/> NONCLINICAL				
COMMENTS / SPECIAL INSTRUCTIONS: NEW NDA. Assigned DDOP Clinical Team for this new NDA: CDTL=Ellen Maher; Geoffrey Kim/ Ellen Maher; Katie DeLorenzo/Amna Ibrahim. Indication: the treatment of patients with unresectable locally advanced or metastatic medullary thyroid cancer. Applicant sent it via eDR, the link is above. The Applicant requested for a priority review. Filing Meeting Day 30 Aug 6, 2010 (actual meeting to be scheduled); Day 74 Sept 19, 2010 (actual meeting to be scheduled); Midcycle Oct 7, 2010 (actual meeting to be scheduled) Clinical's questions to IRT: <ul style="list-style-type: none"> • Please comment on whether additional studies should be done by the applicant. • Please comment on whether the risk of QT prolongation and arrhythmia is adequately explained in the package insert. 				
SIGNATURE OF REQUESTOR Lisa Skarupa		METHOD OF DELIVERY (Check one) <input type="checkbox"/> DFS <input type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND		

PRINTED NAME AND SIGNATURE OF RECEIVER

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Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22405

ORIG-1

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PHARMACEUTICA
LS INC

Zictifa (Vandetanib)

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/s/

LISA M SKARUPA
07/15/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): OSE for DRISK		FROM: Lisa Skarupa, DDOP RPM HFD 150		
DATE July 15, 2010	IND NO.	NDA NO. 022405	TYPE OF DOCUMENT eDR link: \cdsesub1\EVSPROD\NDA022405\0000	DATE OF DOCUMENT July 7, 2010
NAME OF DRUG Vandetanib, ZD6474 ZICTIFA Tablets, 100 and 300 mg	PRIORITY CONSIDERATION Applicant request priority review	CLASSIFICATION OF DRUG NME	DESIRED COMPLETION DATE Primary Reviews Nov 29 th , 2010. PDUFA Jan 7, 2011	
NAME OF FIRM: AstraZeneca Pharmaceuticals LP				
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 type="checkbox"/> OTHER (<i>SPECIFY BELOW</i>):				
II. BIOMETRICS				
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III. BIOPHARMACEUTICS				
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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: Assigned DDOP Clinical Team for this new NDA: CDTL=Ellen Maher ; Geoffrey Kim/ Ellen Maher; Katie DeLorenzo/Amna Ibrahim. Indication: the treatment of patients with unresectable locally advanced or metastatic medullary thyroid cancer. Applicant sent it via eDR, here is the link: \cdsesub1\EVSPROD\NDA022405\0000 The Applicant requested for a priority review.				
Filing Meeting Day 30	Aug 6, 2010 (actual meeting to be scheduled)			
Day 74	Sept 19, 2010 (actual meeting to be scheduled)			
Midcycle	Oct 7, 2010 (actual meeting to be scheduled)			
SIGNATURE OF REQUESTER Lisa Skarupa		METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input checked="" type="checkbox"/> DARRTS		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22405

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/s/

LISA M SKARUPA
07/15/2010



FOOD AND DRUG ADMINISTRATION

Meeting Date and Time: June 10, 2010, 11:00 a.m.
Meeting Type: Type B
Meeting Category: Pre-NDA meeting
Meeting Location: Bldg. 22, Room 1313
Application Number: IND 060042
Product Name: PF-02341066
Received Briefing Package March 27, 2009
Sponsor Name: AstraZeneca
Meeting Requestor: Natalie S. Doman
Meeting Chair: Virginia Ellen Maher, M.D., Medical Team Leader, DDOP
Meeting Recorder: Diane Hanner, RPM

Meeting Attendees:

- Donna Francher, Vice President, Global Product Development
- Peter Langmuir, M.D., Senior Director, Medical Science
- Jessica Read, Statistician
- Debra Shiozawa, Ph.D., Director, US Regulatory Affairs
- James Vasselli, M.D., Director, Clinical Research
- Alan Webster, B.Sc., M.Sci., Global Product Statistician
- Antoine Yver, Vice President, Clinical Development, Oncology & Infection
- Natalie Doman, Associate Director, Regulatory Affairs

FDA Attendees

- Robert Justice, M.D., Director, DDOP
- Anthony Murgo, M.D., Acting Deputy Director, DDOP
- Virginia Ellen Maher, M.D., Medical Team Leader, DDOP
- Ian Waxman, M.D., Medical Officer, DDOP
- Shenghui Tang, Ph.D., Acting Biostatistics Teamleader, DBV
- Brenda Gehrke, Ph.D., Pharmacology Toxicology Reviewer, DDOP
- Diane Hanner, M.P.H., M.S.W., Senior Program Management Officer, DDOP

BACKGROUND:

Vandetanib has been developed for the treatment of patients with unresectable locally advanced or metastatic medullary thyroid cancer. Vandetanib received orphan drug designation on October 21, 2005 and a fast track status on December 22, 2005. The sponsor submitted a meeting request on March 15, 2010. FDA sent its preliminary responses to the questions on June 2, 2010.

DISCUSSION:**Question 1:**

Does the Agency agree that the proposed additional safety analyses of Study 58, as described in the information package, will permit better assessment of the benefit-risk profile?

FDA Response:

Yes. However, the development of adverse events is not directly related to the duration of exposure since patients who remain on therapy for a prolonged period, by definition, have tolerated the study drug.

Meeting Discussion: The sponsor's planned safety analyses are acceptable.

Question 2:

AstraZeneca would like the Agency's view on our plans for the updated safety and survival analyses.

FDA Response:

The safety update data cut-off date of June 1, 2010, is acceptable as long as your application is submitted within approximately 6 months of this cut-off date.

Meeting Discussion: The application will be submitted in July 2010. It will contain efficacy data up to July 2009. The safety update will contain additional safety data up to June 2010. This is acceptable.

Question 3:

Does the Agency agree to the plans for a safety update, with a 1 June 2010 data cut-off, be submitted not later than month-4 (or potentially may be submitted by month-3) if this NDA is granted a priority review?

FDA Response: Yes.

Meeting Discussion: No discussion needed.

Question 4:

Based on the data summary presented, AstraZeneca would appreciate the Agency's advice on any key considerations we should address in the submission and any recommendations on the data package.

FDA Response: Death in the absence of progression was only considered a PFS event if death occurred within 3 months of the last evaluable RECIST assessment. Additionally, corrections were made for calcified lesions and the appearance of new hypodense or hypo-intense liver lesions. In your submission, please provide a PFS analysis including all death events, regardless of time from last assessment, and all progression events, without any correction for calcified lesions or the appearance of new hypodense or hypo-intense liver lesions. This analysis should use a data cutoff date of July 31, 2009. Please include in your submission your justifications for incorporating these modifications into your primary PFS analysis.

PFS and response rate data were less robust in your open-label phase II trial D4200C00008 than in your randomized phase III trial. The median PFS was >2 months longer in the phase III trial and the objective response rate was twice as high (20% vs. 45%). Please include in your submission possible explanations for these differences in efficacy endpoint results between trials.

Meeting Discussion: Within one month of submission, the sponsor will provide two additional sensitivity analyses, one in which all deaths in the absence of progression are considered a PFS event and one in which calcified and hypodense lesions are assessed for progression.

The sponsor will also submit additional information on the difference in PFS and response rate between the phase 2 and phase 3 studies.

An interim analysis of overall survival will be provided with a cut-off date of July 2009. The final analysis will be available in approximately 2012. This study was not powered for overall survival.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

IND-60042

GI-1

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LS LP

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/s/

VIRGINIA E MAHER
07/08/2010

Fax



DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150

Parklawn Building

5600 Fishers Lane, Rockville, MD 20857

To: Omaira Melendez Nesbit, PharmD

From: Amy Baird, CSO

Fax: 302-886-2822

Fax: 301-827-4590

Phone: 302-886-2762

Phone: 301-594-5779

Pages (including cover): 30

Date: July 15, 2005

Re: IND 60,042 ZD6474. Industry meeting held June 13, 2005.

Urgent **For Review** **Please Comment** **Please Reply** **Please Recycle**

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● **Comments:**

Attached are the official FDA meeting minutes from the June 13, 2005, industry meeting in which we discussed AZD6474 for the treatment of thyroid cancer. Please call should you have any questions.

Thank you,

Amy Baird

INDUSTRY MEETING MINUTES

MEETING DATE: June 13, 2005 **TIME:** 3:30pm **LOCATION:** C

IND/NDA IND 60,042

Meeting Request Submission Date: 4-7-05
Briefing Document Submission Date: 5-16-05
Additional Submission Dates:

DRUG: ZD6474

SPONSOR/APPLICANT: AstraZeneca

TYPE OF MEETING: EOP2. Discuss development plan for ZD6474 in the treatment of thyroid carcinoma with mutation in the RET gene.

Proposed Indication: Treatment of thyroid carcinoma with mutation in the RET gene.

FDA PARTICIPANTS:

Robert Justice, M.D., Acting Director, DODP
Ramzi Dagher, M.D., Clinical Team Leader, DODP
Qin Ryan, M.D., Clinical Reviewer, DODP
Rajeshwari Sridhara, Ph.D., Statistical Team Leader, DBI
Shenghui Tang, Ph.D., Statistical Reviewer, DBI
Gene Williams, Ph.D., Biopharm Reviewer, OCPB (pre-only)
Amy Baird, Consumer Safety Officer, DODP

AstraZeneca participants:

Ronald C. Falcone, Ph.D., Dir., US Regulatory Affairs
Lawrence Way, Dir., Global Regulatory Affairs
Omaira Melendez Nesbit, Pharm.D., Assoc. Dir., US Reg. Affairs
Peter Langmuir, M.D., Sr. Dir., Medical Science
Jeannie Hou, M.D., Assoc. Dir., Clinical Research
Alan Webster, B.Sc., M.Sc., Global Product Statistician
Anderson Ryan, Ph.D., Sr. Translational Science Strategist
Menna Holcombe, M.Sc., Reg. Affairs Manager, US Reg. Affairs
Donna Francher, ZD6474 Global Product Director
Gert Kolvenbag, M.D., Development Team Leader
Samuel Wells, M.D., Principal Investigator

MEETING OBJECTIVES:

Discuss sponsor's questions in briefing document dated May 16, 2005.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

- 1. The ongoing phase II study D4200C00008 is a single-arm, open-label study that will enroll a total of 30 patients with locally advanced or metastatic hereditary MTC, all of whom have a defined mutation in the RET gene (please refer to protocol in Appendix G). Preliminary data show 1 partial response out of 5 evaluable patients and significant declines ($\geq 50\%$ decrease from baseline) in the biomarker CTN in all 7 patients that were evaluable at one month on study. The primary endpoint of the study is to demonstrate an objective response rate of $\geq 20\%$, using RECIST criteria, and secondary endpoints include biochemical and symptomatic response to demonstrate further evidence of clinical benefit. Hereditary MTC is a rare disease, and there is no effective therapy for patients with locally advanced or metastatic disease. ZD6474 represents a targeted approach to the treatment of this disease by inhibiting the activity of the constitutively activated RET protooncogene, which is the critical pathogenic factor in this disease. Mutations in the RET gene are defined prior to entry into the study. AstraZeneca therefore believes that the current design of study D4200C00008 is suitable for registration of ZD6474 in patients with locally advanced or metastatic hereditary MTC. Does the Agency agree?**

FDA Response:

Approval based upon this single study is problematic for the following reasons:

If you are relying on response rate as a surrogate endpoint reasonably likely to predict clinical benefit (strategy for accelerated approval), there is no evidence that response rate in this population is a surrogate for survival or symptom benefit. With various combination chemotherapy regimens producing a 15-20% response rate in this disease setting, no effect on survival has been demonstrated.

The adequacy of a single arm study to support accelerated approval would depend upon the number of CRs and PRs, duration of response, and a risk-benefit judgment. Further evaluation would be required to confirm benefit.

The database of 30 patients is likely to be too small for an appropriate risk benefit evaluation.

- 2. Mutation or rearrangement of the RET gene, leading to activation of RET tyrosine kinase signaling, are seen in some patients with sporadic MTC or PTC. To study the efficacy of ZD6474 in this setting, AstraZeneca is proposing to conduct a second study in 60 patients with locally advanced or metastatic MTC or PTC whose tumors, either due to point mutations or chromosomal inversion or translocation, have constitutive activation of the**

RET protooncogene. This proposed study will be a randomized, placebo-controlled study, and patients on the placebo arm will be allowed to receive ZD6474 at disease progression or after 6 months on study. The primary endpoint will be objective response rate, using RECIST criteria. However, given the clinical benefit that could occur in the absence of objective responses, the primary endpoint will be supported by the secondary endpoints of biochemical and symptomatic response. Biochemical response will include changes in CTN and CEA (for patients with MTC), or thyroglobulin (for patients with PTC). Symptomatic response will include measures of quality of life, including disease-related diarrhea symptoms, weight gain and pain control. The primary and secondary endpoints together will be able to demonstrate substantial evidence of clinical benefit. AstraZeneca therefore believes that this study will be suitable for registration of ZD6474 in patients with locally advanced or metastatic MTC and PTC with mutation in the RET gene. Does the Agency agree?

FDA Response:

Objective response rate in this disease is not supportive of clinical benefit in itself. An alternative strategy would be to consider symptom benefit as the primary endpoint in a double blinded study. You should focus on the most relevant symptoms and submit a proposal for our review with a complete SAP.

We are concerned about the proposed small size of this study. The large number of secondary endpoints being evaluated and potentially used to support approval is also problematic.

In defining the patient population, patients with locally advanced disease should have inoperable lesions.

- 3. For the ongoing study D4200C00008, germline mutations in the RET gene are detected and defined using an available DNA-based test that is used in clinical practice. For the proposed randomized study, patients with MTC will have RET mutations detected using the same DNA-based test that is currently being used in study D4200C00008, while patients with PTC will have rearrangements involving the RET gene detected using an RNA-based assay. These tests are highly specific at detecting specific mutations and rearrangements in the RET gene, and are accepted standard techniques for identifying those patients who would be eligible for a therapeutic approach targeted to the activated RET tyrosine kinase. AstraZeneca believes that these tests are appropriate to define those patients with MTC or PTC whose tumors have mutations or rearrangements in the RET gene and to determine eligibility for the clinical studies with ZD6474 proposed in this document. Does the Agency agree?**

FDA Response:

Please submit information on the specifications, method and sensitivity of the assays that you are currently using for enrollment in D4200. You should submit an algorithm for use of these assays in defining the population that will be eligible for the proposed randomized study.

You will need to have further discussions with DODP and CDRH regarding the development of a commercial assay(s) that will be used to identify the target population eligible for treatment.

4. **ZD6474 has been shown in pre-clinical studies to inhibit the activity of the activated RET oncogene, and preliminary results from the clinical study D4200C00008 demonstrate clinical activity of ZD6474 in patients with hereditary MTC who carry a germline mutation of RET. AstraZeneca believes that the pre-clinical and clinical data together support inclusion of the mechanism of action of ZD6474, as an inhibitor of activated RET, within the label. Does the Agency agree?**

FDA Response:

We will consider this labeling issue during our review of any submitted NDA.

5. **AstraZeneca believes that the pre-clinical package of toxicology studies described in section 4.3 will be adequate to support an indication in patients with locally advanced or metastatic hereditary MTC, or with locally advanced or metastatic MTC or PTC with mutation in the RET gene. Does the Agency agree?**

FDA Response:

The six-month study in the rat and the nine-month study in the dog appear to be adequate to fulfill the requirements for long-term toxicology testing for your proposed indication at this time.

Page 5
IND 60,042

The meeting ended at 4:30pm.

Amy Baird
Consumer Safety Officer

Concurrence Chair: _____
Ramzi Dagher, M.D.
Clinical Team Leader

Attachments: Sponsor's slides presented at meeting.

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/s/

Amy Baird

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