

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022405Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

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

PMR/PMC Description: 1719-1 To evaluate the potential for a serious risk of carcinogenicity, conduct a long-term (2 year) rodent carcinogenicity study in the rat. Submit the carcinogenicity protocol for a Special Protocol Assessment (SPA) prior to initiating the study.

PMR/PMC Schedule Milestones:	Special Protocol Assessment Submission:	<u>12/31/2011</u>
	Final Protocol Submission:	<u>03/30/2012</u>
	Study Completion:	<u>Not applicable</u>
	Final Report Submission:	<u>12/31/2014</u>

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

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

The proposed indication for vandetanib in NDA 22405 is for the treatment of patients with unresectable locally advanced or metastatic medullary thyroid cancer. Carcinogenicity studies are generally not required to support marketing for therapeutics intended to treat patients with advanced cancer, therefore, carcinogenicity studies were not requested or required for marketing for this indication. Carcinogenicity studies are now being required based on the prognosis of patients with medullary thyroid cancer in the clinical trial used to support marketing (Study 58). The overall prognosis of patients with medullary thyroid cancer is relatively prolonged with a 10 year overall survival rate of approximately 40% in patients with distant metastases. It is possible that a patient with newly diagnosed, locally advanced or metastatic unresectable medullary thyroid cancer may have a life expectancy that exceeds 10 years from the date of diagnosis. The median number of years from diagnosis until entry on study 58 was 6 years, however, there were several patients who were treated within 2 years of diagnosis. In addition, the median time of exposure to vandetanib was ~90 weeks, indicating that patients with MTC will be chronically exposed to the drug for relatively long periods of time. Finally, the estimated time when 50% of the patients enrolled on the trial will have died is estimated to be over 5 years (2012) from the start of the trial (2007). This signifies that at least 50% of the patients will be living 5 years after first being exposed to vandetanib despite having progressive medullary thyroid cancer.

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

Results of the clinical trial used to support marketing (Study 58) indicate that the median time of exposure to vandetanib was ~90 weeks and that patients with medullary thyroid cancer will be chronically exposed to the drug for relatively long periods of time. Carcinogenicity is a safety concern with drug chronic exposure, particularly for drugs in pharmacologic classes with previous demonstration 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 vandetanib. To address this concern a 2 year carcinogenicity study in the rat is being required to assess the potential for vandetanib to cause carcinogenicity.

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

If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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

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

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

A long-term rodent carcinogenicity study in the rat

Required

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

Continuation of Question 4

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

Agreed upon:

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

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

Attachment B: Sample PMR/PMC Development Template

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

PMR/PMC Description: 1719-2 To evaluate the potential for a serious risk of carcinogenicity, conduct a rodent carcinogenicity study in the mouse. Submit the carcinogenicity protocol for a Special Protocol Assessment (SPA) prior to initiating the study.

PMR/PMC Schedule Milestones:	Special Protocol Assessment Submission:	<u>03/31/2012</u>
	Final Protocol Submission:	<u>06/30/2012</u>
	Study Completion:	<u>Not applicable</u>
	Final Report Submission:	<u>12/31/2013</u>
	Other:	<u>MM/DD/YYYY</u>

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

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

The proposed indication for vandetanib in NDA 22405 is for the treatment of patients with unresectable locally advanced or metastatic medullary thyroid cancer. Carcinogenicity studies are generally not required to support marketing for therapeutics intended to treat patients with advanced cancer, therefore, carcinogenicity studies were not requested or required for marketing for this indication. Carcinogenicity studies are now being required based on the prognosis of patients with medullary thyroid cancer in the clinical trial used to support marketing (Study 58). The overall prognosis of patients with medullary thyroid cancer is relatively prolonged with a 10 year overall survival rate of approximately 40% in patients with distant metastases. It is possible that a patient with newly diagnosed, locally advanced or metastatic unresectable medullary thyroid cancer may have a life expectancy that exceeds 10 years from the date of diagnosis. The median number of years from diagnosis until entry on study 58 was 6 years, however, there were several patients who were treated within 2 years of diagnosis. In addition, the median time of exposure to vandetanib was ~90 weeks, indicating that patients with MTC will be chronically exposed to the drug for relatively long periods of time. Finally, the estimated time when 50% of the patients enrolled on the trial will have died is estimated to be over 5 years (2012) from the start of the trial (2007). This signifies that at least 50% of the patients will be living 5 years after first being exposed to vandetanib despite having progressive medullary thyroid cancer.

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

Results of the clinical trial used to support marketing (Study 58) indicate that the median time of exposure to vandetanib was ~90 weeks and that patients with medullary thyroid cancer will be chronically exposed to the drug for relatively long periods of time. Carcinogenicity is a safety concern with drug chronic exposure, particularly for drugs in pharmacologic classes with previous demonstration 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 vandetanib. To address this concern a rodent carcinogenicity study in the mouse is being required to assess the potential for vandetanib to cause carcinogenicity.

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

If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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

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

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

A rodent carcinogenicity study in the mouse

Required

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

Continuation of Question 4

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

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

Agreed upon:

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

-
- Other
-

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

PMR/PMC Development Template

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

PMR/PMC Description: 1719-3 Conduct a randomized dose-finding trial in which patients with progressive or symptomatic medullary thyroid cancer will be randomized to vandetanib 300 mg or 150 mg daily. The trial will include analyses of the safety and activity of the 150 mg dose of vandetanib. Safety assessments will include evaluations of vortex keratopathy and corneal stromal changes, with ophthalmology examination every 6 months with corneal photographs of abnormalities. Safety assessments will also include evaluation of heart failure using serial echocardiograms in all patients. A primary endpoint will include overall response rate.

PMR/PMC Schedule Milestones: Final protocol Submission Date: 09/30/2011
Study/Clinical trial Completion Date: 07/31/2014
Final Report Submission Date: 12/31/2014
Other: _____

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

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

There are currently no treatments approved for medullary thyroid cancer. Patients with symptomatic or progressive medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease have an unmet need.

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

The proposed dose of 300 mg was associated with life-threatening toxicity. Post-hoc analysis suggested that the lower dose may have comparable efficacy with lower predicted toxicity. In light of the long natural history of the patient population for which this drug is indicated, it is incumbent on the Applicant to maximize the risk-benefit profile for this drug in this disease.

There was a 31% incidence of vortex keratopathy observed in the clinical trial of vandetanib in medullary thyroid cancer. Formal evaluation of a large subset of patients enrolled on a clinical trial with formal ophthalmologic examination including slit lamp exam and archived pictures will better define this toxicity and the risks to patients treated with vandetanib.

There appears to be a safety signal related to heart failure in the clinical experience with vandetanib. Formal evaluation with the use of scheduled echocardiograms or MUGA scans in a randomized clinical trial setting will be able to capture these signals.

Finally, it was determined that only a clinical trial, a randomized dose-finding clinical trial, (rather than a nonclinical or observational study) will be sufficient to assess a known serious risk of vortex keratopathy and corneal stromal changes, to assess signals of excessive toxicity at the studied dose and heart failure, and to identify an unexpected, serious risk of an adverse effect on overall survival.

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

If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study:** all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial:** any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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

- This study will be performed in patients with progressive, symptomatic locally advanced or metastatic medullary thyroid cancer. The primary endpoint will be overall response rates and descriptive statistics will be used to evaluate the comparison of the two doses. safety data, including ECGs, will be collected and analyzed to compare safety profiles of the different doses.
- The applicant will be asked to evaluate heart failure in the randomized, dose finding study in medullary thyroid cancer.
- The applicant will be asked to evaluate vortex keratopathy in the randomized, dose finding study in medullary thyroid cancer.

Required

- Observational pharmacoepidemiologic study
 Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 Thorough Q-T clinical trial
 Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 Pharmacokinetic studies or clinical trials
 Drug interaction or bioavailability studies or clinical trials
 Dosing trials

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

The proposed dose of 300 mg was associated with life-threatening toxicity. Post-hoc analysis suggested that the lower dose may have comparable efficacy with lower predicted toxicity. In light of the long natural history of the patient population for which this drug is indicated, it is incumbent on the Applicant to maximize the risk-benefit profile for this drug in this disease.

There was a 31% incidence of vortex keratopathy observed in the clinical trial of vandetanib in medullary thyroid cancer. Formal evaluation of a large subset of patients enrolled on a clinical trial with formal ophthalmologic examination including slit lamp exam and archived pictures will better define this toxicity and the risks to patients treated with vandetanib.

There appears to be a safety signal related to heart failure in the clinical experience with vandetanib. Formal evaluation with the use of scheduled echocardiograms or MUGA scans in a randomized clinical trial setting will be able to capture these signals.

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

Agreed upon:

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

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

Attachment B: Sample PMR/PMC Development Template

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

PMR/PMC Description: 1719-4 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).

PMR/PMC Schedule Milestones: Final protocol Submission Date: Submitted
Study/Clinical trial Completion Date: 12/31/2013
Final Report Submission Date: 05/30/2014
Other: _____

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

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

There are currently no treatments approved for medullary thyroid cancer. Patients with symptomatic or progressive medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease have an unmet need.

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

Overall survival is a key secondary endpoint of the applicant's pivotal study. This requirement will provide data regarding this endpoint.

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

If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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

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

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

The applicant will be asked to submit the overall survival data from the randomized clinical trial of vandetanib 300 mg vs. placebo in medullary thyroid cancer (study 58).

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
Overall survival is a key secondary endpoint of the applicant's pivotal study. This requirement will provide data regarding this endpoint.
 - Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

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

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

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
04/07/2011

KATHERINE M FEDENKO
04/08/2011

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

PATIENT LABELING REVIEW

Date: February 24, 2011

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

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

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

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

Subject: DRISK Review of Patient Labeling (Medication Guide)

Drug Name(s): Vandetanib Tablets

Application Type/Number: NDA 22-405

Applicant/sponsor: AstraZeneca Pharmaceuticals LP

OSE RCM #: 2010-1557

1 INTRODUCTION

This review is written in response to a request by the Division of Drug Oncology Products (DDOP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide (MG) for Vandetanib Tablets.

On July 7, 2010, AstraZeneca Pharmaceuticals LP submitted New Drug Application (NDA 22-405), for Vandetanib Tablets. Vandetanib is indicated for the treatment of patients with unresectable locally advanced or metastatic medullary thyroid cancer.

The proposed REMS is being reviewed by DRISK and will be provided to DDOP under separate cover.

DRISK conferred with DMEPA and a separate DMEPA review of the carton and container, and patient labeling will be forthcoming.

2 MATERIAL REVIEWED

- Draft Vandetanib Tablets Medication Guide (MG) received on July 7, 2010, revised by the review division throughout the current review cycle and received by DRISK on February 10, 2011.
- Draft Vandetanib Tablets Medication Guide (MG) Prescribing Information (PI) received on July 7, 2010, revised by the review division throughout the current review cycle and received by DRISK on February 10, 2011.

3 RESULTS OF REVIEW

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

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

In our review of the MG, we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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

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

/s/

LATONIA M FORD
02/24/2011

LASHAWN M GRIFFITHS
02/25/2011

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Memorandum

****PRE-DECISIONAL AGENCY MEMO****

Date: February 22, 2011

To: Lisa Skarupa
Regulatory Project Manager
Division of Drug Oncology Products (DDOP)

From: Zarna Patel, PharmD
Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications
(DDMAC)

**Subject: Drug: Zictifa (vandetanib) Tablets
NDA: 022405**

DDMAC has reviewed the proposed Medication Guide, submitted for consult to DDMAC on July 16, 2010, for Zictifa (vandetanib) Tablets.

Our comments are based on the proposed labeling circulated to the review team on February 2, 2011.

Thank you for the opportunity to comment on the proposed Medication Guide.

If you have any questions on the comments for the Medication Guide, please contact Zarna Patel at 301.796.3822 or zarna.patel@fda.hhs.gov.

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

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/s/

ZARNA PATEL
02/22/2011

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications**

*****Pre-decisional Agency Information*****

Memorandum

Date: 2/15/2011

To: Lisa Skarupa, Regulatory Project Manager
Division of Drug Oncology Products

From: James Dvorsky, Regulatory Reviewer
Division of Drug Marketing, Advertising, and Communications

Subject: Comments on draft labeling (Package Insert) for Vandetanib
NDA 022405

In response to your labeling consult request on July 16, 2010, we have reviewed the draft Package Insert for vandetanib and offer the following comments. Note that these comments are based upon the label version as of February 2, 2011.

Package Insert Labeling:

Section	Statement	Comment
Highlights, Warnings and Precautions, Bullet #2	(b) (4)	(b) (4)
Highlights, Warnings and Precautions, Bullet #4	(b) (4)	(b) (4)

		(b) (4)
2 Dosage and Administration	(b) (4)	
2.1 Dosage Adjustment	<p>“...interrupt dosing until QTcF returns to less than 450 ms, then resume at a reduced dose.”</p>	<p>This statement fails to include important material facts related to reducing the dose. It is not until the end of 2.1 that dose reduction is explained. It is recommended to move the sentence, “The 300-mg daily dose can be reduced to 200 mg...and then to 100mg” immediately following the statement under question in order to qualify how the dose should be reduced immediately following instruction to do so.</p>
5.3 Interstitial lung disease	<p>“Interstitial Lung Disease (ILD) or pneumonitis have been observed with vandetanib and deaths have been reported (b) (4)</p>	(b) (4)
6.1 Clinical Studies Experience	(b) (4)	
6.1	(b) (4)	

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/s/

JAMES S DVORSKY
02/15/2011

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: November 22, 2010

TO: Lisa Skarupa, Regulatory Project Manager
Katherine DeLorenzo, Medical Officer
Geoffrey Kim, Medical Officer
Division of Drug Oncology Products

FROM: Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Branch 2
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch 2
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

NDA: 22405

APPLICANT: AstraZeneca Pharmaceuticals LP

DRUG: Zictifa™ (vandetanib)

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATION: Medullary Thyroid Cancer

CONSULTATION REQUEST DATE: 8/6/2010

DIVISION ACTION GOAL DATE: 12/7/10

PDUFA DATE: 1/7/11

I. BACKGROUND:

AstraZeneca seeks approval of vandetanib for the treatment of patients with unresectable locally advanced or metastatic medullary thyroid cancer (MTC). MTC is relatively unresponsive to conventional doses of radiation therapy and to all tested chemotherapeutic regimens.

The applicant presents data from a phase II study, D4200C00058, entitled, “An International, Phase II, Randomized, Double-Blinded, Placebo-Controlled, Multi-Center Study to Assess the Efficacy of ZD6474 (ZACTIMA™) versus Placebo in Subjects with Unresectable Locally Advanced or Metastatic Medullary Thyroid Cancer.” This pivotal study was designed to demonstrate a clinically significant and consistent benefit for vandetanib in prolonging progression-free survival (PFS), with a planned long-term follow-up for overall survival. The study ensured a reliable assessment of the primary endpoint (PFS), with independent review of radiographic images and sensitivity analyses to assess consistency across pre-specified subgroups of clinical relevance.

Three clinical sites were inspected in accordance with the CDER Clinical Investigator Data Validation Inspection using the Bioresearch Monitoring Compliance Program (CP 7348.811); that of Dr. Martin Schlumberger (site number 2801), Dr. Rossella Elisei (site number 2501), and Dr. Barbara Jarzab (site number 1701). These sites were selected for inspection because they all had relatively high enrollment numbers, and there are insufficient domestic data. The study sponsor, AstraZeneca Pharmaceuticals LP, and a CRO, (b) (4) were inspected in accordance with the CDER Sponsor/Monitor/CRO Inspection using the Bioresearch Monitoring Compliance Program (CP 7348.810).

II. RESULTS (by Site):

Name of CI or Sponsor/CRO, Location	Protocol #: and # of Subjects:	Inspection Date	Final Classification
CI#1: Site #2801 – Dr. Martin Schlumberger IGR Onco, 94 Villejuif, Rue Camille Desmoulins Villejuif Cedex 94805, France	Protocol: D4200C00058 Site Number: 2801 Number of Subjects: 35	9/20/2010- 9/23/2010	Pending Interim classification: VAI
CI#2: Site #2501 – Dr. Rossella Elisei AZ. Ospedsliero- Univeritaria Ospedale Cisanello Dipartimento di Endocrinologia e metabolismo Via Paradisa 2	Protocol: D4200C00058 Site Number: 2501 Number of Subjects: 24	9/27/2010- 9/29/2010	Pending Interim classification: VAI
CI#3: Site #1701 – Dr. Barbara Jarzab Zakład Medycyny Nuklearnej I Endokrynologii Onkologicznej Centrum Ul. Wybrzeze Armii Krajowej 15 Gliwice 44-101, Poland	Protocol: D4200C00058 Site Number: 1701 Number of Subjects: 20	10/25/2010- 10/29/2010	Pending Interim classification: NAI

Name of CI or Sponsor/CRO, Location	Protocol #: and # of Subjects:	Inspection Date	Final Classification
CRO: (b) (4)	<u>Protocol:</u> D4200C00058 <u>Sites:</u> 2801, 2501, 1701 and 2901	10/26/10- 10/29/10	Pending Interim classification: NAI
Sponsor: AstraZeneca Pharmaceuticals LP 1800 Concord Pike Wilmington, DE 19803	<u>Study:</u> D4200C00058 <u>Sites:</u> 2801, 2501, 1701 and 2901.	11/1/10- 11/10/10	Pending Interim classification: VAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

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

- 1. CI#1:** – Dr. Martin Schlumberger
(Site Number 2801)
IGR Onco, 94 Villejuif,
Rue Camille Desmoulins
Villejuif Cedex 94805, France

- a. What was inspected:** The site screened 39 subjects, 35 of those were randomized and treated. The study records of 21 subjects were audited in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance, primary and secondary efficacy endpoints, clinical laboratory results, concomitant medications, adverse events, and reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent documents.

Note: A complete review of the EIR was not done by the time this CIS was written. The general observations described below are based on preliminary communication from the field investigator and a preliminary review of the EIR. An inspection summary addendum will be generated if conclusions change upon complete review of the EIR.

- b. General observations/commentary:** Generally, the investigator's execution of the protocol was found to be adequate. The primary efficacy endpoint data were verifiable against source records at the site. The FDA field investigator reviewed subject records, CRFs and source documents, assessed inclusion/exclusion criteria satisfaction and verified subject treatment regimens. There was no evidence of under-reporting protocol violations or AEs. However, there were multiple instances where protocol-specified inclusion/exclusion criteria were not met, yet, subjects were randomized and treated; a direct violation of the protocol. Specifically, of the 35 subjects who were randomized at

this site 18 failed to meet 1 or more inclusion/exclusion criteria for study D4200C00058. In addition, the site allowed persons not listed on the site's "Delegation of Responsibilities within the Study Site Team," to perform study-related functions, and the site failed to report all SAEs to the sponsor in accordance with the protocol.

Consistent with the routine clinical investigator compliance program assessments, the inspection verified data found in source documents and compared those measurements with that reported by the sponsor to the agency in NDA 22405. A Form FDA 483 was issued to the clinical investigator citing 1 inspectional observation.

Observation 1: An investigation was not conducted in accordance with the investigational plan.

Specifically for Study D4200C00058:

- a. According to the Case Report Forms, 18 of 35 subjects randomized did not meet all inclusion/exclusion criteria. The site received a correspondence from the sponsor of the study, dated September 7, 2007, advising that no waivers to the inclusion/exclusion criteria were going to be granted. The subjects are: E2801001, E2801002, E2801004, E2801005, E2801006, E2801007, E2801009, E2801010, E2801011, E2801012, E2801013, E2801014, E2801017, E2801021, E2801024, E2801030, E2801031, and E2801033. In addition, the study files have no documentation from the sponsor allowing their continuation in the study. Subjects E2801030, E2801031, and E2801033 were randomized on or after September 29, 2007. The table below lists, by subject, the inclusion/exclusion criteria that the subject failed, the subject's actual laboratory measurement and ICD signing date.

Subject Number (Site 2801)	Failed I/E Criteria	Actual Measurement	Date ICD signed
001	#8 – E (Calcium: must be 2.12 to 2.56 mmol/l)	2.1 mmol/l	1/16/07
002	#8 – E (Calcium)	2.1 mmol/l	1/24/07
004	#8 – E (Calcium)	2.11 mmol/l	1/31/07
005	#2 (Concomitant Medications) & #8 – E (Potassium: must be ≥ 4 to 5.3 mmol/l)	Deroxat/3.7 mmol/l	2/26/07
006	#8 – E (Calcium)	2 mmol/l	3/7/07
007	#8 – E (Calcium/Potassium)	2.03 mmol/l/3.7 mmol/l	3/12/07
009	#8 – E Calcium)	2.1 mmol/l	3/23/07
010	#10 – I	Negative Pregnancy	3/19/07
011	#8 – E (Calcium)	2.11 mmol/l	6/7/07
012	#8 – E (Potassium)	3.8 mmol/l	5/4/07
013	#8 – E (Calcium)	2.7 mmol/l	5/4/07
014	#8 – E (Potassium)	3.7 mmol/l	4/16/07
017	#8 – E (Calcium/Potassium)	2.1 mmol/l/3.2 mmol/l	5/7/07

Subject Number (Site 2801)	Failed I/E Criteria	Actual Measurement	Date ICD signed
021	#9 – E (ALP: must be 20-130 u/l) & #3 – I (Must have confirmed dx of MTC)	#9E – 693 u/l #3I – No Previously confirmed dx MCT	7/11/07
024	#7 – E (Creatinine Clearance: must be >50 ml/min)	28 ml/min	8/29/07
030	#8 – E (Potassium)	3.6 mmol/l	10/10/07
031	#10 – I	Negative Pregnancy	9/27/07
033	#17 - E (previous or current malignancy) & #9 – I (tumor collection sample provided)	#17E - Previous or current malignancies #9I – Tumor Collection Sample not provided	10/3/07

- b. The site allowed personnel to perform study-related functions that were not authorized to perform under the investigational plan because they were not listed on the study personnel identification list entitled "Delegation of Responsibilities within the Study Site Team." At least 27 prescriptions of the investigational drug were issued and signed by individuals not listed on the study personnel identification list. In addition, the site allowed individuals not listed on the study personnel identification list to perform study visits.

When queried by the FDA field investigator, Dr. Schlumberger stated that this was an oversight on his part but that he had full confidence in the competence of the individuals who performed study-related functions but were not listed on the study personnel identification list entitled "Delegation of Responsibilities within the Study Site Team."

- c. The protocol indicates that Serious Adverse Events should be reported to the sponsor within 1 day of awareness of its occurrence. Subject E2801005 was hospitalized twice between visit 5 and visit 6. The first hospitalization on (b) (6) was due to vomit episodes and the second hospitalization on (b) (6) was due to septicemia. There is no documentation at the site that shows these reports were submitted to the sponsor in accordance with the protocol.

However, a review of the data listings of AEs and SAEs found in the application does list both of these SAEs appropriately. It remains unclear as to whether the site reported these SAEs to the sponsor within 1 day of the site becoming aware of them.

DSI reviewer's Notes: DSI reviewer Lauren Iacono-Connors presented and discussed all of the inspectional findings above with the review division (DDOP) Medical Officers, Dr. Katherine Delorenzo and Dr. Geoffrey Kim, and Medical Team Leader, Dr. Ellen Maher, during a NDA 22405 review team meeting on November 2, 2010. The DSI reviewer requested feedback from Dr. Maher et al., as to whether these inspectional observations might impact data reliability generated by this site for these subjects. On November 5, 2010, Dr. Maher

provided a response via email, stating that DDOP does not think that these protocol violations will alter the subject's clinical outcome and therefore, the analyses of the study data should be unaffected. DSI and DDOP are in agreement that the site's poor protocol compliance, with respect to adherence to inclusion/exclusion criteria, are of concern, but that the specific findings discussed above are unlikely to have significant impact on primary efficacy and safety analyses.

There were several subjects that were enrolled by this site that presented with what appeared to be significant screening laboratory test deviations. With respect to Subject E2801021, the ALP level at screening was significantly above acceptable levels and therefore a possible safety concern. Assessment of data listings and site source records revealed that there were no reported SAEs for this subject. With respect to Subject E2801024, the creatine clearance was well below acceptable levels for study randomization and also raises a possible safety concern. This subject did have SAEs reported while on study; a cerebrovascular accident on (b) (6), and myopathy reported on (b) (6); however, the randomization scheme revealed that this subject was randomized to placebo.

- c. Assessment of data integrity:** Notwithstanding the regulatory violations noted above, the overall primary efficacy and safety data for Dr. Schlumberger's site, associated with Study D4200C00058 submitted to the Agency in support of NDA 22405, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communication from the field investigator and a preliminary review of the EIR. An inspection summary addendum will be generated if conclusions change upon final review of the EIR.

- 2. CI#2:** Dr. Rosella Elisei
(Site Number 2501)
AZ. Ospedsliero- Univeritaria
Ospedale Cisanello
Dipartimento di Endocrinologia e metabolismo
Via Paradisa 2

- a. What was inspected:** The site screened 34 subjects, 24 of those were randomized and treated. The study records of 24 subjects were audited in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance, primary and secondary efficacy endpoints, clinical laboratory results, concomitant medications, adverse events, and reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent documents.

Note: A complete review of the EIR was not done by the time this CIS was written. The general observations described below are based on preliminary communication from the field investigator and a preliminary review of the EIR.

An inspection summary addendum will be generated if conclusions change upon complete review of the EIR.

- b. General observations/commentary:** Generally, the investigator's execution of the protocol was found to be adequate. The primary efficacy endpoint data were verifiable against source records at the site. The FDA field investigator reviewed subject records, CRFs and source documents, assessed inclusion/exclusion criteria satisfaction and verified subject treatment regimens. There was no evidence of under-reporting protocol violations or AEs. However, there were multiple instances where protocol-specified inclusion/exclusion criteria were not met, yet, subjects were randomized and treated; a direct violation of the protocol. Specifically, of the 24 subjects who were randomized at this site 11 failed to meet inclusion/exclusion criteria for study D4200C00058.

Consistent with the routine clinical investigator compliance program assessments, the inspection verified data found in source documents and compared those measurements with that reported by the sponsor to the agency in NDA 22405. A Form FDA 483 was issued to the clinical investigator citing 1 inspectional observation.

Observation 1: An investigation was not conducted in accordance with the investigational plan.

Specifically for Study D4200C00058:

According to the Case Report Forms, 11 of 24 subjects randomized did not meet all inclusion/exclusion criteria. The site received a correspondence from the sponsor of the study, dated September 7, 2007, advising that no waivers to the inclusion/exclusion criteria were going to be granted. The subjects are: E2501002, E2501003, E2501006, E2501011, E2501012, E2501015, E2501016, E2501017, E2501024, E2501026, and E2501028. In addition, the study files have no documentation from the sponsor allowing their continuation in the study. Specifically, all 11 subjects failed to meet Inclusion Criteria 9:

“All subjects (other than those with hereditary MTC who have a documented germ line RET mutation) must submit an archived tumor collection sample. If an archived tumor sample is not available prior to 2 weeks of randomization, a fresh tumor sample must be obtained in its place. The tumor sample must be obtained by the investigative site and shipped to its destination prior to randomization.”

DSI reviewer's Notes: A review of the EIR and limited exhibits revealed that all but Subject 2501024, had tumor samples available but they were shipped after subject randomization. In the case of Subject 2501024, no record of tumor sample shipment was found at the site. DSI reviewer Lauren Iacono-Connors presented and discussed these inspectional findings above with the review division (DDOP) Medical Officers, Dr. Katherine Delorenzo and Dr. Geoffrey Kim, and Medical Team Leader, Dr. Ellen Maher, during a NDA 22405 review team meeting on November 2, 2010. The DSI reviewer requested feedback from Dr. Maher et al., as to whether the inspectional observation will

impact data reliability generated by this site for these subjects. On November 5, 2010, Dr. Maher provided a response via email, stating that that this protocol violation will not alter the subject's clinical outcome and therefore, the analyses of the study data would be unaffected. She stated that Inclusion Criteria 9 was no longer relevant to the study and efficacy endpoint(s). Briefly, Dr. Maher explained that the study was initially designed to collect tumor samples from all patients with sporadic medullary thyroid cancer. However, specimens were not required for patients with hereditary disease. The initial study design had co-primary endpoints, PFS in the ITT population and PFS in patient's whose tumors contained the RET mutation. Amendment 5 of the D4200C00058 protocol modified the design so that the sole primary endpoint was PFS in the ITT population. The reason for this amendment was that the sponsor had a large number of samples in which they could not tell whether a RET mutation did or did not exist.

- c. Assessment of data integrity:** Notwithstanding the regulatory violations noted above, the overall primary efficacy and safety data for Dr. Elisei's site, associated with Study D4200C00058 submitted to the Agency in support of NDA 22405, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communication from the field investigator and a preliminary review of the EIR. An inspection summary addendum will be generated if conclusions change upon final review of the EIR.

- 3. CI#3:** Dr. Barbara Jarzab
(Site Number 1701)
Zakład Medycyny Nuklearnej I
Endokrynologii Onkologicznej
Centrum Ul. Wybrzeże Armii
Krajowej 15 Gliwice 44-101,
Poland

- a. What was inspected:** The site screened 23 subjects, 20 were randomized and treated. The study records of all subjects were audited in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance and reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent documents.

Note: The EIR was not available at the time this CIS was written. The EIR is currently being finalized and will be submitted to DSI upon completion. The general observations described below are based on preliminary communication from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

- b. General observations/commentary:** Generally, the investigator's execution of the protocol was found to be adequate. The primary efficacy endpoint data were verifiable

against source records at the site. The FDA field investigator reviewed subjects' records, CRFs and source documents, for the primary efficacy values and verified their treatment regimens. There was no evidence of under-reporting AEs. The study was found to be well documented and controlled.

Consistent with the routine clinical investigator compliance program assessments, the inspection verified data found in source documents and compared those measurements with that reported by the sponsor to the agency in NDA 22405. No Form FDA 483 was issued.

- c. Assessment of data integrity:** The data for Dr. Jarzab's site, associated with Study D4200C00058 submitted to the Agency in support of NDA 22405, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon final review of the EIR.

4. CRO: [REDACTED] (b) (4)

- a. What was inspected:** The CRO was inspected in accordance with the Sponsor/Monitor/CRO data validation compliance program, CP 7348.810. The study was conducted at 61 clinical sites in 24 countries and randomized 331 subjects. The CRO was responsible for performing as the Central Imaging Reader under contract with the sponsor to determine progression free survival for all subjects randomized. Specifically, the inspection covered organization and personnel, selection and qualifications of independent radiologists and the adjudicator, their functions, imaging/data management, blinding procedures and overall compliance with the Charter. The primary efficacy endpoint data were assessed for all subjects randomized by 4 clinical study sites; Site 1701 (Dr. Barbara Jarzab, 20 subjects and 185 timepoints), Site 2501 (Dr. Rossella Elisei; 24 subjects and 162 time points), Site 2801 (Dr. Martin Schlumberger; 35 subjects and 269 time points), and Site 2901 (Dr. B. Zonnenberg; 12 subjects and 73 time points).

Note: The EIR was not available at the time this CIS was written. The EIR is currently being finalized and will be submitted to DSI upon completion. The general observations described below are based on preliminary communication from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

- b. General observations/commentary:** Records and procedures were clear, and generally well organized. The CRO appeared to function in accordance with the Charter and SOPs in support of Study D4200C00058. Overall, CRO actions and functions appeared adequate. The primary efficacy endpoint data were verifiable at the CRO site for the 4

audited clinical sites, considering a total of 91 subjects. No objectionable conditions were noted. No Form FDA 483 was issued.

Briefly, this was a global study. A total of 61 clinical study sites sent 331 subjects' images (3170 time points; screening and follow-up visits) to (b) (4) and they were read by 4 primary independent radiologists and one adjudicator. The handling of study-generated images by the CRO site was reviewed. All subjects' CTs and/or MRIs were provided to the CRO with a completed data transmittal form (DTF) from the clinical study centers. The CRO ensured that subjects' CT scans or MRI images were verified against their DTFs. Once verified, they were digitalized, cropped and de-identified. The CT scans or MRI images were prepared for reads using a system called BioTrack, and the system used for actual reads was called BioRead. The system validation of both the BioTrack and BioRead systems was assessed during the inspection.

The FDA field investigator also reviewed the 4 readers' and the adjudicator's qualifications and training (such as mock reads) and verified that the Charter for the independent reads for study protocol D4200C00058 was followed. Subject efficacy endpoints, generated by the CRO, were compared with that found in the data listings submitted to NDA 22405 for Site 1701 (Dr. Barbara Jarzab), Site 2501 (Dr. Rossella Elisei), Site 2801 (Dr. Martin Schlumberger), and Site 2901 (Dr. B. Zonnenberg). No discrepancies were observed.

- c. **Assessment of data integrity:** Based on a preliminary review of the inspectional findings the study appears to have been conducted adequately. The data generated by the CRO, PFS endpoints, as it pertains to Study D4200C00058 were audited in accordance with the sponsor-monitor oriented BIMO compliance program, CP 7348.810. The findings are that the data from this CRO submitted to the agency as part and in support of NDA 22405 appear reliable.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

5. Sponsor: AstraZeneca Pharmaceuticals LP
1800 Concord Pike
Wilmington, DE 19803

- a. **What was inspected:** The sponsor was inspected completing the Sponsor/Monitor/CRO data validation compliance program, CP 7348.810. The study, D4200C00058, was conducted at 61 Centers in 24 countries and screened 437 subjects, 331 of which were randomized. The inspection covered adherence to Protocol, and review of the firm's SOPs, including monitoring SOPs, Ethics Committee/IRB approvals, completed Form FDA 1572s, monitoring reports, communications with the sites, subjects' randomization, drug accountability and review of data management from the clinical study sites to the submission of the NDA to the Agency.

The FDA field investigator specifically reviewed and compared 91 subjects' electronic case report form from 4 clinical study sites; Site 1701 (Dr. Barbara Jarzab, 20 subjects), Site 2501 (Dr. Rossella Elisei; 24 subjects), Site 2801 (Dr. Martin Schlumberger; 35 subjects), and Site 2901 (Dr. B. Zonnenberg; 12 subjects) with the data listing which was submitted to NDA 22405. The FDA field investigator paid particular attention to these 4 clinical sites' monitoring reports, ethics committee approvals, drug accountabilities, adverse and serious adverse events, and communications with the sponsor.

Note: The EIR was not available at the time this CIS was written. The EIR is currently being finalized and will be submitted to DSI upon completion. The general observations described below are based on preliminary communication from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

- b. General observations/commentary:** Records and procedures were clear, and generally well organized. There was nothing to indicate under-reporting of AEs/SAEs. Overall, site monitoring appeared adequate with the exception of Site 2801 (see further discussion below). The primary efficacy endpoint data were verifiable at the sponsor site for all 91 subjects from the 4 audited clinical sites. There was no evidence of underreporting protocol violations. Written procedures for monitoring, data management and oversight of contractors were reviewed and no objectionable conditions were noted.

However, review of study records at the firm revealed that out of 331 subjects randomized into the study 73 failed to meet 1 or more entry criteria. This information was reported in the NDA 22405 in the data listings (Clinical Study Report Appendix 12.2.2). Notably, for Site 2801 (Dr. Schlumberger), records indicated that of 35 subjects randomized at this site 18 did not meet 1 or more entry criteria. In addition, the firm failed to comply with its' own monitoring plan for Site 2801. The firm's study management agreement stated that the first interim monitoring visit will be conducted within 2 weeks following the first subject randomization for each site. The first monitoring visit for Site 2801 did not occur until approximately 8 weeks after the first subject (E2801001) was randomized. Finally, the firm did not always submit IND safety reports to the FDA within a timely manner.

At the conclusion of the inspection, an FDA-483, Inspectional Observations form, was issued to management for deficiencies in monitoring and oversight of study conduct. A Form FDA 483 was issued to the Sponsor citing 1 inspectional observation.

Observation 1: Failure to ensure that the study is conducted in accordance with the protocol and/or investigation plan.

Specifically, for clinical study D4200C00058:

- a. Seventy three out of 331 randomized subjects that entered into the study did not meet their inclusion/exclusion criteria.
- b. The Firm's study management agreement, dated January 20, 2006, states that the first interim visit will be conducted within 2 weeks following the "first subject in" at the site. The first subject in at Site 2801 (E2801001) was randomized on January 26, 2007, and the next monitoring visit was not conducted until March 21, 2007. By March 21, 2007 this site had randomized 5 subjects who did not meet 1 or more entry criteria; E2801001, E2801002, E2801004, E2801005 and E2801006. The details on subjects and entry criteria not met for Site 2801 can be found in the Table under Section II of this report (CI# 1, Dr. Schlumberger)
- c. Eight out of 144 IND safety reports were not reported to the FDA within a timely manner. This included three 7 day IND reports and five 15 day IND reports.

DSI reviewer's Notes: *In previous discussions held between DSI and the review division medical officers on inspectional findings of Sites 2801 and 2501, DSI was informed that the protocol deviations reported for both of these sites related to entry criteria violations were not clinically significant and should not impact analyses of study data. These 2 sites account for a total of 59 randomized subjects, 29 of which were randomized with inclusion/exclusion criteria protocol violations.*

The review division may wish to assess the remaining ~44 subjects randomized into the study with inclusion/exclusion criteria violations to determine suitability of their data for study analysis.

- c. **Assessment of data integrity:** The data generated at this site, as it pertains to Study D4200C00058 were audited in accordance with the sponsor-monitor oriented BIMO compliance program, CP 7348.810. Notwithstanding the inspectional observations noted above, the findings are that the data from this Sponsor submitted to the agency in support of NDA 22405 appear reliable.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Based on the review of preliminary inspectional findings for clinical investigators Dr. Schlumberger, Dr. Elisei, Dr. Jarzab, a study CRO (b) (4) and study sponsor, AstraZeneca, the study data collected appear reliable. Dr. Schlumberger, Dr. Elisei, and study sponsor AstraZeneca were issued a Form FDA 483 citing inspection observations.

A Form FDA 483 was issued to Dr. Schlumberger noting protocol deviations with respect to inclusion/exclusion criteria compliance. In addition, the site allowed persons not listed on the site's "Delegation of Responsibilities within the Study Site Team," to perform

study-related functions, and the site failed to report all SAEs to the sponsor in accordance with the protocol. A Form FDA 483 was issued to Dr. Elisei noting protocol deviations with respect to inclusion/exclusion criteria compliance. The DSI reviewer discussed all of the inspectional findings with the review division (DDOP) Medical Officers, Dr. Katherine Delorenzo and Dr. Geoffrey Kim, and Medical Team Leader, Dr. Ellen Maher, during a NDA 22405 review team meeting on November 2, 2010. The DSI reviewer requested feedback on whether these inspectional observations might impact data reliability generated by these sites for these subjects. On November 5, 2010, Dr. Maher provided a response via email, stating that DDOP does not think that these protocol violations will alter the subject's clinical outcome and therefore, the analyses of the study data should be unaffected. DSI and DDOP are in agreement that these observations should not impact overall integrity of site-generated data as related to primary safety and efficacy analyses.

The inspection of the sponsor, AstraZeneca, resulted in inspectional observations that essentially parallel those reported for Dr. Schlumberger's site in that the sponsor's monitoring activities and oversight of study compliance may have permitted the inspectional observations at Site 2801 to persist and accumulate. Written procedures for monitoring, data management and oversight of contractors were reviewed and no objectionable conditions were noted. However, the firm failed to comply with its' own monitoring plan for Site 2801. The firm's study management agreement stated that the first interim monitoring visit will be conducted within 2 weeks following the first subject randomization for each site. The first monitoring visit for Site 2801 did not occur until approximately 8 weeks after the first subject (E2801001) was randomized, and after 5 subjects had been randomized by Site 2801 who did not meet all entry criteria. The site continued to randomize ineligible subjects throughout the conduct of the study. It appears that the site was not brought into compliance by the sponsor throughout the enrollment period despite protocol deviations having been identified by study monitors.

In discussions held between DSI and the review division medical officers on inspectional findings of Sites 2801 and 2501, DSI confirmed that the protocol deviations reported for both of these sites related to entry criteria violations should not significantly impact analyses of study data. These 2 sites account for a total of 59 randomized subjects, 29 of which were randomized with inclusion/exclusion criteria protocol violations. Review of study records at the firm revealed that out of 331 subjects randomized into the study 73 failed to meet 1 or more entry criteria. The review division may wish to assess the remaining ~44 subjects randomized into the study with inclusion/exclusion criteria violations to determine suitability of their data for study analysis.

The review division may consider each inspectional observation outlined in each of the Form FDA 483s, as described above, and sensor subject-specific or site-specific data from study analyses as appropriate. However, although regulatory violations were noted as described above, it appears that they are unlikely to significantly impact primary safety and efficacy analyses. The final reports (EIRs) for these inspections have not been reviewed to date.

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

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

{See appended electronic signature page}

Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

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Tejashri Purohit-Sheth, M.D.
Branch Chief
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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LAUREN C IACONO-CONNORS
11/22/2010

JEAN M MULINDE
11/22/2010
Reviewed and signed for Dr. Tejashri Purohit-Sheth

Interdisciplinary Review Team for QT Studies Consultation: QT Assessments Review

NDA	22405
Brand Name	ZICTIFA
Generic Name	Vandetanib
Sponsor	AstraZeneca
Indication	Treatment of patients with unresectable locally advanced or metastatic medullary thyroid cancer (MTC)
Dosage Form	Tablets
Drug Class	Tyrosine kinase inhibitor
Therapeutic Dosing Regimen	300 mg q.d.
Duration of Therapeutic Use	Till disease progression or DLT
Maximum Tolerated Dose	300 mg q.d.
Submission Number and Date	SDN/001, July 7, 2010
Review Division	DDOP/HFD 150

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

The focus for the IRT review is to quantify QTc prolongation following 300-mg dose of vandetanib. Substantial and sustained QTc prolongation was observed, as evident by data collected from multiple clinical trials.

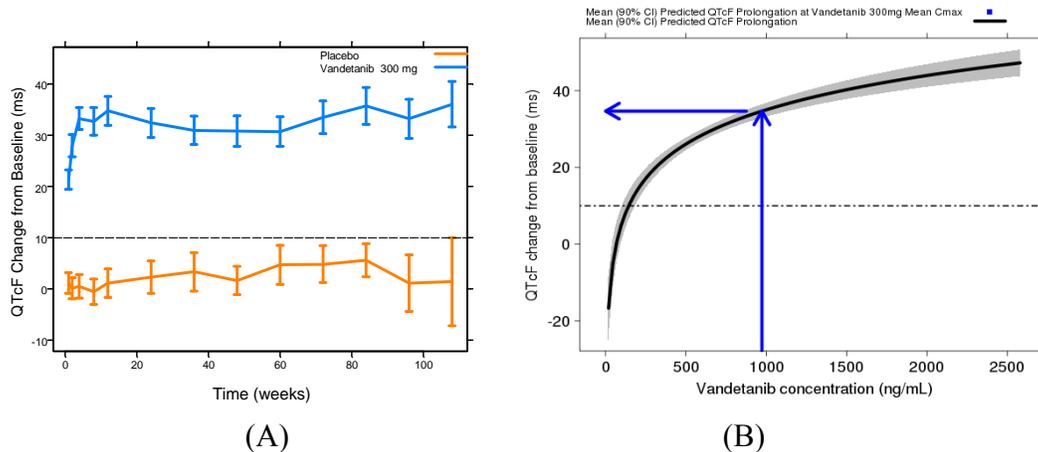
- At the dose of 300 mg, vandetanib is associated with substantial (mean effect over 30 ms) and concentration-dependent QTc prolongation.
 - As observed in 231 medullary thyroid cancer patients receiving vandetanib in the pivotal phase 3 clinical trial (i.e., Study D4200C00058), the mean QTc intervals were higher than 30 ms at multiple visits beyond Visit 4, with the upper bounds of two-sided 90% confidence intervals (CI) greater than 33 ms (Figure 1 A). The QTc prolongation is concentration-dependent. Based on the established exposure-response relationship, the expected mean (90% CI) QTc change from baseline (Δ QTc) at the dose of 300 mg was 35 (33-36) ms (Figure 1 B). In addition, about 35.5% of the patients in vandetanib 300-mg arm experienced greater than 60 ms increase in QTc interval.
 - Similar concentration-QTc relationships were established using data in about 30 patients with locally advanced or metastatic hereditary medullary thyroid carcinoma receiving an initial dose of 300-mg vandetanib in Study D4200C00008 (Section 4.4).
- QTc prolongation is sustained over time.

- Following a single dose of vandetanib, QTc prolongation (i.e., upper 90% CI > 10 ms) was sustained over 28 days post-dose (the last observation time point) in Study D4200C00021 (Section 4.3) in 28 healthy subjects with the maximum vandetanib exposure 42.5% lower than the steady state exposure of vandetanib at 300-mg dose (Figure 2). The sustained QTc prolongation is likely to be associated with the long half-life of vandetanib (19 days).
- As shown in Study D4200C00058, no meaningful reductions in the mean changes of QTc intervals (together with the 90% CIs) were observed following long-term treatment with vandetanib up to 108 weeks (around 2 years) (Figure 1 A). This contradicts the sponsor's assertions that the QTc effect is more tolerable with time.

In addition, QTc prolongations in special patient populations were evaluated using clinical observations from Study D4200C00058. The results were summarized as follows.

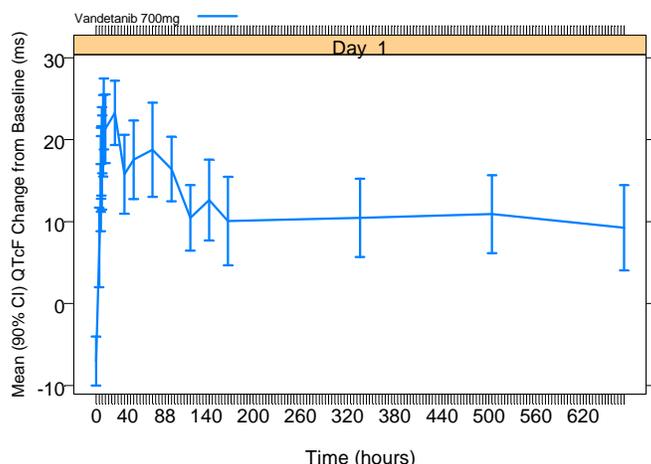
- Higher proportions of patients with Δ QTc > 60 ms, or QTc > 480 ms or QTc > 500 ms were observed in patients with mild to moderate renal impairment as compared to patients with normal renal function (Table 11). The increased QTc effect in patients with compromised renal function may be explained by the increased steady-state exposure of vandetanib (Figure 13). Therefore, dose reduction may be considered in this patient group.
- Caution is required when vandetanib is coadministered with CYP3A4 inducers. CYP3A4 inducers decrease vandetanib exposure but increase exposures of the major metabolites (N-desmethyl vandetanib and N-oxide-vandetanib). Vandetanib, N-desmethyl vandetanib, and N-oxide-vandetanib are all hERG channel blockers. Therefore, the effect of CYP3A4 inducers on the QTc effect is unclear.
- Vandetanib-associated-QTc effects appear to be similar in patients with different body weight (Table 14).
- A slightly larger QTc effect was observed in female patients as compared to male patients (Table 13).

Figure 1: QTc Prolongation Observed in Trial D4200C00058 Using 300-mg Dose



Note: A) Δ QTcF vs. Time Profile
B) Concentration- Δ QTcF Relationship

Figure 2: QTcF vs. Time Profile Observed in Study D4200C00021



Note: Vandetanib exposure in Study D4200C00021 is 45% lower than the steady state exposure of vandetanib at 300-mg dose.

1.2 QT INTERDISCIPLINARY REVIEW TEAM'S COMMENTS

- In the sponsor's study reports, QTc effect was evaluated by using QTcB (Bazett's correction) only. As shown in all vandetanib trials we evaluated (Figure 10, Figure 14 and Figure 17), Bazett's correction method overcorrects heart rate effect. As a result, QTcB tends to underestimate the QTc effect when a drug, like vandetanib, slows down heart rate (Figure 3). Therefore, we consider Bazett's correction method is inappropriate. In the FDA's analysis, we used QTcF (Fridericia's correction method), which has been shown as a better correction method in most vandetanib trials.
- Given the magnitude of QTc prolongation along with cardiotoxicities like cardiac failure and hypertension, more detailed assessments of cardiac safety including an integrated cardiac safety report with review of all deaths and cardiac AEs by an independent cardiologist would have been appropriate.
- There have been two documented cases of TdP in the clinical program. Given the large effect size (with the mean of 35 ms at the 300 mg dose) arrhythmia due to QT prolongation could have played a role in any unobserved death adjudicated as disease progression in the absence of an ECG shortly before the death. It is to be noted that ECGs were collected only once every 12 weeks in the blinded and open label treatment phases of the study.
- Even intensive ECG monitoring does not mitigate the risk of serious ventricular arrhythmia and sudden death. We defer these risk-benefit considerations pertaining to drug approval, (including consideration of baseline co-morbidities and expected survival) to the review division. Table 1 summarizes the indication,

language used in PI, and/or risk mitigation strategy for approved oncology products with similar effect size in QT intervals.

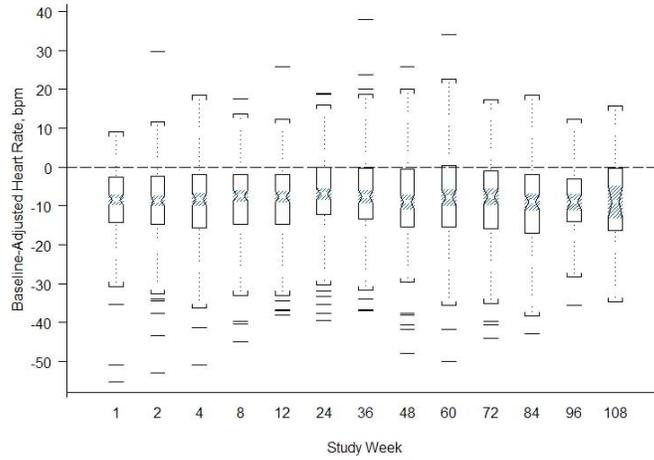
Table 1: Summary of Approved Oncology Products With Similar QTc Interval Prolongations

Drug Name	Indication	Related AE	Regulatory Action
Arsenic trioxide	Acute pro-myelocytic leukemia who are refractory to, or have relapsed from, retinoid and anthracycline chemotherapy	TdP	Boxed Warning
Nilotinib	Imatinib resistant and newly diagnosed CML	Sudden deaths	Boxed Warning, REMS-medication guide and communication plan
Toremifene (NDA 20497/ (b) (4))	Advanced breast cancer	None reported but post-marketing exposure very limited	Boxed Warning proposed by QT-IRT based on effect size
Sunitinib	advanced renal cell cancer& GIST tumors	TdP	W & P statement

- The risk for arrhythmia related death can be minimized with in-patient monitoring and continuous telemetry. Even with frequent ECG monitoring proposed, all events may be not captured in the outpatient setting. For example subjects with a QTc interval under 470 ms at 4-8 weeks or 3 months ECG may develop diarrhea or electrolyte abnormalities when discharged or receive outpatient treatment with a concomitant medication that increases QT prolongation thereby predisposing them to further QT prolongation and related AEs.
- Given the sustained QTc prolongation following a single dose of vandetanib and the long $t_{1/2}$ of the drug (19 days), withdrawal, dose interruption or dose-reduction due to QT prolongation still places the patient at increased risk for a prolonged period of time till the drug clears.
- A theoretical risk mitigation strategy the sponsor could consider, in consultation with their experts could be prophylactic treatment with a blocker of inward late sodium or calcium current like ranolazine or and prophylactic ICD placement.
- The sponsor should submit a REMS plan if the division is considering approval. We defer final decisions regarding appropriate elements of the REMs to be included based on efficacy vs. risk considerations to the review division We

suggest a medication guide, communication plan and ETASU in order that providers and patients are aware of risk and ECG monitoring is in place (see section 2.2). An informed consent should be included so that the patient is aware about the risk for sudden death. Similar procedures should be followed for ongoing and future clinical trials for other indications.

Figure 3: Heart Rate Change from Baseline in Study D4200C00058



2 PROPOSED LABEL

2.1 SPONSOR'S PROPOSED LABEL CONTRAINDICATIONS

(b) (4)

WARNINGS AND PRECAUTIONS

(b) (4)

2.2 QT-IRT RECOMMENDATIONS

Our recommendations are suggestions only. We defer final labeling decisions to the review division.

Boxed Warning:

(b) (4)

Contraindications:

(b) (4)

Warning and Precautions:

(b) (4)

12.4 QT/QTc Prolongation

3 BACKGROUND

3.1 PRODUCT INFORMATION

Vandetanib is a new molecular entity (small molecule) that is an inhibitor of the primary receptor of Vascular Endothelial Growth Factor (VEGF) with additional activity against Epidermal Growth Factor receptor (EGFR) tyrosine kinase and oncogenic RET kinase.

In this application (NDA 22405) the sponsor is seeking approval for ZICTIFA (Vandetanib 300 mg daily) for the treatment of patients with unresectable locally advanced or metastatic medullary thyroid cancer (MTC).

The DDOP clinical reviewer (Michael Brave, MD) in a memo dated October 28, 2009 expressed concern regarding significant toxicity with vandetanib for a small improvement

in median PFS. He also commented that the serum half-life of vandetanib, (19 days) is quite long, and the drug accumulates several fold with multiple dosing (8-fold accumulation reported in patients with MTC in study 58). This raises the concern that patients may receive sub-therapeutic doses early during treatment, and later during treatment may be exposed to undue toxicity.

QT prolongation (mean effect: 100-mg dose, 10 to 20 ms; 300-mg dose, 20 to 30 ms) along with hypertension and heart failure has been reported in vandetanib trials. There are 2 reported cases of torsade de pointes (TdP) occurring in patients receiving vandetanib at the 300-mg dose.

3.2 MARKET APPROVAL STATUS

Vandetanib is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

The effects of vandetanib have been explored in vitro, using the human ether-a-go-go gene (hERG) assay (see report: TSZ36). Vandetanib was active with an IC₅₀ of 0.4 µM. The N-desmethyl (M382558) and the N-oxide (M447882) metabolites of vandetanib were also active, with IC₅₀ values of 1.3 and 4.0 µM, respectively (see report: 0048SZ).

A canine Purkinje fiber study (see report: TSD1293) demonstrated that vandetanib caused a concentration-dependent increase in action potential duration (APD₉₀), with the changes achieving statistical significance at concentrations of 1 µM and greater. The effect was greater at low frequency stimulation, indicating that at low heart rates the effect of vandetanib may be increased. Increases in action potential duration were more pronounced under low potassium conditions.

In conscious telemetered dogs, oral administration of vandetanib had no effect on cardiovascular parameters at the doses used (5, 15 and 40 mg/kg), except for a decrease in heart rate at the highest dose (see report: TKD1045). In contrast, intravenous administration of vandetanib to anaesthetized dogs (see report: 0276SD) caused an increase in heart rate corrected QT interval (QTcV) over the 0.67-13.4 mg/kg dose range. The QTcV increase was up to 15%, peaking at a total plasma exposure of approximately 1.4 µM, but with no further increase at higher exposures. Vandetanib also caused a dose-dependent increase in T – wave amplitude. There were no indications from this study that vandetanib causes coronary constriction, leading to local ischemia.

Vandetanib caused dose-related increases in femoral diastolic blood pressure in both anaesthetized dog studies where vandetanib was administered alone

3.4 PREVIOUS CLINICAL EXPERIENCE

The pivotal study in this submission is a Phase III, randomized, double-blinded, placebo controlled, multicentre study (Study D4200C00058) to assess the efficacy and safety of vandetanib 300 mg once daily in 331 patients with unresectable locally advanced or metastatic MTC (231 patients receiving vandetanib and 99 patients receiving placebo (1 patient randomized to placebo died before receiving study drug). Along with Study D4200C00058, 10 additional studies provide supportive safety data for the use of 300-mg vandetanib monotherapy in a total of 1839 patients.

Cardiac AEs reported in NSCLC program and other cancers

Source: ISS from NDA (b) (4) and Response document dated October 15, 2009

There have been a total of 2 confirmed cases of Torsade de Pointes at the 300-mg dose. One patient with NSCLC in Study D4200C00057 developed TdP. Another patient with papillary thyroid cancer in Study D4200C00079 (Study 79) treated with vandetanib 300 mg has also developed confirmed TdP.

Around 1940 patients received vandetanib for the treatment of NSCLC (1071 in combination with chemotherapy and the remainder as monotherapy). The safety profile of vandetanib is primarily based on the safety profile described in the Phase III NSCLC studies D4200C00032, D4200C00036, and D4200C00057, hereafter referred to as Studies 32, 36 and 57, respectively. Studies 32 and 36 used the 100 mg dose of vandetanib in combination with chemotherapy, and Study 57 used the 300 mg dose of vandetanib as monotherapy.

Hypertension was reported more often in patients who received vandetanib compared to placebo both in pooled studies and in Studies 32 and 36 separately. The sponsor reports that hypertension was readily treated with antihypertensive agents, most commonly calcium-channel blockers, and uncommonly led to withdrawal. One patient in Study 36 receiving vandetanib was reported as having hypertensive crisis. In both Study 32 (0.6% versus 0.3%) and Study 36 (1.5% versus 0.0%), more patients receiving vandetanib experienced an ischemic cerebrovascular event compared to patients receiving chemotherapy alone. Similar numbers of patients in both arms of both studies developed cardiac events (*listed in Table 2.7.4.01.2.1.2. of the ISS for NDA (b) (4)*

In study 57, Hypertension was reported more frequently in the vandetanib arm than the erlotinib arm and CTCAE Grade 3 or higher events of hypertension were also more common with vandetanib (3.9% versus 0.3%, respectively). The sponsor reports that the hypertension was readily treatable and rarely led to withdrawal. One case of hypertensive crisis was also reported in the vandetanib arm in this study. In this study, the incidence of ischemic cerebrovascular grouped events was similar between the treatment arms (1.0% versus 0.7% of patients, for vandetanib and erlotinib, respectively).

Heart failure in NSCLC monotherapy studies

Four patients receiving vandetanib developed AEs related to heart failure (cardiac failure, right ventricular failure, left ventricular failure, cardiomyopathy-see table below), compared to one receiving erlotinib (reported as diastolic dysfunction). One patient receiving vandetanib developed cardiac failure, which was fatal. In the 300-mg monotherapy pool, a total of 10 patients out of 1839 (0.5%) had reported incidences of cardiac failure. Four of these patients died.

At the 300-mg dose, vandetanib, like other inhibitors of VEGF, may be associated with an increased risk of heart failure.

Table 2.7.4.02.2.1.1 Study 57: Summary of patients who had at least 1 AE by PT, arranged by SOC
Safety analysis set

System organ class / Preferred term	Number (%) of patients [a]	
	Vandetanib 300mg (N=623)	Erlotinib 150mg (N=614)
Cardiac disorders	46 (7.4)	32 (5.2)
Atrial fibrillation	11 (1.8)	7 (1.1)
Palpitations	9 (1.4)	1 (0.2)
Myocardial infarction	6 (1.0)	2 (0.3)
Tachycardia	4 (0.6)	9 (1.5)
Cyanosis	3 (0.5)	1 (0.2)
Cardio-respiratory arrest	3 (0.5)	0
Acute myocardial infarction	3 (0.5)	1 (0.2)
Ventricular fibrillation	2 (0.3)	0
Pericardial effusion	2 (0.3)	1 (0.2)
Cardiac failure	2 (0.3)	0
Bundle branch block right	2 (0.3)	0
Bradycardia	2 (0.3)	0
Atrial flutter	2 (0.3)	1 (0.2)
Ventricular tachycardia	1 (0.2)	0
Torsade de Pointes	1 (0.2)	0
Tachyarrhythmia	1 (0.2)	1 (0.2)
Sinus tachycardia	1 (0.2)	1 (0.2)
Sinus bradycardia	1 (0.2)	0

Table 2.7.4.02.2.1.1 Study 57: Summary of patients who had at least 1 AE by PT, arranged by SOC
Safety analysis set

System organ class / Preferred term	Number (%) of patients [a]	
	Vandetanib 300mg (N=623)	Erlotinib 150mg (N=614)
Right ventricular failure	1 (0.2)	0
Postinfarction angina	1 (0.2)	0
Left ventricular failure	1 (0.2)	0
Cardiopulmonary failure	1 (0.2)	0
Cardiomyopathy	1 (0.2)	0
Cardiac arrest	1 (0.2)	0
Atrioventricular block first degree	1 (0.2)	1 (0.2)
Arrhythmia	1 (0.2)	0
Angina pectoris	1 (0.2)	0
Ventricular extrasystoles	0	1 (0.2)
Supraventricular tachycardia	0	1 (0.2)
Myocardial ischaemia	0	1 (0.2)
Extrasystoles	0	2 (0.3)
Diastolic dysfunction	0	1 (0.2)
Cardiovascular disorder	0	1 (0.2)
Atrioventricular block	0	1 (0.2)
Arrhythmia supraventricular	0	1 (0.2)

[a] Number (%) of patients with AEs, sorted by SOC followed by PT, in decreasing order of frequency (sorted by actual treatment, vandetanib then erlotinib).
A patient can have one or more PT reported under a given SOC but is only counted once within a PT.

/art/prod_1588/astrazeneca/oncology/d4200/d4200n00004saf/program/reports/ae201.sas ae201c.lst 01OCT2009:11:11 art_srv

Reviewers Comment: Vandetanib is not only a known torsadogen, but at the proposed therapeutic dose of 300 mg is also associated with other cardiotoxic effects including congestive heart failure and hypertension.

ECGs:

For the purposes of the Phase III vandetanib development program, QTcB prolongation was defined as:

- A single QTc value of ≥ 550 millisecond (ms) or an increase of ≥ 100 ms from baseline;

OR

- Two consecutive QTc measurements, within 48 hours of one another, where either of the following criteria are met for both QTc values (the second being the mean of 3 consecutive ECGs):
 - A QTc interval ≥ 500 ms, but < 550 ms;

OR

- An increase of ≥ 60 ms, but <100 ms from baseline QTc to a QTc value ≥ 480 ms (≥ 460 ms in Study 06)

Table 99 Summary of number of patients with a QTc (Bazett) prolongation (Studies 32 & 36 - Safety analysis set)

	Number (%) of patients			
	Vandetanib 100 mg + docetaxel (N=689)	Placebo + docetaxel (N=690)	Vandetanib 100 mg + pemetrexed (N=260)	Placebo + pemetrexed (N=273)
Patients with a protocol defined QTcB prolongation	13 (1.9)	0	1 (0.4)	0
QTcB prolongation single value[a]	8 (1.2)	0	1 (0.4)	0
Absolute value > 550 ms	1 (0.1)	0	0	0
Change from baseline > 100 ms	8 (1.2)	0	1 (0.4)	0
Both	1 (0.1)	0	0	0
QTcB prolongation two consecutive values[b]	8 (1.2)	0	0	0
Confirmation value absolute value > 500 ms	4 (0.6)	0	0	0
Confirmation value change from baseline > 60 ms [c]	6 (0.9)	0	0	0
Both	2 (0.3)	0	0	0

** Confirmed QTc prolongation as per protocol.

[a] QTcB prolongation single value: QTc ≥ 550 ms, or QTc increase from baseline ≥ 100 ms (does not need confirmation).

[b] QTcB prolongation consecutive values: QTc ≥ 500 and QTc < 550 ms, or QTc increase from baseline ≥ 60 .

[c] For Study 06 QTc must be ≥ 460 ms, for studies 32 and 36 QTc must be ≥ 480 ms.

Reasons for QTc prolongation are not mutually exclusive.

Table 151 Summary of number of patients with a QTc (Bazett) prolongation (Study 57 - Safety analysis set)

	Number (%) of patients	
	Vandetanib 300 mg (N=623)	Erlotinib 150mg (N=614)
Patients with a protocol defined QTcB prolongation	40 (6.4)	1 (0.2)
QTcB prolongation single value[a]	19 (3.0)	0 (0.0)
Absolute value > 550ms	8 (1.3)	0 (0.0)
Change from baseline > 100ms	18 (2.9)	0 (0.0)
Both	7 (1.1)	0 (0.0)
QTcB prolongation two consecutive values[b]	30 (4.8)	1 (0.2)
Confirmation value absolute value > 500ms	21 (3.4)	1 (0.2)
Confirmation value change from baseline > 60 ms [c]	24 (3.9)	0 (0.0)
Both	15 (2.4)	0 (0.0)

** Confirmed QTc prolongation as per protocol.

[a] QTcB prolongation single value: QTc \geq 550ms, or QTc increase from baseline \geq 100ms (does not need confirmation).

[b] QTcB prolongation consecutive values: QTc \geq 500 and QTc <550ms, or QTc increase from baseline \geq 60 to \geq 480ms.

Reasons for QTc prolongation are not mutually exclusive.

Reviewer’s Comment: The sponsor only reports QTcB. There are more outliers with the 300-mg mono-therapy dose. Following Visit 7 (Day 85) ECGs were performed only every 3 months until discontinuation of study medication.

Cardiac AE s related to QT prolongation

The sponsor reported that a total of 12 patients in studies across the vandetanib clinical program (NDA 22409), who received study treatment had an AE reported as one of the above MedDRA preferred terms “Sudden death”, “Sudden cardiac death”, “Torsades de Pointes”, “Cardiac fibrillation”, “Ventricular arrhythmia”, “Ventricular fibrillation”, “Ventricular flutter”, “Ventricular tachycardia”, and “Ventricular tachyarrhythmia”. in a response document to DDOP. This included the two reports of TdP. The sponsor reported one sudden death each in subjects on placebo+ docetaxel, vandetanib 100 mg + docetaxel, vandetanib 300 mg and 3 sudden deaths on erlotinib,

Reviewer’s Comment: Given the large effect size, QT prolongation may have contributed to any of the deaths reported as primarily or secondarily due to NSCLC (175 on randomized treatment and 200 after safety follow –up, listed in table 48 of the CSR for Study 57) in the absence of an ECG shortly prior to the event, especially the unobserved deaths. Again, following Visit 7 (Day 85) ECGs were performed every 3 months until discontinuation of study medication.

Cases of TdP

- Patient E0701006 (Study 79)

This patient with metastatic thyroid cancer had a history dyspnoea at exertion, right bundle block and transient ischaemic attack (TIA). The patient began study drug on 21-Jan-2008. On (b) (6) he visited his physician for routine medical examination. The examination of the physician revealed blood pressure of 160/90 mmHg and a peripheral irregularly heart rate of 44 beats/min. To exclude a sinus bradycardia with extrasystoles,

the doctor advised him to do ten knee-bends. Following this exercise the patient became unconscious and went into cardiac arrest. Artificial respiration and cardiac massage were started. During the defibrillation the patient developed TdP and finally returned to sinus rhythm and spontaneous respiration. During these actions the patient also developed seizures. He was hospitalized and transferred to the intensive care unit. He received a two chamber implantable cardioverter defibrillator (ICD) due to several episodes of torsade de pointes and ventricular tachycardia. At baseline the patients ECG was normal except for right bundle branch block and no QTc prolongation. The Investigator considered the event related to study medication and hydrochlorothiazide+losartan.

- Patient E1304012 –Study 57

Source: CSR for Study 57

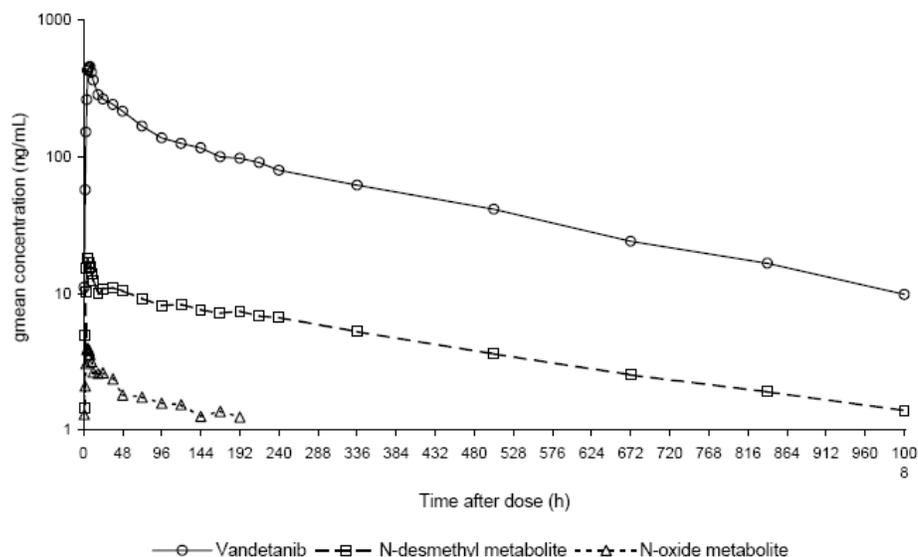
This case concerned a 74 year old female patient with metastatic NSCLC since 2003. The patient began study drug on 15 August 2007 and presented to the hospital emergency room on (b) (6) with a history of dizzy spells and fatigue and feeling generally unwell with nausea and diarrhea. She had started levofloxacin 8 days earlier. Whilst undergoing ECG monitoring the patient experienced paroxysms of ventricular arrhythmias, including an episode of torsade de pointes and study drug was discontinued on the same day ((b) (6)). Laboratory values indicated low electrolyte levels, which prompted electrolyte replacement with magnesium and potassium. The patient received a loading dose of amiodarone to treat the arrhythmias; blood pressure was 116/62 and pulse was 70 beats per minute and regular but with occasional premature ventricular contractions. Subsequent ECGs showed QT of 434 ms and QTc of 481 ms (11 November 2007), QT of 550 ms, QTc of 554 ms (12 November 2007) QT of 550 ms and QTc of 554 ms (13 November 2007) and QT of 500 ms and QTc of 508 ms (14 November 2007) and QT of 554 ms and QTc of 539 ms (15 November 2007). Findings included T wave inversions that had not been seen on previous ECGs undertaken during the study and troponins were found to be elevated (1.19 ng/mL).

Reviewer's Comments: The elevated QTc later was also due to amiodarone but TdP was clearly associated to vandetanib and electrolyte abnormalities.

3.5 CLINICAL PHARMACOLOGY

The mean plasma concentration-profiles vandetanib, N-desmethyl-vandetanib and vandetanib-N-oxide after single 800-mg dose of vandetanib are shown in Figure 4. The exposure ratio of the metabolites of vandetanib is shown in Table 2. The exposures of N-desmethyl vandetanib is 11.1% and 17.1 % of the exposure achieved by vandetanib at weeks 12 and 24.

Figure 4: Sponsor’s Mean Plasma Concentration-Time Profiles for Vandetanib, N-Desmethyl Vandetanib and N-Oxide Vandetanib after a Single 800 mg Dose



(Source: Figure 7 from Summary report of Clinical Pharmacology)

Table 2: Summary of Accumulation Ratio and Exposure ratio of N-Desmethyl-Vandetanib and Vandetanib-N-Oxide to Vandetanib.

	Week 12		Week 24	
	Exposure ratio	Accumulation ratio	Exposure ratio	Accumulation ratio
Study 57 (300 mg vandetanib)				
N-desmethyl	0.111	2.323	0.171	3.473
N-oxide	0.014	1.608	0.022	1.924

All values presented are arithmetic means.
For Study 57 Week 12 and 24 data were compared with Week 1 data.

(Source: Table 8 from Summary report of Clinical Pharmacology)

Appendix 5.1 summarizes the key features of vandetanib’s clinical pharmacology.

4 SPONSOR SUBMITTED ECG RESULTS

4.1 OVERVIEW

The focus of our quantitative analysis is to evaluate the magnitude of QTc prolongation following 300-mg dose of vandetanib. Because no thorough/dedicated QT study has been conducted by the sponsor, the evaluation is based on the ECG and exposure data collected during the clinical development program.

The sponsor performed intensive ECG monitoring in the pivotal Phase III study (Study D4200C00058). Therefore, data collected in this trial serve as the primary basis for our quantitative assessment, including central tendency analysis, categorical analysis and exposure-response analysis. The study design and data analysis was discussed in detail in Section 4.2.

The quantitative evaluation results obtained from Study D4200C00058 were further supported by the analyses results from additional clinical trials, including Study D4200C00021 (Section 4.3) and Study D4200C00008 (Section 4.4).

The sponsor submitted waveforms to the ECG warehouse for 3 clinical trials, studies D4200C00021, D4200C00044, and D4200C00058. ECG and PK data are available for all above-mentioned trials.

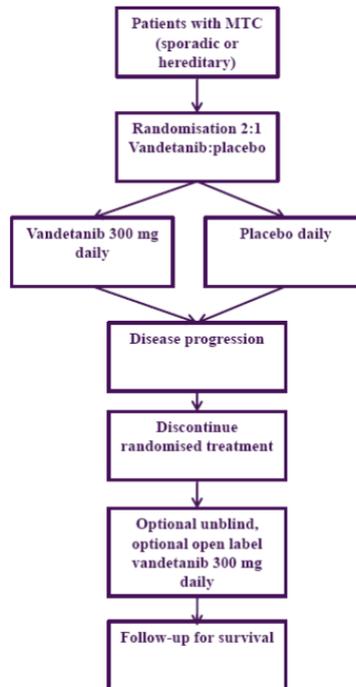
4.2 ECG MONITORING IN THE PIVOTAL TRIAL (STUDY D4200C00058)

4.2.1 Trial Design:

4.2.1.1 Overall Trial Design

The sponsor conducted one phase 3 pivotal trial (Study D4200C00058) entitled “An International, Phase III, Randomized, Double-Blinded, Placebo- Controlled, Multi-Center Study to Assess the Efficacy of ZD6474 versus Placebo in Subjects with Unresectable Locally Advanced or Metastatic Medullary Thyroid Cancer”. The main objective was to evaluate the efficacy of vandetanib in patients with MTC. QTc-related assessment was included as one of the secondary objectives. The design was depicted in Figure 5. Briefly, patients were randomized in a 2:1 ratio to receive vandetanib 300-mg once daily oral dose or matched placebo, continuing on blinded treatment until they had objective disease progression, provided they did not meet any other withdrawal criteria. Upon disease progression, patients were discontinued from blinded study treatment and then unblinded and given the option to begin open label treatment with vandetanib 300 mg (or receive a permanently reduced dose, if applicable), or enter follow-up for survival status.

Figure 5: Flow Chart to the Study Design



4.2.1.2 Exclusion Criteria

To manage patient risk, the following QT-related exclusion criteria were included:

- Any concomitant medications that may have affected QTc or induced CYP3A4 function (with the exception of somatostatin or somatostatin analog) and/or any prohibited medications referenced in the Amended CSP, Appendix E
- Potassium <4.0 mmol/L despite supplementation, or above the Common Terminology Criteria for Adverse Events (CTCAE) grade 1 upper limit. Magnesium below the normal range despite supplementation, or above the CTCAE grade 1 upper limit. Serum calcium above the CTCAE grade 1 upper limit. In instances when the serum calcium was below the normal range, the calcium adjusted for albumin was to be obtained and substituted for the measured serum value. Exclusion was to then be based on the calcium adjusted for albumin values falling below the normal limit. $\text{Corrected Calcium} = \text{Ca} + 0.8 \times (4 - \text{serum albumin})$
- Significant cardiac event (e.g., myocardial infarction), superior vena cava syndrome, New York Heart Association (NYHA) classification of heart disease ≥ 2 , within 12 weeks before randomisation, or presence of cardiac disease that in the opinion of the investigator increased the risk of ventricular
- History of arrhythmia (multifocal premature ventricular contractions, bigeminy, trigeminy, ventricular tachycardia) that was symptomatic or required treatment (CTCAE grade 3), symptomatic or uncontrolled atrial fibrillation despite treatment, or asymptomatic sustained ventricular tachycardia. Patients with atrial fibrillation controlled by medication were permitted.

- Congenital long QT syndrome or 1st degree relative with unexplained sudden death under 40 years of age
- QT prolongation with other medications that required discontinuation of that medication
- Presence of left bundle branch block (LBBB)
- QTc with Bazett's correction unmeasurable or ≥ 480 ms on screening electrocardiogram (ECG). Note: if a patient had QTc interval ≥ 480 ms on screening ECG, the screening ECG could have been repeated 2 times (at least 24 hours apart) for a total of 3 ECGs. The average QTc from the 3 screening ECGs had to be < 480 ms for the patient to be eligible for the study.) If a patient was receiving a medication with possible association with Torsades de Pointes (see Appendix E, Table 2 of the Amended CSP [Appendix 12.1.1] before study entry, and the medication could not be discontinued before study treatment, then the screening QTc had to be < 460 ms.
- Any concomitant medications that may have affected the QTc interval or induced CYP3A4 function.

4.2.1.3 Protocol Defined QTc Prolongation and Dose Intervention:

During the trial, QTc (QTcB) values above preset thresholds of 500 and 550 ms (or changes from baseline of 60 and 100 ms) were deemed to require intervention. Dose interruption was required for a single QTc value of ≥ 550 ms or an increase of ≥ 100 ms from baseline. For a QTc interval ≥ 500 ms, but < 550 ms, or an increase of ≥ 60 ms but < 100 ms from baseline QTc to a QTc value ≥ 480 ms, treatment could continue but a repeat ECG (in triplicate, with the average calculated) had to be obtained within 48 hours. If QTc prolongation was confirmed by the average of these 3 ECGs, dose interruption was required. Treatment was resumed at a lower dose after the QTc recovered to < 480 ms or baseline. QTc values above these thresholds are referred to as protocol-defined QT prolongation.

4.2.1.4 ECG and PK Assessment:

ECG Assessment:

A 12-lead ECG was collected at the screening, within 21 days before the first dose, baseline values for QTc were collected on day 1 prior to first dose. Subsequently ECG data were collected on days 7, 14, 28, 56, 84 (weeks 1, 2, 4, 8 and 12) and then every 12 weeks until discontinuation of treatment. The ECG was performed 4-8 hours after the drug was administered orally. Additional 12-lead ECGs were to be performed during the post-prolongation period in the event of QTc prolongation.

Baseline QTc was determined by the average of no fewer than 3 consecutive ECGs (within 5 to 10 minutes of one another) on Day 1 (Visit 2). If the screening QTc was obtained with 3 consecutive ECGs within 3 days before Day 1 (Visit 2), then the screening QTc was considered the baseline, and repeat ECGs were not necessary on Day 1. ECGs were to be performed at the same time throughout the study, after the patient had taken study drug on the assessment days. A post-dose ECG was not required on Day 1

(Visit 2). Additional 12-lead ECGs were to be performed during the post-prolongation period in the event of QTc prolongation.

12-lead ECGs were assessed at post-progression weeks 0, 1, 2, 4, 8, and 12, and every 12 weeks thereafter until discontinuation of post-progression open-label vandetanib study treatment. ECGs were to be performed at the same time throughout the study, approximately 4 to 8 hours after patients took their study drug on the assessment days. Additional 12-lead ECGs were to be performed in the event of QTc prolongation and during the post-prolongation period, as defined in Section 3.3.1 of the Amended CSP.

PK Assessment:

Blood samples were collected on days 7, 14, 28, 56, 84 (weeks 1, 2, 4, 8 and 12) and then every 12 weeks until discontinuation of treatment. Blood samples were collected as soon as possible following ECG collection. PK sampling was not performed with the baseline ECG or following additional ECG during QT prolongation.

Reviewer's Comment: The sampling scheme is adequate as the PK and ECG data were collected at 4-8 hours after dosing which corresponds to peak concentrations of vandetanib and its metabolites (see Clin Pharm Table).

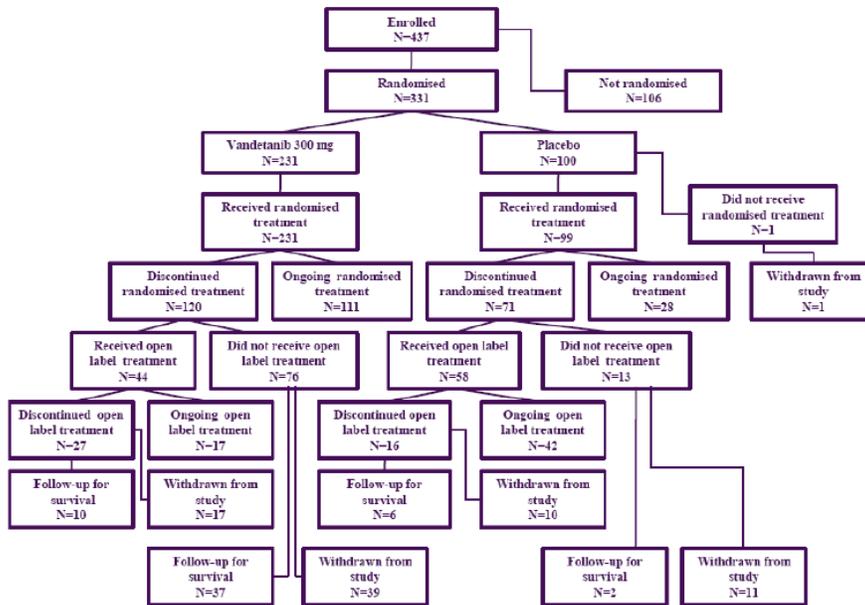
4.2.1.5 ECG Collection:

ECGs were read centrally by an external contract organization, appointed by AstraZeneca, with results communicated back to the sites within 72 hours. ECGs were transmitted electronically to the vendor for the central read, where the QT interval was interpreted. Only QTcB has been reported. Further details about ECG acquisition and interpretation are unavailable.

4.2.2 Sponsor's Results

4.2.2.1 Study Subjects

331 patients (vandetanib 300 mg-231, placebo-100) with unresectable locally advanced or metastatic hereditary or sporadic MTC were randomized in the study with discontinuation of blinded study treatment at Day 75. Sponsor's summary of subject disposition is shown below.



Derived from Table 11.1.1 and Table 11.1.2. These tables present this information in tabular format and include summaries of reasons for discontinuation of treatment and reasons for withdrawal from study.

The term 'enrolled' means that informed consent was received.

Number of patients randomised = the Full Analysis Set (equivalent to the ITT population).

Data cut-off date = 31 July 2009.

4.2.2.2 The Sponsor's Analyses

The sponsor's QTc analyses were based on QTcB.

4.2.2.2.1 Central Tendency Analysis

The sponsor's results on changes from baseline at multiple visits using QTcB were summarized in Table 3 and Table 4. The mean changes from baseline over time were plotted in Figure 6.

Table 3: Summary of QTc (Bazett) over Time whilst on Randomized Treatment - Change from Baseline (Safety Analysis Set)

Assessment timepoint	Summary statistics	Vandetanib 300mg (N=231)	Placebo (N=99)	Total (N=330)
Week 1	n	221	96	317
	Mean	13.0	1.0	9.4
	SD	18.61	13.04	17.96
	Min	-79.3	-39.3	-79.3
	Max	62.0	27.7	62.0
	Median	14.7	1.2	8.5
Week 2	n	224	92	316
	Mean	19.4	-0.0	13.8
	SD	20.84	14.13	21.07
	Min	-45.3	-31.7	-45.3
	Max	69.0	32.5	69.0
	Median	20.5	-1.7	11.5
Week 4	n	225	97	322
	Mean	25.9	0.3	18.2
	SD	19.50	14.84	21.67
	Min	-22.7	-40.8	-40.8
	Max	81.0	47.3	81.0
	Median	24.3	-0.7	18.2
Week 8	n	227	97	324
	Mean	25.6	-1.1	17.6
	SD	23.97	16.09	25.09
	Min	-58.3	-37.7	-58.3
	Max	97.3	33.3	97.3
	Median	26.3	0.3	16.7
Week 12	n	222	90	312
	Mean	27.6	1.7	20.1
	SD	25.32	16.98	26.01
	Min	-50.3	-32.3	-50.3
	Max	135.7	88.3	135.7
	Median	28.7	1.8	20.0
Week 24	n	213	73	286
	Mean	26.7	1.5	20.3
	SD	23.82	16.69	24.77
	Min	-49.7	-46.7	-49.7

Baseline QTcB is defined as the average of up to 3 values, obtained within the same visit closest to and preceding the first dose of randomized treatment.
 NC = not calculable.

Assessment timepoint	Summary statistics	Vandetanib 300mg (N=231)	Placebo (N=99)	Total (N=330)
Week 24	Max	89.0	33.3	89.0
	Median	27.0	1.7	20.3
Week 36	n	191	57	248
	Mean	24.7	3.8	19.9
	SD	23.36	17.22	23.77
	Min	-61.3	-24.7	-61.3
	Max	78.0	53.5	78.0
	Median	25.8	1.0	19.6
Week 48	n	179	49	228
	Mean	23.8	0.2	18.7
	SD	24.61	13.26	24.63
	Min	-78.7	-45.0	-78.7
	Max	81.0	40.0	81.0
	Median	26.0	1.0	17.7
Week 60	n	163	41	204
	Mean	23.5	4.9	19.8
	SD	23.53	17.91	23.68
	Min	-66.0	-46.3	-66.0
	Max	88.7	36.0	88.7
	Median	23.0	4.3	20.4
Week 72	n	144	37	181
	Mean	24.7	5.7	20.8
	SD	22.56	16.51	22.75
	Min	-64.0	-30.7	-64.0
	Max	83.3	57.0	83.3
	Median	25.0	4.7	20.7
Week 84	n	131	35	166
	Mean	27.4	5.4	22.8
	SD	25.50	13.63	25.13
	Min	-41.7	-23.7	-41.7
	Max	95.0	49.0	95.0
	Median	27.3	6.3	20.0
Week 96	n	76	18	94

Baseline QTCB is defined as the average of up to 3 values, obtained within the same visit closest to and preceding the first dose of randomized treatment.
NC = not calculable.

Assessment timepoint	Summary statistics	Vandetanib 300mg (N=231)	Placebo (N=99)	Total (N=330)
Week 96	Mean	25.5	4.0	21.4
	SD	20.14	14.55	20.93
	Min	-29.7	-20.7	-29.7
	Max	74.7	29.3	74.7
	Median	25.8	5.7	21.2
Week 108	n	43	12	55
	Mean	29.6	0.5	23.3
	SD	21.13	17.62	23.62
	Min	-13.7	-28.7	-28.7
	Max	83.7	34.3	83.7
	Median	26.0	-1.5	24.3
Week 120	n	16	4	20
	Mean	19.0	-3.1	14.6
	SD	15.34	8.50	16.71
	Min	-11.7	-10.7	-11.7
	Max	40.3	8.7	40.3
	Median	20.2	-5.2	12.8
Week 132	n	1	0	1
	Mean	44.0	NC	44.0
	SD	NC	NC	NC
	Min	44.0	NC	44.0
	Max	44.0	NC	44.0
	Median	44.0	NC	44.0

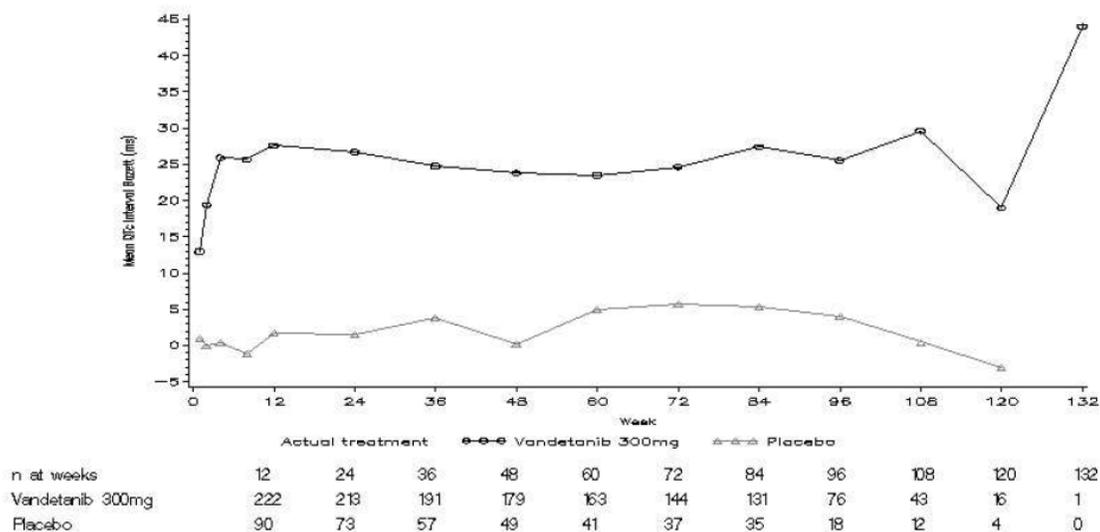
Table 4: Summary of QTc (Bazett) over Time whilst on Open Label Treatment - Change from Baseline (Open Label Analysis Set)

Assessment timepoint	Summary statistics	Vandetanib 300mg (N=231)	Placebo (N=99)	Total (N=330)
Week 1	n	221	96	317
	Mean	13.0	1.0	9.4
	SD	18.61	13.04	17.96
	Min	-79.3	-39.3	-79.3
	Max	62.0	27.7	62.0
	Median	14.7	1.2	8.5
Week 2	n	224	92	316
	Mean	19.4	-0.0	13.8
	SD	20.84	14.13	21.07
	Min	-45.3	-31.7	-45.3
	Max	69.0	32.5	69.0
	Median	20.5	-1.7	11.5
Week 4	n	225	97	322
	Mean	25.9	0.3	18.2
	SD	19.50	14.84	21.67
	Min	-22.7	-40.8	-40.8
	Max	81.0	47.3	81.0
	Median	24.3	-0.7	18.2
Week 8	n	227	97	324
	Mean	25.6	-1.1	17.6
	SD	23.97	16.09	25.09
	Min	-58.3	-37.7	-58.3
	Max	97.3	33.3	97.3
	Median	26.3	0.3	16.7
Week 12	n	222	90	312
	Mean	27.6	1.7	20.1
	SD	25.32	16.98	26.01
	Min	-50.3	-32.3	-50.3
	Max	135.7	88.3	135.7
	Median	28.7	1.8	20.0
Week 24	n	213	73	286
	Mean	26.7	1.5	20.3
	SD	23.82	16.69	24.77
	Min	-49.7	-46.7	-49.7

Assessment timepoint	Summary statistics	Vandetanib 300mg (N=231)	Placebo (N=99)	Total (N=330)
Week 24	Max	89.0	33.3	89.0
	Median	27.0	1.7	20.3
Week 36	n	191	57	248
	Mean	24.7	3.8	19.9
	SD	23.36	17.22	23.77
	Min	-61.3	-24.7	-61.3
	Max	78.0	53.5	78.0
	Median	25.8	1.0	19.6
Week 48	n	179	49	228
	Mean	23.8	0.2	18.7
	SD	24.61	13.26	24.63
	Min	-78.7	-45.0	-78.7
	Max	81.0	40.0	81.0
	Median	26.0	1.0	17.7
Week 60	n	163	41	204
	Mean	23.5	4.9	19.8
	SD	23.53	17.91	23.68
	Min	-66.0	-46.3	-66.0
	Max	88.7	36.0	88.7
	Median	23.0	4.3	20.4
Week 72	n	144	37	181
	Mean	24.7	5.7	20.8
	SD	22.56	16.51	22.75
	Min	-64.0	-30.7	-64.0
	Max	83.3	57.0	83.3
	Median	25.0	4.7	20.7
Week 84	n	131	35	166
	Mean	27.4	5.4	22.8
	SD	25.50	13.63	25.13
	Min	-41.7	-23.7	-41.7
	Max	95.0	49.0	95.0
	Median	27.3	6.3	20.0
Week 96	n	76	18	94
Assessment timepoint	Summary statistics	Vandetanib 300mg (N=231)	Placebo (N=99)	Total (N=330)
Week 96	Mean	25.5	4.0	21.4
	SD	20.14	14.55	20.93
	Min	-29.7	-20.7	-29.7
	Max	74.7	29.3	74.7
	Median	25.8	5.7	21.2
	Week 108	n	43	12
Mean		29.6	0.5	23.3
SD		21.13	17.62	23.62
Min		-13.7	-28.7	-28.7
Max		83.7	34.3	83.7
Median		26.0	-1.5	24.3
Week 120	n	16	4	20
	Mean	19.0	-3.1	14.6
	SD	15.34	8.50	16.71
	Min	-11.7	-10.7	-11.7
	Max	40.3	8.7	40.3
	Median	20.2	-5.2	12.8
Week 132	n	1	0	1
	Mean	44.0	NC	44.0
	SD	NC	NC	NC
	Min	44.0	NC	44.0
	Max	44.0	NC	44.0
	Median	44.0	NC	44.0

(Source: CSR P-1829, Table 11.3.8.1.7.1)

Figure 6: Plot of Mean Change from Baseline (QTcB) on Randomized Treatment over Time (Safety Analysis Data)



(Source: CSR P-1819, Figure 11.3.8.1.4.1)

4.2.2.2.2 Categorical Analysis

A total of 19 patients in the vandetanib arm had a protocol-defined QTc prolongation compared with none of the patients in the placebo arm while on randomized treatment or during the 60-day follow-up period after the last dose of randomized treatment. As shown in Table 5, 18 (7.8%) patients had a protocol-defined QTc prolongation during randomized treatment and 4 patients had this after randomized treatment, which was defined as occurring during the 60-day follow-up period. Three of the patients who had protocol-defined QTc prolongation during the 60-day follow-up period also had this during randomized treatment.

The median time from first dose of vandetanib to first QTc prolongation during randomized treatment was 174 days (range, 18 to 516 days). The median period until QTc recovered (defined as the period from confirmed QTc prolongation until return to QTc value of 480 ms) was 27 days (range 1 to 191 days) for all patients who had a QTc prolongation.

A total of 3 (1.3%) patients in the vandetanib arm had QTc \geq 550 ms or increase from baseline \geq 100 ms, based on a single value during randomized treatment (see Table 5). Two (0.9%) patients (E0013006 and E1901004) in the vandetanib arm discontinued treatment due to an AE of QTc prolongation or electrocardiogram QT prolonged. Both of these patients met the criteria for protocol-defined QTc prolongation. In addition, 1 patient (E0021003) in the vandetanib arm had an AE of prolonged QTc that was CTCAE grade 4, but the patient did not meet the criteria for protocol-defined QTc prolongation, and there were no accompanying AEs that would confirm such a grade.

A total of 3 (1.3%) patients in the vandetanib arm had QTc \geq 550 ms or increase from baseline \geq 100 ms, based on a single value during randomized treatment) (see Table 5). Two (0.9%) patients (E0013006 and E1901004) in the vandetanib arm discontinued treatment due an AE of QTc prolongation or electrocardiogram QT prolonged. Both of these patients met the criteria for protocol-defined QTc prolongation. In addition, 1 patient (E0021003) in the vandetanib arm had an AE of prolonged QTc that was CTCAE grade 4, but the patient did not meet the criteria for protocol defined QTc prolongation, and there were no accompanying AEs that would confirm such a grade.

A total of 14 patients had QTc prolongation while receiving vandetanib 300 mg during randomized treatment, but QTc prolongation also occurred in patients during dose reductions to 200 or 100 mg or during dose interruption.

Patients with protocol-defined QTc prolongation are summarized for those who received a Group 1 defined or Group 2 defined concomitant medication. A total of 3 (9.7%) of 31 patients in the vandetanib arm who were treated with a Group 1 concomitant medication had protocol-defined QTc prolongation during randomized treatment and 1 (3.2%) of 4 patients had this event after randomized treatment. Of those taking Group 2 concomitant medications, 5 (8.8%) patients in the vandetanib arm had QTc prolongation during randomized treatment and 2 (3.5%) patients had QTc prolongation after randomized treatment.

Maximum QTc values compared with baseline during randomized treatment are summarized. Overall, 25/231 (10.8%) patients in the vandetanib arm had a maximum QTc (Bazett's) value of \geq 500 ms compared with 1/99 (1.0%) patients in the placebo arm. (Source: CSR P-169)

Table 5: Summary of Patients with a QTc (Bazett) Prolongation during and after Randomised Treatment (Safety Analysis Set)

			Number (%) of patients				
			Vandetanib 300mg (N=231)	Placebo (N=99)	Total (N=330)		
During	QTc prolongation	No	213 (92.2)	99 (100.0)	312 (94.5)		
		Yes	18 (7.8)	0 (0.0)	18 (5.5)		
	If yes, reason	QTcB prolongation single value ^a	3 (1.3)	0 (0.0)	3 (0.9)		
		Absolute value \geq 550ms	1 (0.4)	0 (0.0)	1 (0.3)		
		Change from baseline \geq 100ms	3 (1.3)	0 (0.0)	3 (0.9)		
		Both	1 (0.4)	0 (0.0)	1 (0.3)		
		QTcB prolongation ² consecutive values ^b	15 (6.5)	0 (0.0)	15 (4.5)		
		Confirmation value absolute value \geq 500ms	9 (3.9)	0 (0.0)	9 (2.7)		
		Confirmation value change from baseline \geq 60 ms (to =480ms)	10 (4.3)	0 (0.0)	10 (3.0)		
		Both	4 (1.7)	0 (0.0)	4 (1.2)		
		If no, reason	Single value meeting criteria ^c with subsequent value not meeting criteria ^c	45 (19.5)	1 (1.0)	46 (13.9)	
			Single value meeting criteria ^c with no subsequent value recorded	0 (0.0)	0 (0.0)	0 (0.0)	
			No values meeting criteria for prolongation	184 (79.7)	98 (99.0)	282 (85.5)	
		After	QTc prolongation	No	30 (13.0)	12 (12.1)	42 (12.7)
				Yes	4 (1.7)	0 (0.0)	4 (1.2)

During /after randomised treatment	___Number (%) of patients___				
		Vandetanib 300mg (N=231)	Placebo (N=99)	Total (N=330)	
If yes, reason	QTcB prolongation single value ^a	2 (0.9)	0 (0.0)	2 (0.6)	
	Absolute value \geq 550ms	1 (0.4)	0 (0.0)	1 (0.3)	
	Change from baseline \geq 100ms	2 (0.9)	0 (0.0)	2 (0.6)	
	Both	1 (0.4)	0 (0.0)	1 (0.3)	
	QTcB prolongation 2 consecutive values ^b	2 (0.9)	0 (0.0)	2 (0.6)	
	Confirmation value absolute value \geq 500ms	2 (0.9)	0 (0.0)	2 (0.6)	
	Confirmation value change from baseline \geq 60 ms (to \geq 480ms)	2 (0.9)	0 (0.0)	2 (0.6)	
	Both	2 (0.9)	0 (0.0)	2 (0.6)	
	If no, reason	Single value meeting criteria ^c with subsequent value not meeting criteria ^c	3 (1.3)	0 (0.0)	3 (0.9)
		Single value meeting criteria ^c with no subsequent value recorded	0 (0.0)	0 (0.0)	0 (0.0)
No values meeting criteria for prolongation		30 (13.0)	12 (12.1)	42 (12.7)	

Derived from [Table 11.3.8.1.8.1](#).

^a QTcB prolongation single value: QTc \geq 550ms, or QTc increase from baseline \geq 100ms (does not need confirmation).

^b QTcB prolongation 2 consecutive values: QTc \geq 500 and QTc $<$ 550ms, or QTc increase from baseline \geq 60 but $<$ 100ms (to \geq 480ms). Two consecutive QTc values.

^c QTcB prolongation single value: QTc \geq 500 and QTc $<$ 550ms, or QTc increase from baseline \geq 60 (to \geq 480ms).

Reasons for QTC prolongation are not mutually exclusive.

After refers to the 60-day follow-up period after last dose of randomised treatment. If the patient entered open label prior to the end of the 60-day follow-up period, then any QTc prolongations that occurred after the first dose of open label are summarised in the open label version of this table and are excluded from this table.

(Source: CSR P-167, Table 54)

4.2.2.2.3 Safety Analysis

A total of 48 deaths (14.5%; 32 on vandetanib, 15 on placebo) occurred in patients in this study at the time of data cut-off (31 July 2009). Of these, one patient on placebo died before receiving study treatment. The sponsor attributes MTC as a primary or secondary cause of death in 24 subjects compared to 14 in the placebo arm (Table 47 in the CSR for study 58).

There was 1 death reported in the vandetanib arm due to arrhythmia and cardiac failure (E2301006, Table 49 in the CSR for Study 58), (b) (6) days from the start of randomized treatment. This patient, a 42-year-old man with sporadic MTC who had disease in the cervical LNs and extensive metastatic disease to the lungs, mediastinal lymph nodes, and liver had a history of junctional tachycardia treated with propranolol. The patient's medications included: propranolol, levothyroxine, metoclopramide, clonazepam, aspirin, oral prednisone, and amitriptyline. Vandetanib treatment was started on 15 August 2007 and reduced to 100 gm qd for a rash. The patient had been receiving propranolol for years and he came into study on propranolol but was stopped on 9/12/07 because he had become bradycardic and re-started on October 8, 2008 since he had SVT. When the patient returned a week later he had no complaints and was feeling "fine". The patient's heart rate was 90 bpm but on repeat ECGs performed 18 October 2008, the mean QTcB was found to be prolonged at 498ms (by central ECG vendor). On (b) (6), the patient called the investigator complaining of severe tiredness and feeling very poorly. He was instructed to go to the hospital where he was found to be tachycardic and hypotensive with a blood pressure of 80/60 and a creatinine value of 2.8 mg/dL. Cardiac isoenzymes were normal; ECG showed sinus tachycardia without ischemic changes. Vandetanib treatment was stopped on (b) (6). On the first night in the hospital, the patient had a cardiac arrest but was quickly resuscitated requiring further intravenous pressors and intubation. An echocardiogram showed a LV ejection fraction estimated to be 10% to 15% with normal RV function. There was minimal aortic insufficiency and the left ventricle was dilated with normal wall thicknesses. The patient's condition continued to improve and he was extubated on (b) (6). However, he died suddenly on (b) (6). There were no ECG strips available at the time of the patient's death, but the cardiac monitor is reported to have shown ventricular tachycardia. ECGs performed within the week before death all were read by the central ECG vendor as having prolonged QTcB intervals of 547, 556 and 538 ms respectively; however, the patient received IV amiodarone on (b) (6).

Reviewer's Comment:

- *This case illustrates persistent QTc prolongation even with drug withdrawal due to long $t_{1/2}$ of vandetanib. Although there is confounding due to amiodarone and CHF, there is association to study drug.*
- *Again after week 12 in the blinded or open label treatment phases, ECGs have been collected only every 12 weeks, so arrhythmia related death cannot be excluded for any of the deaths attributed to disease progression in the absence of an ECG shortly before the death.*

Two subjects were discontinued from the vandetanib arm due to QT prolongation (table 51 of the CSR for study 58). Nineteen subjects in the vandetanib arm had dose interruptions due to QT prolongation (Table 41 in the CSR for study 58).

Cardiac AEs on randomized and open label treatment are summarized below.

Table 11.3.2.2.1 Summary of patients who had at least 1 AE by PT, arranged by SOC whilst on randomized treatment

Final SAS Safety analysis set					
SOC Name Preferred Term	Vandetanib 300mg (N=231)		Placebo (N=99)		Total number (%) of patients (N=330)
	Number (%) of patients [a]	Event rate (per 1000 pt years)	Number (%) of patients [a]	Event rate (per 1000 pt years)	
Cardiac Disorders	30 (13.0)	100.0	13 (13.1)	138.8	43 (13.0)
Palpitations	6 (2.6)	18.6	2 (2.0)	20.0	8 (2.4)
Angina Pectoris	4 (1.7)	12.3	1 (1.0)	9.8	5 (1.5)
Bradycardia	4 (1.7)	12.3	0 (0.0)	0.0	4 (1.2)
Sinus Bradycardia	4 (1.7)	12.3	0 (0.0)	0.0	4 (1.2)
Tachycardia	2 (0.9)	6.1	2 (2.0)	19.6	4 (1.2)
Bundle Branch Block Left	2 (0.9)	6.1	1 (1.0)	9.9	3 (0.9)
Atrial Fibrillation	2 (0.9)	6.0	0 (0.0)	0.0	2 (0.6)
Arrhythmia	1 (0.4)	3.0	1 (1.0)	9.9	2 (0.6)
Cardiac Failure	1 (0.4)	3.0	0 (0.0)	0.0	1 (0.3)
Cardiac Failure Acute	1 (0.4)	3.0	0 (0.0)	0.0	1 (0.3)
Coronary Artery Occlusion	1 (0.4)	3.0	0 (0.0)	0.0	1 (0.3)
Cyanosis	1 (0.4)	3.0	0 (0.0)	0.0	1 (0.3)
Hypertrophic Cardiomyopathy	1 (0.4)	3.0	0 (0.0)	0.0	1 (0.3)
Nodal Arrhythmia	1 (0.4)	3.0	0 (0.0)	0.0	1 (0.3)
Pericarditis	1 (0.4)	3.0	0 (0.0)	0.0	1 (0.3)
Supraventricular Extrasystoles	1 (0.4)	3.0	0 (0.0)	0.0	1 (0.3)
Ventricular Tachycardia	1 (0.4)	3.0	0 (0.0)	0.0	1 (0.3)
Arrhythmia Supraventricular	0 (0.0)	0.0	1 (1.0)	9.8	1 (0.3)
Pericardial Effusion	0 (0.0)	0.0	1 (1.0)	9.8	1 (0.3)
Pericardial Haemorrhage	0 (0.0)	0.0	1 (1.0)	9.8	1 (0.3)
Sinus Tachycardia	0 (0.0)	0.0	1 (1.0)	9.8	1 (0.3)
Supraventricular Tachycardia	0 (0.0)	0.0	1 (1.0)	9.8	1 (0.3)

SOC = System Organ Class, PT = Preferred Term.

[a] Number (%) of patients with AEs, sorted by SOC followed by PT, in decreasing order of frequency in the vandetanib arm.
A patient can have one or more PT reported under a given SOC.

Event rate = (No. of pats. with event / total duration of follow-up until 1st event for all pats. in group) x 1000

/art/prod_2511/astrazeneca/oncology/d4200/d4200c00058/prog/reports/ae201.sas ae201a.lst 07JUN2010:20:33 art_rvw

Table 11.3.2.2.2 Summary of patients who had at least 1 AE by PT, arranged by SOC whilst on open label treatment

Final SAS Open label analysis set					
SOC Name Preferred Term	Vandetanib 300mg [b] (N=44)		Placebo [b] (N=58)		Total number (%) of patients (N=102)
	Number (%) of patients [a]	Event rate (per 1000 pt years)	Number (%) of patients [a]	Event rate (per 1000 pt years)	
Cardiac Disorders	2 (4.5)	77.4	8 (13.8)	133.0	10 (9.8)
Palpitations	2 (4.5)	77.4	1 (1.7)	15.1	3 (2.9)
Arrhythmia	0 (0.0)	0.0	1 (1.7)	15.1	1 (1.0)
Atrioventricular Block	0 (0.0)	0.0	1 (1.7)	15.0	1 (1.0)
Bradycardia	0 (0.0)	0.0	1 (1.7)	15.0	1 (1.0)
Bundle Branch Block Left	0 (0.0)	0.0	1 (1.7)	14.9	1 (1.0)
Myocardial Infarction	0 (0.0)	0.0	1 (1.7)	14.7	1 (1.0)
Sinus Tachycardia	0 (0.0)	0.0	1 (1.7)	14.7	1 (1.0)
Stress Cardiomyopathy	0 (0.0)	0.0	1 (1.7)	15.0	1 (1.0)
Tachycardia	0 (0.0)	0.0	1 (1.7)	15.1	1 (1.0)

SOC = System Organ Class, PT = Preferred Term.

[a] Number (%) of patients with AEs, sorted by SOC followed by PT, in decreasing order of frequency in the total column.

[b] Treatment labels refer to the treatment received whilst the patient was on actual treatment. Patients in the vandetanib column received at least 1 dose of vandetanib whilst on actual treatment. Patients in the placebo column only received placebo whilst on actual treatment.

A patient can have one or more PT reported under a given SOC.

All patients received vandetanib whilst on open label treatment.

Event rate = (No. of pats. with event / total duration of follow-up until 1st event for all pats. in group) x 1000

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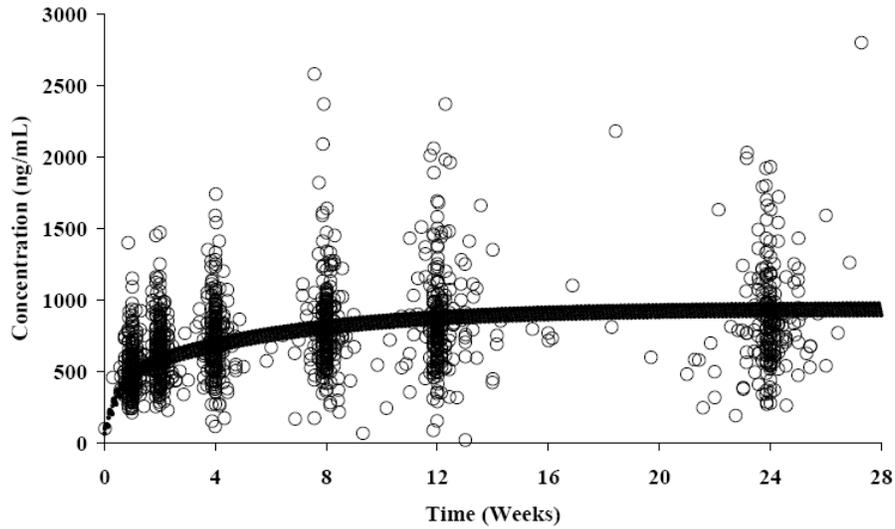
Reviewer's Comments: The number of subjects with cardiac AEs seems similar in both groups. Given the small number of subjects in the open label phase, no definitive conclusions can be made.

4.2.2.2.4 Clinical Pharmacology

Pharmacokinetic Analysis

PK data from study 58 was used to develop a population PK model to perform exposure-response analysis for QTc. The population predicted vandetanib PK profile and observed concentrations are shown in Figure 7.

Figure 7: Sponsor's Population Predicted Vandetanib PK Profile

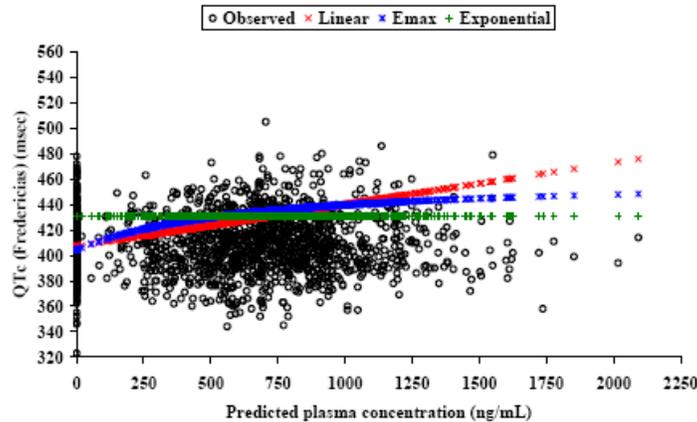


(Source: Figure 75 from Population PK report of study D4200C00058)

Exposure-Response Analysis

An exposure-response analysis was performed by the sponsor utilizing the observed QTcF values and predicted plasma concentrations of vandetanib. A population PK model was developed using non-linear mixed effects modeling approach and the individual predicted concentrations from this model was used to conduct exposure-response analysis for QTcF. The relationship between QTcF and predicted vandetanib concentrations were investigated using linear and non-linear models and are shown in Figure 8. An increase in QTcF was observed with increasing concentration. A mean QTcF prolongation of 33.5 ms at 800 ng/ml concentrations of vandetanib was predicted from the model. The steady state C_{max} , 4 hours post-dose on day 56, was predicted to be 810 ng/ml. The mean QTcF as a function of time after first dose is shown in Figure 9.

Figure 8: Sponsor's QTcF versus Predicted Plasma Concentrations of Vandetanib and Modeled Relationships for 300 mg Daily Vandetanib



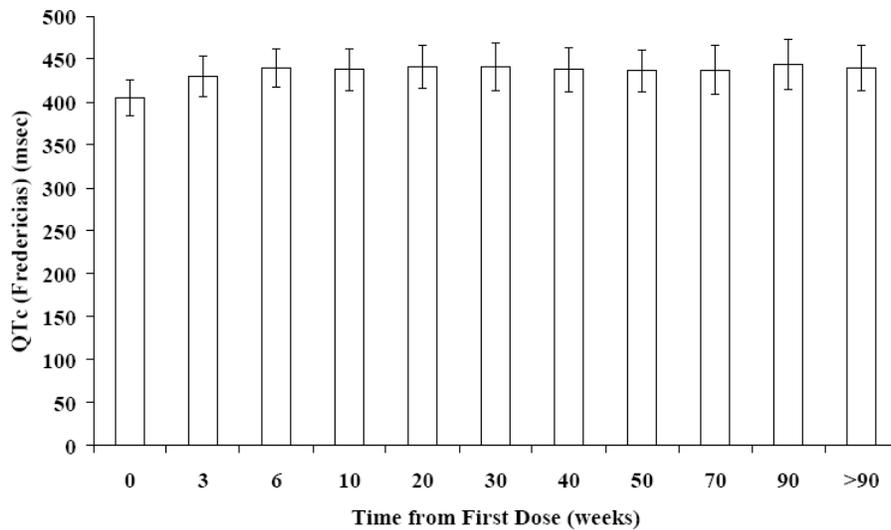
(Source: Figure 91 from Population PK report of study D4200C00058)

Table 6: Sponsor’s Predicted Mean QTcF at Plasma Concentrations of 800 ng/ml

Mean QTc ± SE (ms)	33.9 ± 0.477
Median (ms)	33.5
SD (ms)	7.23
Minimum value (ms)	19.6
Maximum value (ms)	70.1
Count	230

(Source: Table 32 from Population PK report of study D4200C00058)

Figure 9: Sponsor’s QTcF as a Function of Time from the First Dose



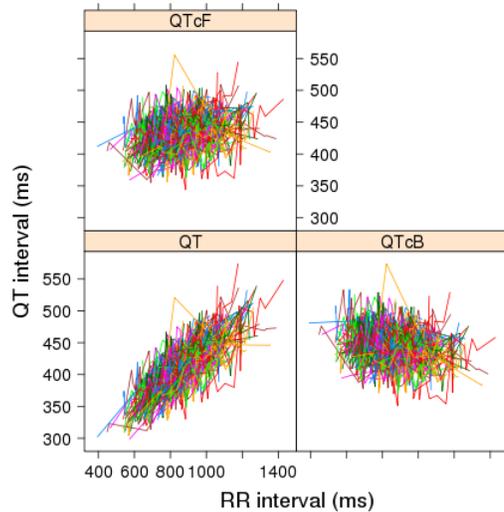
(Source: Figure 90 from Population PK report of study D4200C00058)

4.2.3 REVIEWERS’ ASSESSMENT

4.2.3.1 Evaluation of the QT/RR Correction Method

The relationship between different correction methods and RR is presented in Figure 10. In FDA’s analysis, Fridericia correction method was used as the primary correction method. Bazett’s correction tends to overcorrect the heart rate effect. As a result, QTcB tends to underestimate the QTc effect when a drug, like vandetanib, slows down heart rate. Therefore, we consider Bazett’s correction method is inappropriate.

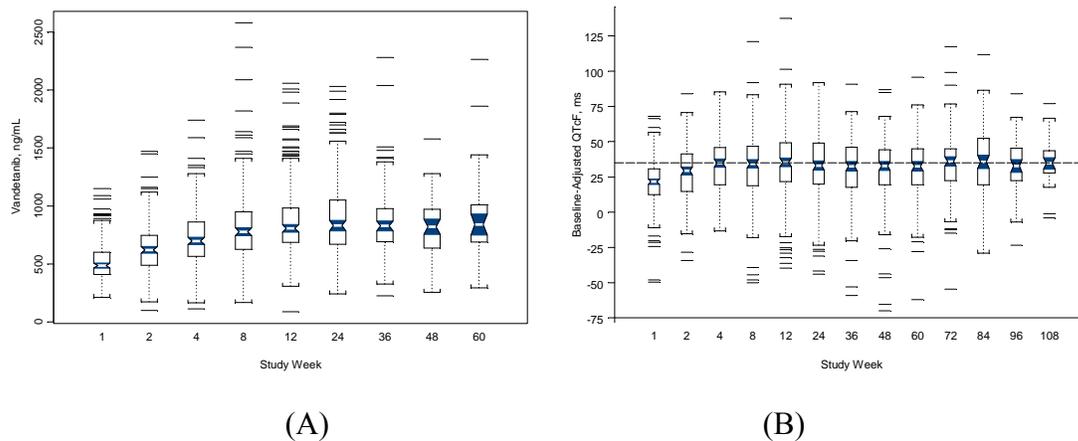
Figure 10: QT, QTcB and QTcF vs. RR (Each Subject's Data Points are Connected with a Line)



4.2.3.2 Central Tendency Analysis

The observed concentration of vandetanib with time was shown in Figure 11A. The steady state median concentration of vandetanib ranged from 810 ng/ml to 840 ng/ml between weeks 12 to 60. The observed change from baseline in QTcF with time was shown in Figure 11. The dotted line denoted 35 ms Δ QTcF which was the predicted mean effect of the reviewer's exposure-response model. The mean Δ QTcF at different visits stratified by treatment groups were summarized in Table 7.

Figure 11: Vandetanib Concentration vs. Time (A) and Δ QTcF vs. Time (B)



Box plot: The central line represents the median. The top and bottom of the box represents the 25th and 75th percentile of the observed data. The top and bottom of the whisker represents the 5th and 95th percentile of the observed data

Table 7: Mean and 95% CI of Δ QTcF

Time in weeks	Placebo				Vandetanib 300 mg			
	N	Mean Δ QTcF	Lower 90% CI	Upper 90% CI	N	Mean Δ QTcF	Lower 90% CI	Upper 90% CI
1	98	1.12	-0.885	3.13	216	21.3	19.4	23.2
2	94	0.0869	-1.98	2.16	223	27.9	25.8	30.1
4	88	0.482	-1.83	2.79	208	33.2	31.1	35.4
8	91	-0.57	-3.05	1.91	216	32.7	30	35.4
12	80	1.11	-1.69	3.9	206	34.8	31.9	37.6
24	63	2.29	-0.877	5.46	189	32.4	29.6	35.2
36	50	3.3	-0.456	7.05	167	30.9	28.2	33.7
48	43	1.61	-1.14	4.36	159	30.8	27.8	33.8
60	38	4.68	0.844	8.51	150	30.7	27.8	33.6
72	35	4.8	1.2	8.4	125	33.5	30.3	36.7
84	30	5.57	2.35	8.78	121	35.7	32.1	39.3
96	17	1.08	-4.45	6.6	65	33.2	29.4	37
108	11	1.39	-7.2	9.99	38	36	31.6	40.5

4.2.3.3 Categorical Analysis

Error! Reference source not found. Table 8 listed the number of subjects whose QTcF values were ≤ 450 ms, between 450 ms and 480 ms, greater than 480 ms, and greater than 500ms. In addition, the categorical analysis results for Δ QTcF were summarized in Table 9.

Table 8: Categorical Analysis for QTcF

Treatment	N	QTcF \leq 450 ms	450<QTcF \leq 480 ms	QTcF>480 ms	QTcF>500 ms
Vandetanib	231	87 (37.7%)	105 (45.5%)	39 (16.9%)	10 (4.3%)
Placebo	99	89 (89.9%)	10 (10.1%)	0 (0%)	0 (0%)

Table 9: Categorical Analysis of Δ QTcF

Treatment	N	Δ QTcF \leq 30 ms	30< Δ QTcF \leq 60	Δ QTcF>60 ms
Vandetanib	231	25 (10.8%)	124 (53.7%)	82 (35.5%)
Placebo	99	88 (88.9%)	9 (9.1%)	2 (2%)

4.2.3.4 Exposure-Response Assessments

4.2.3.4.1 Exposure-Response Modeling

The relationship between Δ QTcF and vandetanib concentrations was visualized in Figure 12 and a concentration-dependent prolongation of QTc interval was observed upon daily administration of 300-mg of vandetanib in the pivotal study. The relationship between Δ QTcF and vandetanib concentrations was described using a log-linear model and the parameter estimates of the model were provided in Table 10. The QTcF change from baseline (90% confidence interval) at drug concentration of 973 ng/ml, the mean of the highest observed concentrations, was predicted to be 34.7 (32.9-36.4) ms.

Figure 12: Δ QTcF vs. Vandetanib Concentration in Study 58

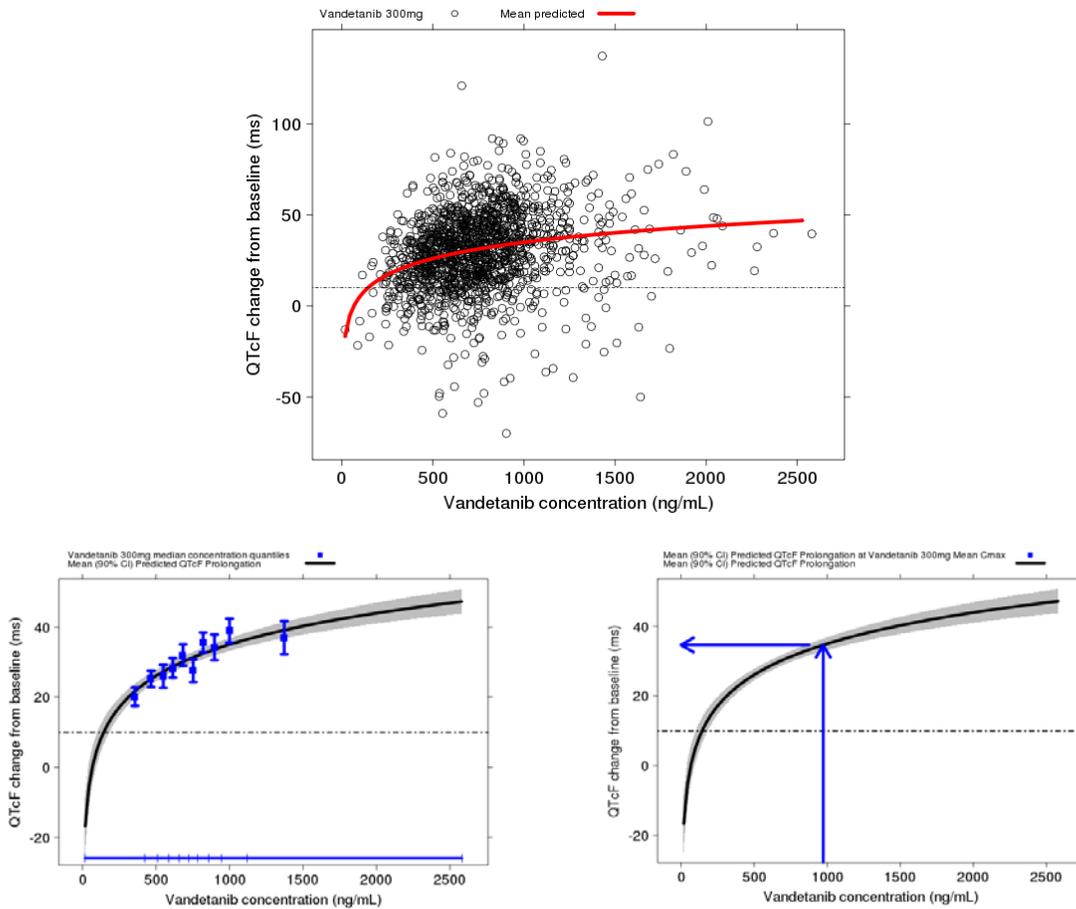


Table 10: Parameter Estimates for the Log-linear Model for Study 58

Parameter	Estimate	Lower 95% CI	Upper 95% CI
Intercept (ms)	-54	-68.6	-39.4
Slope (ms per log ng/mL)	12.9	10.6	15.1

4.2.3.4.2 Effect of Intrinsic and Extrinsic Factors on QTc Prolongation

4.2.3.4.2.1 Renal Impairment

Table 11 listed the number of subjects whose observed Δ QTcF values were greater than 60 ms, QTcF values greater than 480 ms and 500 ms based on their renal functions. The proportion of subjects with QTcF > 500 ms was higher in patients with moderate renal impairment (14%) compared to normal patients (4%). Similarly higher proportion of subjects with Δ QTcF > 60 ms was observed in patients with moderate renal impairment (57%) compared to normal patients (34%). It is to note that patients with severe renal impairment were excluded from the Phase 3 study.

Table 11: Categorical Analysis for Δ QTcF and QTcF Based on Renal Function

	N	Δ QTcF >60 (ms)	QTcF >480 (ms)	QTcF >500 (ms)
Normal (CRCL \geq 80)	167	57 (34.1 %)	25 (15 %)	6 (3.6 %)
Mild(50 \geq CRCL < 80)	56	21 (37.5 %)	12 (21.4 %)	3 (5.4 %)
Moderate(30 \geq CRCL < 50)	7	4 (57.1 %)	2 (28.6 %)	1 (14.3 %)

The drug clearance reduced from 11.7 L/h for normal patients to 8.32 L/h for patients with severe renal impairment. This corresponded to an increase in AUC from 3861 ng·h/mL to 6064 ng·h/mL. There was no change in C_{max} in the single dose study in patients with compromised renal functions. However, due to the change in drug clearance, the steady state concentration of the drug is expected to be different in patients with renal impairment compared to normal subjects. Data for the steady state concentrations of the drug in renally impaired patients has not been provided by the sponsor. Thus, a simulation was performed to calculate the drug concentration at steady state in normal patients and patients with renal impairment. The simulated concentration-time profiles are shown in Figure 13. The steady state C_{max} and C_{min} for normal patients and patients with severe renal impairment are shown in Table 12.

Figure 13: Concentration vs. Time Profiles for Patients with Normal Renal Function and Patients with Renal Impairment

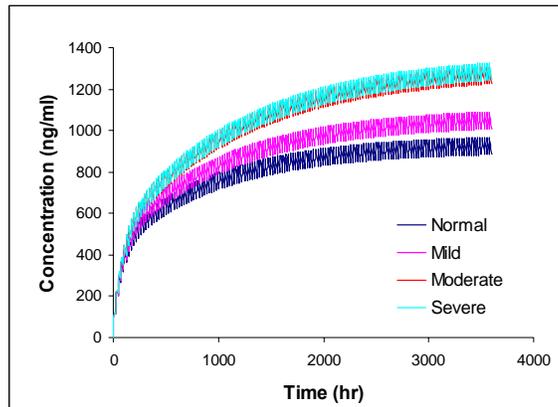


Table 12: Predicted Steady-State Concentrations and Δ QTcF for Patients with Normal Renal Function and Patients with Renal Impairment

	$C_{\max,ss}$ (ng/ml)	$\Delta QTcF$ at $C_{\max,ss}$ (ms)	$C_{\min,ss}$ (ng/ml)	$\Delta QTcF$ at $C_{\min,ss}$ (ms)
Normal	960	35	884	33
Severe	1320	39	1244	38

The results suggested that the increased QTc effect in patients with compromised renal function may be explained by the increased steady-state exposure of vandetanib. Therefore, a dose reduction may be considered in this patient group.

4.2.3.4.2.2 Gender

Vandetanib-associated-QTc effects appear to be slightly higher in female patients as compared to male patients. Table 13 listed the number of males and females whose observed $\Delta QTcF$ values were greater than 60 ms, QTcF values greater than 480 ms or 500 ms. The proportion of subjects with $\Delta QTcF > 60$ ms was slightly higher in females (39%) compared to males (33%). Similarly, slightly higher proportion of subjects with QTcF > 480 ms was observed among females (22%) compared to males (13%). The proportion of subjects with QTcF > 500 ms was similar between both groups.

Table 13: Categorical Analysis for $\Delta QTcF$ and QTcF Based on Gender

	N	$\Delta QTcF > 60$ (ms)	QTcF > 480 (ms)	QTcF > 500 (ms)
Male	134	44 (32.8%)	18 (13.4%)	6 (4.5%)
Female	97	38 (39.2%)	21 (21.6%)	4 (4.1%)

4.2.3.4.2.3 Body weight

Vandetanib-associated-QTc effects appear to be similar in patients with different body weight. An increase in highest drug concentration achieved was observed with decreasing body weight in patients. Thus, a categorical analysis was performed to determine if body weight also influenced QTc prolongation. Patients were divided into two groups based on a body weight cut-off of 60 kg. Table 14 listed the number of subjects in different groups based on body weight whose observed $\Delta QTcF$ values were greater than 60 ms, QTcF values greater than 480 ms and 500 ms. While a higher proportion of patients with low body weight (≤ 60 kg) had $\Delta QTcF > 60$ ms. Opposite trend was observed for QTcF > 480 ms and > 500 ms.

Table 14: Categorical analysis for $\Delta QTcF$ and QTcF Based on Body Weight

	N	$\Delta QTcF > 60$ (ms)	QTcF > 480 (ms)	QTcF > 500 (ms)
Weight ≤ 60 kg	70	32 (45.7%)	10 (14.3%)	1 (1.4%)
Weight > 60 kg	157	49 (31.2%)	29 (18.5%)	9 (5.7%)

4.2.3.4.2.4 CYP3A4 Inducers

Caution is required when vandetanib is co-administered with CYP3A4 inducers in patients. The C_{\max} of vandetanib was unaltered and the AUC was reduced by 40% when vandetanib was given in combination with rifampicin compared to vandetanib alone in a

single dose Phase 1 study. This suggested that a lower steady-state concentration of the parent drug is expected when vandetanib is co-administered with an inducer. However, both AUC and C_{max} of the N-desmethyl metabolite increased 266% and 414% for vandetanib in combination with rifampicin compared to vandetanib alone. Also, the C_{max} of N-oxide metabolite was increased by 179%. Thus higher steady concentrations of the metabolites are expected which have been reported active in hERG assays. Based on the data provided, it is difficult to quantify the effect of co-administration of inducers on QTc prolongation.

4.3 ECG MONITORING IN STUDY D4200C0021

Study D4200C0021 is a phase I study conducted in 28 healthy male volunteers to assess the effect of co-administration of a single oral dose of vandetanib and a single intravenous dose of ondansetron on cardiac repolarization. This crossover study included two treatment arms- a) 700-mg vandetanib coadministered with 32-mg ondansetron and b) 700-mg vandetanib coadministered with placebo. The trial is useful because it included intensive ECG and PK sampling to cover the entire profile up to 28 days post a single dose of vandetanib (treatment b). The main limitation for the trial is that although the sponsor used a single dose of 700 mg, the maximum exposures achieved in this study were 42.5% lower than those observed at steady state following 300-mg daily dosing.

Based on the study data, different QT correction (i.e., Fridericia and Bazett's correction) methods were evaluated (Figure 14). Fridericia's correction method provided better correction for heart rate, therefore was chosen in the analysis.

Figure 14: QT, QTcB and QTcF vs. RR plot for Study 21 (Each Subject's Data Points are Connected with a Line)

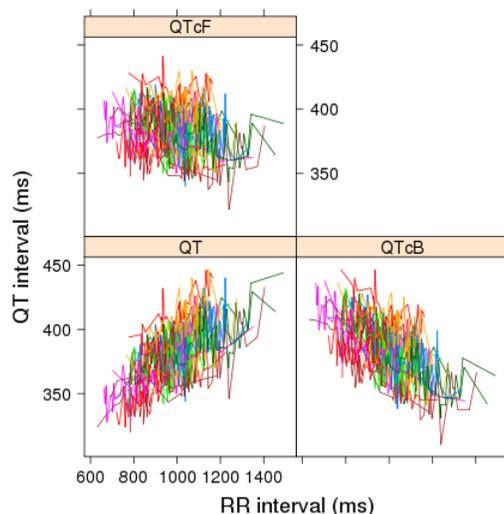


Figure 15 demonstrated vandetanib concentration vs. time profile and Δ QTcF vs. time profiles. Following a single dose of vandetanib, QTc prolongation (i.e., upper 90% CI > 10 ms) was sustained over 28 days post-dose (the last observation time point). The sustained QTc prolongation is likely to be associated with the long half-life of vandetanib (19 days). The exposure-response analysis results were shown in Figure 16.

Because the exposure range observed in Study D4200C0021 is too low, the established exposure-response relationship should not be used to predict QTc interval under steady state exposure at 300-mg dose level.

Figure 15: Vandetanib Concentration versus Time (A) and Δ QTcF versus Time (B) Profile in Study 21

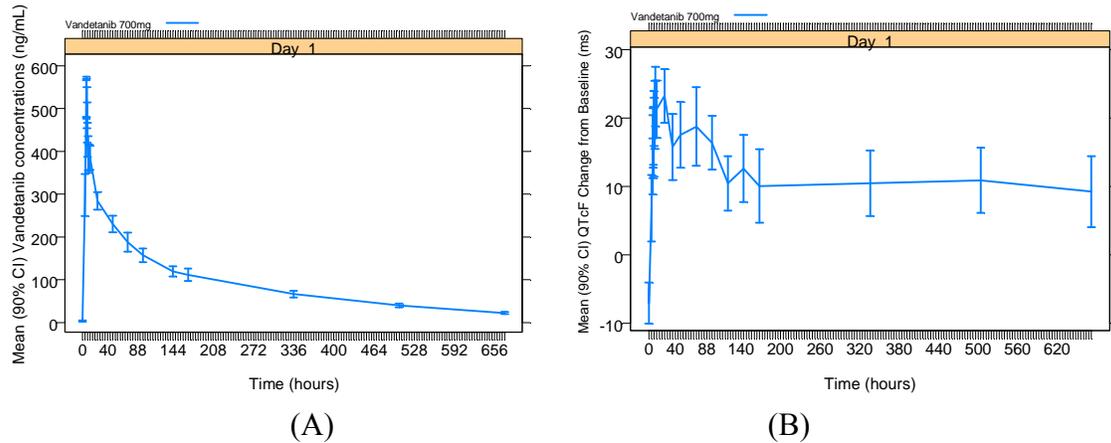
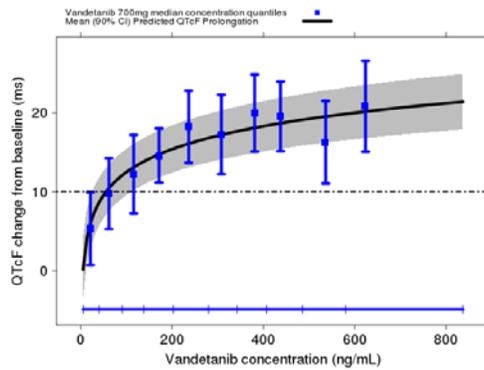


Figure 16: Vandetanib Concentration versus Δ QTcF Relationship



4.4 ECG MONITORING IN STUDY D4200C0008

Study D4200C0008 is an open-label, phase II study to determine the efficacy and tolerability of vandetanib in 35 patients with locally advanced or metastatic hereditary medullary thyroid carcinoma. Of these, 30 patients received initial treatment with vandetanib 300 mg. ECG and PK samples were collected at multiple visits during the treatment. The study is useful because therapeutic dose (i.e., 300 mg) is used in the trial.

Error! Reference source not found. Figure 17 indicated that Fridericia correction method provided adequate correction for the heart rate effect. The relationship between Δ QTcF and vandetanib concentrations was described using a log-linear model and the parameter estimates of the model were provided in Table 15. The parameter estimates were similar to the results obtained from Study D4200C00058. The QTcF change from baseline (90% confidence interval) at drug concentration of 1110 ng/ml, the mean of the

highest concentrations observed in subjects is predicted to be 35.2 (30.8-39.6) ms. The results further confirm the finding in Study D4200C00058.

Figure 17: QT, QTcB and QTcF vs. RR plot for Study 8 (Each Subject's Data Points are Connected with a Line)

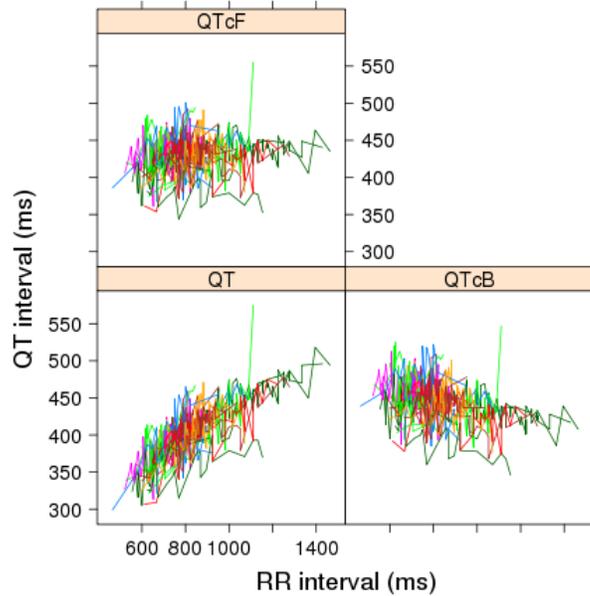


Table 15: Parameter estimates for the log-linear model for study 8

Parameter	Estimate	Lower 95% CI	Upper 95% CI
Intercept (ms)	-43.5	-62.2	-24.7
Slope (ms per log ng/mL)	11.2	8.3	14.2

4.5 CLINICAL ASSESSMENTS

4.5.1 Safety assessments

Events identified to be of clinical importance per the ICH E 14 guidelines i.e. significant ventricular arrhythmias and sudden death have occurred in the vandetanib clinical program.

4.5.2 ECG assessments

Waveforms from the ECG warehouse were reviewed. Key statistics according to the ECG warehouse automated algorithm are listed below. T wave abnormalities, including, flattening notching, biphasic T waves, U waves, T wave asymmetry were observed in all studies. Overall increased high frequency noise (> 40% of ECGs in most studies) and poor T wave signal (> 20% of ECGs) was common in all studies. Consistent with known prolongers with torsadogenic potential like sotalol, several T wave abnormalities like flattening, notching, asymmetry biphasic T waves and T-U waves were noted; more frequently in study 57 compared to 58 (see ECGs). Overall ECG acquisition was poor,

but given that the study is in a patient population with high co-morbidities and QT bias was within values we see in similar patient studies. ECGs submitted are acceptable.

Waveforms under NDA - (b) (4)

Study 32: ECGs not annotated in lead II-40.5%, ECGs with poor T wave signal-20.2%, ECGs with significant QT bias- 1.7%

Study 36: ECGs not annotated in lead II-46%, ECGs with poor T wave signal-21.2%, ECGs with significant QT bias-2.16%

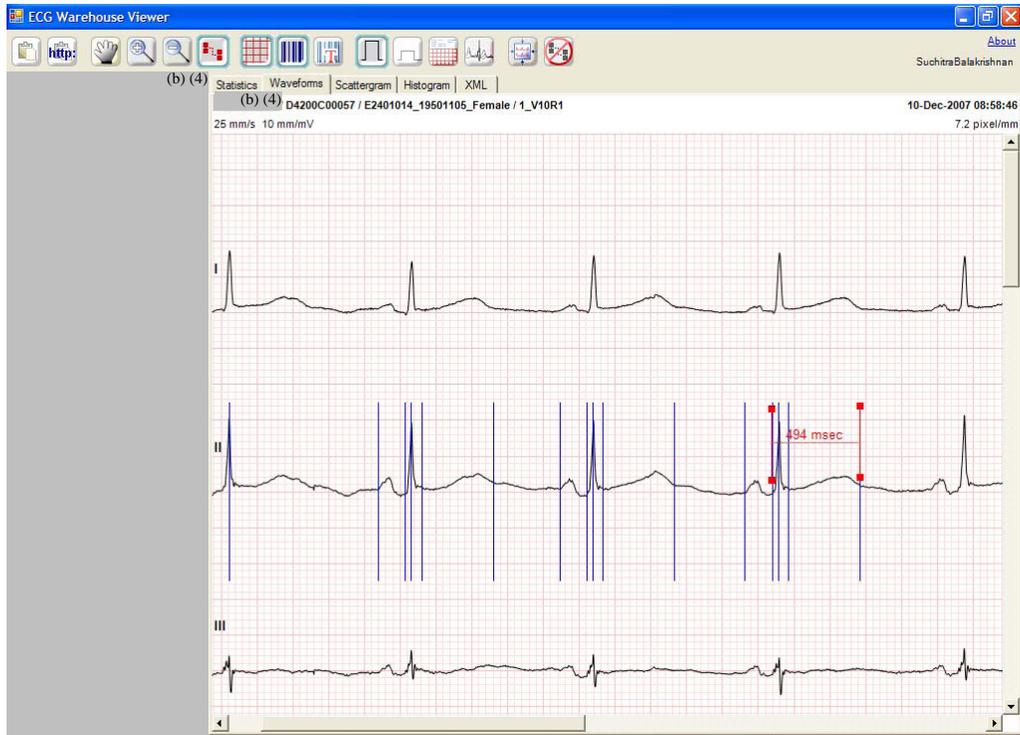
Study 57- ECGs not annotated in lead II- 46%, ECGs with poor T wave signal-21.5%, ECGs with significant QT bias- 3.4%

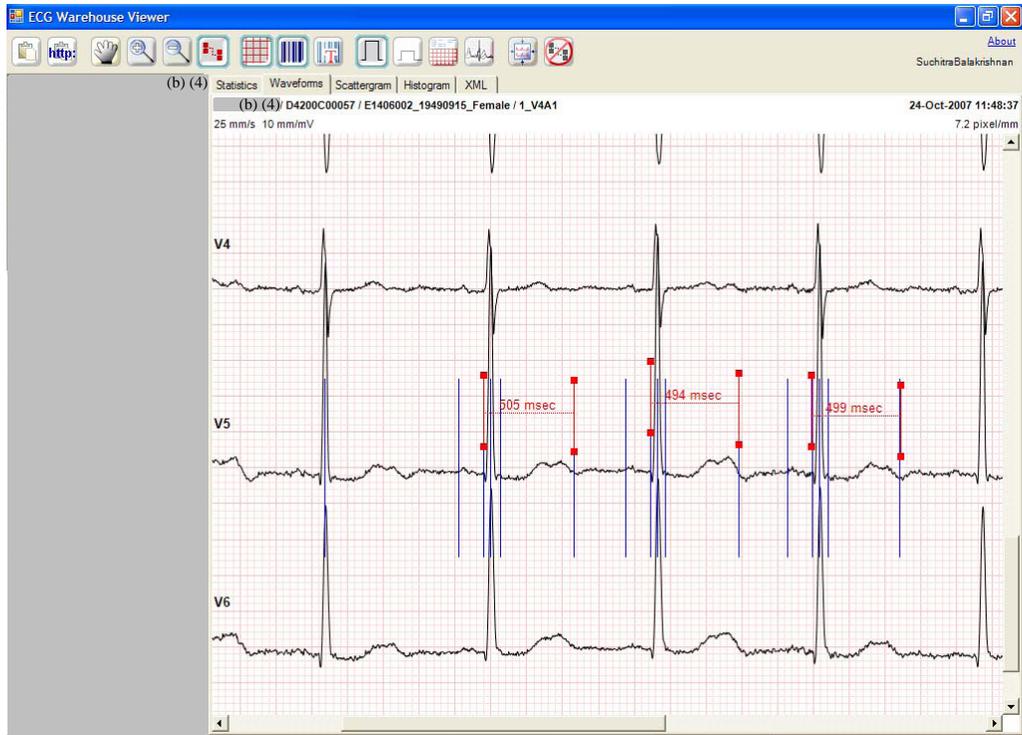
Waveforms under NDA 22405:

Study 21 (HV study):-ECGs not annotated in lead II-< 1%, ECGs with QT bias-6.62%, ECGs with poor T wave signal- 88%, ECGs with T offset bias-3%, -

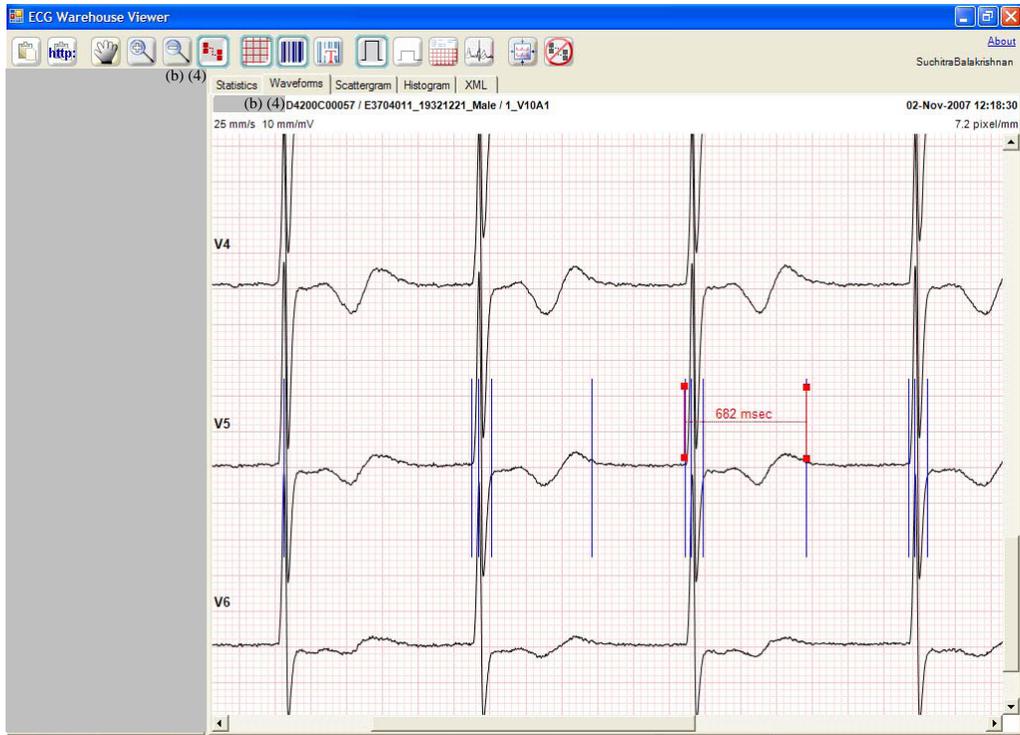
Study 44:- ECGs not annotated in lead II-44%, ECGs with poor T wave signal (22%) ECGs with QT bias 5.77%.

Study 58:- ECGs not read in primary lead-41% ECGs with QT bias 3.9%, ECGs with poor Twave signal-20%





QT=405 ms, but QT-U (appropriate in this case) = 649 ms



4.5.3 PR and QRS Interval

PR and QRS data are not reported (ISS submitted to NDA (b) (4) and NDA 22405 were reviewed). We reviewed the datasets and found no clinically relevant changes in the PR and QRS intervals. The mean changes from baseline were summarized in Table 16.

Table 16: Mean Changes from Baseline for PR and QRS Intervals

Interval	Mean change (90% CI)
PR	1.1 (0.2-1.9)
QRS	0.7 (0.2- 1.3)

5 APPENDIX

5.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Table 1 Vandetanib: Highlights of Clinical Pharmacology

Therapeutic dose	300 mg	
Maximum tolerated dose	300 mg	
Principal adverse events	Rash, diarrhea, hypertension	
Maximum dose tested	Single Dose	1200 mg
	Multiple Dose	600 mg once daily
Exposures achieved at maximum tested dose	Single Dose 1200 mg	C_{max} gmean 752.5 ng/ml CV% = 20.64 (n=5) AUC 102200 ng.h/ml CV% = 15.3 % (n=5)
	Multiple Dose 600 mg after 29 daily doses	C_{max} 1270 and 3520 ng/ml (n=2) AUC ₀₋₂₄ 29053 and 63188 ng.h/ml (n=2)
Range of linear PK	100 to 1200 mg single dose 100 to 600 mg multiple dose (single daily dosing)	
Accumulation at steady state	Estimated mean (\pm SD) population accumulation ratio of 7.7 ± 3.31 from Study 58 (dosed once daily). The median accumulation ratio was 12-fold (range 9- to 20-fold) for 100 mg once-daily dosing in Study 01 based on non compartmental analysis.	
Metabolites	N-desmethyl vandetanib: similar potency to vandetanib against isolated VEGFR-2 ($IC_{50} = 0.070 \mu M$) and EGFR ($IC_{50} = 0.170 \mu M$) and in HUVEC cellular assays when evaluated against proliferation induced by VEGF, EGF and bFGF. Vandetanib-N-oxide: approximately 5-fold less potent against isolated VEGFR-2 tyrosine kinase than vandetanib (IC_{50} values of 0.2 and 0.04 μM respectively). Approximately 50-fold less potent than vandetanib in the HUVEC cellular assay.	
Absorption	Absolute/relative bioavailability	Absolute oral bioavailability not assessed. Relative bioavailability of the vandetanib tablet (ie, the commercial formulation) to the solution in vivo (Study 30) was 106% (95% CI 99% to 113%).
	t_{max}	Vandetanib: median 5h (range 1 to 24h) taken from Study 01 Day 15, 100 mg. N-desmethyl vandetanib: 5h (range 3 to 7h), vandetanib N-oxide: 7h (range 4 to 12h). Data taken from Study 26 (rifampicin interaction study vandetanib +placebo) 300 mg single dose.

Table 1 Vandetanib: Highlights of Clinical Pharmacology

Distribution	V_d/F	$V_d/F = 7450$ L from Study 58 population PK analysis.
	% bound	90% (in vitro). 93% (range 92.0% to 94.5%) ex vivo from Study 16 (single 800 mg dose in volunteers). 93% (range 90.3% to 95.3%) ex vivo (Study 50) colorectal cancer 100 mg.
Elimination	Route	~44% faecal, ~25% urine during 21-day collection period.
	Terminal $t_{1/2}$	Mean for vandetanib 19.6 days based on population PK analysis from Study 58. N-desmethyl vandetanib 168.2h (28.5%), vandetanib N-oxide not calculable. Data taken from Study 26 rifampicin interaction study (vandetanib +placebo) 300 mg single dose.
	CL/F	CL/F 13.2 L/h (300 mg) based on population PK analysis from Study 58.
Intrinsic factors	Age	No effect of age on PK based on population analysis of Study 58.
	Sex	No effect of sex on PK based on population analysis of Studies 58.
	Race	Population analyses of Phase III Studies 32/36 did not identify race as having impact on PK parameters. No difference evident in CL/F between D4200L00004 (Chinese) 7.07 L/h (90% CI 5.6 to 8.4), Study 43 (Japanese) 5.5L/h (4.3 to 6.7) and Study 01 (western) 8.5 L/h (6.4 to 10.4).
	Hepatic and renal impairment	Renal impairment – AUC increased by 46% (mild), 62% (moderate) and 79% (severe). No change in C_{max} . Hepatic impairment - AUC of vandetanib unchanged in mild (AUC ratio 1.04 [CI 0.86, 1.26]), moderate (0.94 [0.78, 1.15]) and severely impaired (0.93 [0.76, 1.14]), compared to subjects with normal hepatic function. C_{max} unchanged for subjects with mild and moderate hepatic impairment but showed a significant decrease of approximately 29% in subjects with severe hepatic impairment compared with subjects with normal hepatic function.

Table 1 Vandetanib: Highlights of Clinical Pharmacology

Extrinsic factors	Drug interactions	Rifampicin (CYP3A4 inducer) reduced vandetanib AUC by ~40% (C_{max} unaltered). Itraconazole (CYP3A4 inhibitor) increased vandetanib AUC by 9% (C_{max} unaltered).
	Food effects	Food had no effect on AUC. Food reduced C_{max} by 11%. (Food = standard high fat breakfast).
Expected high clinical exposure scenario	Severe renal impairment. AUC increased by ~1.8-fold.	

AUC	Area under the concentration-time curve.
bFGF	Basic fibroblast growth factor
CI	Confidence interval.
CL/F	Total body clearance of drug from plasma after an oral dose (apparent oral clearance).
C_{max}	Maximum plasma (peak) drug concentration after single dose administration.
CV	Coefficient of variation.
CYP	Cytochrome oxidase.
EGF	Endothelial growth factor receptor
EGFR	Epidermal growth factor receptor.
g_{mean}	Geometric mean.
HUVEC	Human umbilical vein endothelial cells.
IC_{50}	Concentration at which the activity is inhibited by 50%.
PK	Pharmacokinetic.
SD	Standard deviation.
$t_{1/2}$	Half-life.
t_{max}	Time to reach peak or maximum concentration or maximum response following drug administration.
V_d/F	Volume of distribution at steady state after an oral dose.
VEGFR-2	Vascular endothelial growth factor receptor-2.
VEGF	Vascular endothelial growth factor receptor.

5.2 TABLE OF STUDY ASSESSMENTS IN STUDY 58

Blinded Study Treatment

Visit (Visit window ± 3 days for each visit starting at Visit 2)	1 (Screening)	2	3	4	5	6	7 etc	75 Disc of blinded study treatment ^a	400 60-day follow-up	Survival follow-up
Week		0	1	2	4	8	12, etc Visits every 12 weeks			
Day	-21 to 0	1	7	14	28	56	84, etc			
Written informed consent	X									
Physical examination ^{b,1}	X	X	X	X	X	X	X	X	X	
Demographics	X									
Medical/surgical history ^c	X									
Inclusion/exclusion criteria	X									
Extent of disease	X									
RECIST assessment ^{d, e, f}	X						X	X		
WHO PS	X	X					X	X	X	
12-lead ECG ^{g,h}	X	X	X	X	X	X	X	X	X	
Vital signs ⁱ	X	X	X	X	X	X	X	X	X	
Concomitant medication ^j	X	X	X	X	X	X	X	X	X	
AE review ^k	X	X	X	X	X	X	X	X	X	
Weight ^l	X	X	X	X	X	X	X	X	X	
Blood samples for clinical laboratory tests ¹	X	X	X	X	X	X	X	X	X	
24-hour urinalysis ^m	X						X	X		
Urinalysis ^{n,1}	X	X	X	X	X	X	X	X	X	
Blood samples for CTN/CEA ^o	X	X			X	X	X	X	X	
Blood samples for biomarkers ^p		X			X	X	X	X	X	
PK blood sampling for vandetanib ^q			X	X	X	X	X	X		

Visit (Visit window ± 3 days for each visit starting at Visit 2)	1 (Screening)	2	3	4	5	6	7 etc	75 Disc of blinded study treatment ^a	400 60-day follow-up	Survival follow-up
Week		0	1	2	4	8	12, etc Visits every 12 weeks			
Day	-21 to 0	1	7	14	28	56	84, etc			
Pregnancy test for female patients of childbearing potential ^f	X									
Mandatory tumour collection sample ^g	X									
Optional fresh tumour biopsy ^h	X						X			
Randomization to vandetanib/placebo		X								
Vandetanib/placebo dispensed/returned ^a		X					X	X		
Administration of first dose of vandetanib/placebo		X								
FACT-G QoL questionnaire ^v	X						X	X		
Brief Pain Inventory ^w	X		X	X	X	X	X			
Stool frequency ^w	X		X	X	X	X	X			
Analgesic use ^w	X		X	X	X	X	X			
Survival follow-up ^x										X
Ophthalmologic examination ^y	X	Follow-up exam occurred at Visit 9 and/or discontinuation								

^a Patients who chose to enter post-progression open-label vandetanib treatment completed the discontinuation of blinded study treatment visit (see [Table 2](#)).

^b After height at screening was recorded, it was not repeated unless clinically indicated. The Visit 2 (Day 1) assessments were only to be taken if the screening assessments were collected more than 7 days earlier.

^c All historical CTN/CEA values within the last 3 years were to be recorded.

^d Radiographic studies were performed at screening (ie, within 3 weeks before date of randomisation), then once every 12 weeks up to and including discontinuation of blinded study treatment, unless patients had withdrawn consent. Patients who discontinued study treatment for reasons other than disease progression continued to have objective tumour assessments every 12 weeks until progression was documented, unless the patient withdrew consent.

- ^e For patients with objective response of CR or PR, an additional confirmatory scan was to be performed ≥ 4 weeks following the date of first response.
- ^f If new hypo-dense or hypo-intense lesions appeared in the liver within the first 2 scheduled RECIST follow up assessments, the baseline CT/MRI was to be re-examined, and if in retrospect iso-dense or iso-intense lesions were identified in the same location, then these were to be recorded as non-target lesions at baseline, and followed for subsequent progression as defined by unequivocal size increase. If no iso-dense or iso-intense lesions were identified on retrospective review of the baseline, then these lesions had to be recorded as new lesions.
- ^g At screening, a 12-lead ECG was performed to ensure a QTc value of < 480 ms for eligibility. If the QTc value was ≥ 480 , the screening ECG could have been repeated up to 2 times (at least 24 hours apart). The average of these screening ECGs (up to 3 ECGs) had to be < 480 ms to confirm patient eligibility. If a patient was receiving a medication with possible association with Torsades de Pointes (see Appendix E of the Amended CSP) prior to study entry that could not be discontinued before study treatment, then the screening QTc had to be < 460 ms and an additional ECG had to be obtained 4 to 8 hours after the first dose of vandetanib.
- ^h Baseline QTc was determined by the average of no less than 3 consecutive ECGs (within 5 to 10 minutes of one another) on Day 1 (Visit 2). If the screening QTc was obtained with 3 consecutive ECGs within 3 days before Day 1 (Visit 2), then the screening QTc was considered the baseline, and repeat ECGs were not necessary on Day 1. ECGs were to be performed at the same time throughout the study, after the patient had taken study drug on the assessment days. A post-dose ECG was not required on Day 1 (Visit 2). Additional 12-lead ECGs were to be performed during the post-prolongation period in the event of QTc prolongation.
- ⁱ Vital signs included BP, pulse, and temperature. BP and pulse were to be taken after the patient had been sitting for 5 minutes and before any blood sampling was performed.
- ^j At screening, all prior anti-cancer therapy and all concomitant medications were recorded. All new concomitant medication started during the 60 calendar days after the last dose of study drug had to be reported. When a patient entered post-progression open-label vandetanib treatment, they were followed continuously for concomitant medications until the post-progression 60-day follow-up visit. All medications prohibited in this study were to have been withdrawn within 2 weeks of randomisation, and were to be avoided for up to 4 weeks following discontinuation of study treatment.
- ^k AEs were captured from the signing of the informed consent and graded according to CTCAE version 3. AEs were followed for 60 days following the last dose of study drug. All SAEs and study drug related AEs were followed until resolution unless the investigator determined that the event was unlikely to resolve due to the patient's underlying condition.
- ^l The Visit 2 (Day 1) assessments were only to be taken if the screening assessments were collected more than 7 days earlier. Blood and urine samples were sent to the central laboratory for analysis.
- ^m For hereditary MEN2a/MEN2b patients only, a 24-hour urine/urinalysis for catecholamines, metanephrine, and normetanephrine was required. Only patients with elevated levels were followed every 12 weeks up to and including discontinuation of blinded study treatment. Patients were to avoid alcohol, coffee, tea, tobacco, and strenuous exercise prior to collection.
- ⁿ Urine analysis for proteins, blood, and glucose for all patients were performed for safety. All urine samples were sent to the central laboratory for analysis.
- ^o Patients had to fast overnight (no food or drink except for water past midnight) for approximately 8 hours before testing for CTN and CEA levels. Medication could be administered with sips of water before the blood draw. At screening (Visit 1), CTN/CEA testing was conducted in an interval of 0, 1, 4, and 8 hours (total of 4 blood draws); the average of the 4 blood draws determined the baseline CTN/CEA level. Although the blood draw at time 0 had to be drawn while the patient was fasting, the fast did not need to be maintained for the 1-, 4-, and 8-hour blood draws. At all subsequent visits (beginning on Day 1, Visit 2), patients had to fast overnight (approximately 8 hours) prior to testing for CTN/CEA levels – only 1 draw was required. CTN/CEA blood samples were sent to the central laboratory for analysis. For patients with a biochemical CR, repeat serum tumour marker levels were obtained at least 4 weeks after patients achieved a biochemical CR, and had to remain within normal limits to be considered a biochemical CR.
- ^p At each time indicated, two 5 mL blood samples were required. A total of 5 mL of venous blood was drawn to prepare plasma to determine VEGF, VEGFR-2, and bFGF levels. In addition, 5 mL of venous blood was

drawn to prepare serum to determine serum protein expression profiles. These blood samples were sent to the central laboratory for analysis (refer to Appendix M of the Amended CSP).

^q Blood samples for the determination of plasma levels of vandetanib were to be obtained from patients enrolled in the study. These samples were to be taken as soon as possible following each ECG starting at Visit 3 and each visit thereafter, up to and including discontinuation of blinded study drug. A PK sample was not required with the baseline ECG on Day 1 (Visit 2), nor was one required following ECG during QTc prolongation.

^r Females of childbearing potential had to have a negative pregnancy test during screening within 3 days before Day 1 (Visit 2).

^s All patients with sporadic MTC had to submit a suitable archived tumour sample before randomisation. In the event that a suitable archived sample was not available within 2 weeks prior to randomisation, a fresh tumour sample had to be obtained in its place prior to randomisation. The archived sample was to be searched for first. In the event a fresh sample had to be obtained, the screening laboratory tests were to be performed to confirm eligibility prior to the procedure to ensure that patients were not subjected to an unnecessary procedure. Patients with hereditary MTC who had a documented germline mutation in RET were not required to provide a mandatory tumour sample (unless a primary documentation defining RET mutation status could not be demonstrated), but would be eligible for the optional tumour biopsies. If a patient underwent the fresh biopsy procedure, this specimen satisfied the first optional tumour biopsy submission.

^t Optional fresh tumour biopsies were collected from patients who consented to this exploratory part of the study. The first biopsy was obtained prior to the first dose of study drug, and the second biopsy was obtained at Week 12 \pm 7 days after randomisation, unless the patient withdrew consent. Patients did not have to consent to the optional fresh tumour biopsies to participate in the study; however, it was strongly recommended that patients who did consent to the optional procedure underwent both the pre and post dose vandetanib biopsies to characterise the effects of vandetanib on RET, EGFR, and VEGFR signalling pathways in tumours. Screening laboratory tests were to be performed prior to the procedure to confirm eligibility to ensure that patients were not subjected to an unnecessary procedure.

^u Vandetanib or placebo was dispensed every 12 weeks while on study. Any unused study medication had to be returned at each visit. Drug accountability had to be performed as indicated in Section 3.5.5 of the Amended CSP.

^v During the last week of the screening period (Day -7 to Day 0), the FACT-G questionnaire was self-reported through patient questionnaires once a day, for 4 days to establish baseline, then every 12 weeks thereafter during blinded study treatment, up to and including to the discontinuation of blinded study treatment visit. Patients were asked to complete QoL assessments over the course of the past 7 days. The FACT-G questionnaire was reported before the patient was given the results of their tumour assessments.

^w During the last week of the screening period (Day -7 to Day 0), the BPI, stool frequency, and analgesic use were self-reported by the patient using a paper diary once a day for 4 days to establish baseline, then every week thereafter during blinded study treatment, up to the discontinuation of blinded study treatment visit. Patients were asked to report their pain, stool frequency, and analgesic use over the course of the past 24 hours. While patients were asked to report all analgesic use, only opioids were used for the analysis.

^x All patients continued to be followed for survival unless consent was withdrawn. In addition to survival information, the names and dates of the first and all subsequent anti-cancer therapies post-study were collected. The patient, patient's family, or the patient's physician had to be contacted every 12 weeks for survival information until death, or until \geq 50% of patients had died. A statement of death electronic CRF was to be completed during the study when a patient died. It was permissible to obtain survival information by telephone contact.

^y The ophthalmologic examination was to be completed at Visit 1 (Screening) and Visit 9. The exception was when a patient discontinued prior to Visit 9, or had already completed Visit 9 prior to the requirement for the ophthalmologic examination – in these situations an ophthalmology examination had to be performed at the discontinuation visit (Visit 75). The ophthalmologic examinations consisted of at least a slit lamp examination, colour vision, and visual field examinations. The results of the eye examination were to be sent to AstraZeneca.

Post-progression open label vandetanib treatment

Post-progression visit (Visit window ± 3 days for each visit starting at Visit 2)	75 Disc of blinded study treatment ^a	301 ^a	302	303	304	305	306 etc	350 Discontin-- ation of PP open-label study treatment	400 60- day follow -up	Survival
Post-progression week	0	0	1	2	4	8	12 Visits every 12 weeks			
Post-progression day	0	1	7	14	28	56	84, etc			
Blinded vandetanib/placebo returned ^b	X									
Open-label vandetanib dispensed/returned ^c	X	X					X	X		
Physical exam	X	X	X	X	X	X	X	X	X	
RECIST Assessment ^d	X	X					X	X		
12-lead ECG ^e	X	X	X	X	X	X	X	X	X	
Vital signs	X	X	X	X	X	X	X	X	X	
Concomitant medication ^f	X	X	X	X	X	X	X	X	X	
AE review ^g	X	X	X	X	X	X	X	X	X	
Weight	X	X	X	X	X	X	X	X	X	
Blood samples for clinical laboratory tests	X	X	X	X	X	X	X	X	X	
Urinalysis	X	X	X	X	X	X	X	X	X	
Blood samples for CTN/CEA ^h	X	X					X	X	X	
Optional fresh tumour biopsy ⁱ							X			
FACT-G QoL questionnaire	X									
Blood samples for biomarkers	X									

Post-progression visit (Visit window ± 3 days for each visit starting at Visit 2)	75 Disc of blinded study treatment ^a	301 ^a	302	303	304	305	306 etc	350 Discontin-- ation of PP open-label study treatment	400 60- day follow -up	Survival
Post-progression week	0	0	1	2	4	8	12 Visits every 12 weeks			
Post-progression day	0	1	7	14	28	56	84, etc			
PK blood sampling for vandetanib	X									
Survival follow-up ^j										X
Ophthalmologic examination ^k		X	Follow-up examination was to occur at Visit 308 and/or discontinuation (see footnote 'k')							

^a Visit 301 was to occur within 4 weeks from the discontinuation visit. Cases where Visit 301 could not be performed within 4 weeks of Visit 75 were handled on an individual basis through contact the AstraZeneca study physician. All non-RECIST scheduled assessments for Visit 301 only needed to be performed if the previous discontinuation of blinded study treatment visit (Visit 75) assessments were completed > 7 days prior to Visit 301. See Footnote D for RECIST assessments.

^b Any unused blinded vandetanib or placebo had to be returned at the discontinuation of blinded study treatment visit. Drug accountability had to be performed.

^c Open-label vandetanib was dispensed at the discontinuation of blinded study treatment visit and every 12 weeks thereafter until discontinuation of post-progression open label treatment. Any unused study drug had to be returned at each visit. Drug accountability had to be performed.

^d The scan from the discontinuation of blinded study treatment visit was used to establish the baseline assessment for RECIST for post-progression open-label treatment.

^e 12-lead ECGs were assessed at post-progression weeks 0, 1, 2, 4, 8, and 12, and every 12 weeks thereafter until discontinuation of post-progression open-label vandetanib study treatment. ECGs were to be performed at the same time throughout the study, approximately 4 to 8 hours after patients took their study drug on the assessment days. Additional 12-lead ECGs were to be performed in the event of QTc prolongation and during the post-prolongation period, as defined in Section 3.3.1 of the Amended CSP (Appendix 12.1.1).

^f Patients who entered post-progression open-label treatment were followed continuously for concomitant medications up to and including the post-discontinuation 60-day follow-up visit.

^g AEs were followed for 60 days after the last dose of open-label vandetanib. All SAEs and study drug-related AEs were to be followed until resolution unless the investigator considered that the event was unlikely to resolve due to the patient's underlying condition.

^h Patients had to fast overnight (approximately 8 hours) before testing for CTN/CEA levels – only 1 draw was required. Appropriate medication could have been administered with sips of water prior to the blood draw. CTN/CEA blood samples had to be sent to the central laboratory for analysis. For patients with a biochemical CR, repeat serum tumour marker levels had to be obtained at least 4 weeks after patients achieved that response, and had to remain within normal limits to be considered a biochemical CR.

ⁱ Optional fresh tumour biopsies were collected from patients who consented to this exploratory part of the study. The second biopsy was obtained at Week 12 (± 7 days) after randomisation, unless the patient withdrew consent.

- j Patients could have continued on post-progression open-label treatment until another anti-cancer therapy (other than the study drug) was administered, or another discontinuation criterion was met. All patients continued to be followed for survival unless they had withdrawn their consent. In addition to survival information, the names and dates of the first and all subsequent anti-cancer therapies post-study were collected. The patient, patient's family, or the patient's physician was contacted every 12 weeks for survival information until death, or until $\geq 50\%$ of patients had died. A statement of death electronic CRF was to be completed at any point during the study when a patient had died. It was permissible to obtain survival information by telephone contact.
- k The ophthalmologic examination was to be completed at Visits 301 and 308. When this examination was completed at the discontinuation visit [Visit 75] the examination at Visit 301 was not required. If the patient discontinued before Visit 308, or had already completed their Visit 308 prior to the requirement for the ophthalmologic exam, an ophthalmology examination had to be performed at the discontinuation visit (Visit 350). The ophthalmologic examinations consisted of at least a slit lamp examination, colour vision, and visual field examinations. The eye examination was to be sent to AstraZeneca.

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/s/

HAO ZHU
10/22/2010

Anshu Marathe
10/22/2010

SUCHITRA M BALAKRISHNAN
10/22/2010

NORMAN L STOCKBRIDGE
10/22/2010

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date: October 22, 2010

Application Type/Number: NDA 022405

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

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

From: Denise V. Baugh, PharmD, BCPS, Safety Evaluator
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Label and Labeling Review

Drug Name(s): Zictifa (Vandetanib) Tablets
100 mg and 300 mg per tablet

Applicant: IPR Pharmaceuticals, Inc.

OSE RCM #: 2010-1541

1 INTRODUCTION

This review responds to a request from the Division of Drug Oncology Products (DDOP) for the Division of Medication Error and Analysis' (DMEPA's) assessment of labels and labeling of Zictifa (Vandetanib) for their vulnerability to medication errors.

2 METHODS AND MATERIALS

Using Failure Mode and Effects Analysis,¹ the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the container labels and labeling submitted by the Applicant on July 7, 2010, (See Appendix A; no image of insert labeling).

3 CONCLUSIONS AND RECOMMENDATIONS

Our evaluation noted areas where information on the label and labeling can be clarified and improved upon to minimize the potential for medication errors. Section 3.1 (Comments to the Division) contains our recommendations for the insert labeling. Section 3.2 (Comments to the Applicant) contains our recommendations for the container labels. We request these recommendations be communicated to the Applicant prior to approval of this NDA.

We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Sarah Simon, OSE Project Manager, at 301-796-5205.

3.1 COMMENTS TO THE DIVISION

3.1.1 *Insert Labeling*

- A. We note an abbreviation 'CTCAE' which appears in Section 2.1 Dosage Adjustment under the heading 'Full Prescribing Information'. We recommend you spell out the words associated with this acronym with its initial use so that it is not misinterpreted.
- B. Revise the typographical error, 'Unncommon' which appears in the second paragraph after Table 1 in Section 6.1 to read 'Uncommon'.
- C. Delete the (b) (4) which follows the statement, 'How to Store Zictifa' in the patient information section of the insert labeling.

3.2 COMMENTS TO THE APPLICANT

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.

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

B. Container Labels

1. The established name is presented in [REDACTED] (b) (4). This presentation is difficult to read because of the insufficient color contrast. Increase the color contrast for the established name to increase its visibility.
2. We note that the container labels for both strengths utilize the same color scheme [REDACTED] (b) (4). Revise the color scheme of the container labels so that each container label is distinctively different from the other. Additionally, ensure that the color used for the strengths is not the same color used for the proprietary name. When colors overlap in either situation, it minimizes the prominence of information and the ability to differentiate between the strengths.
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.



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

/s/

DENISE V BAUGH
10/22/2010

TODD D BRIDGES
10/22/2010

CAROL A HOLQUIST
10/22/2010

RPM FILING REVIEW
(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)

Application Information		
NDA # 022405 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: (b) (4) Established/Proper Name: vandetanib Dosage Form: Tablets Strengths: 100 mg and 300 mg		
Applicant: iPR Pharmaceuticals, Inc. Agent for Applicant (if applicable): AstraZeneca Pharmaceuticals LP, Authorized US Agent		
Date of Application: July 7, 2010 Date of Receipt: July 7, 2010 Date clock started after UN:		
PDUFA Goal Date: January 7, 2011	Action Goal Date (if different):	
Filing Date: September 5, 2010	Date of Filing Meeting: August 16, 2010	
Chemical Classification: (1,2,3 etc.) (original NDAs only) NME = 1		
Proposed indication(s)/Proposed change(s): ZICTIFA is indicated for the treatment of patients with unresectable locally advanced or metastatic medullary thyroid cancer (MTC).		
Type of Original NDA: New Molecular Entity AND (if applicable) Type of NDA Supplement:		<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html <i>and refer to Appendix A for further information.</i>		
Review Classification:		<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device	
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical	

Other:	benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): IND 60,042; NDA (b) (4); DMFs (b) (4)				
Goal Dates/Names/Classification Properties				
PDUFA and Action Goal dates correct in tracking system? <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	YES	NO	NA	Comment
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			GOAL date January 7, 2011
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i>	X			GOAL date October 10, 2010
Application Integrity Policy				
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>	YES	NO	NA	Comment
<i>If yes, explain in comment column.</i>		X		
<i>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</i>				
User Fees				
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	YES	NO	NA	Comment
X				
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send UN letter and contact user fee staff.</i>	Payment for this application:			
	<input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees:			
	<input type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).</i>				

505(b)(2) (NDAs/NDA Efficacy Supplements only)		YES	NO	NA	Comment
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?				X	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).				X	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))? <i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i>				X	
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm				X	
If yes, please list below:					
Application No.	Drug Name	Exclusivity Code		Exclusivity Expiration	
<i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i>					
Exclusivity		YES	NO	NA	Comment
Does another product have orphan exclusivity for the same indication? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm			X		
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i>					
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (NDAs/NDA efficacy supplements only) If yes, # years requested: <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>				X	

Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?		X		
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>				

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission , does it follow the eCTD guidance ¹ ? If not , explain (e.g., waiver granted).	X			
Index: Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including: <input type="checkbox"/> legible <input type="checkbox"/> English (or translated into English) <input type="checkbox"/> pagination <input type="checkbox"/> navigable hyperlinks (electronic submissions only) If no , explain.	X			
Controlled substance/Product with abuse potential: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted? <i>If yes, date consult sent to the Controlled Substance Staff:</i>			X	
BLAs only: Companion application received if a shared or divided manufacturing arrangement?				

If yes, BLA #				
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Forms and Certifications				
<p><i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature? <i>If foreign applicant, both the applicant and the U.S. agent must sign the form.</i>	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature? <i>Forms must be signed by the APPLICANT, not an Agent.</i> <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>	X			
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? (<i>Certification is not required for supplements if submitted in the original application</i>) <i>If foreign applicant, both the applicant and the U.S. Agent must sign the certification.</i> <i>Note: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>	X			

Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>				Submissions via e-submission.

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	X			
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>			X	Orphan Drug Designation
<p>If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</p> <p><i>If no, request in 74-day letter</i></p>			X	
<p>If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)</p> <p><i>If no, request in 74-day letter</i></p>			X	
<p><u>BPCA</u> (NDAs/NDA efficacy supplements only):</p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)</i></p>				

Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review. Submission 7.12.2010</i>	X			
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request in 74-day letter.</i>	X			
Is the PI submitted in PLR format?	X			
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request PLR format in 74-day letter.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC? Sent 7.16.2010.	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X			
REMS consulted to OSE/DRISK?			X	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA? OSE Consult sent. 7.15.2010.	X			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				

Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent: QT-IRT consult on 7.15.2010; SEALD consult on 7.15.2010.</i>	X			

Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): EOP2 June 13, 2005 <i>If yes, distribute minutes before filing meeting</i>	X			
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): June 10, 2010 <i>If yes, distribute minutes before filing meeting</i>	X			
Any Special Protocol Assessments (SPAs)? Date(s): SPA Study 58 Minutes May 26, 2006 <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	X			

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

ATTACHMENT

MEMO OF FILING MEETING

DATE: August 16, 2010

BLA/NDA/Supp #: NDA 22405

PROPRIETARY NAME: Zactifa™

ESTABLISHED/PROPER NAME: vandetanib

DOSAGE FORM/STRENGTH: Tablets: 100 mg and 300 mg

APPLICANT: iPR Pharmaceuticals, Inc.; AstraZeneca Pharmaceuticals LP, Authorized US Agent

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): ZICTIFA is indicated for the treatment of patients with unresectable locally advanced or metastatic medullary thyroid cancer (MTC).

BACKGROUND: NDA 022405 is another submission for vandetanib from AstraZeneca. AstraZeneca on behalf of iPR Pharmaceuticals had submitted vandetanib for Non Small Cell Lung Cancer under NDA (b) (4). For this NDA submission (NDA 22405), AstraZeneca is submitting vandetanib under a new indication, unresectable locally advanced or metastatic medullary thyroid cancer. The clinical studies run in the US to support the proposed indication were conducted under IND Application 60,042 (product name ZD 6474). AstraZeneca listed 14 trials conducted prior to this NDA submission. Vandetanib was granted orphan drug designation in the treatment of medullary thyroid carcinoma, (b) (4) on October 21, 2005. Vandetanib is a new molecular entity. AstraZeneca is requesting priority review.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Lisa Skarupa	Y
	CPMS/TL:	Alice Kacuba	N
Cross-Discipline Team Leader (CDTL)	Ellen Maher, M.D.		Y
Clinical	Reviewer:	Geoffrey Kim –efficacy data Katherine DeLorenzo –safety data	Y
	TL:	Ellen Maher, M.D.	Y

Social Scientist Review (<i>for OTC products</i>)	Reviewer:	NA	
	TL:	NA	
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	NA	
	TL:	NA	
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	NA	
	TL:	NA	
Clinical Pharmacology	Reviewer:	Pengfei Song	Y
	TL:	Young-Jin Moon, Qi Liu	Y
Pharmacogenomics (Clinical Pharmacology)	Reviewer:	Roseane Charlab Orbach	N
	TL:	Issam Zineh	N
Biostatistics	Reviewer:	Somesh Chattopadhyay	Y
	TL:	Shenghui Tang	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Brenda Gehrke	Y
	TL:	Leigh Verbois	Y
Statistics (carcinogenicity)	Reviewer:	NA	
	TL:	NA	
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	NA	
	TL:	NA	
Product Quality (CMC)	Reviewer:	Wendy Wilson, John Duan, Debasis Ghosh	Y
	TL:	Hari Sarker	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	NA (tablet)	
	TL:	NA	
CMC Labeling Review (<i>for BLAs/BLA supplements</i>)	Reviewer:	NA	
	TL:	NA	
Facility Review/Inspection	Reviewer:	NA	
	TL:	NA	

OSE/DMEPA (proprietary name)	Reviewer:	Denise Baugh	N
	TL:	Todd Bridges	N
OSE/DRISK (REMS)	Reviewer:	Latonia Ford	N
	TL:	Claudia Karwoski	N
DDMAC	Reviewer:	Keith Olin	N
	TL:	Stephanie Victor	N
Clinical (DSI)	Reviewer:	Lauren Iacono-Connor	N
	TL:	Tejashri Purohit-Sheth	N

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments: none</p>	<input type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input checked="" type="checkbox"/> YES Date if known: <input type="checkbox"/> NO <input checked="" type="checkbox"/> To be determined Reason: NME.

<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

Comments:	
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<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? • Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments: Facilities have been entered into EES for inspection.</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review (BLAs/BLA supplements only)</u></p> <p>Comments:</p>	<p>Not Applicable</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Director, Office of Oncology Drug Products.	
21st Century Review Milestones (see attached) (optional):	
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input type="checkbox"/> Standard Review <input checked="" type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system.
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input checked="" type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

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

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

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

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

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

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

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

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

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

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

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

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/s/

LISA M SKARUPA
09/23/2010

DSI CONSULT: Request for Clinical Inspections

Date: 8.5.2010

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

Through: Katherine DeLorenzo, MD (Safety) MO/ DDOP
Geoffrey Kim, MD (Efficacy) MO/DDOP
Virginia Maher, MD CDTL/DDOP
Robert Justice, MD Division Director/ DDOP

From: Lisa Skarupa, RPM/DDOP

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA-022405
Applicant/ Applicant contact information (to include phone/email):
Drug Proprietary Name: Zictifa™ (vandetanib)
NME: Yes
Review Priority: Priority

Study Population includes < 17 years of age: No
Is this for Pediatric Exclusivity: No

Proposed New Indication(s): (b) (4)

PDUFA: January 7, 2011
Action Goal Date: December 7, 2010
Inspection Summary Goal Date: November 1, 2010

II. Protocol/Site Identification

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
IGR Onco, 94 Villejuif, Rue Camille Desmoulins Villejuif Cedex 94805, France Site 2801 Phone: 01.42.11.42.61 PI: Martin Schlumberger	D4200C000 58	35 total subjects	Largest site, substantial amount of AE's
AZ. Ospedsliero- Univeritaria Ospedale Cisanello Dipartimento di Endocrinologia e metabolismo Via Paradisa 2 Pisa 56124, Italy Site 2501 Phone: 39.050.995.120 PI: Dr. Rosella Elisei	D4200C000 58	24 total subjects	Large number of patients with a substantial amount of AE's
Zaklad Medycyny Nuklearnej I Endokrynologii Onkologicznej Centrum Ul. Wybrzeze Armii Krajowej 15 Gliwice 44-101, Poland Site 1701 Phone: 48 32 278 93 01 PI: Prof. Barbara Jarzab	D4200C000 58	20 total subjects	Large number of patients with no protocol violations

III. Site Selection/Rationale

We have chosen three sites for inspection based on the following issues:

- There were a significant number of patients treated at each site.
- Given the number of patients, there were a substantial number of AE's recorded.
- The Polish site, although it enrolled 20 patients, had zero protocol violations recorded.

Domestic Inspections:

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify):

International Inspections:

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify) This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites. The sites requested are the three sites with the highest enrollment. The largest domestic site enrolled 11 patients. Site 1701 was also selected because they had no protocol violations.

Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DSI.

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

Should you require any additional information, please contact Lisa Skarupa, RPM at 301-796-2219 or Katherine DeLorenzo, medical officer (safety) at 301-796-7547.

Concurrence: (as needed)

_____ Medical Team Leader
_____ Medical Reviewer
_____ Division Director (for foreign inspection requests or requests for 5 or more sites only)

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/

LISA M SKARUPA
08/05/2010

KATHERINE A DELORENZO
08/05/2010

VIRGINIA E MAHER
08/06/2010

ROBERT L JUSTICE
08/06/2010