

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022405Orig1s000

STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES-TEAM LEADER'S MEMO

NDA/Serial Number: 22-405 / S-000

Drug Name: [REDACTED] (vandetanib)

Indication(s): Treatment of patients with unresectable locally advanced or metastatic medullary thyroid cancer.

Applicant: IPR Pharmaceuticals, Inc. and AstraZeneca Pharmaceuticals LP

Date(s): Submitted: July 7, 2010
PDUFA: January 7, 2011
Review Completed: December 16, 2010

Review Priority: Priority

Biometrics Division: Division of Biometrics V (HFD-711)

Primary Reviewer: Somesh Chattopadhyay, Ph.D.

Secondary Reviewer: Shenghui Tang, Ph.D., Team Leader

Concurring Reviewer: Rajeshwari Sridhara, Ph.D., Division Director

Medical Division: Division of Drug Oncology Products (HFD-150)

Clinical Team: Geoffrey Kim, M.D., Medical Reviewer
Katherine Delorenzo, M.D., Medical Reviewer
Virginia Maher, M.D., Medical Team Leader

Project Manager: Ms. Lisa Skarupa

Keywords: Double-blind, intent-to-treat, interim analysis, Kaplan-Meier product limit, logrank test, multiple endpoints, proportional hazards, randomization, subgroup analysis, survival analysis.

The applicant has submitted results from one multicenter, phase III, randomized, double-blind, placebo-controlled clinical trial (Study D4200C00058) comparing vandetanib (b) (4) to placebo in patients with unresectable locally advanced or metastatic medullary thyroid cancer (MTC). Study D4200C00058 randomized a total of 331 patients, 231 to vandetanib arm and 100 to placebo arm. The vandetanib arm showed statistically significant improvement over placebo with respect to PFS as determined by the independent central review in the ITT patient population [hazard ratio=0.352, 95% confidence interval: (0.235, 0.527), log-rank test, two-sided p-value<0.0001]. Vandetanib arm did not show improvement over placebo with respect to OS assessment in the ITT patient population [hazard ratio=0.893, 95% confidence interval: (0.490, 1.629), 99.993% confidence interval: (0.271, 2.944), log-rank test, two-sided p-value=0.7131]. The overall response rate was 44.6% in the vandetanib arm and 1% in the placebo arm based on the responses assessed by the independent review. No adjustment to the level of significance was made for multiple secondary endpoints. Therefore, p-values are not interpretable for the secondary endpoints. For further details regarding the design, data analyses, and results of this phase 3 study, please refer to the statistical review by Dr. Somesh Chattopadhyay (December 16, 2010). In addition, the overall safety database including studies in other indications, showed toxicities and adverse reactions including large amount of QT/QTc prolongation including 2 torsades, sudden deaths, Stevens-Johnson syndrome and interstitial lung disease. For further details regarding the safety profile for vandetanib, please refer to the medical review by Drs. Geoffrey Kim and Katherine DeLorenzo (December 9, 2010). The application was discussed at the Oncologic Drug Advisory Committee meeting on December 2, 2010. The committee voted unanimously to require the applicant to evaluate additional doses as a post-marketing requirement to determine the optimal dose as 49.4% of patients in the vandetanib arm had dose reduction in this clinical trial.

This team leader concurs with the recommendations and conclusions of the statistical reviewer (Dr. Somesh Chattopadhyay) of this application. The inference regarding favorable benefit-risk profile for the use of vandetanib in patients with unresectable locally advanced or metastatic medullary thyroid cancer with an estimated 10 year survival rate of 40%, is deferred to the clinical review team.

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/s/

SHENGHUI TANG
12/16/2010

RAJESHWARI SRIDHARA
12/16/2010



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
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CLINICAL STUDIES

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Applicant: IPR Pharmaceuticals, Inc. and AstraZeneca Pharmaceuticals LP

Date(s): Submitted: July 7, 2010
PDUFA: January 7, 2011
Review Completed: December 15, 2010

Review Priority: Priority

Biometrics Division: Division of Biometrics V (HFD-711)

Statistical Reviewer: Somesh Chattopadhyay, Ph.D.

Concurring Reviewers: Shenghui Tang, Ph.D., Team Leader
Rajeshwari Sridhara, Ph.D., Director

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1. EXECUTIVE SUMMARY

1.1. Conclusions and Recommendations

The applicant has submitted results from one multicenter, phase III, randomized, double-blind, placebo-controlled clinical trial (Study D4200C00058) comparing vandetanib (b) (4) to placebo in patients with unresectable locally advanced or metastatic medullary thyroid cancer (MTC). The vandetanib arm showed statistically significant improvement over placebo in progression-free survival (PFS) as assessed by independent central radiology review in all randomized patients. However, the vandetanib arm did not show statistically significant improvement with respect to overall survival (OS) at the time of the final PFS analysis. Therefore, the clinical benefit of vandetanib in MTC is not clear particularly since the natural history of this disease is long with an estimated 10-year survival rate of 40%. Moreover, the overall safety database that also includes studies in other indications, showed toxicities and adverse reactions including large amount of QT/QTc prolongation, sudden deaths, Stevens-Johnson syndrome and interstitial lung disease and increased incidence of rare serious adverse reactions like torsade de pointe. The application was discussed at the Oncologic Drug Advisory Committee meeting on December 2, 2010. The committee voted unanimously to require the applicant to evaluate additional doses as a post-marketing requirement to determine the optimal dose. The judgment of meaningfulness of the improvement in PFS in light of the toxicities and lack of significant improvement in OS is deferred to the clinical review team.

1.2. Brief Overview of Clinical Studies

This application is based on one Phase III trial (Study D4200C00058 or Study 58) and two uncontrolled single-arm Phase II studies (D4200C00008 and D4200C00068). This review is primarily based on the Phase III study. Study 58 was a multicenter, international, randomized, double-blind, placebo-controlled, Phase III study to evaluate the efficacy of vandetanib compared to placebo in patients with unresectable locally advanced or metastatic MTC. 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. First patient was enrolled on November 23, 2006. The data cut-off date was July 31, 2009. A total of 331 patients were randomized, 231 to vandetanib and 100 to placebo. Of the randomized patients, 190 were men and 141 were women, 315 were White, and the median age was 51 years (age range: 18 to 84 years). Randomized patients were enrolled at 60 centers in 23 countries. There were 73 patients from US and 0.6% of the patients reported their race as Black. The primary efficacy endpoint was progression-free survival (PFS) as assessed by the independent central radiology review. The secondary efficacy endpoints were overall response rate (ORR) as determined by central review, disease control rate (DCR), duration of response, overall survival (OS) and biochemical response [measured by calcitonin (CTN) and carcinoembryonic antigen (CEA)].

1.3. Statistical Issues and Findings

Statistical Issues:

1. The study was designed to have a 2:1 randomization for vandetanib to placebo. However, actually 231 patients were randomized to vandetanib and 100 patients to placebo. Thus the randomization ratio actually was greater than 2:1. In this study, randomization was stratified by site in blocks of 3. If a site did not use all the randomization numbers in a given block, it would be expected that the ratio of patients assigned to the vandetanib group relative to those assigned to the placebo group would not be equal to 2. The applicant explained that in this study, these incomplete blocks, by random chance, had a ratio that was greater than 2 more often than they had a ratio that was less than 2 and consequently, the ratio overall was greater than 2.
2. The censoring rules of FDA and the applicant were different for primary PFS analysis based on IRC review. Following is a list of censoring rules that are different for FDA's and the applicant's analyses.
 - PFS for the patients with investigator-determined, but without IRC determined progression have been censored at their last RECIST assessment prior to discontinuation of study drug for FDA's analysis. The applicant's analysis of PFS used the IRC assessment beyond investigator assessed progression and study drug discontinuation in these cases. While the sponsor's analysis may address informative censoring and conform to ITT analysis, this analysis includes effect of non-protocol treatment beyond investigator determined progression.
 - For the patients who received radiation during the study period, FDA's analysis censored PFS at the last RECIST assessment prior to radiation therapy. The applicant's analysis did not censor these patients for radiation therapy.
 - PFS for the patients who had no baseline measurable disease by the IRC has been censored at Day 1 in FDA's analysis. The applicant's analysis did not censor them at Day 1.
3. FDA's analysis of PFS based on investigator's assessment did not match with that reported in the Clinical Study Report. One reason for this discrepancy is that in the submitted dataset the date of progression or censoring based on investigator's assessment was missing for 15 subjects although the result reported in the Clinical Study Report did not reflect that. There may be additional unknown reasons as well.
4. FDA's calculation of response rate does not include responses that occurred after discontinuation of study drug and crossover to open-label vandetanib whereas the applicant included those responses in the calculation of response rate.
5. The validity of the patient-reported outcome instruments employed is questionable. Moreover, the quality of life endpoints are not interpretable if blinding is not properly maintained. It is not clear if the blinding is broken due to difference in adverse events. Therefore, this review considers those endpoints exploratory.

6. Based on the planned number of events, the study had actually 90% power to detect a doubling in median PFS at 2-sided 5% level of significance. However, the application did not precisely specify the power; power was stated only to be greater than 80%.
7. The study was originally planned to have two co-primary analyses to compare PFS between the two treatment arms in all patients who received at least one dose of vandetanib/placebo and in patients who had RET mutation and received at least one dose of vandetanib/placebo. The required number of events and the related number of patients were calculated based on the analysis of PFS for all patients. The protocol specified that 90 events would be required to detect doubling of PFS in all patients at a 2-sided 2.5% level of significance with 80% power and this would provide 80% power at 2-sided 2.5% level of significance to detect a hazard ratio of 0.32 in the patients with RET mutation assuming that there would be 50% patients with RET mutation. However, the co-primary analysis population of patients with a known RET mutation was removed from the study in protocol amendment 5 (18 May 2009) because assays used to identify RET mutation were unable to establish mutation status in 41% of the patients.
8. The applicant derived the hazard ratio estimate and its confidence interval based on the results from the log-rank test whereas FDA used the Cox proportional hazards model to derive these numbers.
9. Type I error rate has not been adjusted for analysis of multiple secondary endpoints. Therefore, p-values for the secondary endpoints are not interpretable.
10. The PFS improvement in the vandetanib arm is consistent across various subgroups. All the subgroup analyses presented are considered exploratory or hypothesis generating and no formal inference may be drawn.

Findings:

Study 58 randomized a total of 331 patients, 231 to vandetanib arm and 100 to placebo arm. The vandetanib arm showed statistically significant improvement over placebo with respect to PFS as determined by the independent central review in the full analysis set (FAS) [hazard ratio=0.352, 95% confidence interval: (0.235, 0.527), log-rank test, two-sided p-value<0.0001]. Vandetanib arm did not show improvement over placebo with respect to OS assessment in the FAS [hazard ratio=0.893, 95% confidence interval: (0.490, 1.629), 99.993% confidence interval: (0.271, 2.944), log-rank test, two-sided p-value=0.7131]. However, no adjustment to the level of significance was made for multiple secondary endpoints. Therefore p-values are not interpretable for the secondary endpoints. The overall response rate was 44.6% in the vandetanib arm and 1% in the placebo arm based on the responses assessed by the independent review. The analysis of PFS as determined by the independent central review in FAS is presented in Table 1. The corresponding OS analysis is presented in Table 2.

Table 1: Analysis of PFS Based on Independent Review in FAS (FDA Analysis)

Treatment	Number of Patients	Number (%) Failed	Median in Months¹ (95% CI)	Hazard Ratio² Vandetanib/Placebo (95% CI)	P-value³
Vandetanib	231	59 (25.54%)	NE (22.6, NE)	0.352 (0.235, 0.527)	<0.0001
Placebo	100	41 (41.00%)	16.4 (8.3, 19.7)		

¹: Kaplan-Meier estimate. ²: Based on Cox model. ³: Based on two-sided log-rank test. NE: Not estimable.

Table 2: Analysis of OS in FAS

Treatment	Number of Patients	Number (%) Failed	Median in Months¹ (95% CI)	Hazard Ratio² Vandetanib/ Placebo (95% CI)	P-value³
Vandetanib	231	32 (13.85%)	NE (29.3, NE)	0.893 (0.490, 1.629)	0.7131
Placebo	100	16 (16.00%)	NE (NE, NE)		

¹: Kaplan-Meier estimate. ²: Based on Cox model. ³: Based on two-sided log-rank test. NE: Not estimable.

2. INTRODUCTION

2.1. Overview

Carcinoma of the thyroid is the most common malignancy of the endocrine system. Most cases of thyroid cancer (85%–95%) are well-differentiated tumors (papillary or follicular); other less common types include medullary and anaplastic. About 5% to 10% of thyroid cancers are medullary carcinoma. Medullary thyroid cancer (MTC) is a distinct subtype, arising from the parafollicular cells (C-cells) of the thyroid.

MTC presents either as a sporadic cancer or as part of a hereditary syndrome. The sporadic form accounts for 75% of cases; in the remainder, MTC occurs as part of 1 of 3 hereditary syndromes: Multiple Endocrine Neoplasia (MEN) type 2a, MEN type 2b, or Familial Medullary Thyroid Carcinoma (FMTC). Each of these syndromes is inherited as an autosomal dominant trait, and each is characterized by a distinct genotype and clinical phenotype.

2.1.1. Background

Vandetanib (b) (4) is a new molecular entity and as reported by the Applicant is a selective 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. Both EGFR and VEGF signaling pathways are anti-cancer targets. Angiogenesis, the process of new blood vessel formation, is critical for the growth of all solid tumors and both VEGF and its primary receptor are critical to this process. EGFR is a membrane-bound receptor of the erbB family that is frequently over-expressed and activated to a phosphorylated state in non-small cell lung cancer (NSCLC). Once activated, the tyrosine kinase moiety of EGFR initiates a complex cascade of phosphorylation resulting in cell mobility, proliferation, protection from apoptosis and metastasis. A dual VEGFR/EGFR signaling inhibitor has therapeutic potential in diseases such as NSCLC where both signaling pathways are implicated, preventing new blood vessel development, and slowing or halting tumor growth independently of whether the tumor was sensitive or resistant to EGFR inhibitors. However, well conducted randomized studies in NSCLC have not demonstrated benefit with vandetanib. In addition, according to the Applicant inhibition of RET signalling has the potential to broaden the pharmacological activity of vandetanib to include those disease settings with aberrant RET signalling such as medullary thyroid cancer (MTC), a disease in which all three signalling pathways may play a role.

2.1.2. Regulatory History

This application is based on a single Phase III and multiple Phase II trials. The trials were conducted under IND 60,042. The study protocol for the Phase III trial D4200C00058 was submitted for a Special Protocol Assessment (SPA) on February 16, 2006. No agreement was reached on the SPA. The Pre-NDA meeting was held on June 10, 2010.

Vandetanib was also investigated in patients with solid tumors other than MTC. In addition to the Phase III study in MTC, 4 other Phase III studies have been conducted with vandetanib. These Phase III studies investigated the efficacy of vandetanib in patients with refractory NSCLC: 2 in combination with chemotherapy and 2 as monotherapy. The primary objective of prolongation of PFS was met for vandetanib in combination with docetaxel (vs. docetaxel), but was not met for vandetanib in combination with pemetrexed (vs. pemetrexed). The primary objective of prolongation of PFS was also not met for vandetanib vs. erlotinib. None of these studies demonstrated improvement in overall survival. The primary objective of improvement in OS was also not met for vandetanib vs. placebo in patients following treatment with an EGFR inhibitor. (b) (4)

2.1.3. Specific Studies Reviewed

This application is based on one Phase III trial (Study D4200C00058 or Study 58) and two uncontrolled single-arm Phase II studies (D4200C00008 and D4200C00068). This review is primarily based on the Phase III study. Study 58 was a multicenter, international, randomized, double-blind, placebo-controlled, Phase III study to evaluate the efficacy of vandetanib compared to placebo in patients with unresectable locally advanced or metastatic MTC. 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. First patient was enrolled on November 23, 2006. The data cut-off date was July 31, 2009.

A total of 331 patients were randomized, 231 to vandetanib and 100 to placebo. Of the randomized patients, 190 were men and 141 were women, 315 were White, and the median age was 51 years (age range: 18 to 84 years). Randomized patients were enrolled at 60 centers in 23 countries. There were 73 patients from US.

2.2. Data Sources

Data used for this review are from the electronic submission dated July 7, 2010. The path is <\\Cdseub1\EVSPROD\NDA022405\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\mtc\5351-stud-rep-contr\d4200c00058\crt>.

3. STATISTICAL EVALUATION

3.1. Evaluation of Efficacy

The applicant has submitted efficacy results from one Phase III study (Study D4200C00058 or Study 58) titled “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” and two uncontrolled single-arm Phase II studies (D4200C00008 and D4200C00068). This review will be primarily based on the Phase III study.

3.1.1. Study Objectives

3.1.1.1. Primary Objective

The primary objective of study 58 was to demonstrate an improvement in progression-free survival (PFS) with vandetanib as compared to placebo in patients with unresectable locally advanced or metastatic MTC.

3.1.1.2. Secondary Objectives

The secondary objectives were:

1. To demonstrate an improvement in the objective response rate (ORR), disease control rate (DCR), and duration of or response (DOR) with vandetanib as compared to placebo.
2. To demonstrate an improvement in overall survival (OS) in patients with MTC who have been treated with vandetanib as compared to placebo.
3. To demonstrate an improvement in biochemical response with vandetanib as compared to placebo, as measured by calcitonin (CTN) and carcinoembryonic antigen (CEA).
4. To demonstrate a delay in time to worsening of pain (TWP) among patients with MTC after treatment with vandetanib as compared to placebo.
5. To determine the pharmacokinetics (PK) of vandetanib in this patient population and investigate any influence of patient demography and pathophysiology on the PK.
6. To assess the relationship between PK and time interval between the start of the Q wave and the end of the T wave, (corrected for heart rate) (QTc), safety, efficacy, and biomarkers.
7. To determine the safety and tolerability of vandetanib treatment in MTC patients.
8. To determine the mutational status of the RET proto-oncogene in deoxyribonucleic acid (DNA) extracted from tumor samples

3.1.1.3. Exploratory Objectives

1. To investigate the effect of treatment with vandetanib as compared to placebo on diarrhea in patients with MTC.
2. To explore changes in plasma VEGF, VEGFR-2, and basic fibroblast growth factor (bFGF) levels in patients treated with vandetanib as compared to placebo, and their relationship to efficacy.
3. To explore changes in serum protein profiles in patients treated with vandetanib as compared to placebo, and their relationship with efficacy and disease progression.
4. To measure EGFR expression levels in tumor tissue in patients treated with vandetanib as compared to placebo, and determine the relationship between expression levels and efficacy.
5. To investigate changes in tumor biomarkers of inhibition of RET, VEGFR, and EGFR signaling pathways.
6. To demonstrate a delay in TWP among patients with MTC who have no pain at baseline defined as requiring <10mg/day morphine sulfate or equivalent after treatment with vandetanib as compared to placebo.
7. To demonstrate a delay in TWP among patients with MTC who have pain at baseline defined as requiring ≥ 10 mg/day morphine sulfate or equivalent after treatment with vandetanib as compared to placebo.
8. To demonstrate a reduction in the use of opioid analgesic medication in patients with MTC who have pain at baseline requiring ≥ 10 mg/day morphine sulfate or equivalent after treatment with vandetanib as compared to placebo.
9. To demonstrate an improvement in weight in patients with MTC who have been treated with vandetanib as compared to placebo.
10. To demonstrate a delay in the time to decline in WHO performance status (TDPS) in patients treated with vandetanib as compared to placebo.
11. To investigate the effects of vandetanib as compared to placebo on patient quality of life (QoL) as measured by the Functional Assessment of Cancer Therapy General Scale (FACT-G).

3.1.2. Study Design

This study was a multicenter, international, randomized, double-blind, placebo-controlled, Phase III study to evaluate the efficacy of vandetanib compared to placebo in patients with unresectable locally advanced or metastatic MTC.

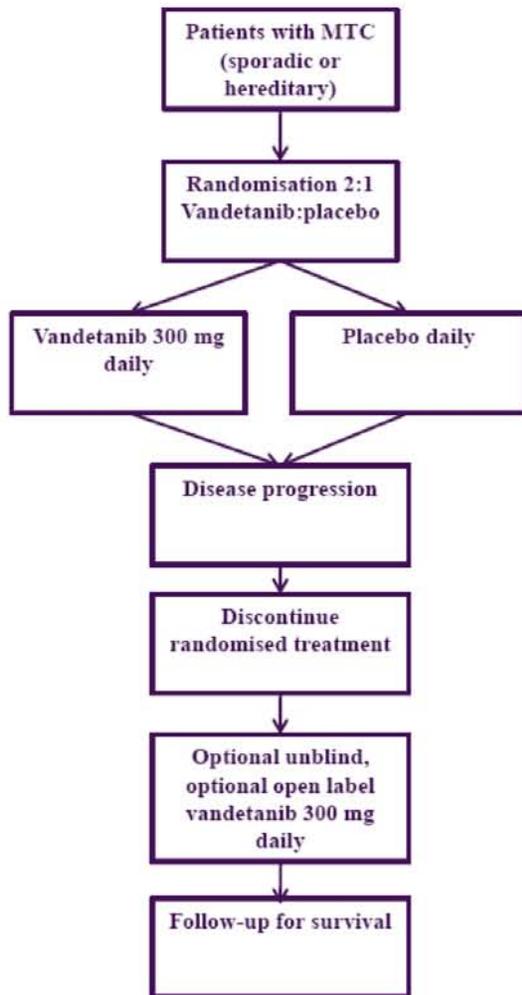
Patients were randomized in a 2:1 ratio to receive vandetanib 300 mg once daily oral dose or matched placebo, continuing on blinded treatment until they had objective disease progression, provided they did not meet any other withdrawal criteria. Upon disease progression as determined by investigator, 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.

Based on Protocol Amendment 6, investigators had the option to unblind any subjects remaining on randomized therapy, whether or not disease progression had occurred. Any patient who was unblinded as a result of Amendment 6 had to either enter the open-label phase of the study or discontinue blinded therapy and be followed for survival. Once unblinding occurred, patients could not stay on blinded therapy. Survival follow-up would continue until at least 50% of the patients die. Patients who are receiving open label vandetanib could continue for as long as the investigator believes the patients are receiving clinical benefit.

Major inclusion criteria included previously confirmed histological diagnosis of unresectable locally advanced or metastatic hereditary or sporadic MTC, life expectancy of at least 12 weeks, WHO performance status 0 to 2, presence of a measurable tumor and CTN ≥ 500 pg/mL.

The study design is presented in Figure 1.

Figure 1: Study Design Flow Chart



Source: Clinical study report submitted in the NDA.

Reviewer's Comments:

The study was designed to have a 2:1 randomization for vandetanib to placebo. However, actually 231 patients were randomized to vandetanib and 100 patients to placebo. Thus the randomization ratio actually was greater than 2:1. In this study, randomization was stratified by site in blocks of 3. If a site did not use all the randomization numbers in a given block, it would be expected that the ratio of patients assigned to the vandetanib group relative to those assigned to the placebo group would not be equal to 2. The applicant explained that in this study, these incomplete blocks, by random chance, had a ratio that was greater than 2 more often than they had a ratio that was less than 2 and consequently, the ratio overall is greater than 2.

3.1.3. Schedule of Assessments

Radiologic evaluation using modified Response Evaluation Criteria in Solid Tumors (RECIST) was performed every 12 weeks. Patients were evaluated until objective progression, and then followed for survival, regardless of whether they continued post-progression treatment, unless they withdrew consent. All medical images were reviewed at the site and by a centrally appointed Contract Research Organization (b) (4)

The central review data were used for primary efficacy analysis.

3.1.4. Efficacy Endpoints

Primary endpoints:

- Progression-free survival (PFS) as determined by the central review.

Secondary endpoints:

- Objective response rate (ORR) by RECIST as determined by the central review, disease control rate (DCR) and duration of response (DOR)
- Overall survival (OS)
- Biochemical response (CTN and CEA)

Patient reported outcome endpoint:

- Time to worsening of pain (TWP)

Progression-free survival (PFS) was defined as the time from randomization to objective disease progression or death from any cause in the absence of progression, provided death occurred within 3 months from the last evaluable RECIST assessment.

Patients who had not progressed or died (within 3 months of their last evaluable RECIST assessment) at the time of analysis were censored at the time of their last evaluable central read RECIST assessment (i.e., the last central read RECIST assessment must have had a visit

response of CR/PR or SD for censoring in the absence of progression). This included patients who were lost to follow-up or had withdrawn consent.

Progression and response were assessed using modified RECIST. The modifications included a calcification correction and allowing investigators to retrospectively assess whether or not a hypodense or hypointense lesion in the liver seen in the first 2 follow-up assessments was present at baseline and, if so, they were instructed to record these lesions as non-target lesions at baseline and not treat their discovery as progression. The primary analysis of PFS used these 2 modifications of the RECIST criteria.

ORR was defined as the percentage of patients with a best objective response (BOR) of CR or PR. BOR was determined based on data up to the point of the first RECIST progression according to all available central read RECIST assessments. If the patient had not progressed according to the central read before discontinuation of randomized treatment, any available scans performed after the patient discontinued randomized treatment were considered up until the point of progression according to the central read, regardless of whether these assessments were performed whilst on open label treatment. For patients who had not progressed according to the central read at the time of the analysis, data were included up to their last evaluable central read RECIST assessment.

DCR was defined as the percentage of patients with a BOR of CR, PR, or stable disease ≥ 24 weeks following randomization. DCR was only derived from best objective responses according to the central read RECIST assessments. All available central read RECIST assessments were considered in the derivation, regardless of whether the patient was taking subsequent therapy or open label treatment at the time of the assessment.

OS was defined as the time from randomization to death.

Biochemical response rate was defined as the percentage of patients with a best biochemical response (CTN or CEA) of CR or PR. The following definitions were used to calculate the CTN or CEA biochemical response at each follow-up assessment for each patient:

- Complete Response (CR): Complete normalization of the CTN level (≤ 10 pg/ml for men and ≤ 5 pg/ml for women) confirmed by a repeat assessment > 4 weeks later.
- Partial Response (PR): A decrease in the CTN level of at least 50% from baseline confirmed by a repeat assessment > 4 weeks later.
- Progressive Disease (PD): An increase in the CTN level of at least 50% from baseline confirmed by a repeat assessment > 4 weeks later.
- Stable disease (SD): The change in the CTN level from baseline does not meet the criteria for CR, PR, or PD.
- Not evaluable (NE): The CTN level was missing at the baseline assessment and/or the follow-up assessment.

The CEA biochemical response rate was derived in the same way as the CTN biochemical response using CEA levels. Complete normalization of CEA was defined as a value ≤ 2.5 pg/ml.

Time to worsening of pain (TWP) was a composite endpoint derived from opioid analgesic use and the worst pain item of the Brief Pain Inventory (BPI) questionnaires. Responses for opioid analgesic use and responses for the worst pain item were derived by comparing follow-up assessments to baseline or the previous visit. These responses were then used to derive a worsening in pain, defined as a response of worsening in at least 1 of the 2 components (opioid analgesic use or worst pain item) that was not followed by an overall response (determined by combining the response for opioid analgesic use and the response for worst pain) of improvement in the next 14 days. TWP was defined as the time to the date of the assessment of the component that led to the first confirmed worsening from the date of randomization. If both components had a response of worsening at the same visit, then the earliest assessment date was used in the derivation of TWP. For worst pain, worsening was defined as a ≥ 2 point increase from baseline, improvement was defined as a ≥ 2 point decrease from baseline worst-pain item score with no increase from baseline of ≥ 10 mg/day of morphine sulphate equivalent, otherwise no change. For opioid analgesic use, worsening was defined as an increase from baseline of ≥ 10 mg/day of morphine sulphate equivalent, improvement was defined as a decrease from previous visit by $>50\%$ of opioid analgesic use with no increase of ≥ 2 point from baseline worst-pain item score, otherwise no change.

Reviewer's comments:

1. The censoring rules of FDA and the applicant were different for primary PFS analysis based on IRC review. Following is a list of censoring rules that are different for FDA's and the applicant's analyses.
 - PFS for the patients with investigator-determined, but without IRC determined progression have been censored at their last RECIST assessment prior to discontinuation of study drug for FDA's analysis. The applicant's analysis of PFS used the IRC assessment beyond investigator assessed progression and study drug discontinuation in these cases. While the sponsor's analysis may address informative censoring and conform to ITT analysis, this analysis includes effect of non-protocol treatment beyond investigator determined progression.
 - For the patients who received radiation during the study period, FDA's analysis censored PFS at the last RECIST assessment prior to radiation therapy. The Applicant's analysis did not censor these patients for radiation therapy.
 - PFS for the patients who had no baseline measurable disease by the IRC has been censored at Day 1 in FDA's analysis. The applicant's analysis did not censor them at Day 1.
2. FDA's calculation of response rate does not include responses that occurred after discontinuation of study drug and crossover to open-label vandetanib whereas the applicant included those responses in the calculation of response rate.
3. The validity of the patient-reported outcome instruments employed is questionable. Moreover, the quality of life endpoints are not interpretable if blinding is not properly maintained. It is not clear if the blinding is broken due to difference in adverse events. Therefore, this review considers those endpoints exploratory.

3.1.5. Sample Size Considerations

The sample size was calculated based of the primary endpoint PFS. Assuming 2:1 randomization (vandetanib: placebo), in order to detect a doubling of median PFS at 5% significance level (2-sided) with more than 80% power, at least 90 events were required. Assuming median PFS of 12 months in the control group, a non-linear recruitment period of 22 months and a minimum follow-up of 6.7 months, approximately 232 patients were to be recruited in to the study, i.e., the total length of the study was estimated to be 28.7 months in order to observe 90 PFS events. The study was not powered for OS.

Reviewer's comments:

1. Based on the planned number of events, the study had actually 90% power to detect a doubling in median PFS at 2-sided 5% level of significance. However, the application did not precisely specify the power; power was stated only to be greater than 80%.
2. The study was originally planned to have two co-primary analyses to compare PFS between the two treatment arms in all patients who received at least one dose of vandetanib/placebo and in patients who had RET mutation and received at least one dose of vandetanib/placebo. The required number of events and the related number of patients were calculated based on the analysis of PFS for all patients. The protocol specified that 90 events would be required to detect doubling of PFS in all patients at a 2-sided 2.5% level of significance with 80% power and this would provide 80% power at 2-sided 2.5% level of significance to detect a hazard ratio of 0.32 in the patients with RET mutation assuming that there would be 50% patients with RET mutation. (b) (4)

3.1.6. Interim Analyses

No interim analysis was planned or performed for PFS.

The analysis of OS performed at the time of the final analysis of all other data was treated as an interim analysis of OS with the final analysis to be performed at the time that at least 50% of the patients randomized have died. The significance level for OS will be adjusted for these repeat analyses using Lan and DeMets methodology (Lan and DeMets 1983), based on the actual number of deaths at the time of the first analysis and the number of deaths that will be required for the final analysis based on actual recruitment.

Reviewer's comment:

Based on the data cut-off date of July 31, 2009 for the primary analysis of PFS, there were 48 deaths. Total number of patients enrolled in the trial was 331. Therefore, the final analysis of OS will be performed after 166 deaths. At the time of the first OS analysis 28.9% of deaths that are

required for the final analysis occurred and the alpha for that analysis is 0.00007 according to Lan-DeMets method when overall alpha for OS is 0.05. However, alpha was not adjusted for multiple secondary endpoints. Therefore, all the reported nominal p-values for secondary endpoints are not interpretable.

3.1.7. Efficacy Analysis Methods

3.1.7.1. Analysis Populations

The following analysis sets were used in this study:

Full Analysis Set (ITT population) - all randomized patients

Per Protocol Analysis Set - All randomized patients excluding those who had at least 1 significant protocol deviation believed by the sponsor to have a potential impact on the efficacy outcomes of the study.

Safety Analysis Set - All randomized patients who received at least 1 dose of randomized treatment (i.e., at least one dose of vandetanib/placebo).

PK Analysis Set - All randomized patients with valid plasma concentrations of vandetanib who were identified as being randomized to the vandetanib group.

Open-label Analysis Set – All randomized patients who received at least one dose of open label treatment.

3.1.7.2. Analysis of Primary Endpoint

The primary analysis of PFS was based on PFS derived from all available central read RECIST assessments; this included any available information on central read RECIST scans performed whilst on randomized treatment, after discontinuation of randomized treatment and after first dose of open label treatment. Other methods of deriving PFS were considered as part of sensitivity analyses in support of the primary analysis.

A log-rank test was performed for the primary analysis of PFS based on the ITT population. Results are presented in terms of an estimate of the hazard ratio (vandetanib:placebo) associated confidence interval, and p-value.

Point estimates of the median PFS were provided for each treatment group, and PFS was displayed graphically using Kaplan-Meier plots. In addition, the proportion of patients who had PFS at 6 months, 1 year and 2 years after randomization was summarized by randomized treatment. These were produced for PFS as derived for the primary analysis only (i.e., derived from all available central read RECIST assessments).

The progression status of patients at the time of analysis was summarized. This included the number (%) of patients who had progression, along with the type of progression event (i.e., RECIST progression or death). The reasons that patients had not progressed were also presented (i.e., alive without progression, lost to follow-up, etc.). This was produced for PFS as derived for the primary analysis only (i.e., derived from all available central read RECIST assessments).

Reviewer's comment:

The applicant derived the hazard ratio estimate and its confidence interval based on the results from the log-rank test whereas FDA used the Cox proportional hazards model to derive these numbers.

3.1.7.3. Analysis of Secondary Endpoints

The analysis of objective response rate was performed using logistic regression including treatment as the only covariate based on the ITT population. Results are presented in terms of an estimate of the odds ratio (vandetanib:placebo) alongside the p-value from changes in log-likelihood and likelihood confidence intervals.

The number (%) of patients with an objective response according to all the available central read RECIST assessments was summarized. The summary also included details of the number (%) of patients within each BOR category.

Analysis of disease control rate (DCR) was similar to that of objective response rate.

Duration of response was summarized, where possible, in terms of the median duration of response.

A log rank test was performed for the primary analysis of OS based on the ITT population. OS was displayed graphically using Kaplan-Meier plots. In addition, the proportion of patients who had OS at 6 months, 1 year, and 2 years after randomization was summarized by randomized treatment. OS was analyzed at the time of the analysis of all other endpoints and will be analyzed a second time when at least 50% of the patients have died. At the time of the first analysis 48 patients had died and at the second analysis the expectation is that at least 166 patients will have died. Therefore, 28.9% of the final number of deaths had occurred at the first analysis of OS. The significance level for this first analysis was 0.02% with corresponding 99.98% confidence intervals presented. At the proposed survival update for this study the significance level will be 4.98% with corresponding 95.02% confidence intervals.

Reviewer's comment:

Type I error rate has not been adjusted for analysis of multiple secondary endpoints. Therefore, p-values for the secondary endpoints are not interpretable.

3.1.7.4. Patient Reported Outcome Analyses

A log rank test was performed for the primary analysis of TWP. The primary analysis used TWP as derived using both information on worst pain and opioid analgesic use. Results of each analysis are presented in terms of HRs, CIs and associated p-values. Point estimates of the median TWP are presented for each treatment group and TWP was displayed graphically using Kaplan-Meier plots. The analysis of TWP was considered the primary analysis for patient reported outcome data; all other analyses of PROs were considered to be exploratory.

Reviewer's comment:

The TWP results are not interpretable because there was no adjustment in Type I error rate for multiple secondary and patient reported outcome endpoints. In addition, the validity of the patient-reported outcome instruments employed is questionable due to higher proportion of patients experiencing toxicity which could potentially unblind the treatment assignment. Analysis of this endpoint is also not valid with a large percentage of missing data (only 50% overall compliance rate).

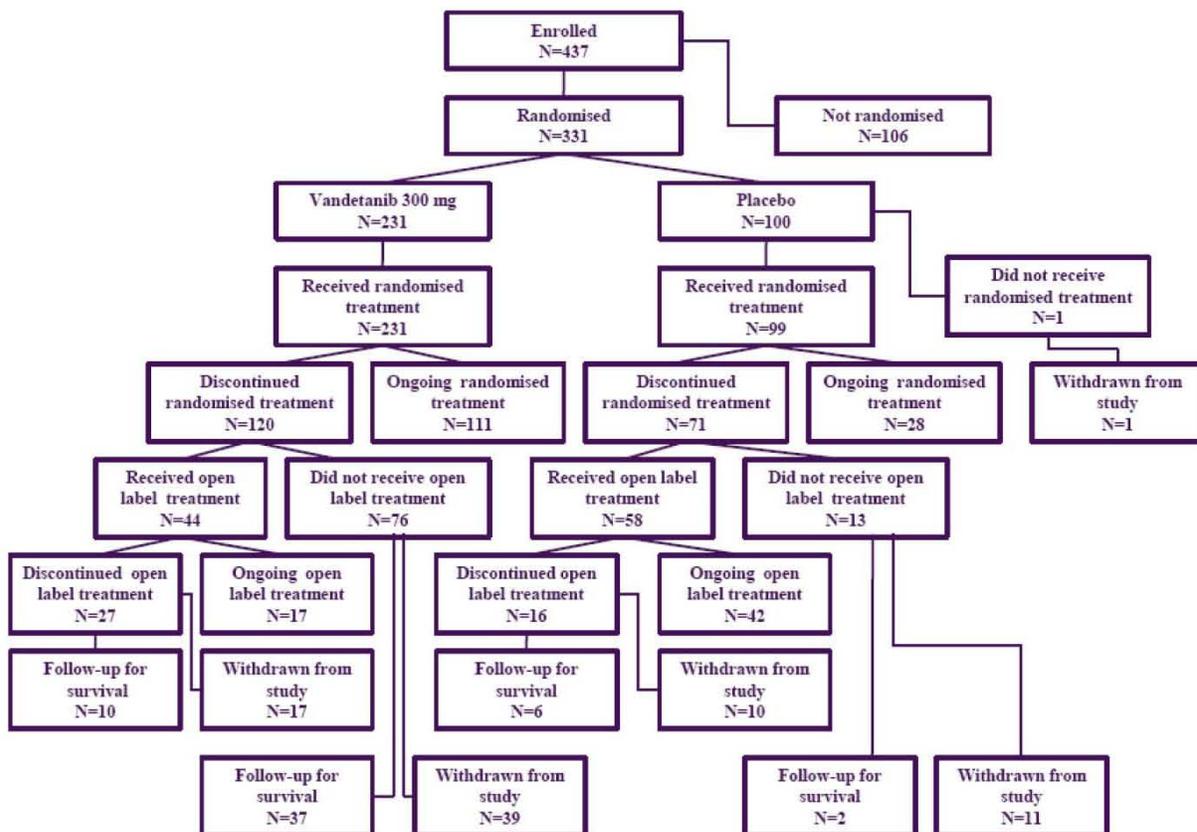
3.1.8. Sponsor's Results and FDA Statistical Reviewer's Findings/Comments

A total of 331 patients were randomized to receive either vandetanib (231 patients) or placebo (100 patients). Patients were recruited at 60 centers in 23 countries. The data cut-off date for this study was July 31, 2009.

3.1.8.1. Patient Disposition

The patient disposition is presented in Figure 2.

Figure 2: Patient Disposition



Source: Clinical study report submitted in the NDA.

3.1.8.2. Baseline Characteristics

The treatment arms were well balanced with respect to general demographic characteristics (gender, race and age) at baseline. The study population consisted of 57.4% male. Majority of the patients were Caucasian (95%). The mean and median age of patients at randomization was 51.5 and 51 years, respectively, with an overall age range of 18 to 84 years. Approximately 21% of patients were elderly. The study recruited patients from 23 countries. Approximately 22% patients were from US. A summary of demographic characteristics at baseline is presented in Table 3.

Important baseline characteristics are presented in Table 4. Approximately 64% patients enrolled in this study had a WHO PS of 0, 32% had WHO PS 1 and the rest 4% had WHO PS 2. Almost 90% patients had sporadic MTC. Median time from diagnosis to randomization was 6.1 years and this time difference was as high as 35.2 years for one patient. The median baseline sum of longest diameters by IRC was 11.8 cm. There was a higher percentage of patients with hereditary

MTC in vandetanib arm (12%) than in placebo arm (5%). There also was a higher percentage of patients with WHO performance status 0 in vandetanib arm (67%) than in placebo arm (58%). Time from diagnosis to randomization and baseline sum of longest diameters were similar between two arms.

Table 3: Demographic Characteristics: Gender, Race and Age at Randomization in FAS

		Vandetanib (N=231)	Placebo (N=100)	All (N=331)
Gender	Female	97 (41.99%)	44 (44%)	141 (42.60%)
	Male	134 (58.01%)	56 (56%)	190 (57.40%)
Race	Black	1 (0.43%)	1 (1%)	2 (0.60%)
	White	218 (94.37%)	97 (97%)	315 (95.17%)
	Oriental	8 (3.46%)	1 (1%)	9 (2.72%)
	Other	4 (1.73%)	1 (1%)	5 (1.51%)
Age Group in Years	<65	182 (78.79%)	80 (80%)	262 (79.15%)
	≥65	49 (21.21%)	20 (20%)	69 (20.85%)
Age in Years at Randomization	Mean, SD	50.72, 14.14	53.41, 12.02	51.53, 13.58
	Min, Max	18, 83	26, 84	18, 84
	Q1, Median, Q3	41, 50, 63	44.5, 52.5, 62	42, 51, 62
Geographic region	US	52 (22.51%)	21 (21%)	73 (22.05%)
	Non-US	179 (77.49%)	79 (79%)	258 (77.95%)

Table 4: Baseline Characteristics

		Vandetanib (N=231)	Placebo (N=100)	All (N=331)
Medullary Thyroid Cancer	Hereditary	28 (12.12%)	5 (5%)	33 (9.97%)
	Sporadic	203 (87.88%)	95 (95%)	298 (90.03%)
WHO Performance Status	0	154 (66.67%)	58 (58%)	212 (64.05%)
	1	67 (29.00%)	38 (38%)	105 (31.72%)
	2	10 (4.33%)	4 (4%)	14 (4.23%)
Time From Diagnosis to Randomization (Years)	N	230	100	330
	Mean, SD	8.0, 6.6	7.8, 7.0	7.9, 6.7
	Min, Max	0.1, 31.2	0.3, 35.2	0.1, 35.2
	Q1, Median, Q3	2.6, 6.3, 11.6	2.4, 5.6, 11.1	2.6, 6.1, 11.4
Baseline Sum of Longest Diameters by IRC (cm)	N	211	88	299
	Mean, SD	13.4, 8.8	14.5, 9.8	13.7, 9.1
	Min, Max	2.0, 45.1	2.0, 47.1	2.0, 47.1
	Q1, Median, Q3	6.3, 12.1, 18.5	6.2, 11.1, 21.9	6.3, 11.8, 19.9

3.1.8.3. Primary Efficacy Analysis

FDA’s primary efficacy analysis comparing progression-free survival (PFS) between vandetanib and placebo in FAS based on independent central review using log-rank test is presented in Table 5. The applicant’s primary PFS analysis is presented in Table 6. The corresponding Kaplan-Meier plots are given in Figure 3 and Figure 4, respectively. The PFS improvement in vandetanib arm over placebo arm was statistically significant (log-rank test, nominal two-sided p-value < 0.0001) in both FDA’s and Applicant’s analyses. The hazard ratios of vandetanib over placebo and 95% confidence intervals for PFS were 0.352 [95% CI: (0.235, 0.527)] and 0.46 [95% CI: (0.31, 0.69)] in FDA’s and applicant’s analyses, respectively.

Table 5: Analysis of PFS Based on Independent Review in FAS (FDA Analysis)

Treatment	Number of Patients	Number (%) Failed	Median in Months ¹ (95% CI)	Hazard Ratio ² Vandetanib/Placebo (95% CI)	P-value ³
Vandetanib	231	59 (25.54%)	NE (22.6, NE)	0.352 (0.235, 0.527)	<0.0001
Placebo	100	41 (41.00%)	16.4 (8.3, 19.7)		

¹: Kaplan-Meier estimate. ²: Based on Cox model. ³: Based on two-sided log-rank test. NE: Not estimable.

Figure 3: Kaplan-Meier Plot of PFS in FAS Based on Independent Review (FDA Analysis)

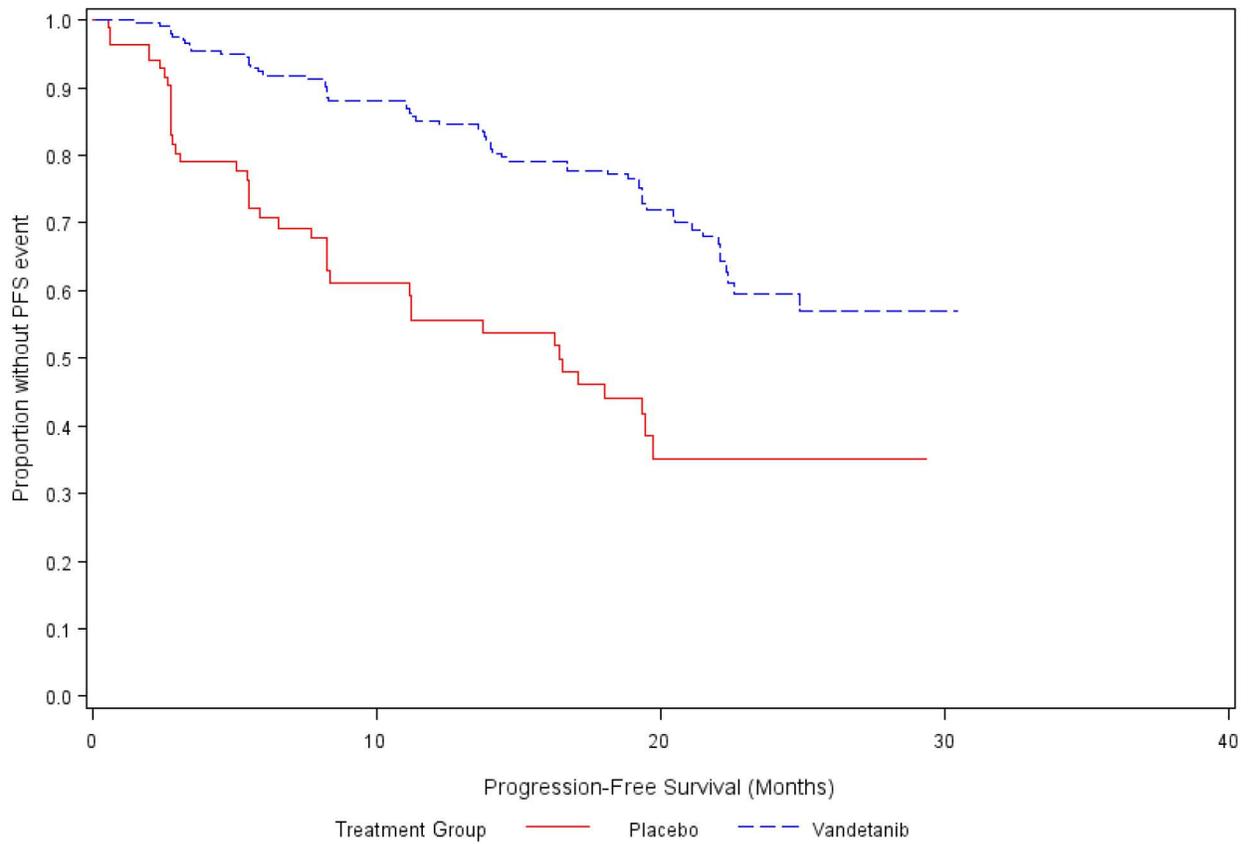
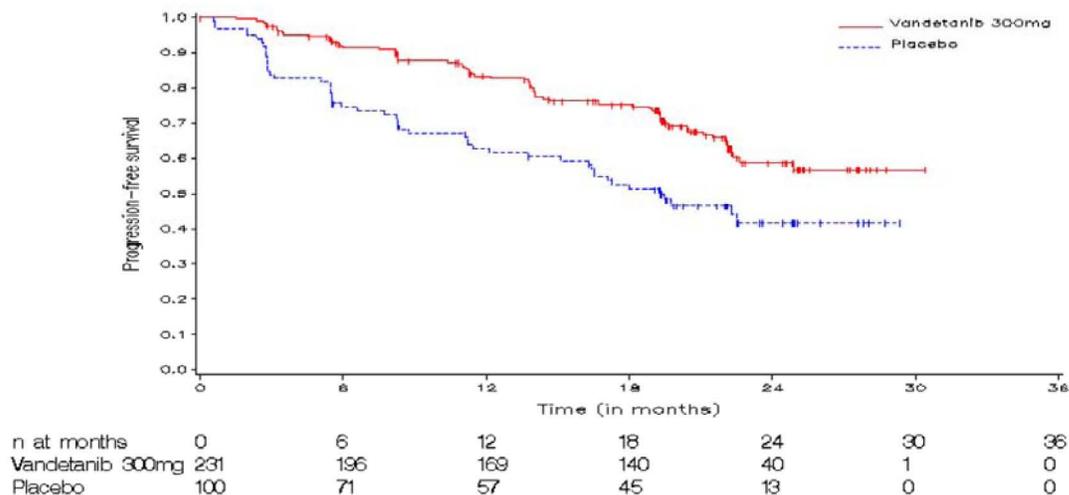


Table 6: Analysis of PFS Based on Independent Review in FAS (Applicant’s Analysis)

Randomised treatment	N	Number (%) of events	Treatment effect (vandetanib:placebo)		
			Hazard ratio	95% CI	2-sided p-value
Vandetanib 300mg	231	73 (31.6)	0.46	(0.31, 0.69)	0.0001
Placebo	100	51 (51.0)			

Source: Table 16 of Clinical Study Report

Figure 4: Kaplan-Meier Plot of PFS in FAS Based on Independent Review (Applicant’s Analysis)



Source: Figure 3 of the Clinical Study Report

3.1.8.4. Sensitivity Analysis of Primary Efficacy Endpoint

There was some imbalance in baseline WHO performance status (67% in vandetanib vs. 58% in placebo arm with WHO PS 0) and MTC type (12% in vandetanib vs. 58% in placebo arm with hereditary disease). Results from the analyses of PFS based on independent review adjusting for WHO performance status (0 vs. 1 and 2) and MTC type (hereditary vs. sporadic) using Cox proportional hazards models are presented in Table 7. In all of the models, the PFS hazard ratios and their confidence intervals were similar to that of the model with treatment as the only covariate.

Table 7: PFS Hazard Ratios of Vandetanib to Placebo Adjusted for Baseline WHO Performance Status and MTC Type (Based on Independent Review)

Covariates in Addition to Treatment in the Cox Model	PFS Hazard Ratio Vandetanib/Placebo (95% CI)
WHO Performance Status (0 vs. 1 and 2)	0.352 (0.235, 0.526)
MTC Type (hereditary vs. sporadic)	0.356 (0.237, 0.535)
WHO Performance Status and MTC Type	0.355 (0.236, 0.532)

FDA’s analysis of PFS based on investigator assessment (site read) is presented in Table 8. The applicant’s analysis of investigator assessed PFS is presented in Table 9: Analysis of PFS Based on Investigator’s Assessment in FAS (Applicant’s Analysis)Table 9. Additional sensitivity analyses have been presented in Appendix A.

Table 8: Analysis of PFS Based on Investigator’s Assessment in FAS (FDA Analysis)

Treatment	Number of Patients	Number (%) Failed	Median in Months ¹ (95% CI)	Hazard Ratio ² Vandetanib/ Placebo (95% CI)	P-value ³
Vandetanib	221	101 (45.70%)	22.3 (19.8, 27.6)	0.464 (0.338, 0.638)	<0.0001
Placebo	95	62 (65.26%)	8.3 (7.6, 13.5)		

¹: Kaplan-Meier estimate. ²: Based on Cox model. ³: Based on two-sided log-rank test.

Figure 5: Kaplan-Meier Plot of PFS Based on Investigator’s Assessment in FAS (FDA Analysis)

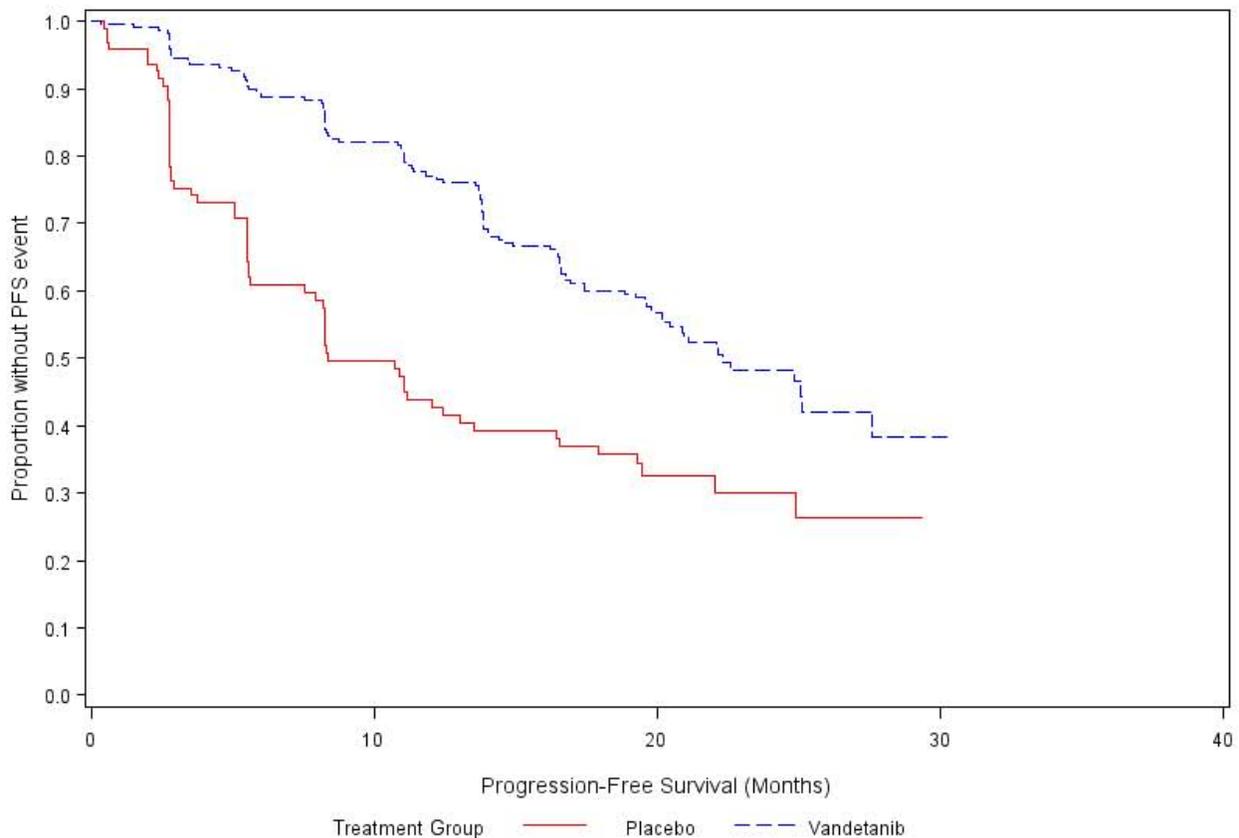


Table 9: Analysis of PFS Based on Investigator’s Assessment in FAS (Applicant’s Analysis)

Treatment	Number of Patients	Number (%) Failed	Hazard Ratio Vandetanib/ Placebo (95% CI)	P-value
Vandetanib	231	101 (43.7%)	0.40 (0.27, 0.58)	<0.0001
Placebo	100	62 (62.0%)		

Reviewer's Comment:

FDA's analysis of PFS based on investigator's assessment did not match with that reported in the Clinical Study Report. One reason for this discrepancy is that in the submitted dataset the date of progression or censoring based on investigator's assessment was missing for 15 subjects although the result reported in the Clinical Study Report did not reflect that. There may be additional unknown reasons as well.

3.1.8.5. Secondary Efficacy Analyses

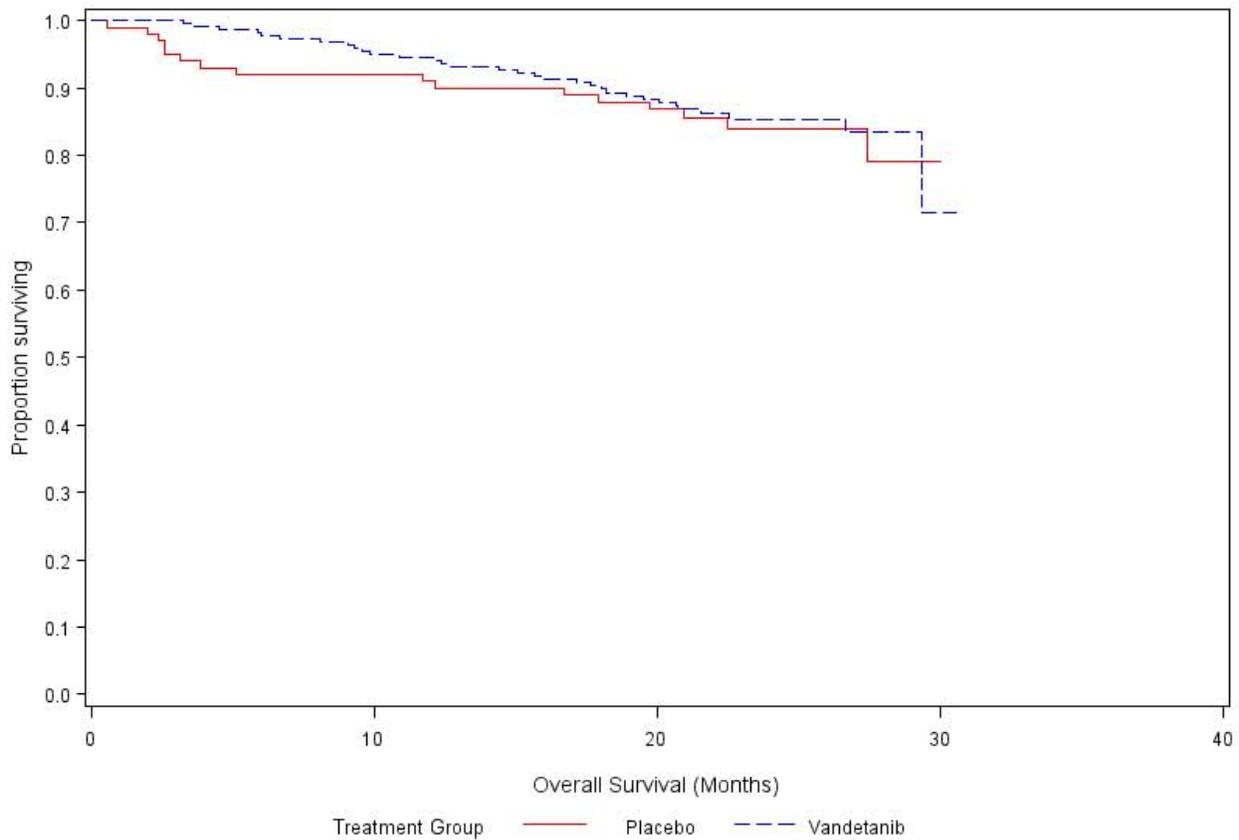
The analysis of secondary endpoint OS in FAS based on the data with cut-off dates July 31, 2009, which is considered as an interim analysis of OS, is presented in Table 10. The corresponding Kaplan-Meier plots are given in Figure 6. There were only 48 deaths as of July 31, 2009 cut-off date. The final OS analysis will be conducted after 50% of the enrolled patients (166) die. Although the study was not powered for OS, Lan-DeMets alpha spending function has been used to adjust for multiple OS analysis. Vandetanib did not show statistically significant improvement in OS over placebo in FAS (log-rank test, nominal two-sided p-value 0.7131). The hazard ratio for OS was 0.893 [95% CI: (0.490, 1.629)]. According to the Lan-DeMets alpha spending function for O'Brien-Fleming boundary, the alpha for the interim OS analysis would be 0.00007. A 99.993% confidence interval for OS hazard ratio is (0.271, 2.944).

Table 10: Analysis of OS in FAS (July 31, 2009 Cut-off)

Treatment	Number of Patients	Number (%) Failed	Median in Months¹ (95% CI)	Hazard Ratio² Vandetanib/ Placebo (95% CI)	P-value³
Vandetanib	231	32 (13.85%)	NE (29.3, NE)	0.893	0.7131
Placebo	100	16 (16.00%)	NE (NE, NE)	(0.490, 1.629)	

¹: Kaplan-Meier estimate. ²: Based on Cox model. ³: Based on two-sided log-rank test. NE: Not estimable.

Figure 6: Kaplan-Meier Plot of OS in FAS (May 17, 2008 Cut-off)



The tabulation of response rates based on independent review for each of FDA’s analysis and applicant’s analysis are presented in Table 11. The response rate in vandetanib arm was approximately 45% in both analyses. The response rate for placebo arm was 13% in applicant’s analysis and 1% in FDA’s analysis.

Table 11: Response Rate Based on Independent Review

		Randomization Group	
		Vandetanib (N=231)	Placebo (N=100)
FDA’s Analysis	Response Rate	44.6%	1%
	(95% CI)	(38.1%, 51.2%)	(0%, 5.4%)
	Complete Response	0	0
Applicant’s Analysis	Partial Response	103 (44.6%)	1 (1%)
	Response Rate	45.0%	13.0%
	Complete Response	0	0
	Partial Response	45.0%	13.0%

Reviewer's Comments:

1. There was no adjustment in type I error rate for multiple secondary endpoints. Therefore, p-values for the secondary endpoints are not interpretable.
2. According to the Lan-DeMets alpha spending function for O'Brien-Fleming boundary, alpha spent at the interim OS analysis should be 0.00007 (calculated using East Version 5). The applicant noted this number as 0.0002. A 99.98% confidence interval for OS hazard ratio is (0.286, 2.793).
3. The response rates calculated by FDA differ from those calculated by the applicant because FDA's calculation does not include responses that occurred after discontinuation of study drug and crossover to open-label vandetanib whereas the applicant included those responses in the calculation of response rate.

3.2. Evaluation of Safety

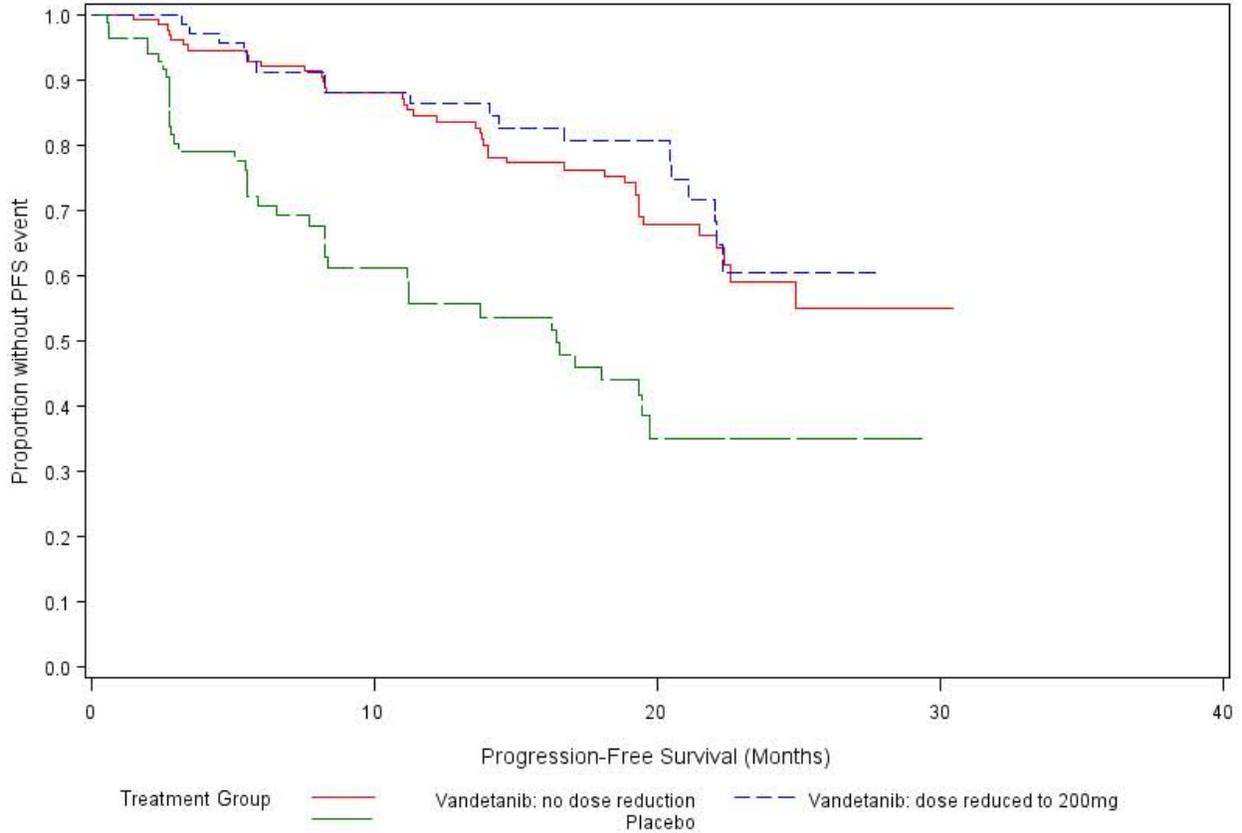
Following is a brief summary of safety results based on the studies submitted in the application. For a detailed safety evaluation, please refer to the clinical review of this application.

Adverse events of particular concern included interstitial lung disease, Stevens- Johnson Syndrome, torsades de pointe, and cerebrovascular events. There were 2 cases of torsades noted in the vandetanib safety database. This is of significant concern given the relatively low numbers of patients treated. The most common ($\geq 5\%$) grade 3-4 adverse reactions in the vandetanib-treated patients were diarrhea, QTc prolongation, hypertension, and fatigue.

In Study 58, deaths not directly attributed to disease progression and occurring within 30 days of the last dose of study drug were reported in 7 (3%) vandetanib-treated patients and 1 (1%) placebo treated patient. The seven deaths on the vandetanib arm were secondary to staphylococcal sepsis, aspiration pneumonia, respiratory arrest, pneumonia, and in one patient due to both acute cardiac failure and arrhythmia. In the Integrated Summary of Safety (ISS), deaths not directly attributed to disease progression were reported in 60 (4%) vandetanib-treated patients with sudden death, cardiac failure, dyspnea, pulmonary hemorrhage, pneumonia, pulmonary embolism, respiratory failure, and aspiration pneumonia as the causes of death in > 3 patients.

In Study 58, dose reduction was reported in 49.4% of vandetanib-treated patients and 15.2% placebo-treated patients. An exploratory Kaplan-Meier plot showing the estimated survival function of PFS in patients treated with vandetanib 300 mg without dose reduction, patients treated with vandetanib 300 mg and later reduced to 200 mg dose, and patients treated with placebo is presented in Figure 7.

Figure 7: Kaplan-Meier Plot of PFS in Vandetanib Patients without Dose Reduction, Vandetanib Patients with Dose Reduction and Placebo Patients



Reviewer's Comments:

1. Vandetanib appears to have severe toxicity in patients. Some of the serious adverse reactions like QTc prolongation appear to have been reduced with a lower dose.
2. There did not seem to be any loss of PFS effect with dose reduction.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1. Gender, Race and Age

Efficacy by gender was analyzed by exploratory analysis of PFS and is presented in Table 12. Efficacy by age group (<65 years, ≥65 years) was also analyzed by exploratory analysis of PFS and is presented in Table 13. More than 95% patients were white and the next largest group was black which consisted of less than 3% patient. Therefore, no exploratory PFS analysis by race is conducted. All PFS analyses in this section are based on independent review.

Table 12: Exploratory Analysis of PFS by Gender

Gender	Treatment	Number of Patients	Number (%) Failed	Median in Months ¹ (95% CI)	Hazard Ratio ² Vandetanib/ Placebo (95% CI)
Female	Vandetanib	97	21 (21.65%)	NE (22.3, NE)	0.316 (0.158, 0.631)
	Placebo	44	14 (31.82%)	19.4 (11.2, NE)	
Male	Vandetanib	134	38 (28.36%)	NE (22.3, NE)	0.367 (0.223, 0.605)
	Placebo	56	27 (48.21%)	11.1 (5.9, 17.1)	

¹: Kaplan-Meier estimate. ²: Based on Cox model. NE: Not estimable.

Table 13: Exploratory Analysis of PFS by Age Group

Age Group	Treatment	Number of Patients	Number (%) Failed	Median in Months ¹ (95% CI)	Hazard Ratio ² Vandetanib/ Placebo (95% CI)
<65 Years	Vandetanib	182	46 (25.27%)	NE (24.9, NE)	0.398 (0.249, 0.637)
	Placebo	80	29 (36.25%)	19.3 (11.2, NE)	
≥ 65 Years	Vandetanib	49	13 (26.53%)	22.3 (19.4, NE)	0.211 (0.092, 0.482)
	Placebo	20	12 (60.00%)	5.5 (2.8, 13.8)	

¹: Kaplan-Meier estimate. ²: Based on Cox model. NE: Not estimable.

Reviewer's Comment:

Vandetanib is effective across all age group and gender with respect to PFS but it appears to be more effective in patients ≥ 65 years of age than in patients < 65 years of age.

4.2. Other Special/Subgroup Populations

Exploratory analysis of PFS by geographic region (US and Non-US), MTC type, calcitonin doubling time, symptomatic versus asymptomatic, time from original diagnosis to randomization, time from last documented progression to randomization and baseline sum of

longest diameters are presented in Table 14, Table 15, Table 16, Table 17, Table 18, Table 19 and Table 20, respectively. Asymptomatic patients were defined by FDA as those who had baseline average stool frequency <4/day, baseline average pain = 0 and baseline WHO PS = 0. All PFS analyses are based on independent review.

Table 14: Exploratory Analysis of PFS by Geographic Region

Geographic Region	Treatment	Number of Patients	Number (%) Failed	Median in Months¹ (95% CI)	Hazard Ratio² Vandetanib/ Placebo (95% CI)
US	Vandetanib	52	14 (26.92%)	22.6 (20.5, NE)	0.460 (0.192, 1.107)
	Placebo	21	8 (38.10%)	19.4 (2.8, NE)	
Non-US	Vandetanib	179	45 (25.14%)	NE (24.9, NE)	0.323 (0.205, 0.509)
	Placebo	79	33 (41.77%)	16.4 (8.3, 19.7)	

¹: Kaplan-Meier estimate. ²: Based on Cox model. NE: Not estimable.

Table 15: Exploratory Analysis of PFS by MTC Type

MTC Type	Treatment	Number of Patients	Number (%) Failed	Median in Months¹ (95% CI)	Hazard Ratio² Vandetanib/ Placebo (95% CI)
Hereditary	Vandetanib	28	6 (21.43%)	NE (16.7, NE)	0.237 (0.047, 1.190)
	Placebo	5	2 (40.00%)	7.7 (2.6, NE)	
Sporadic	Vandetanib	203	53 (26.11%)	NE (22.6, NE)	0.365 (0.240, 0.555)
	Placebo	95	39 (41.05%)	16.5 (8.3, 19.7)	

¹: Kaplan-Meier estimate. ²: Based on Cox model. NE: Not estimable.

Table 16: Exploratory Analysis of PFS by Calcitonin Doubling Time

Calcitonin Doubling Time	Treatment	Number of Patients	Number (%) Failed	Median in Months¹ (95% CI)	Hazard Ratio² Vandetanib/ Placebo (95% CI)
< 6 Months	Vandetanib	91	23 (25.27%)	NE (22.3, NE)	0.418 (0.202, 0.862)
	Placebo	31	11 (35.48%)	19.3 (5.5, NE)	
≥ 6 Months	Vandetanib	116	26 (22.41%)	NE (22.3, NE)	0.301 (0.173, 0.525)
	Placebo	58	25 (43.10%)	16.4 (8.3, 19.7)	
< 24 Months	Vandetanib	165	41 (24.85%)	NE (22.6, NE)	0.327 (0.199, 0.537)
	Placebo	60	26 (43.33%)	11.1 (6.6, NE)	
≥ 24 Months	Vandetanib	42	8 (19.05%)	NE (21.1, NE)	0.307 (0.120, 0.788)
	Placebo	29	10 (34.48%)	17.1 (11.2, NE)	

¹: Kaplan-Meier estimate. ²: Based on Cox model. NE: Not estimable.

Table 17: Exploratory Analysis of PFS by Baseline Symptom

Asymptomatic vs. Any Symptoms	Treatment	Number of Patients	Number (%) Failed	Median in Months ¹ (95% CI)	Hazard Ratio ² Vandetanib/ Placebo (95% CI)
Any Symptoms	Vandetanib	129	38 (29.46%)	24.9 (22.1, NE)	0.314 (0.188, 0.524)
	Placebo	58	25 (43.10%)	8.3 (5.5, 19.3)	
Asymptomatic	Vandetanib	102	21 (20.59%)	NE (NE, NE)	0.383 (0.198, 0.741)
	Placebo	42	16 (38.10%)	19.7 (11.2, NE)	

¹: Kaplan-Meier estimate. ²: Based on Cox model. NE: Not estimable.

Table 18: Exploratory Analysis of PFS by Time from Original Diagnosis to Randomization

Time From Original Diagnosis to Randomization	Treatment	Number of Patients	Number (%) Failed	Median in Months ¹ (95% CI)	Hazard Ratio ² Vandetanib/ Placebo (95% CI)
< 6 Years	Vandetanib	108	34 (31.48%)	22.3 (22.0, NE)	0.368 (0.216, 0.627)
	Placebo	54	24 (44.44%)	16.4 (6.6, 19.4)	
≥ 6 Years	Vandetanib	122	25 (20.49%)	NE (NE, NE)	0.340 (0.183, 0.633)
	Placebo	46	17 (36.96%)	16.5 (11.1, NE)	

¹: Kaplan-Meier estimate. ²: Based on Cox model. NE: Not estimable.

Table 19: Exploratory Analysis of PFS by Time from Last Documented Progression to Randomization

Time from Last Documented Progression to Randomization	Treatment	Number of Patients	Number (%) Failed	Median in Months ¹ (95% CI)	Hazard Ratio ² Vandetanib/ Placebo (95% CI)
< 2 Months	Vandetanib	110	23 (20.91%)	NE (NE, NE)	0.329 (0.180, 0.602)
	Placebo	51	20 (39.22%)	16.5 (8.2, NE)	
≥ 2 Months	Vandetanib	118	36 (30.51%)	24.9 (22.1, NE)	0.329 (0.187, 0.578)
	Placebo	48	21 (43.75%)	16.4 (7.7, 19.4)	
< 6 Months	Vandetanib	158	41 (25.95%)	NE (22.6, NE)	0.407 (0.250, 0.665)
	Placebo	73	27 (36.99%)	16.5 (8.3, NE)	
≥ 6 Months	Vandetanib	70	18 (25.71%)	24.9 (20.5, NE)	0.245 (0.118, 0.506)
	Placebo	26	14 (53.85%)	16.4 (5.5, 19.4)	

¹: Kaplan-Meier estimate. ²: Based on Cox model. NE: Not estimable.

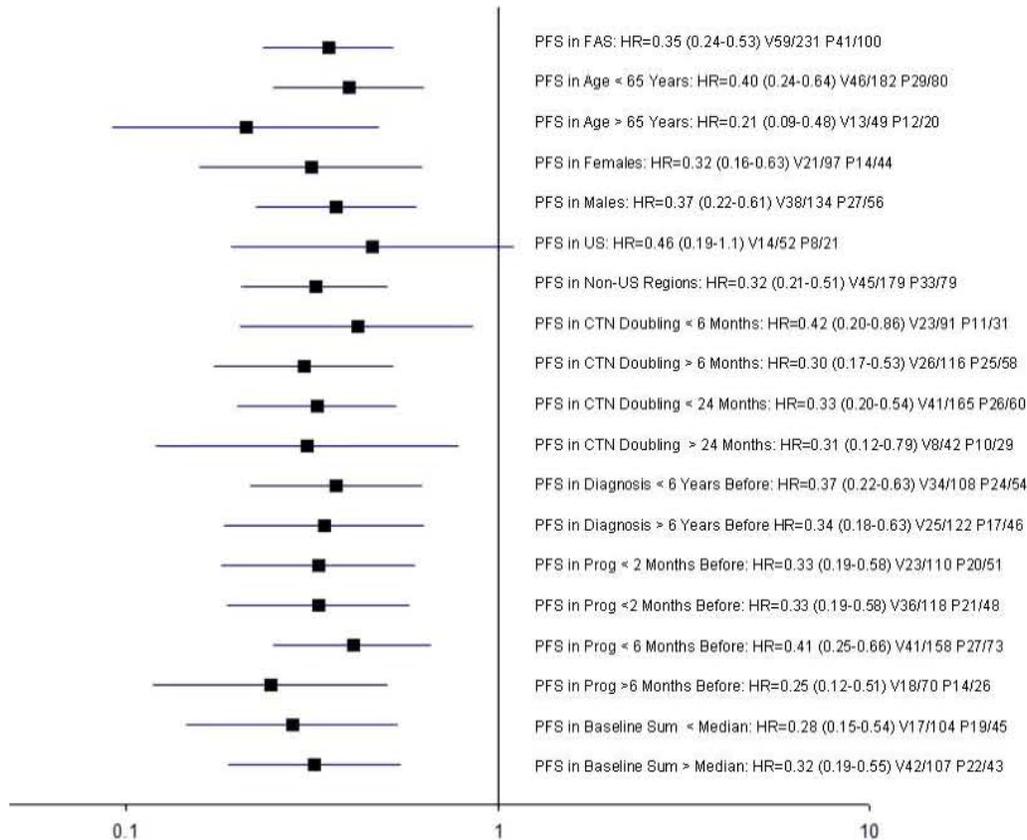
Table 20: Exploratory Analysis of PFS by Baseline Sum of Longest Diameters

Baseline Sum of Longest Diameters (SLD)	Treatment	Number of Patients	Number (%) Failed	Median in Months ¹ (95% CI)	Hazard Ratio ² Vandetanib/ Placebo (95% CI)
<Median SLD for All Patients	Vandetanib	104	17 (16.35%)	NE (NE, NE)	0.280
	Placebo	45	19 (42.22%)	19.7 (11.2, NE)	(0.145, 0.541)
≥ Median SLD for All Patients	Vandetanib	107	42 (39.25%)	22.3 (20.4, NE)	0.320
	Placebo	43	22 (51.16%)	11.1 (5.1, 16.5)	(0.188, 0.547)

¹: Kaplan-Meier estimate. ²: Based on Cox model. NE: Not estimable.

Figure 8 presents a forest plot of hazard ratios and 95% confidence intervals for PFS by demographic and baseline characteristics. It should be noted that the horizontal scale in the forest plot is a logarithmic scale.

Figure 8: Forest Plot of Hazard Ratios and 95% Confidence Intervals for PFS by Demographic and Baseline Characteristics



Reviewer's Comments:

1. All the subgroup analyses presented in this section are considered exploratory or hypothesis generating and no formal inference may be drawn.
2. The PFS improvement in the vandetanib arm is consistent across various subgroups.

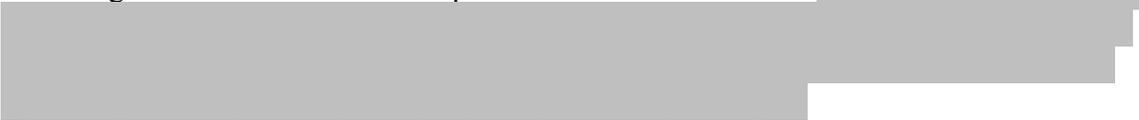
5. SUMMARY AND CONCLUSIONS

This application is based on one Phase III trial (Study D4200C00058 or Study 58) and two uncontrolled single-arm Phase II studies (D4200C00008 and D4200C00068). This review is primarily based on the Phase III study. Study 58 was a multicenter, international, randomized, double-blind, placebo-controlled, Phase III study to evaluate the efficacy of vandetanib compared to placebo in patients with unresectable locally advanced or metastatic MTC. 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. First patient was enrolled on November 23, 2006. The data cut-off date was July 31, 2009. A total of 331 patients were randomized, 231 to vandetanib and 100 to placebo. Randomized patients were enrolled at 60 centers in 23 countries. There were 73 patients from US. Only 0.6% of the patients were Black. The primary efficacy endpoint was progression-free survival (PFS) as assessed by the independent central radiology review. The secondary efficacy endpoints were overall response rate (ORR) as determined by central review, disease control rate (DCR), duration of response, overall survival (OS) and biochemical response [measured by calcitonin (CTN) and carcinoembryonic antigen (CEA)].

The vandetanib arm showed statistically significant improvement over placebo with respect to PFS as determined by the independent central review in the full analysis set (FAS) [hazard ratio=0.352, 95% confidence interval: (0.235, 0.527), log-rank test, two-sided p-value<0.0001]. Vandetanib arm did not show improvement over placebo with respect to OS assessment in the FAS [hazard ratio=0.893, 95% confidence interval: (0.490, 1.629), 99.993% confidence interval: (0.271, 2.944), log-rank test, two-sided p-value=0.7131]. However, no adjustment to the level of significance was made for multiple secondary endpoints. Therefore p-values are not interpretable for the secondary endpoints. The overall response rate was 44.6% in the vandetanib arm and 1% in the placebo arm based on the responses assessed by the independent review.

5.1. Statistical Issues and Collective Evidence

1. The study was designed to have a 2:1 randomization for vandetanib to placebo. However, actually 231 patients were randomized to vandetanib and 100 patients to placebo. Thus the randomization ratio actually was greater than 2:1. In this study, randomization was stratified by site in blocks of 3. If a site did not use all the randomization numbers in a given block, it would be expected that the ratio of patients assigned to the vandetanib group relative to those assigned to the placebo group would not be equal to 2. The applicant explained that in this study, these incomplete blocks, by random chance, had a ratio that was greater than 2 more often than they had a ratio that was less than 2 and consequently, the ratio overall was greater than 2.
2. The censoring rules of FDA and the applicant were different for primary PFS analysis based on IRC review. Following is a list of censoring rules that are different for FDA's and the applicant's analyses.
 - PFS for the patients with investigator-determined, but without IRC determined progression have been censored at their last RECIST assessment prior to discontinuation of study drug for FDA's analysis. The applicant's analysis of PFS

- used the IRC assessment beyond investigator assessed progression and study drug discontinuation in these cases. While the sponsor's analysis may address informative censoring and conform to ITT analysis, this analysis includes effect of non-protocol treatment beyond investigator determined progression.
- For the patients who received radiation during the study period, FDA's analysis censored PFS at the last RECIST assessment prior to radiation therapy. The Applicant's analysis did not censor these patients for radiation therapy.
 - PFS for the patients who had no baseline measurable disease by the IRC has been censored at Day 1 in FDA's analysis. The applicant's analysis did not censor them at Day 1.
3. FDA's analysis of PFS based on investigator's assessment did not match with that reported in the Clinical Study Report. One reason for this discrepancy is that in the submitted dataset the date of progression or censoring based on investigator's assessment was missing for 15 subjects although the result reported in the Clinical Study Report did not reflect that. There may be additional unknown reasons as well.
 4. FDA's calculation of response rate does not include responses that occurred after discontinuation of study drug and crossover to open-label vandetanib whereas the applicant included those responses in the calculation of response rate.
 5. The validity of the patient-reported outcome instruments employed is questionable. Moreover, the quality of life endpoints are not interpretable if blinding is not properly maintained. It is not clear if the blinding is broken due to difference in adverse events. Therefore, this review considers those endpoints exploratory.
 6. Based on the planned number of events, the study had actually 90% power to detect a doubling in median PFS at 2-sided 5% level of significance. However, the application did not precisely specify the power; power was stated only to be greater than 80%.
 7. The study was originally planned to have two co-primary analyses to compare PFS between the two treatment arms in all patients who received at least one dose of vandetanib/placebo and in patients who had RET mutation and received at least one dose of vandetanib/placebo. The required number of events and the related number of patients were calculated based on the analysis of PFS for all patients. The protocol specified that 90 events would be required to detect doubling of PFS in all patients at a 2-sided 2.5% level of significance with 80% power and this would provide 80% power at 2-sided 2.5% level of significance to detect a hazard ratio of 0.32 in the patients with RET mutation assuming that there would be 50% patients with RET mutation. (b) (4)

 8. The applicant derived the hazard ratio estimate and its confidence interval based on the results from the log-rank test whereas FDA used the Cox proportional hazards model to derive these numbers.
 9. Type I error rate has not been adjusted for analysis of multiple secondary endpoints. Therefore, p-values for the secondary endpoints are not interpretable.
 10. The PFS improvement in the vandetanib arm is consistent across various subgroups. All the subgroup analyses presented are considered exploratory or hypothesis generating and no formal inference may be drawn.

5.2. Conclusions and Recommendations

The applicant has submitted results from one multicenter, phase III, randomized, double-blind, placebo-controlled clinical trial (Study D4200C00058) comparing vandetanib [REDACTED]^{(b) (4)} to placebo in patients with unresectable locally advanced or metastatic medullary thyroid cancer (MTC). The vandetanib arm showed statistically significant improvement over placebo in progression-free survival (PFS) as assessed by independent central radiology review in all randomized patients. However, the vandetanib arm did not show statistically significant improvement with respect to overall survival (OS) at the time of the final PFS analysis. Therefore, the clinical benefit of vandetanib in MTC is not clear particularly since the natural history of this disease is long with an estimated 10-year survival rate of 40%. Moreover, the overall safety database that also includes studies in other indications, showed toxicities and adverse reactions including large amount of QT/QTc prolongation, sudden deaths, Stevens-Johnson syndrome and interstitial lung disease and increased incidence of rare serious adverse reactions like torsade de pointe. The application was discussed at the Oncologic Drug Advisory Committee meeting on December 2, 2010. The committee voted unanimously to require the applicant to evaluate additional doses as a post-marketing requirement to determine the optimal dose. The judgment of meaningfulness of the improvement in PFS in light of the toxicities and lack of significant improvement in OS is deferred to the clinical review team.

APPENDIX A: ADDITIONAL EXPLORATORY SENSITIVITY ANALYSES OF PFS

Several sensitivity analyses of PFS have been conducted by the FDA reviewer to verify the robustness of the PFS results. The p-values reported are nominal values and are not adjusted for multiple analyses. Three of them are presented below.

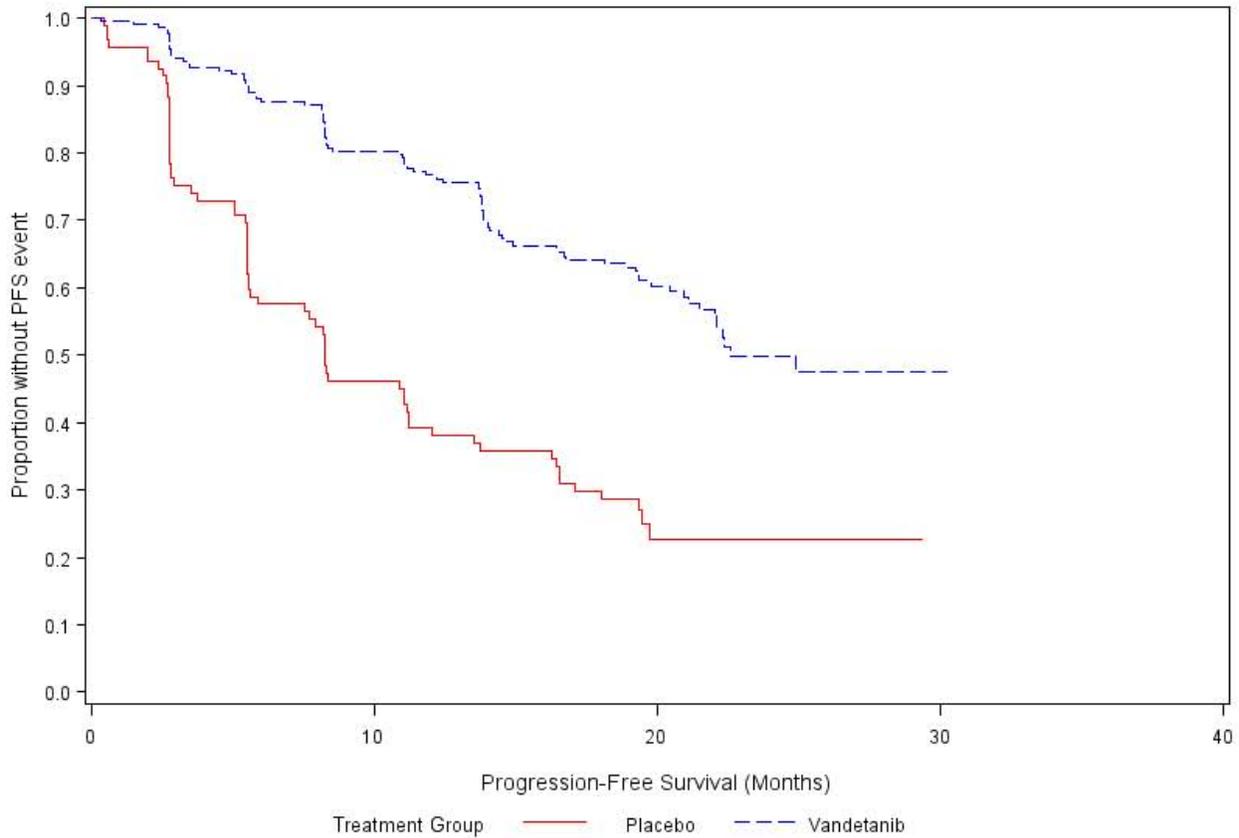
Sensitivity Analysis 1: In this sensitivity analysis, the earlier of investigator determined and independent review determined PFS event/censoring is used for each patient. The results are presented in Table 21 and the Kaplan-Meier estimates are presented in Figure 9.

Table 21: Sensitivity Analysis of PFS Based on Earlier of Investigator and Independent Determination

Treatment	Number of Patients	Number (%) Failed	Median in Months ¹ (95% CI)	Hazard Ratio ² Vandetanib/ Placebo (95% CI)	P-value ³
Vandetanib	221	90 (40.72%)	22.6 (21.5, NE)	0.361 (0.262, 0.497)	<0.0001
Placebo	95	67 (70.53%)	8.3 (5.6, 11.2)		

¹: Kaplan-Meier estimate. ²: Based on Cox model. ³: Based on two-sided log-rank test. NE: Not estimable.

Figure 9: Kaplan-Meier Plot of PFS Based on Earlier of Investigator and Independent Determination



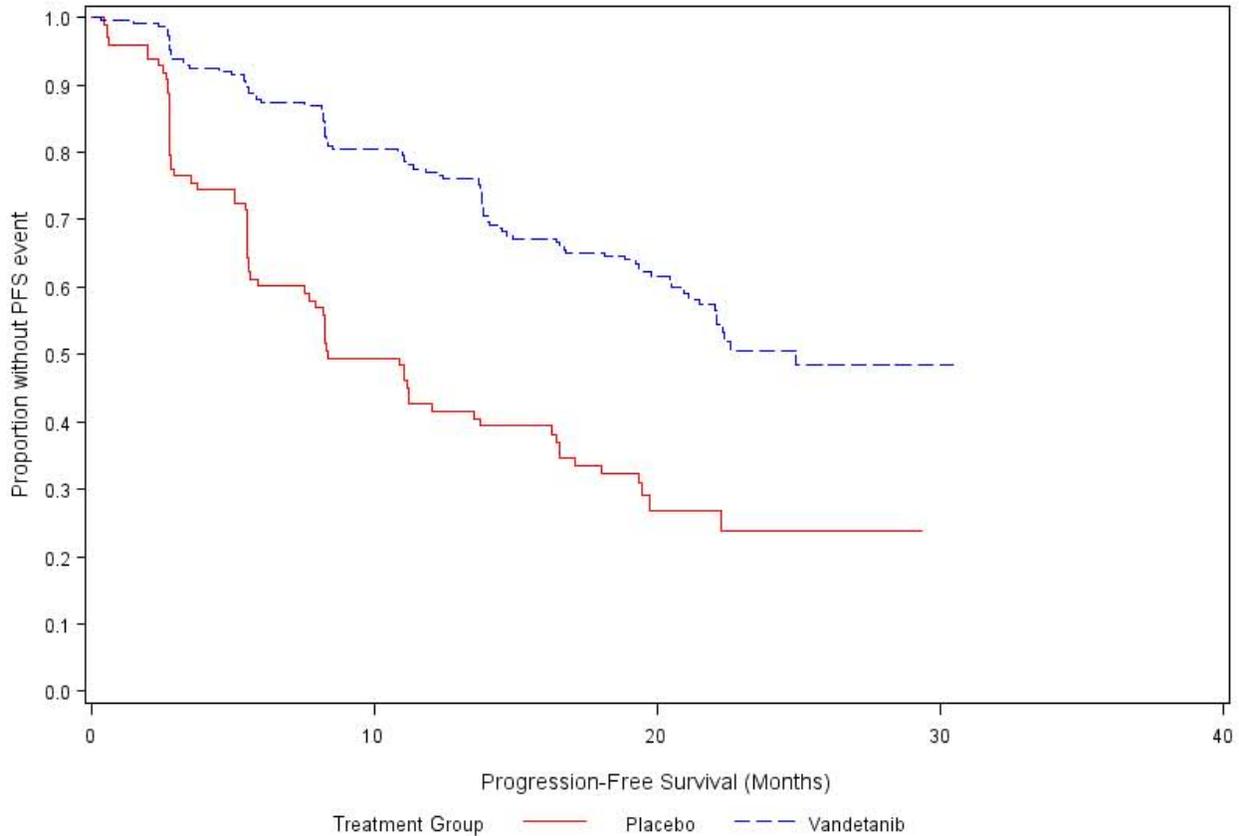
Sensitivity Analysis 2: This sensitivity analysis is mainly based on independent review with the exception when investigator assessed progression date is earlier than the event or censoring date by independent review, in which case investigator assessed date and event are used. The results are presented in Table 22 and the Kaplan-Meier estimates are presented in Figure 10.

Table 22: Sensitivity Analysis of PFS Based on Independent review with Modification if Investigator Determined Earlier Event

Treatment	Number of Patients	Number (%) Failed	Median in Months ¹ (95% CI)	Hazard Ratio ² Vandetanib/ Placebo (95% CI)	P-value ³
Vandetanib	231	92 (39.83%)	24.9 (21.5, NE)	0.387	<0.0001
Placebo	100	68 (68.00%)	8.3 (5.9, 13.8)	(0.282, 0.531)	

¹: Kaplan-Meier estimate. ²: Based on Cox model. ³: Based on two-sided log-rank test. NE: Not estimable.

Figure 10: Kaplan-Meier Plot of PFS Based on Independent review with Modification if Investigator Determined Earlier Event



Sensitivity Analysis 3: In this sensitivity analysis, following rules were used.

- Patients in the vandetanib with investigator-determined, but without IRC-determined progression were treated as if they had progressed
- Patients in the placebo arm with investigator-determined, but without IRC-determined progression were censored at their last RECIST assessment prior to discontinuation of randomized therapy
- The RECIST criteria was applied without modifications
- Patients who received additional therapies were considered to have progressed
- All patients who died without prior documented progression were considered to have progressed 1 day after their last RECIST assessment.

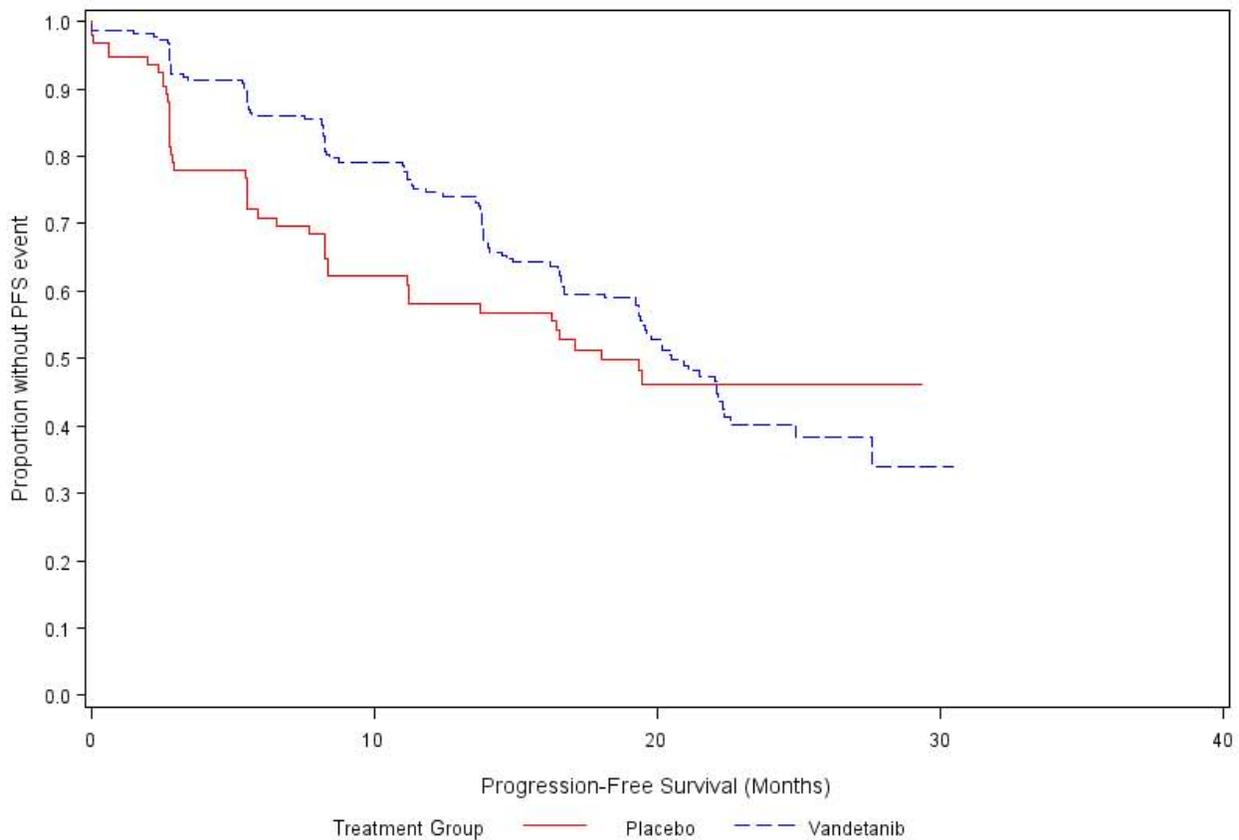
The results are presented in Table 23 and the Kaplan-Meier estimates are presented in Figure 11.

Table 23: Sensitivity Analysis of PFS with Multiple Modifications

Treatment	Number of Patients	Number (%) Failed	Median in Months ¹ (95% CI)	Hazard Ratio ² Vandetanib/ Placebo (95% CI)	P-value ³
Vandetanib	231	109 (47.19%)	20.5 (19.3, 22.3)	0.828 (0.583, 1.176)	0.2905
Placebo	100	44 (44.00%)	18.0 (11.1, NE)		

¹: Kaplan-Meier estimate. ²: Based on Cox model. ³: Based on two-sided log-rank test. NE: Not estimable.

Figure 11: Kaplan-Meier Plot of PFS with Multiple Modifications



Results from the first two sensitivity analyses are similar to that of the primary analysis of PFS. However, the third sensitivity analysis results are much different with two arms not showing a significant difference in spite of having similar number of events as in the other sensitivity analysis. The third analysis creates a worst case scenario and not adapted in practice.

SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer: Somesh Chattopadhyay, Ph.D.
Date: December 15, 2010

Concurring Reviewer(s): Shenghui Tang, Ph.D., Team Leader
Rajeshwari Sridhara, Ph.D., Director

Statistical Team Leader: Shenghui Tang, Ph.D.

Biometrics Division Director: Rajeshwari Sridhara, Ph.D.

cc:

HFD-150/Ms. Lisa Skarupa
HFD-150/Dr. Geoffrey Kim
HFD-150/Dr. Katherine Delorenzo
HFD-150/Dr. Virginia Maher
HFD-711/Dr. Somesh Chattopadhyay
HFD-711/Dr. Shenghui Tang
HFD-711/Dr. Rajeshwari Sridhara
HFD-700/Ms. Lilian Patrician

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/s/

SOMESH CHATTOPADHYAY
12/15/2010

SHENGHUI TANG
12/16/2010

RAJESHWARI SRIDHARA
12/16/2010

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 22405

**Applicant: AstraZeneca (iPR
Pharmaceuticals)**

Stamp Date: July 7, 2010

**Drug Name: Zictifa
(vandetanib)**

NDA/BLA Type: Original

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? ___ YES ___

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Somesh Chattopadhyay, Ph. D.	8/20/2010
Reviewing Statistician	Date
Shenghui Tang, Ph.D.	8/20/2010
Supervisor/Team Leader	Date

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/

SOMESH CHATTOPADHYAY
08/23/2010

SHENGHUI TANG
08/23/2010