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APPLICATION NUMBER:

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MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	22405
Priority or Standard	Priority
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Division / Office	DDOP/OODP
Reviewer Name(s)	Geoffrey Kim (efficacy) Katherine DeLorenzo (safety)
Review Completion Date	March 24, 2011
Established Name	Vandetinib/ ZD6474
Therapeutic Class	Tyrosine Kinase Inhibitor
Applicant	Astra-Zeneca
Formulation(s)	oral
Dosing Regimen	300mg/ daily
Indication(s)	Advanced medullary thyroid carcinoma
Intended Population(s)	Patients with symptomatic or progressive medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease.

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Approval

1.2 Risk Benefit Assessment

The recommendation for approval is based on the single, randomized clinical trial in which vandetanib showed a statistically significant progression free survival advantage compared to placebo in patients with locally advanced or metastatic medullary thyroid cancer (MTC).

The single clinical trial enrolled 331 patients with locally advanced or metastatic MTC. The hazard ratio was 0.35 (95% CI 0.24-0.53); p<0.0001, favoring vandetanib. The median progression free survival (PFS) for vandetanib was not yet reached. There were deaths due to toxicity observed on the vandetanib arm in the randomized trial as well as the cumulative clinical experience with vandetanib. Fifty-five percent (55%) of the patients on the vandetanib arm experienced grade 3 or 4 adverse events. Patients receiving vandetanib experienced a mean prolongation of their QT interval of 35 ms, and sudden death and torsades des pointes have been observed with vandetanib. These risks are outweighed by the marked improvement in PFS. However, a Risk Evaluation and Mitigation Strategy (REMS) will be used to decrease the risk of vandetanib.

MTC, even in the metastatic setting, has a relatively long survival time. Due to the toxicity profile of vandetanib, the application was presented at the December 2, 2010 Oncologic Drugs Advisory Committee. The members of the committee were asked to discuss whether the indication should be limited to patients with progressive, symptomatic medullary thyroid cancer and to comment on whether there are any other subgroups that may be appropriate for treatment with vandetanib in light of the risk-benefit profile. All of the committee members agreed that treatment is not indicated in patients with a low burden or asymptomatic disease. The majority of the committee members agreed with modifying the indication to those with progressive, symptomatic MTC. The proposed patient population has no treatment options which offer a progression free survival prolongation and the robust results demonstrated by vandetanib would provide a new treatment option for these patients.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

On January 21, 2011, FDA formally informed Astra-Zeneca that a REMS is necessary to ensure that the benefits of vandetanib outweigh the risks of QT prolongation and torsades de pointe.

Goal: The goal of the REMS is to educate prescribers about the risk, appropriate monitoring, and management of QT prolongation to help minimize the occurrence of torsades de pointes and sudden death and to inform patients about the serious risks associated with vandetanib.

The REMS plan has multiple components that can be grouped into general categories.

Communication: The communication plan will inform healthcare providers about the risks of vandetanib and notify them that they must enroll in the REMS program prior to prescribing vandetanib. It will also include information on how to register for the REMS program. The applicant will send a Dear Healthcare Provider letter and will communicate with relevant societies and organizations. Information will be provided at various society conventions and on the applicant website. The applicant does not plan to use journal advertising.

Education: Healthcare providers will register for the REMS program. This will be followed by review of an educational pamphlet and/or a slide set that can be viewed over the web. Healthcare providers will then complete 6 questions by telephone or over the web. They will be informed of the correct answer at the completion of each question.

Implementation: After completing these 6 questions and reviewing the answers, the healthcare provider will submit a prescription complete the Vandetanib REMS Program Prescriber Enrollment Form and Vandetanib Prescription Referral Form and submit these to the specialty pharmacy. A specialty pharmacy will be used to dispense vandetanib and each pharmacy must enroll to be part of the REMS program.

Monitoring and Assessment: The applicant will monitor vandetanib distribution and prescription data. One year after the REMS program is initiated, the applicant will begin annual assessment of patient and prescriber understanding of the risks of vandetanib. The REMS program may be modified as a result of these surveys.

1.4 Recommendations for Postmarket Requirements and Commitments

These were discussed with the applicant and will include:

1. To evaluate the potential for a serious risk of carcinogenicity, it is necessary to assess the potential for carcinogenicity by conducting a long-term (2 year) rodent carcinogenicity study in the rat.
2. To evaluate the potential for a serious risk of carcinogenicity, it is necessary to assess the potential for carcinogenicity by conducting a rodent carcinogenicity study in the mouse.
3. Conduct a 2 arm randomized study in which patients with progressive or symptomatic medullary thyroid cancer will be randomized to vandetanib 300mg or 150mg. The safety and activity of the 150 mg dose will be assessed. The primary endpoint should be overall response rate.
4. Evaluate vortex keratopathy and corneal stromal changes with ophthalmology examination every 6 months with corneal photographs of abnormalities in the randomized, dose finding study in medullary thyroid cancer.
5. Evaluate heart failure by use of serial echocardiograms in all patients in the randomized, dose finding study in medullary thyroid cancer.

2 Introduction and Regulatory Background

2.1 Medullary Thyroid Cancer

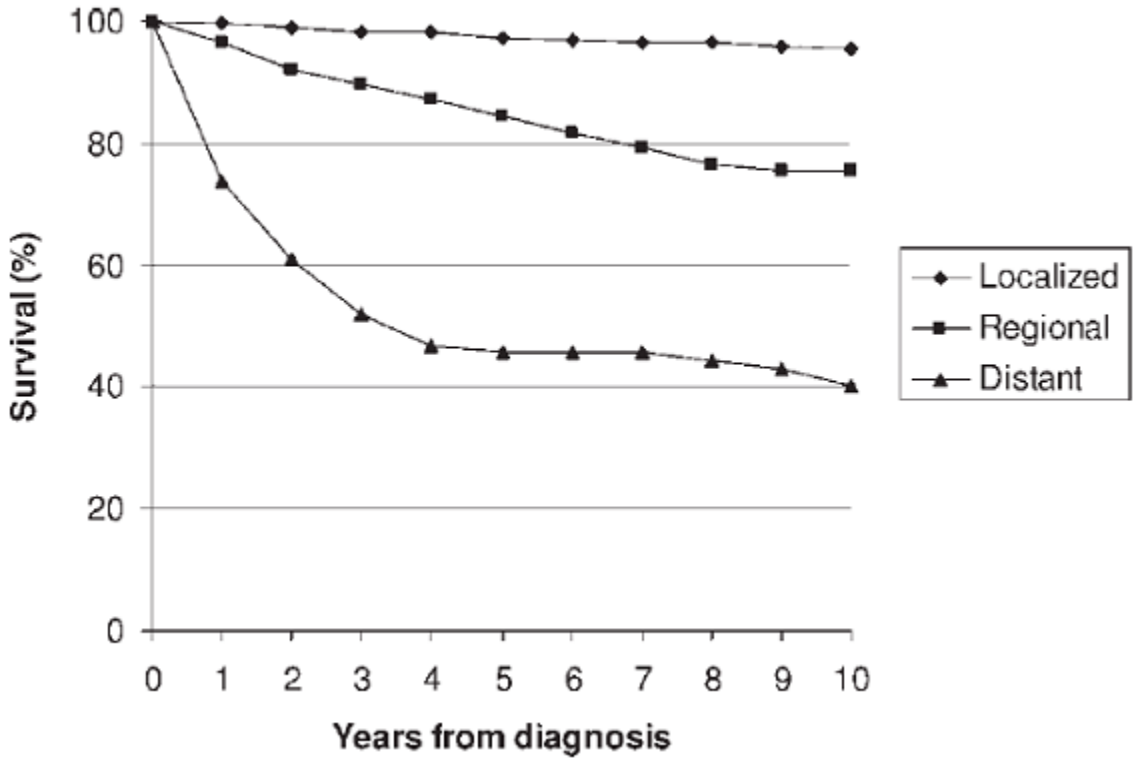
Medullary thyroid cancer (MTC) is a rare tumor arising from the parafollicular C cells of the thyroid. Medullary thyroid cancer represents approximately 5% of all thyroid cancers and the estimated number of new cases of MTC in 2010 is extrapolated to be 1800 (Jemal). Seventy-five (75%) of MTC cases are sporadic, while the remaining 25% are hereditary and are part of the autosomal dominant disorder multiple endocrine neoplasia type 2 (MEN 2). The 3 recognized subtypes of MEN 2 include MEN 2A, characterized by MTC, pheochromocytoma, and hyperparathyroidism; MEN 2B, by MTC and pheochromocytoma; and familial MTC (FMTC), by MTC only. Mutations in the RET proto-oncogene are found in >90% of patients with MEN2A and familial MTC. Somatic mutations in the RET proto-oncogene are found in 40-50% of tumors of patients with sporadic MTC. Mutations in codon 918 which are found in both hereditary and sporadic MTC activate the tyrosine kinase function of the receptor and are associated with poorer outcomes.

There are no hallmark symptoms of medullary thyroid cancer, and patients most often initially present with a thyroid nodule or mass. Patients with localized symptoms, such as dysphagia, dyspnea, or hoarseness, were more likely to have persistent disease following surgery. Systemic symptoms, such as bone pain or diarrhea, most often occur in patients with distant metastases (Kebebew). The etiology of diarrhea may be related to the secretion of calcitonin (CTN), which is produced by the parafollicular C cells of the thyroid (Austin). Calcitonin levels are useful in predicting residual disease after surgery and the doubling time of CTN may have prognostic implications (Barbet). High levels of

CTN as seen in patients with disseminated metastases do not usually cause derangements of calcium metabolism (Austin). Hypocalcemia, however, may be seen in patients with MTC as a result of post-surgical hypoparathyroidism (Rosato).

Early stage disease can be treated surgically with curative intent and patients known to be at risk for the hereditary forms of the disease often undergo prophylactic thyroidectomy. The overall prognosis of MTC is favorable with a 10 year overall survival rates for patients with tumors confined to the thyroid gland of approximately 95%, but with distant metastases present at diagnosis, the 10 year overall survival rate is estimated to be 40% (Roman). Surgery is the mainstay of treatment even with the presence of distant metastases. Other modalities that are used for disease control include radiation therapy, radiofrequency ablation, and radiolabelled antibodies (Terezakis).

Figure 1: 10 year, Disease-Specific Survival by SEER Stage for MTC, 1973-2002



To date, there are no approved systemic agents for the treatment of unresectable MTC. Historically, chemotherapy has been used for advanced disease, however the experience has largely been limited to case series or case reports. The best described agent is doxorubicin with response rates reported to be in the range of 10-25% (Matuszczyk; Shimaoka) Other chemotherapy agents that have been reported in the literature include capecitabine, cisplatin, and DTIC (Shimaoka; Gilliam; Nocera). Due to

the natural history of the disease and the side effect profile of these cytotoxic agents, it is widely recognized that patients with metastatic disease may survive years without systemic treatment and that systemic therapy is usually reserved for patients with rapidly progressive distant metastasis (Kloos, Pacini)

Recently, there have been several clinical trials reporting the use of small molecule tyrosine kinase inhibitors (TKI) in MTC. Tyrosine kinase inhibitors with in vitro activity against RET and vascular endothelial growth factor (VEGF) receptors have been evaluated in early stage clinical trials. These agents include: (b) (4)

Table 1: Tyrosine Kinase Inhibitors in MTC

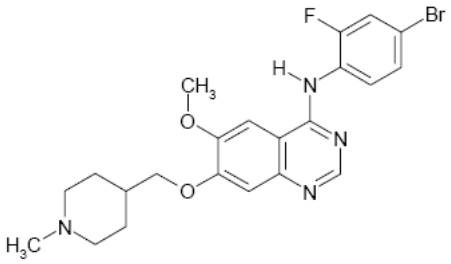
Drug Name	Current status	*In Vitro* Inhibitory Kinase Activity	Responses/ number of patients
Vandetanib	Completed Phase 3	RET, VEGFR2, EGFR	103/231 (45%)

(b) (4)

2.1 Product Information

Vandetanib is a new molecular entity and is a kinase inhibitor.

CAS Registry Number	443913-73-3
Generic Name	Vandetanib

Code Name	ZD6474, M382561, AZ11749412
Chemical Name	*N*-(4-bromo-2-fluorophenyl)-6-methoxy-7- [(1-methylpiperidin-4-yl)methoxy]quinazolin-4-amine
Molecular Formula/Molecular Weight	$C_{22}H_{24}BRFN_4O_2$/475.36 g/mol
Structure or Biochemical Description	
Pharmacologic Class	Kinase inhibitor

2.2 Tables of Currently Available Treatments for Proposed Indications

There are no currently available therapies indicated for unresectable locally advanced or metastatic medullary thyroid cancer.

2.3 Availability of Proposed Active Ingredient in the United States

Please refer to CMC review. Vandetanib is not available in the US.

2.4 Important Safety Issues With Consideration to Related Drugs

Both the Sutent and Votrient labels carry boxed warnings for hepatotoxicity. Refer to section 7.2.6.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The development of vandetanib for the treatment of patients with medullary thyroid cancer was discussed during an end of Phase 2 meeting in May 2005. This was followed by a request for Special Protocol Assessment for the key Phase 3 study in this submission. A non-agreement letter was sent, but the FDA did agree PFS by blinded independent review was an acceptable endpoint for full approval. Further, the FDA agreed to the applicant's plan to use co-primary endpoints, PFS in all patients and PFS in patients whose tumor contained the RET mutation. During follow up discussions, the FDA also agreed to the use of modified RECIST criteria in the assessment of PFS, but

recommended a series of sensitivity analyses using conventional RECIST criteria. The study was conducted from November 2006 to December 2009 and this NDA was submitted in July 2010 with a data cutoff of July 2009.

2.6 Other Relevant Background Information

None

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission contains all required components of the eCTD. The overall quality and integrity of the application appear reasonable.

3.2 Compliance with Good Clinical Practices

The protocol and its 7 amendments were submitted to Independent Ethics Committees (IEC) and/or Institutional Review Boards (IRB) for review, and the study was conducted after written approval.

The protocol and study conduct complied with recommendations of the 18th World Health Congress (Helsinki, 1964) and all applicable amendments approved by the World Medical Assemblies, and the International Conference for Harmonization (ICH) guidelines for Good Clinical Practice (GCP). The protocol also complied with the laws and regulations, as well as any applicable guidelines, of the countries where the studies were conducted.

Informed consent was obtained prior to the conduct of any study-related procedures. The written informed consent form (ICF) was signed, the names filled in and personally dated by the patient or by the patient's legally acceptable representative, and by the person who conducted the informed consent discussion. The ICF used by the Investigator for obtaining the patient's informed consent was reviewed and approved by the Sponsor prior to submission to the appropriate Ethics Committee (IRB/IEC) for approval/favorable opinion. The patient informed consent form was modified according to the local regulations and requirements.

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. Rosella 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).

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. 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.
In discussions held between the Division of Scientific Integrity (DSI) and the review division medical officers on inspectional findings of Sites 2801 and 2501, it was decided that protocol deviations reported for both of these sites 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 Astra Zeneca revealed that out of 331 subjects randomized into the study 73 failed to meet 1 or more entry criteria. Although regulatory violations were noted as described above, it appears that they are unlikely to significantly impact primary safety and efficacy analyses.

Establishment Inspections

Establishment inspections have been completed and were ultimately found to be acceptable.

3.3 Financial Disclosures

Disclosure of financial interests of the investigators who conducted the clinical trials supporting this NDA was submitted in the FDA form 3454. The disclosure was certified by Anthony Rodgers, Vice President, Regulatory Affairs for the applicant. Two sub-investigators in the key study supporting this NDA were found to have financial conflict of interest, in the form of significant payments from the applicant. There were 60 sites where patients were enrolled on the pivotal, Phase 3 trial. The number of patients enrolled at each of the 2 sites at which a sub-investigator had a financial conflict of interest did not drive the efficacy or safety data.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

See final CMC review.

Vandetanib is synthesized and mixed with the following excipients: dibasic calcium phosphate dehydrate, microcrystalline cellulose, crospovidone, povidone, and magnesium stearate. Drug product is them formed into 100 mg and 300 mg tablets which are film coated with hypromellose 2910, PEG300, and titanium dioxide. The vandetanib tablets used in the Phase 3 trial were manufactured using the commercial process and the amounts of each excipient and of the components of the film coating are acceptable. Impurities and residual solvents are also acceptable. Thirty-six months of stability has been demonstrated with 3 batches of 100 mg and 3 batches of 300 mg tablets.

4.2 Clinical Microbiology

Vandetanib is taken orally and is not sterile.

4.3 Preclinical Pharmacology/Toxicology

Vandetanib is a multi-kinase inhibitor. Its IC_{50} values against various clinically relevant kinases are shown in Table 1. Vandetanib was not mutagenic or clastogenic in standard assays. Carcinogenicity studies have not been conducted and, given the long natural history of this disease, will be included in the post marketing requirements. Repeat dose toxicity studies in the rat showed damage to the kidneys, adrenal gland, mesenteric lymph nodes, skin, spleen, and thymus. At high doses, mortality secondary to pulmonary toxicity, cholangitis and pancreatitis was seen. Pericarditis and myocardial fibrosis were also seen at high doses. In other studies, vandetanib appeared to impair autonomic and neuromuscular function in the rat. In repeat dose toxicity studies in the dog, target organs included the gastrointestinal tract, kidneys, spleen, and thymus. Results of embryo-fetal development studies in the rat, showed that vandetanib is embryotoxic, fetotoxic, and teratogenic to rats at exposures equivalent to or lower than those expected at the recommended dose of 300 mg/day. The reproductive and developmental toxicology studies suggest that administration of vandetanib may also impair fertility. Vandetanib will be assigned Pregnancy Category D.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Vandetanib is a kinase inhibitor with activity at multiple kinases. Vandetanib was tested in multiple *in vitro* recombinant enzyme assays to evaluate the potency and selectivity of the compound by determining the IC_{50} values for various protein kinases. Based on these assays vandetanib has potency for vascular endothelial growth factor (VEGF), epidermal growth factor receptor (EGFR), and RET kinase. The N-desmethyl metabolite of vandetanib was found to have similar inhibitory activity to vandetanib for inhibition of VEGF (KDR and Flt-1), EGFR, and bFGF.

4.4.2 Pharmacodynamics

In vivo effects of vandetanib were demonstrated using angiogenesis assays and in human tumor xenograft models in nude mice. In a study on the effect of vandetanib on VEGF165-induced angiogenesis with matrigel plugs in athymic nude mice, treatment with vandetanib decreased the number of vessel nodes and vessel length compared to vehicle in mice. Therefore, treatment with vandetanib showed a dose dependent inhibition of VEGF-induced angiogenesis. Vandetanib has also been shown to inhibit tumor growth in a variety of human cancer xenografts including Calc-6 human lung and PC-3 prostate cancer xenografts of various sizes. One study assessed the effects of vandetanib on the expression of pVEGFR-2 and pEGFR levels in paraffin-embedded sections of human lung or colon tumor xenografts from mice treated with vehicle or vandetanib. A dose of 150 mg/m^2 vandetanib inhibited VEGFR2 phosphorylation in the Calu-6 lung xenograft and pEGRF staining in the LoVo human colon tumor xenograft model. These studies provide some evidence that vandetanib has *in vivo* activity against VEGF and EGFR.

In the Phase 3 study, vandetanib concentration in individual patients (at steady state) was compared to patient outcome in terms of PFS and calcitonin level. No exposure-response relationship was seen for PFS. However, a relationship between drug concentration and the decrease in calcitonin level was seen. In the same study, vandetanib concentration was related to adverse events such as diarrhea and fatigue, but was not related to hypertension or rash. Most vascular endothelial growth factor inhibitors exhibit as relationship between hypertension and drug concentration. Vandetanib concentration is closely related to prolongation in the QTc interval. At 300 mg daily, the mean increase in QT interval was 35 ms, with 35.5% of patients showing a > 60 ms increase in QT over baseline (CTCAE v4 grade 4 toxicity). This increase in QT interval will be discussed further in Section 8. Safety.

4.4.3 Pharmacokinetics

The applicant has conducted several phase 1 studies in healthy volunteers and patients with malignant tumors to evaluate the safety and pharmacokinetics of vandetanib. The Tmax of vandetanib occurs 6 hours (range 4-10 hours) after the dose. The PK of vandetanib is linear over the range of 100 – 600 mg once daily dosing. A high-fat meal did not change the vandetanib exposure. The pharmacokinetics of vandetanib appear to be affected by race; the area under the curve was increased 2-fold in Japanese and Chinese patients when compared to Caucasians.

In the pivotal study, the clearance was 13 L/h, volume of distribution was 7450 L, and half-life was 19 days. In patients receiving daily vandetanib, steady state is achieved at Day 56. There was high inter-individual variability. Vandetanib is 94% bound to human serum albumin and α1-acid-glycoprotein. Two metabolites – N-desmethyl vandetanib (active) and N-oxide vandetanib (inactive) - were identified in plasma, urine and feces. N-desmethyl vandetanib, which is produced by CYP3A4, is present at concentrations between 7 and 17% of vandetanib. N-desmethyl and N-oxide vandetanib have the potential to prolong QTc based on the human ether-a-go-go gene (hERG) assay with IC50 values that were 3- and 10-fold greater, respectively than that for vandetanib. There was no clinically significant effect on exposure to vandetanib in the presence of the potent CYP3A4 inhibitor itraconazole in healthy volunteers. However, the potent CYP3A4 inducer rifampicin reduced exposure to vandetanib by 48% but increased exposure to the active N-desmethyl metabolite. Therefore, the effect of CYP3A4 inducers on the QTc effect is unclear. Patients receiving vandetanib should avoid the use of potent inducers of CYP3A4.

After administration of radio-labeled vandetanib in healthy male subjects, both urine (25%) and fecal (44%) excretion are the major routes of elimination of vandetanib. Data from a single dose pharmacokinetic study in healthy volunteers with renal impairment resulted in a 40% increase in the mean AUC of vandetanib in patients with moderate and severe renal impairment. A dose reduction to 200 mg for patients with moderate and severe renal impairment is recommended.

Single dose pharmacokinetic data from healthy volunteers with hepatic impairment suggests that there were no differences in pharmacokinetics compared to subjects with normal hepatic function. There is limited data in patients with hepatic impairment (serum bilirubin greater than 1.5 times the upper limit of normal). ZICTIFA is not recommended for use in patients with hepatic impairment, as safety and efficacy have not been established.

Substantial and sustained QTc prolongation was observed. The QTc prolongation is concentration-dependant. Based on the exposure-response relationship, the expected mean (90% CI) ΔQTcF at a dose of 300 mg was 35 (33-36) ms.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 2: Studies in NDA 022405

Study number	Study Title	Number of patients and number receiving vandetanib	Dose of vandetanib	Control
D4200C00058 Study 58	An international, Phase III, randomized, double-blinded, placebo-controlled, multi-centre study to assess the efficacy of ZD6474 versus placebo in subjects with unresecatble locally advanced or metastatic medullary thyroid cancer	331 total 231 at 300 mg 58 patients originally randomized to receive placebo received 300 mg in open label phase	300 mg	Placebo
D4200C00008 Study 8	An open-label, two stage, Phase II study to evaluate the efficacy and tolerability of ZD6474 in patients with unresectable locally advanced or metastatic hereditary medullary thyroid carcinoma.	30 at 300 mg	300 mg	None
D4200C00068 Study 68	An Open-Label, Two-Stage, Phase II Study to Evaluate the Efficacy and Tolerability of ZD6474 in Patients With Locally Advanced or Metastatic Hereditary Medullary Thyroid Carcinoma	19 at 100 mg	100 mg	
D4200C00001 Study 1	An open, Phase I, rising multiple-dose tolerability study of ZD6474 in patients with malignant tumors.	25 at 300 mg	300 mg	None

D4200C00002 Study 2	An open-label, mulitcentre Phase II study to assess the response of subjects with metastatic breast cancer, previously treated with anthracycline and taxane therapy with or without capcitabine, to ZD6474.	24 at 300 mg	300 mg	None
D4200C00003 Study 3	A Phase II, randomized, double-blind, 2-part, multicentre study to compare the efficacy of ZD6474 with the efficacy of ZD1839 (Iressa™) in patients with locally advanced or metastatic (IIIB/IV) NSCLC after failure of either first-line and/or second line platinum-based chemotherapy and to assess the activity of ZD6474 in patients following failure of treatment with ZD1839.	83 as initial treatment 37 after gefitinib	300 mg	Gefinitib 250 mg
D4200C00007 Study 7	A randomized, partially blinded, Phase II study to assess the safety, tolerability, and efficacy of ZD6474 alone or in combination with paclitaxel and carboplatin in subjects with previously untreated unresectable locally advanced or metastatic.	73 at 300 mg monotherapy	300 mg	Multiple arms
D4200C00039 Study 39 Japan	A randomized, double-blind, parallel-group, Phase IIa dose-finding multicentre study to assess the efficacy (Objective response) and safety of ZD6474 100, 200 and 300mg/day in patients with advanced or metastatic (Stage IIIb/IV) or recurrent NSCLC who have failed one	18 at 300 mg	300 mg	None

	or two previous chemotherapy regimens at least one of which contained platinum			
D4200C00043 Study 43 (TVE-15-11) Japan	An open, Phase I, rising multiple dose tolerability study of ZD6474 in Japanese patients with solid, malignant tumors	6 at 300 mg	300 mg	None
D4200C00044 Study 44	A Phase III, international, randomized, double-blind, parallel-group, multicentre study to assess the efficacy of ZD6474 plus best supportive care versus placebo plus best supportive care in patients with unresectable advanced or metastatic (Stage IIIb/IV) NSCLC after prior therapy with an epidermal growth factor receptor tyrosine kinase inhibitor (EGFR TKI)	619 at 300 mg	300 mg	Placebo
D4200C00050 Study 50	A Phase I, randomized, open-label study to assess the effect of ZD6474 on vascular permeability in patient with advanced colorectal cancer and liver metastases.	12 at 300 mg	300 mg	None
D4200C00057 Study 57	A Phase III, randomized, double-blind, parallel-group, multicentre study to assess the efficacy of ZD6474 versus erlotinib in patients with unresectable locally advanced or metastatic (Stage IIb/IV) NSCLC after failure of at least one prior cytotoxic chemotherapy	623 at 300 mg	300 mg	Erlotinib

5.2 Review Strategy

The clinical review is based on the clinical study report for Study 58, including the applicant's presentation slides, case report forms, primary data sets for efficacy and toxicity submitted by the applicant, study reports for other vandetanib clinical trials and literature review of MTC. Efficacy is supported by studies 08 and 68. The other studies were used in the review of safety.

5.3 Discussion of Individual Studies/Clinical Trials

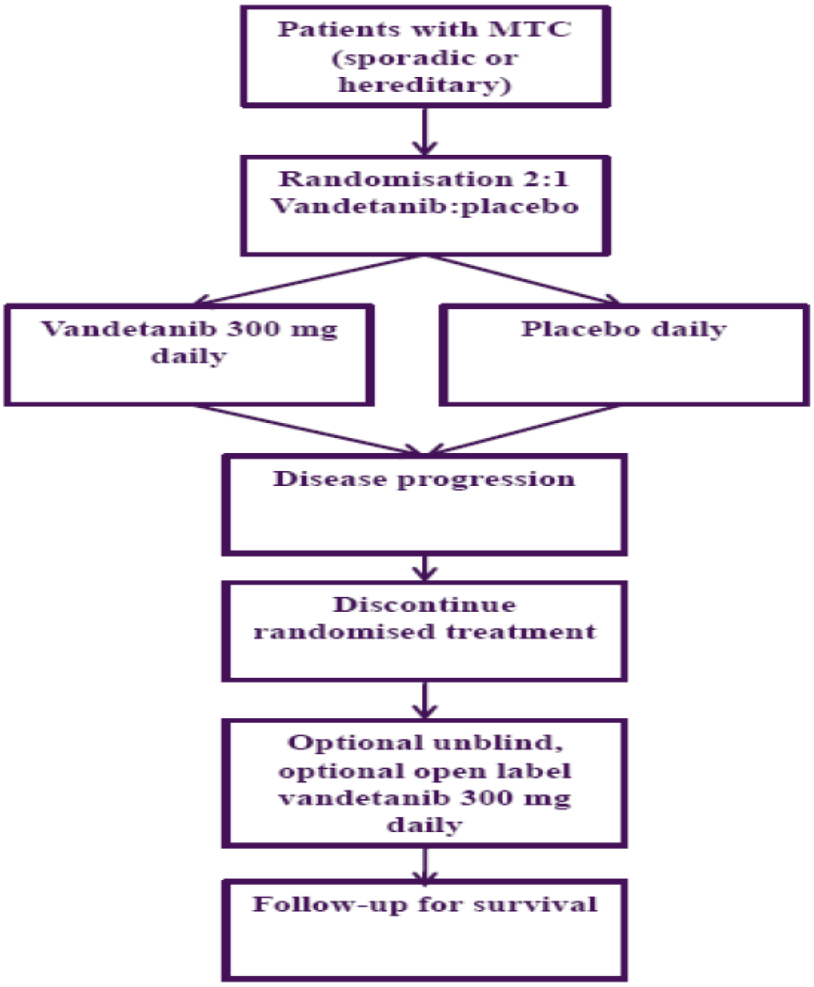
This NDA is based primarily on progression free survival from a single, randomized, double-blinded Phase 3 trial, Study 58

Study Title: An international, Phase III, randomized, double-blinded, placebo-controlled, multi-centre study to assess the efficacy of ZD6474 versus placebo in subjects with unresectable locally advanced or metastatic medullary thyroid cancer.

5.3.1 Study Design

Study 58 was a double-blind, randomized, placebo-controlled Phase 3 trial comparing vandetanib to placebo in patients with unresectable locally advanced or metastatic medullary thyroid cancer.

Figure 2: Study Design Schema



5.3.2 Study Drug Administration and Schedule

Patients were stratified by center to:

1. Vandetanib 300 mg po qd, N = 231
2. Placebo po qd, N = 100

Patients were treated until investigator-determined progression. Patients on both the placebo and vandetanib arm could receive vandetanib after investigator-determined progression.

5.3.3 Study Endpoints

Primary objective
The primary objective of this study was to demonstrate an improvement in progression-free survival (PFS) with ZD6474 as compared to placebo in subjects with unresectable locally advanced or metastatic MTC.

Reviewers Comment: *Conducting a trial with overall survival as the primary endpoint in this patient population would be very difficult to do. Given the long natural history of this disease, it is difficult to determine the clinical benefit of the primary endpoint of progression free survival. In prior meetings, the applicant and the FDA have come to agree that PFS can be used for full approval, provided that the risk/benefit profile favored treatment with vandetanib.*

Secondary objectives

The secondary objectives of the study were:

1. To demonstrate an improvement in the overall objective response rate (ORR), disease control rate (DCR), and duration of response (DOR) with ZD6474 as compared to placebo
2. To demonstrate an improvement in the overall survival (OS) in subjects with MTC who have been treated with ZD6474 as compared to placebo
3. To demonstrate an improvement in biochemical response with ZD6474 as compared to placebo, as measured by CTN and CEA
4. To demonstrate a delay in time to worsening of pain (TWP) among subjects with MTC after treatment with ZD6474 as compared to placebo
5. To determine the pharmacokinetics (PK) of ZD6474 in this subject population and investigate any influence of subject demography and pathophysiology on the PK
6. To assess the relationship between pharmacokinetics (PK) and QTc, safety, efficacy, and biomarkers
7. To determine the safety and tolerability of ZD6474 treatment in MTC subjects
8. To determine the mutational status of the RET proto-oncogene in deoxyribonucleic acid (DNA) extracted from tumor samples.

Exploratory Objectives
The exploratory objectives of the study were:
1. To investigate the effect of treatment with ZD6474 as compared to placebo on diarrhea in subjects with MTC
2. To explore changes in plasma VEGF, VEGFR-2, and bFGF levels in subjects treated with ZD6474 as compared to placebo, and their relationship to efficacy
3. To explore changes in serum protein profiles in subjects treated with ZD6474 as compared to placebo, and their relationship with efficacy and disease progression

4. To measure EGFR expression levels in tumor tissue in subjects treated with ZD6474 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 signalling pathways
6. To demonstrate a delay in time to worsening of pain (TWP) among subjects with MTC who have no pain at baseline (defined as requiring <10mg/day morphine sulfate or equivalent after treatment) with ZD6474 as compared to placebo
7. To demonstrate a delay in time to worsening of pain (TWP) among subjects with MTC who have pain at baseline (defined as requiring ≥ 10mg/day morphine sulfate or equivalent) after treatment with ZD6474 as compared to placebo
8. To demonstrate a reduction in the use of opioid analgesic medication in subjects with MTC who have pain at baseline (defined as requiring ≥ 10mg/day morphine sulfate or equivalent) after treatment with ZD6474 as compared to placebo
9. To demonstrate an improvement in weight in subjects with MTC who have been treated with ZD6474 as compared to placebo
10. To demonstrate a delay in the time to decline in WHO performance status (TDPS) in subjects treated with ZD6474 as compared to placebo.
11. To investigate the effects of ZD6474 as compared to placebo on subject quality of life (QoL) as measured by the FACT-G
12. To determine the relationship between histopathological variables in archival tumor tissue and efficacy of ZD6474
13. To examine the relationship between CTN and CEA expression in archival tumor tissue and plasma
14. To determine the expression status of signaling pathways known to be targets of ZD6474 (VEGFR. EGFR, RET), and their downstream effectors, and the efficacy of ZD6474
15. To determine the mutation status of genes known to play a role in thyroid cancer or other solid tumors

5.3.4 Eligibility Criteria

Inclusion Criteria

For inclusion in the study subjects must have fulfilled all of the following criteria:

1. Provision of written informed consent
2. Female or male aged 18 years and over
3. Previously confirmed histological diagnosis of unresectable, locally advanced or metastatic hereditary or sporadic MTC.
4. Life expectancy of 12 weeks or longer
5. WHO Performance status 0-2
6. Able to swallow study medication

7. Presence of a measurable tumor as defined by:
    a) a solitary lesion measuring ≥2 cm, OR
    b) for multiple lesions
        i. • A technique providing ≤5mm sections: a sum of diameters ≥2cm(no target lesions measuring <1cm and no lymph nodes <1.5cm) OR
        ii. • A technique providing >5mm sections: a sum of diameters ≥4cm(no target lesion measuring <2cm
8. CTN ≥ 500 pg/ml(conventional units) or ≥ 146.3 pmol/L(international standard units)
9. All subjects (other than those with hereditary MTC who have a documented germline RET mutation) must submit a suitable archived tumor collection sample. If an archived tumor sample is not available prior to 2 weeks before 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.
10. Negative pregnancy test for female subjects of childbearing potential

Reviewer's Comments: *Patients were to have measurable, locally advanced or metastatic disease. However, no criteria specifying the pace of disease or whether the patient was in need of treatment were included in the study. This is a particularly important issue in MTC where it is widely recognized that the indolent, natural history of the disease process makes observation of patients an acceptable option, even in the setting of metastatic disease.*

Exclusion Criteria

Any of the following is regarded as a criterion for exclusion from the study:

1. Brain metastases or spinal cord compression, unless treated at least 4 weeks before first dose and stable without steroid treatment for 10 days
2. Any concomitant medications that may affect QTc or induce CYP3A4 function (with the exception of somatostatin or somatostatin analog).
3. Major surgery within 4 weeks before randomization
4. The last dose of prior chemotherapy is received less than 4 weeks prior to randomization
5. Radiation therapy within the last 4 weeks prior to randomization (with the exception of palliative radiotherapy)
6. Serum bilirubin greater than 1.5 x the upper limit of reference range (ULRR)
7. Creatinine clearance <30 ml/min (calculated by Cockcroft-Gault formula)
8. Potassium <4.0 mmol/L despite supplementation, or above the 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 cases where the serum calcium is below the normal range, the

calcium adjusted for albumin is to be obtained and substituted for the measured serum value. Exclusion is to then be based on the calcium adjusted for albumin values falling below the normal limit. Corrected Calcium=Ca + 0.8 X (4-serum albumin)

9. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase (ALP) greater than 2.5 × ULRR, or greater than 5.0 × ULRR if judged by the investigator to be related to liver metastases
10. Significant cardiac event (e.g. myocardial infarction), superior vena cava [SVC] syndrome, New York Heart Association [NYHA] classification of heart disease ≥2, within 12 weeks before randomization, or presence of cardiac disease that in the opinion of the Investigator increases the risk of ventricular arrhythmia
11. History of arrhythmia (multifocal premature ventricular contractions [PVCs], bigeminy, trigeminy, ventricular tachycardia), which is symptomatic or requires treatment (CTCAE grade 3), symptomatic or uncontrolled atrial fibrillation despite treatment, or asymptomatic sustained ventricular tachycardia. Subjects with atrial fibrillation controlled by medication are permitted.
12. Congenital long QT syndrome or 1st degree relative with unexplained sudden death under 40 years of age
13. QT prolongation with other medications that required discontinuation of that medication
14. Presence of left bundle branch block (LBBB)
15. QTc with Bazett's correction unmeasurable or ≥480 msec or greater on screening ECG (Note: If a subject has QTc interval ≥480 msec on screening ECG, the screening ECG may be repeated 2 times [at least 24 hours apart] for a total of 3 ECGs. The average QTc from the three screening ECGs must be <480 msec in order for the subject to be eligible for the study.) If a subject is receiving one of the medications with possible association with Torsades de Pointes prior to study entry, and it cannot be discontinued before study treatment, then the screening QTc must be <460msec.
16. Hypertension not controlled by medical therapy (systolic BP greater than 160 millimeter of mercury [mmHg] or diastolic blood pressure greater than 100 mmHg)
17. Previous or current malignancies of other histologies within the last 5 years, with the exception of tumors associated with MEN2a and MEN2b, in situ carcinoma of the cervix, and adequately treated basal cell or squamous cell carcinoma of the skin
18. Any unresolved chronic toxicity greater than CTCAE grade 2 from previous anticancer therapy
19. Participation in a clinical study and/or receipt of an investigational drug during the last 30 days (participation in the survival follow-up period of a study is not an exclusion)
20. Previous exposure to ZD6474
21. Currently pregnant or breast feeding

22. Involvement in the planning and conduct of the study (applies to both AstraZeneca staff or staff at the investigational site)
23. Previous randomization or treatment in the present study

5.3.5 Duration of Treatment

Subjects could have been discontinued from study treatment and assessments at any time. Subjects continued to receive blinded treatment as long as there was no evidence of tumor progression, they were benefiting from treatment in the opinion of the Investigator, and they did not meet the criteria of discontinuation.

Specific reasons for discontinuing a subject from this study were:

- Disease progression or death
- Voluntary discontinuation by the subject who is at any time free to discontinue his/her participation in the study, without prejudice to further treatment
- Safety reasons as judged by the investigator and/or AstraZeneca
- Severe non-compliance to protocol as judged by the investigator and/or AstraZeneca
- Incorrect enrollment (ie, the subject does not meet the required inclusion/exclusion criteria) of the subject
- Subject lost to follow-up
- Administration of another anti-cancer therapy other than the study medication

Subjects were considered to have withdrawn from the study only if informed consent was withdrawn. In this case, no data was collected after the date of withdrawal of informed consent.

5.3.6 Primary Endpoint Evaluation

Methods of assessment
PFS was determined using data from RECIST assessments performed at baseline, during treatment and during the follow-up period.

Derivation or calculation of outcome variable
Progression free survival was defined from the date of randomization to the date of objective progression or death (by any cause in the absence of progression). Subjects who have not progressed or died at the time of statistical analysis will be censored at the time of their latest objective tumor assessment. This includes subjects who are lost to follow-up or have withdrawn consent. For subjects lost to follow-up without having progressed, death within a further 12 weeks was considered an event; otherwise the subject was censored for PFS at the time of their last tumor assessment date.

The modified RECIST criteria was used to perform the objective tumor assessments and determine a subject's PFS and best overall objective tumor response
Baseline radiological tumor assessments were to be performed no more than 3 weeks before the start of study treatment and at all time points defined in the study plan.
All measurable lesions, up to a maximum of 10 lesions and representative of all involved organs (maximum of 5 lesions per organ), were identified as target lesions and were recorded and measured at baseline. Target lesions were selected on the basis of their size (lesions with the LD) and their suitability for accurate repetitive measurements (by either CT or MRI). A sum of the LD for all target lesions was calculated and reported as the baseline sum LD. The baseline sum LD was used as reference to further characterize the objective tumor response of the measurable dimension of the disease.

In order to increase specificity and be able to accurately measure change, only lymph nodes measuring ≥ 1.5 cm in the longest diameter were accepted as a measurable lesion, assuming 5mm imaging section. Most common sites of metastasis in MTC are local regional lymph nodes in the neck and mediastinum. For slice thickness >5 mm, the minimum measurable lesion size was 2 cm for all measurable lesions.

A subject was determined to have progressed if they had progression of target lesions, clear progression of existing non-target lesions or the appearance of one or more new lesions. Progression of target lesions was defined as at least a 20% increase in the sum of the LD of target lesions taking as references the smallest sum of LD recorded. Death was regarded as a progression event in those subjects who die before documented objective disease progression.

All medical images were reviewed at the site and by a centrally appointed CRO. The central review data was used in preference to the local site review data at the time of the data analyses.

Categorization of the objective tumor response assessments were based on the RECIST criteria for target and non-target lesions. Response were assigned as CR, PR, SD, progressive disease (PD), or not evaluable (NE) at each scheduled visit by the Investigator. For the purposes of analysis the applicant determined visit and overall response using the lesion assessments recorded on the eCRF.

Subjects who discontinued from study treatment for toxicity other than objective disease progression continued to have objective tumor assessments every 12 weeks until progression was documented, unless the subject withdrew consent.

Modifications to RECIST criteria

Calcified tumor lesions can occur in MTC subjects and be seen at baseline imaging or during follow up. It is recognized that there is great difficulty in measuring such lesions, and that an increase in size of the calcified component may represent healing rather

than progression. As a result, it was recommended that such lesions not be assessed as target lesion at baseline unless no other lesions were available for measurement. Calcification within the liver or other lesions may occur during the study, as observed in the phase II study (D4200C00008) in hereditary MTC subjects. Response assessment based upon the presence and potential growth of calcified lesions was modified to recognize that growth in calcified portions of metastases may not represent progression.

As observed in study D4200C00008, (the phase II study in hereditary MTC subjects), new hypo-dense or hypointense lesions may appear in the liver even as subjects exhibit respond in other target lesions, and demonstrate clinical response with improvement in biomarkers. Visualization of non necrotic/cystic lesions may be difficult at baseline due to near iso-density or iso-intensity with normal liver in terms of contrast enhancement as a documented technical limitation of CT and MRI. If new hypo-dense or hypointense lesions appear in the liver within the first 2 scheduled RECIST follow up assessments, the baseline CT/MRI was re-examined and if in retrospect iso-dense or iso-intense lesions were identified in the same location then these were 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 be identified on retrospective review of the baseline then these lesions were recorded as new lesions.

Reviewer's Comments: *These modifications to the RECIST criteria were not previously validated in any comparison clinical trial and are based on a single arm phase II trial in 30 hereditary MTC patients.*

5.3.7 Secondary Endpoint Evaluation

Overall Response Rate (ORR), Disease Control Rate (DCR), Duration of Response (DOR)
The ORR was calculated as the percentage of subjects with a best response of CR or PR. The DCR was calculated as the percentage of subjects with CR or PR or SD ≥ 24 weeks.

DOR was calculated for those subjects who have a best response of CR or PR only. DOR was defined in two ways:

- from the date of randomization until the date of documented objective disease progression or death from any cause in the absence of documented progression, and
- from the date of first documentation of response until date of documented objective disease progression or death from any cause in the absence of documented progression

Overall survival (OS)

OS was calculated from the date of randomization to the date of death.

After withdrawal from study treatment, subjects were followed up for survival every 12 weeks, unless the subject withdrew consent, or death occurred. This will continue until the survival cut-off timepoint (defined as the time when ≥50% subjects have died). Subjects who had not died at the time of the statistical analysis were censored at the time they were last known to be alive.

Biochemical response

Venous blood (approx. 6 ml) was taken for the analysis of CEA and CTN. All samples were sent to the central laboratory for analysis. The following definitions were used to calculate both the CEA response and the CTN response for each subject:

- **Complete Response (CR):** Complete normalization of CEA/CTN level following treatment, as confirmed with a repeat CEA/CTN level
- **Partial Response (PR):** At least a 50% decrease in the CEA/CTN level (represented by a persistent decrease in CEA/CTN over 4 weeks documented by repeat CEA/CTN serum measurement), taking as reference the baseline (mean) level
- **Progressive Disease (PD):** At least a 50% increase in the CEA/CTN (sustained over weeks), taking as reference the baseline (mean) level
- **Stable disease (SD):** Neither sufficient normalization decrease to qualify for PR nor sufficient normalization increase to qualify for PD, taking as reference the baseline (mean) level

For each subject, their best CEA response and their best CTN response will be calculated from assessments performed at baseline and during treatment. Responders are those subjects with a best biochemical response of CR or PR.

The CEA response rate, the CTN response rate and the associated exact 95% confidence intervals (CI) will be summarized for each treatment group. To be assigned a status of PR or CR, changes in serum tumor marker level were confirmed by repeat assessments, no less than 4 weeks after the criteria for PR or CR were first met. For subjects with biochemical CR, repeat serum tumor marker levels were obtained at least 4 weeks after subjects achieved biochemical CR, and had to remain within normal limits in order to be considered a biochemical CR. In the case of stable disease, follow-up CEA/CTN levels met the stable disease criteria at least once after study entry at a minimum interval defined as 12 weeks.

Opioid Analgesic Use
Baseline opioid analgesic use was established using the average reported opioid medication use assessed during 4 days of the screening period in the week immediately prior to randomization.

In subjects with MTC who used ≥10mg/day of morphine sulphate or equivalent at baseline, a response to opioid analgesic use was defined as a decrease in the use of opioid analgesic medication by >50% from baseline lasting for 14 days and was accompanied by no increase in the worst pain severity item of the Brief Pain Inventory (BPI) . The overall response to opioid analgesic use was calculated as the percentage of subjects with a response. Duration of opioid analgesic use response was calculated for those subjects with opioid analgesic response, from the date of first documented response until the date of the subject no longer met the criteria for response.

Time Worsening of Pain (TWP) and Worst Pain Severity

Methods of assessment
A subject's time to worsening of pain was assessed using the opioid analgesic utilization and responses on the worst pain severity question from the BPI instrument.

Derivation or calculation of variable
Baseline score on the worst-pain item for each subject was established using the average of scores on the worst-pain item from the BPI assessments during 4 days in the screening period in the week immediately prior to randomization. In addition, baseline opioid analgesic use was established using the average reported opioid medication use assessed during 4 days of the screening period in the week immediately prior to randomization. Post-baseline weekly visit responses were established for each subject using the worst pain severity score or the opioid analgesic medication use.

At each visit, worsening of pain severity was considered an increase of ≥ 2 points from baseline on the worst-pain item or an increase in opioid analgesic use from baseline of ≥ 10mg/day of morphine sulphate equivalent. At each visit, an improvement of pain severity was considered a decrease of ≥ 2 point from baseline with no increase from baseline in opioid analgesic use of ≥ 10mg/day of morphine sulphate equivalent or decrease in opioid analgesic use from previous visit of > 50% with no increase of ≥ 2 points from baseline on the worst-pain item. If the visit response could not be categorized as either worsening or improvement of pain severity, then the visit response will be categorized as no change.

5.3.8 Major Protocol Amendments

Table 3: Major Protocol Amendments

Number	Date	Amendment
2	30 May 2007	Ophthalmologic examinations were added to the study plan; Inclusion criteria were updated to indicate that the qualifications for a measurable lesion would include

		measurements for lymph nodes, sum of diameters, and size of target lesion; Exclusion criteria were updated to revise serum creatinine requirement to ≤50 mL/min to ≤30 mL/min.
3	15 May 2008	The study was redefined as a Phase 3 study; DCR was calculated as the percentage of patients with CR, PR, or SD ≥24 weeks;
5	18 May 2009	The objectives for the PRO variables were amended, which affected both the secondary and exploratory objectives of the study. PRO variables and statistical methods for PRO variables were also revised for consistency with changes to study objectives; Patient weight was changed from a secondary to an exploratory objective; (b) (4)
6	13 January 2010	The study plan was updated to provide investigators with the option to unblind patients remaining on blinded, randomized therapy. When unblinded, patients could not remain on blinded therapy; they had to either enter the open-label portion of the study or discontinue blinded therapy and be followed for survival. Patients who were not unblinded had to continue in the study outlined in the study plan.

6 Review of Efficacy

Efficacy Summary

This application is based on the primary endpoint of progression free survival (PFS) in a single, randomized, double-blinded study comparing vandetanib with placebo in 331 patients with unresectable, locally advanced or metastatic medullary thyroid cancer.

- The applicant reports an improvement of PFS in patients treated with vandetanib as compared to placebo, with a hazard ratio of 0.46 95% CI (0.31, 0.69) p = 0.0001. The duration of PFS for vandetanib was not reached.
- The applicant reports an overall response rate of 45% for vandetanib as compared to an ORR of 13% for placebo. The duration of response for vandetanib was not reached.
- There was no statistically significant difference in overall survival seen between arms.
- There were few major protocol violations that could have affected the primary endpoint analysis. The most frequent major protocol violation concerned missing

archival tissue for RET mutation analysis (b) (4)

(b) (4) The time to worsening pain endpoint was based on patient opioid use and patient questionnaires. The overall compliance rate with the questionnaires was only 50% with compliance rates of less than 30% seen at multiple timepoints. This large amount of missing data precludes any conclusions being drawn regarding this endpoint. Biochemical responses in CTN and CEA are not validated as clinical endpoints in this disease.

6.1 Indication

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

6.1.1 Methods

Clinical review is based primarily on the CSR for study 58, the applicant's presentation slides, case report forms, primary data sets for efficacy and toxicity submitted by the applicant and literature review of MTC.

6.1.2 Demographics

There was no substantial imbalance between treatment arms with respect to the demographic characteristics of age, sex, and race. There was a higher percentage of patients in the ≥18 to <40 year age category and a lower percentage of patients in the ≥40 to <65 year age category in the vandetanib arm relative to the placebo arm. A total of 95.2% of patients were Caucasian.

Table 4: Patient Demographics

		Vandetanib (n=231)	Placebo (n=100)	Total (n=331)
Baseline Characteristics:				
Age (years):				
	Mean:	50.7	53.4	51.5
	SD:	14.1	12.0	13.6
	Median:	50.0	52.5	51.0
	Min:	18	26	18
	Max:	83	84	84

Gender:				
	Male:	134 (58.0)	56 (56.0)	190 (57.4)
	Female:	97 (42.0)	44 (44.0)	141 (42.6)
Race:				
	Asian:	8 (3.5)	1 (1.0)	9 (2.7)
	Black:	1 (0.4)	1 (1.0)	2 (0.6)
	White:	218 (94.4)	97 (97.0)	315 (95.2)
	Other:	4 (1.7)	1 (1.0)	5 (1.5)

Enrollment of patients with this rare disease involved 23 countries with 22.1% of patients coming from the US.

Table 5: Country of Enrollment

	Vandetanib (n=231)	Placebo (n=100)	Total (n=331)
Country:			
Australia	5	3	8
Austria	3	1	4
Belgium	6	3	9
Brazil	4	2	6
Canada	9	3	12
Czech Republic	3	1	4
Denmark	3	2	5
France	31	14	45
Germany	19	9	28
Hungary	3	1	4
India	5	1	6
Italy	26	12	38
Netherlands	9	4	13
Poland	22	10	32
Portugal	5	2	7
Republic of Korea	4	1	5
Romania	3	1	4
Russia	5	3	8
Serbia	5	2	7
Spain	1	3	4
Sweden	2	0	2

Switzerland	6	1	7
US	52	21	73

Stage of disease at entry was balanced between treatment arms. A total of 94.6% of patients in the 2 treatment groups had Stage IVC disease at entry. In terms of sites of disease, there was no imbalance in the distribution of the metastatic sites. Overall, the most common metastatic sites were hepatic (65.9%), lymph nodes (61.3%), and respiratory 56.2%).

Table 6: Baseline Disease Characteristics

		Vandetanib (n=231)	Placebo (n=100)	Total (n=331)
Primary Tumor:				
	T1	5 (2.2)	1 (1.0)	6 (1.8)
	T2	3 (1.3)	0 (0.0)	3 (0.9)
	T3	2 (0.8)	5 (5.0)	7 (2.1)
	T4a	8 (3.5)	5 (5.0)	13 (3.9)
	T4b	6 (2.6)	1 (1.0)	7 (2.1)
	Tx	207 (89.6)	88 (88.0)	295 (89.1)
Lymph Nodes:				
	N0	29 (12.5)	13 (13.0)	42 (12.7)
	N1a	26 (11.3)	10 (10.0)	36 (10.9)
	N1b	132 (57.1)	59 (59.0)	191 (57.7)
	N2	4 (1.7)	3 (3.0)	7 (2.1)
	N3	0 (0.0)	1 (1.0)	1 (0.3)
	Nx	40 (17.3)	14 (14.0)	54 (16.3)
Metastasis:				
	M0	14 (6.1)	3 (3.0)	17 (5.1)
	M1	216 (93.5)	97 (97.0)	314 (94.9)
	MX	1 (0.4)	0 (0.0)	1 (0.3)
Stage:				
	Stage III	1 (0.4)	2 (2.0)	3 (0.9)
	Stage IVa	8 (3.5)	0 (0.0)	8 (2.4)
	Stage IVb	6 (2.6)	1 (1.0)	7 (2.1)
	Stage IVc	216 (93.5)	97 (97.0)	313 (94.6)

The majority of patients had a history of prior thyroidectomy and lymphadenectomy. Half of the patients had a history of radiation therapy. Twenty percent (20%) of the patients had prior cytotoxic chemotherapy such as doxorubicin and/or cisplatin. Ten percent (10%) of the patients had prior targeted therapy with off-label use of approved agents such as imatinib or use in the context of a different clinical trial.

Table 7: Prior Therapy

	Vandetanib (n=231)	Placebo (n=100)	Total (n=331)
Thyroidectomy	207 (89.6)	92 (92.0)	299 (90.3)
Lymphadenectomy	171 (74.0)	80 (80.0)	251 (75.8)
Prior Systemic Therapy:			
Cytotoxic:	50 (21.6)	18 (18.0)	68 (20.5)
Targeted:	22 (9.5)	11 (11)	33 (10.0)
Radioimmune	10 (4.3)	7 (7.0)	17 (5.1)
Radioisotope	25 (11.0)	9 (9.0)	34 (10.3)
Prior Radiation	117 (51.0)	53 (53.0)	170 (51.3)

The median time from diagnosis of MTC to enrollment on trial was 6 years which underscores the relatively long natural history of this disease.

Table 8: Time from Diagnosis to Enrollment (years)

	Vandetanib (n=231)	Placebo (n=100)	Total (n=331)
Median	6.0	6.0	6.0
Std Error	0.4	0.7	0.4
Range	0-31	0-35	0-35

The median time from last documented progression to enrollment on study was approximately 2 months, but 30% of the patients had last progressed more than 6 months prior to enrolling on trial, and 13 patients had last progressed 3 years before entering the trial. The longest progression free interval was a patient who last progressed almost 9 years before entering the study.

Table 9: Time from last progression (months)

	Vandetanib (n=231)	Placebo (n=98)	Total (n=325)
Median	2.43	1.96	2.14
Std Error	0.92	1.18	0.73
Range	0-107	0-77	0-107
Progressed <6mo	157 (69%)	72 (73%)	229 (70%)
Progressed >6mo	70 (31%)	26 (27%)	96 (30%)

The median sum of the longest diameter of the baseline tumor lesions was 11cm. Eleven percent (11%) of the patients had a baseline sum of less than 4. Fourteen percent (14%) of the patients did not have measurable disease as assessed by independent blinded review of baseline imaging.

Table 10: Baseline sum of lesions (cm)

	Vandetanib (n=211)	Placebo (n=88)	Total (n=299)
Median	12.1	11.1	11.4
Std Error	0.61	1.0	0.53
Range	2.0-45	2.0-47.1	2.0-47.1

Median baseline levels of calcitonin (CTN) and carcinoembryonic antigen are depicted in Table 11. Patients were required to have a CTN level $\geq$ 500 ng/L at entry.

Table 11: Baseline Calcitonin and CEA

	Vandetanib (n=231)	Placebo (n=88)	Total (n=325)
Median CTN ng/L	9620	11696	10242
Std Error	5361	8358	4509
Mean CTN ng/L	29011	35154	30858
Std Dev	80958	82739	81419
Median CEA µg/L	137	194	153
Std Error	248	85	176
Mean CEA µg/L	860	523	759
Std Dev	3749	842	3171

All patients were required to provide an archived tumor sample prior to randomization for RET mutation analysis, although no sample was required for patients with hereditary disease who had a documented germline mutation in RET. Tumor biopsy samples were

obtained using standard core biopsy techniques or by use of fine needle aspiration. RET mutation status was determined by AstraZeneca's Tissue Bank Reception (Alderley Park, Macclesfield, Cheshire UK) by sequencing the 6 most commonly mutated exons in MTC (10, 11, 13, 14, 15, and 16) and by evaluating for the M918T mutation using an amplification refractory mutation system (ARMS) analysis . A RET positive mutation status was defined as having a mutation either observed from the sequencing or ARMS assay. Stringent criteria were chosen to define RET mutation status as negative to minimize the number of patients incorrectly classified in this category. Thus, RET mutation negative status was defined as having the sequencing assay successfully showing wild type sequence at all 6 exons, and the ARMS assay negative for a M918T mutation. Unknown RET mutation status was documented when 1 or more sequencing assay was unsuccessful (non-informative), and none of the successful assays demonstrated a mutation.

Table 12: Genetic Composition

	Vandetanib (n=231)	Placebo (n=100)	Total (n=331)
RET Mutation Positive	137 (59.3)	50 (50.0)	187 (56.5)
RET Mutation Negative	2 (0.9)	6 (6.0)	8 (2.4)
RET Mutation Unknown	92 (39.8)	44 (44.0)	136 (41.1)
Hereditary MTC	28 (12.1)	5 (5.0)	33 (1.0)
Associated Endocrinopathy			
MEN 2a	14 (6.0)	3 (3.0)	17 (5.1)
MEN 2b	7 (3.0)	0 (0.0)	7 (2.1)
Familial MTC	4 (1.7)	1 (1.0)	5 (1.5)
Family History of MTC	12 (5.2)	4 (4.0)	16 (4.8)

6.1.3 Subject Disposition

The first patient was enrolled on 23 November 2006 and the last patient was enrolled in the study on 19 October 2007. The date of data cut-off for the study was 31 July 2009. With 231 patients assigned to the vandetanib arm and 100 patients to the placebo arm, the ratio of the number of patients randomized to vandetanib:placebo exceeded the 2:1 target. Randomization was stratified by site in blocks of 3. If a site did not use all the randomization numbers in a given block, it was expected that the ratio of patients assigned to the vandetanib arm relative to those assigned to the placebo arm would not be equal to 2. 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. All patients received at least 1 dose of randomized treatment except for 1 patient randomized to placebo. Patient E2501032 was randomized to placebo but died of progressive MTC before receiving randomized treatment.

A total of 111 (48.1%) patients in the vandetanib arm continued to receive randomized at the date of data cut-off (31 July 2009), compared with 28 patients (28.0%) in the placebo arm. A total of 120 (51.9%) patients in the vandetanib arm discontinued randomized treatment, compared with 71 (71.0%) patients in the placebo arm. The most common reason for discontinuation was disease progression (71 [30.7%] of patients in the vandetanib arm versus 55 [55.0%] patients in the placebo arm).

Patients who discontinued randomized treatment for disease progression were given the option to be unblinded and receive open label vandetanib or to continue in the study without receiving open label vandetanib.

In the vandetanib arm, 44 patients received open label treatment compared to 58 patients in the placebo arm.

Table 13: Patient Disposition

	Vandetanib	Placebo
Randomized	231	100
Treated	231	99
Ongoing Randomized Treatment	111	28
Discontinued Randomized Treatment	120	71
Permanently Discontinued Study Treatment	76	13
Progressive Disease or Death	41	7
Lost to Follow Up/Patient Decision	23	5
Adverse Event	12	1
Received Open Label Treatment	44	58
Ongoing Open Label Treatment	17	42
Discontinued Open Label Treatment	27	16
Progressive Disease or Death	21	9
Lost to Follow Up/Patient Decision	5	3
Adverse Event	1	4

6.1.4 Analysis of Primary Endpoint(s)

This primary analysis of progression free survival is shown in the table 14. This analysis censors the following patients:

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

Patients with more than 1 censoring-event were censored at the earliest event.

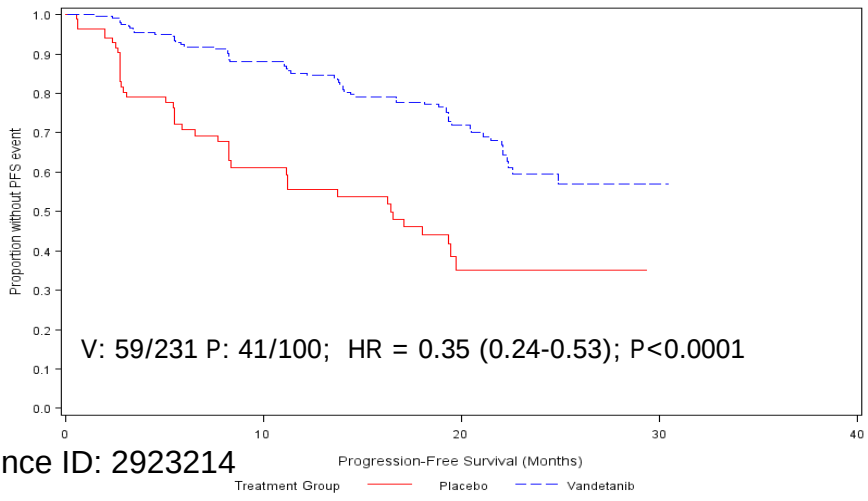
Table 14: Primary Analysis Study 1-FDA (Data Cutoff 7-31-09)

Progression Free Survival	Vandetanib N = 231	Placebo N = 100
Number of Events	59 (25.5%)	41 (41.0%)
Censored	172 (74.5%)	59 (59.0%)
Median PFS	NE (22.6 months, NE)[2]	16.4 months (8.3, 19.7)
Hazard Ratio[1] (95% CI)		0.35 (0.24-0.53)
p-value (logrank test)		<0.0001

[1]Cox proportional hazards model [2]Not estimable

A Kaplan-Meier curve for the comparison of time to PFS, as derived from all available central read RECIST assessments, is presented in Figure 3. As shown in Figure 3, the effects of vandetanib treatment appear to be maintained over time as the curves remain separated and show no appearance of converging through the entire assessment period.

Figure 3: Kaplan-Meier PFS Estimates



The hazard ratio, as calculated by the fda and the applicant, differ due to different censoring criteria, namely differences in handling discordance in progression between the investigator and independent review, the use of additional therapy during randomized treatment, and the absence of baseline disease.

Table 15: FDA and Applicant Primary Analyses

	FDA	Applicant
Events	30%	41%
Censored	70%	59%
Discordance	14%	0
Additional Therapy	2%	0
No Baseline Disease	10%	0
No Event	45%	59%
Hazard Ratio (95% CI)	0.35 (0.24-0.53)	0.46 (0.31-0.69)
p-value	0.0001	0.0001

A summary of the differences between the censoring patterns and calculated hazard ratios as determined by FDA, Investigator assessed, and Independent Radiology Committee readings are depicted in Table 16.

Table 16: FDA, Investigator, and IRC Primary Analysis

	FDA	**Investigator**	**IRC**
Hazard Ratio (95% CI)	0.35[1] (0.24-0.53)	0.40[2] (0.27-0.58)	0.46[2] (0.31-0.69)
Events Resulting in Censoring	Censored at	Censored at	Censored at
No Measurable Disease at Baseline	Day 1	Not Censored	Not Censored
Investigator-Progression Without IRC-Progression	Last RECIST Assessment Prior to Discontinuation of Study Drug	Followed Until IRC-Progression	Followed Until IRC-Progression

Received Radiation Therapy	Last RECIST Assessment Prior to Radiation	Not Censored	Not Censored

In the FDA analysis, 24% of patients were censored in the vandetanib arm and 9% of patients were censored in the placebo arm. Given this evidence of differential censoring, a A sensitivity analysis was conducted in which patient data was handled in the following manner:

- 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; and
- All patients who died without prior documented progression were considered to have progressed 1 day after their last RECIST assessment.

Table 17: Sensitivity Analysis-Primary Endpoint Study 1 (Data Cutoff 7-31-09)

Progression Free Survival	Vandetanib N = 231	Placebo N = 100
Number of Events	109 (47.2%)	44 (44.0%)
Median PFS (95% CI)	20.5 months (19.3, 22.3)	18 months (11.1, NE)
Hazard Ratio[1] (95% CI)		0.83 (0.58, 1.18)
p-value (logrank)		0.29

[1]Cox model

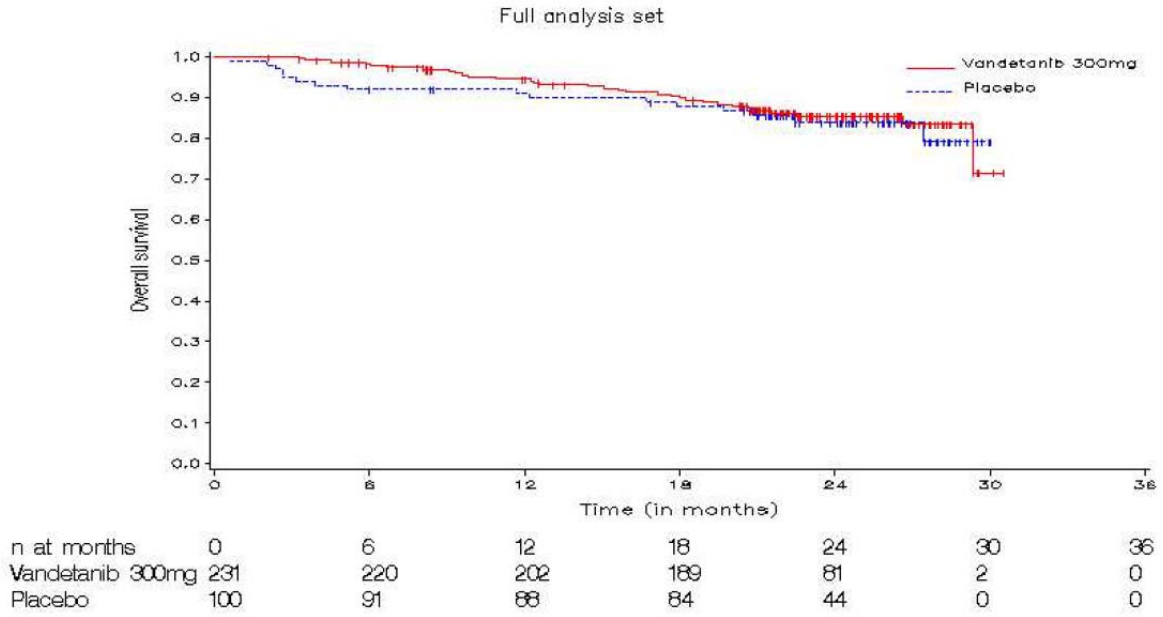
Despite these data handling conventions, the comparison of vandetanib and placebo maintains a hazard ratio < 1.

6.1.5 Analysis of Secondary Endpoints(s)

Overall Survival

Overall survival was a key secondary endpoint, however at the time of the data cutoff, no significant difference between the vandetanib arm and the placebo arm was seen. It is important to note that only 15% of the events have occurred. While this study is not powered for overall survival, a final analysis of this endpoint will occur at 50% of events which currently is anticipated to be in 2012.

Figure 4: Kaplan-Meier OS Estimates



Overall Responses

The table below provides the response rate (RR) and duration of response for patients in Study 58 by the IRC and the investigator-determined RR. It does not include responses which occurred after discontinuation of study drug and crossover to open label vandetanib. It is unusual for the investigator-determined RR to be lower than the IRC-determined RR and the reason for this finding remains unclear. The table also shows the RR in patients with hereditary and sporadic disease. This analysis was performed so that the RR in the Phase 3 study could, in an exploratory manner, be compared to the RR in the Phase 2 studies in hereditary MTC (below). The Phase 2 studies only enrolled patients with hereditary disease.

Table 18: Response Rate Study 58 (Data Cutoff 7-31-09)

Response Rate (CR+PR)	Vandetanib N = 231	Placebo N = 100
Response Rate-IRC	44.6%	1.0%
CR	0	0
PR	44.6%	1.0%
Median Duration of Response	NR	218 days
Response Rate-IRC		
Hereditary	39.0%	0%

Sporadic	44.3%	1.0%
Response Rate-Investigator	39.0%	2.0%

Biochemical Responses

Biochemical response was derived from data collected when patients were receiving randomized treatment. (b) (4)

Table 19: Overall Responses – Calcitonin Levels*

	Vandetanib (n=231)	Placebo (n=100)	Total (n=331)
Complete Responses**	3 (1.3)	0 (0.0)	3 (0.9)
Partial Responses***	157 (68.0)	3 (3.0)	160 (48.0)

* - No correlation between tumor response and calcitonin response.
**-Level of ≤10 pg/ml for men and ≤5pg/ml for women on 2 separate lab measurements at least 4 weeks apart.
*** - A decrease in the CTN level at least 50% from baseline.

Table 20: Overall Responses – CEA Levels*

	Vandetanib (n=231)	Placebo (n=100)	Total (n=331)
Complete Responses**	7 (3.0)	2 (2.0)	9 (2.7)
Partial Responses***	112 (48.5)	0 (0.0)	112 (33.8)

* - No correlation between tumor response and CEA response.
**-Level of ≤2.5 pg/ml on 2 separate lab measurements at least 4 weeks apart.
*** - A decrease in the CEA level at least 50% from baseline.

Time to Worsening Pain

A key secondary endpoint is the time to worsening pain, which is based on patient opioid use and patient questionnaires. Unfortunately, the overall compliance rate with the questionnaires was only 50% with compliance rates of less than 30% seen at multiple timepoints. This large amount of missing data precludes any conclusions being drawn regarding this endpoint.

6.1.6 Other Endpoints

None

6.1.7 Subpopulations

Pre-specified subgroup analyses of PFS conducted by the applicant, are shown below. Note that these data are determined using the applicant's censoring pattern.

Figure 5: Applicant's Prespecified Subgroup Analysis

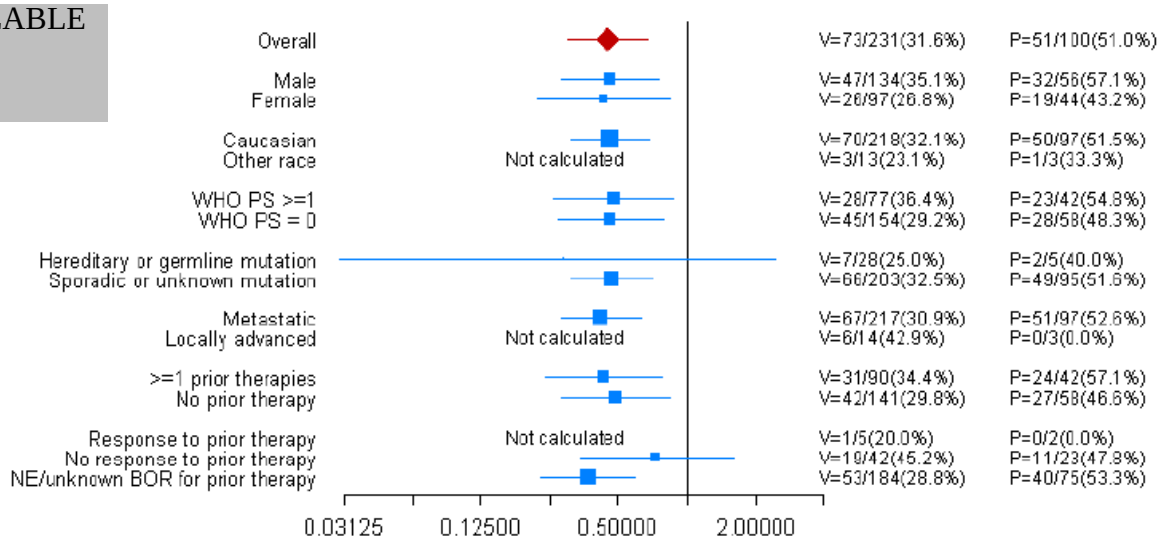
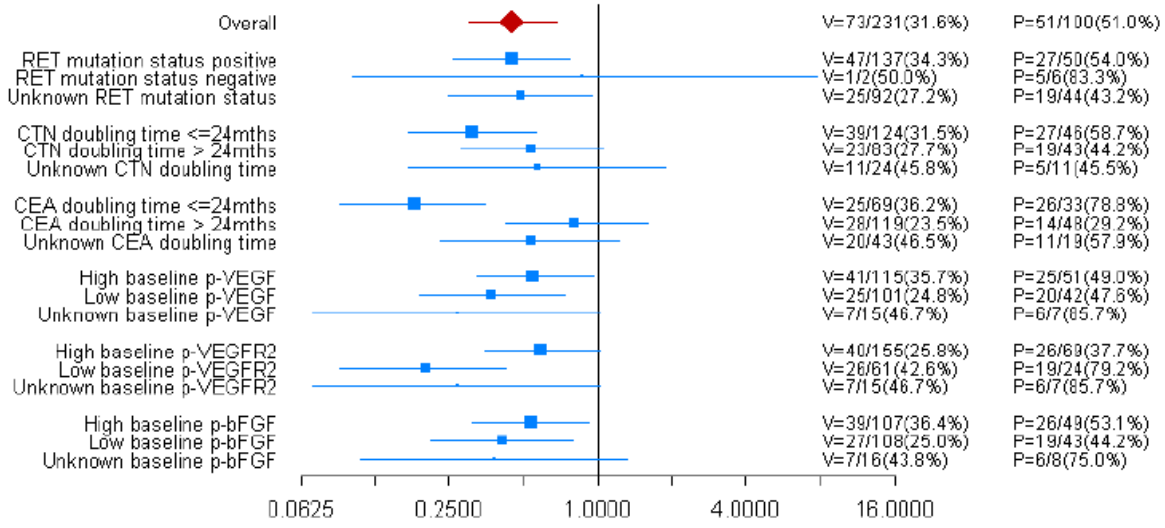


Figure 6: Applicant's Prespecified Subgroup Analysis; Biomarkers



Visual inspection of the forest plots suggest that the PFS benefits observed were generally consistent across all subgroups. However, it appears that patients with a CEA doubling time of <24 months at baseline and patients with low plasma VEGFR2 may have received a greater differential benefit, although the HRs for the complementary subgroups (ie, CEA doubling time >24 months and high plasma VEGFR2) do not suggest a lack of benefit.

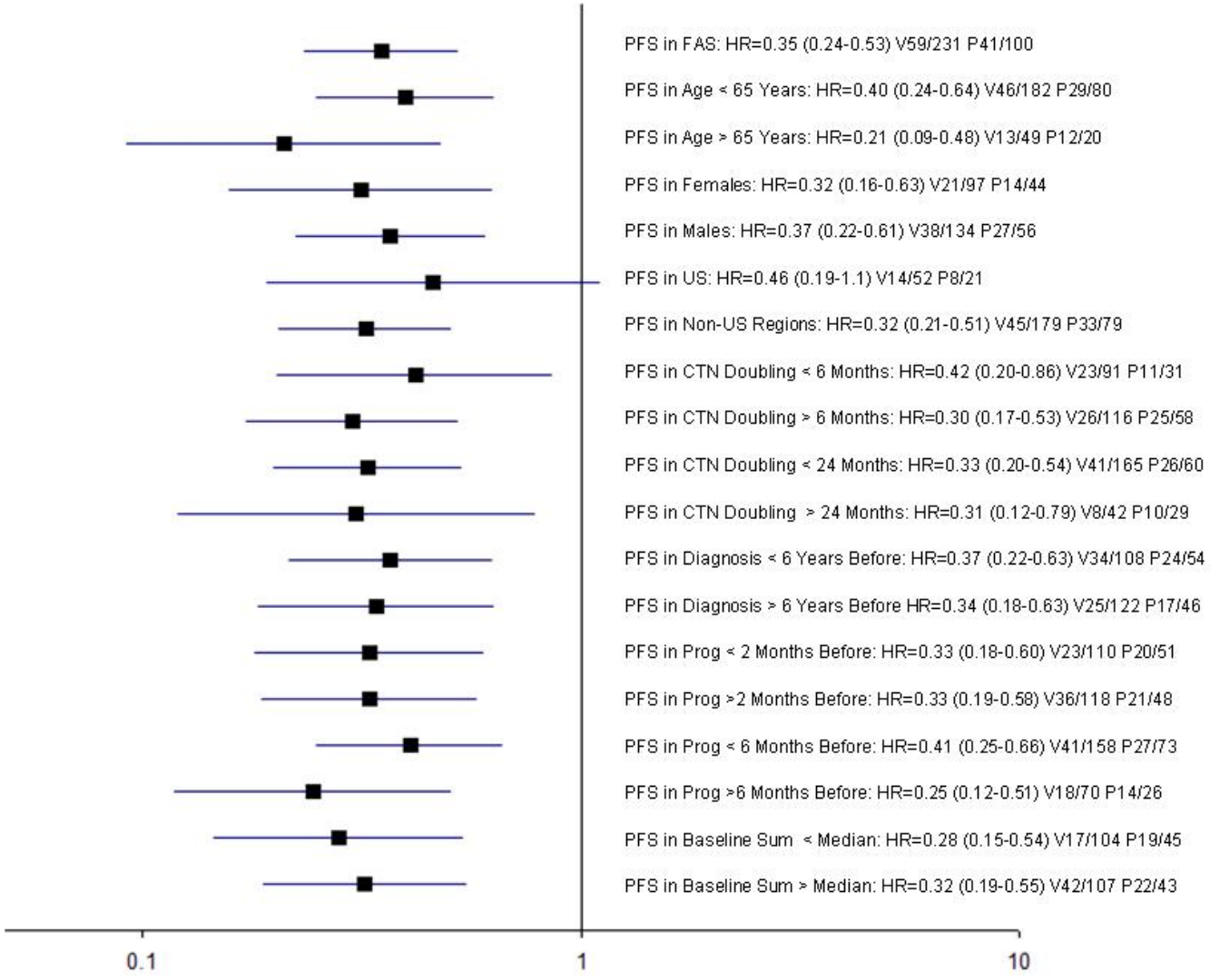
An exploratory subgroup analysis of PFS by age group that was not pre-specified was conducted after unblinding of study data. There was a statistically significant difference in PFS in favor of the vandetanib treatment group in both patients <65 years of age (HR=0.50, 95% CI, 0.32 to 0.80, p=0.0036) and >65 years of age (HR=0.32, 95% CI, 0.14 to 0.74, p=0.0071)

Reviewer's Comment: *CTN and CEA doubling times have not been validated as clinically meaningful subgroups in MTC. Furthermore, the in vitro assays of CTN, CEA, or plasma VEGFR2 have not been validated.*

Post-Hoc Analyses

A series of post-hoc analyses were conducted by the FDA in order to determine whether the improvement in PFS with vandetanib is consistent among the various subsets. The risk ratios were consistent for all subsets including: patients grouped according to last documented progression, time from diagnosis, and baseline tumor burden. The hazard ratio for patients enrolled on trial in the US was 0.46, which was slightly higher than the overall study population, but still suggestive of a benefit for vandetanib among US patients.

Figure 7: FDA Subgroup Analyses

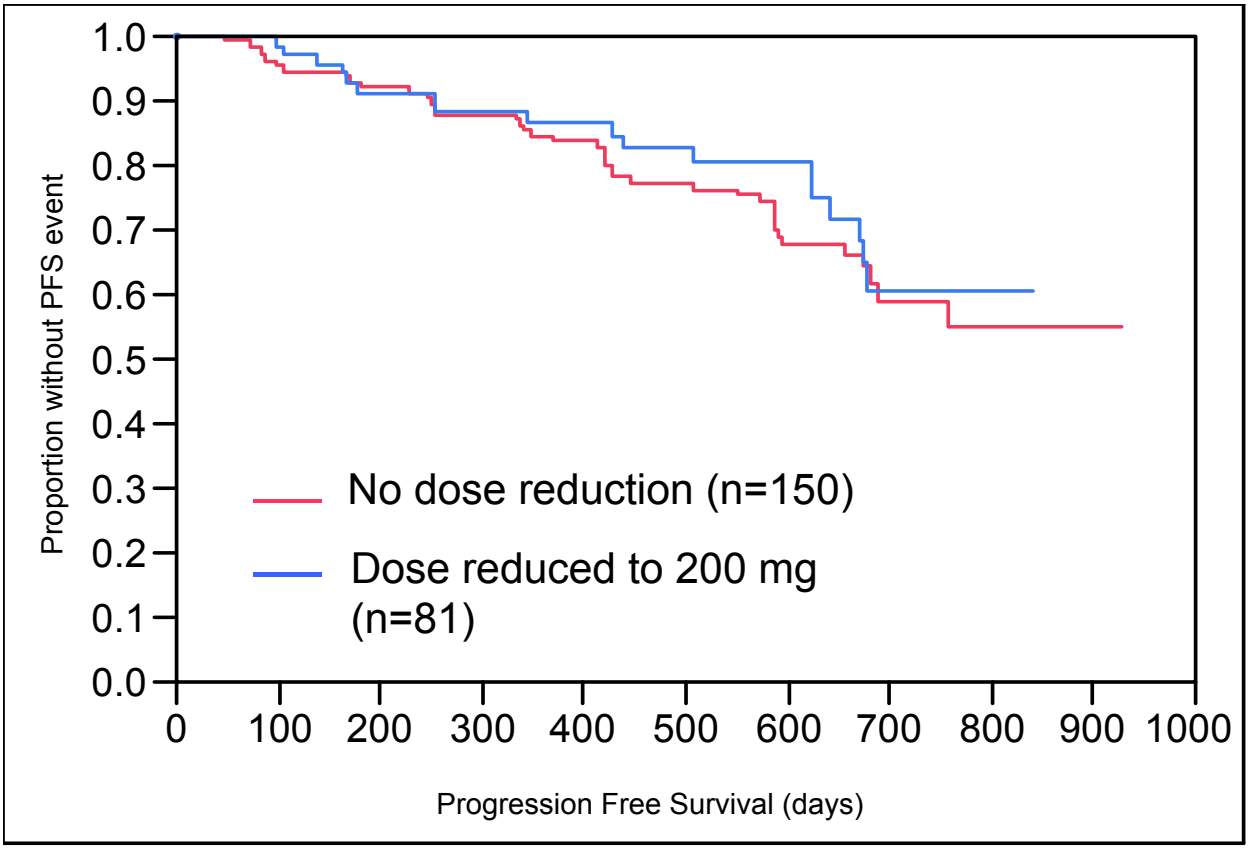


The vast majority of the patients on trial were WHO performance status 0 or 1 (96%); however, there still may be symptoms of pain or diarrhea even among patients with a performance status of 0-1. A post-hoc analysis of symptomatic patients v. asymptomatic patients was performed using a strict definition of asymptomatic, in that, only those patients with a WHO PS of 0 AND a stool frequency less than 4 times per day AND no pain on average at baseline of any type, were considered asymptomatic. The effect of vandetanib on PFS was consistent in both subsets (HR 0.38 95% CI 0.2, 0.75 for asymptomatic v. HR 0.31 95% CI 0.19, 0.53 for symptomatic patients).

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The FDA has performed an exploratory analysis in those patients who required dose reduction to 200 mg and compared them to patients who remained on 300 mg throughout the study. Figure depicts the Kaplan Meier curve comparing PFS for these patients, which demonstrates no clear difference between patient groups. This analysis suggests that patients undergoing dose reduction and those not undergoing a dose reduction benefited equally from treatment with vandetanib.

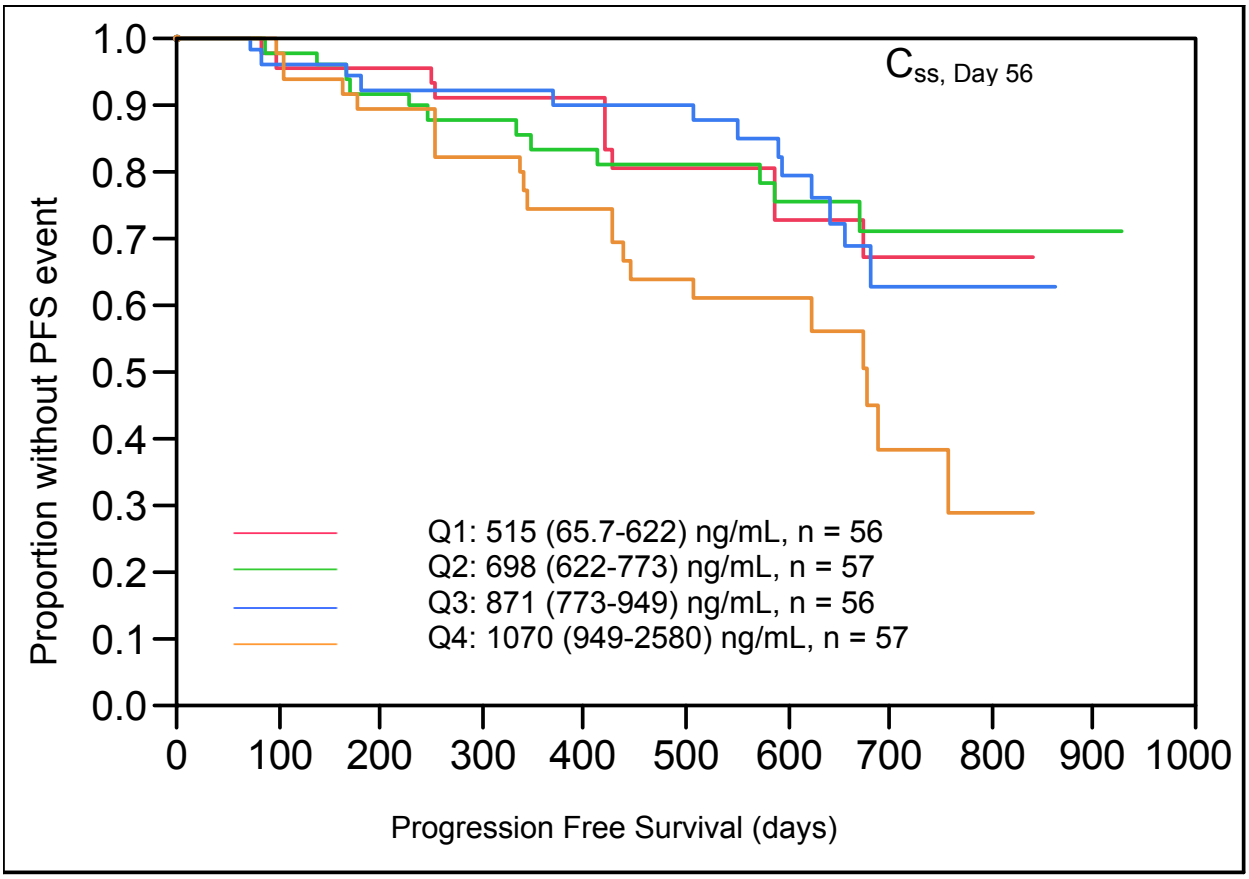
Figure 8: Kaplan Meier PFS Estimates: Dose Reduction v. No Dose Reduction



The FDA has conducted an exploratory analysis on any possible exposure-response relationships seen in Study 58. The trough concentrations at Day 56 were divided into quartiles and a Kaplan-Meier analysis was conducted to assess PFS in patients achieving different concentrations of vandetanib at steady state. The PFS curves of patients in different quartiles were not significantly different from each other, indicating a lack of relationship between steady-state plasma concentrations and PFS over this

range. Administration of lower dosages of vandetanib such as 200 mg or 100 mg would be expected to result in concentrations in the range found in quartile 1.

Figure 9: Exposure-Response Relationship Analysis



6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The median PFS for the vandetanib arm was not met. The median PFS for the placebo arm was 16.4 months (95% CI: 8.3, 19.7).

The median duration of response was not met for either treatment arm at the time of the data cut-off.

6.1.10 Additional Efficacy Issues/Analyses

Two single arm Phase 2 studies have been conducted in patients with hereditary medullary thyroid cancer.

Study 8
Study 8 administered 300 mg of vandetanib to 30 patients with hereditary medullary thyroid cancer. In general, the baseline disease characteristics of patients in Study 8 were more favorable than those in Study 58. However, while treatment was initiated with 300 mg of vandetanib, 80.0% of patients required a dose reduction or interruption. The table below shows the RR by investigator (RECIST criteria without a lower limit for nodal size) and IRC (modified RECIST criteria as in Study 58). While the investigator and IRC RR are similar, only 2 of the 6 patients with an INV response were considered responders by the IRC. Note that this response rate is markedly lower than the 45% RR seen in the Phase 3 trial.

Table 21: Response Rate Study 8 (Data Cutoff 2-22-08)

Response Rate (CR+PR)	Vandetanib 300 mg N = 30	Median Duration of Response (range)
Investigator Response	6 (20.0%)	311 days (137-850)
IRC Response	5 (16.7%)	500 days (337-980)

Study 68
Study 68 administered 100 mg of vandetanib to 19 patients with hereditary medullary thyroid cancer. This dose was chosen because it was estimated that the serum concentration achieved with 100 mg of vandetanib would be comparable to the IC_{50} for the RET gene. Again, the baseline disease characteristics of patients in Study 68 were, in general, more favorable than those in Study 58. Despite initiation of treatment with 100 mg of vandetanib, 21.1% required a dose reduction/interruption. The table below shows the RR by investigator using modified RECIST criteria (as in Study 58). On progression, patients thought to be benefitting could receive 300 mg vandetanib. Four patients choose this option; 3 had SD and 1 had PD.

Table 22: Response Rate Study 68 (Data Cutoff 1-31-08)

Response Rate (CR+PR)	Vandetanib 100 mg N = 19	Median Duration of Response (range)
Investigator Response	3 (15.8%)	168 days (158-245)

Note that while the investigator RR in patients receiving 100 mg of vandetanib in Study 68 appears to be markedly lower than the RR of the hereditary MTC patients in Study 58 (15.8% vs. 39.0%), it is similar to the investigator RR in Study 8 (15.8% vs. 20.0%).

Data Integrity

There were a total of 76 protocol violations. Most of the protocol violations were related to patients with laboratory values outside entry criteria. A large proportion of these patients were enrolled at site 2801. (b) (4) Overall, it is believed that these protocol violations should not impact the overall integrity of site-generated data as related to primary safety and efficacy analyses.

Table 23: Protocol Violations

	Vandetanib (n=231)	Placebo (n=100)	Total (n=331)
All	49	27	76
No measurable tumors at baseline*	9	5	14
Baseline RECIST scan >28 days	2	2	4
Randomized but did not receive treatment	0	1	1
CYP3A4 inducer taken for at least 14 days	0	1	1
No Confirmed Histological Diagnosis	1	0	1
At least 1 dose of incorrect treatment	1	0	1
Previous malignancies within 5 years	1	0	1
Laboratory values outside range	18	11	29
Concomitant medications violation	6	2	8
No serum pregnancy test	3	1	4
QTc unmeasurable or outside specified range	3	1	4
Suitable Archived sample not provided	10	5	15
History of excluded arrhythmia	1	0	1

* - As determined by investigator read.

Overall, there was excellent compliance to protocol mandated imaging assessments. Only 3 imaging assessments were missing and 40 assessments were performed outside the protocol-defined 2 week window.

Table 24: Missing Data

	Vandetanib (n=231)	Placebo (n=100)	Total (n=331)
Missing Time Points	3	0	3
Scans Outside 2wk Window	28	12	40

7 Review of Safety

Safety Summary

The safety of vandetanib was evaluated in 331 patients with advanced or metastatic medullary thyroid cancer in the phase 3 trial D4200C00058 (Study 58), in which patients were randomized to receive either vandetanib 300mg daily or placebo. A summary of important safety results from this study are included below.

- 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%) of placebo treated patients. The seven deaths on the vandetanib arm were secondary to staphylococcal sepsis, aspiration pneumonia, respiratory arrest, pneumonia, and one patient from acute cardiac failure and arrhythmia. Two patients died from sudden death and cardio-respiratory failure after the data cut-off, but are included in the safety analysis as they were initially randomized to vandetanib and died within 30 days of last dose. The patient on the placebo arm died due to gastrointestinal hemorrhage. There was an additional placebo death that Astra-Zeneca included in their totals for deaths on placebo, however in the safety database, the primary cause of death for this patient was listed as disease progression, therefore the FDA did not include this patient as a death from adverse event while on placebo.

  In the ISS database, deaths not directly attributed to disease progression were reported in 60 (4%) vandetanib-treated patients and 30 (3%) of placebo or control group patients. The majority of those deaths were patients randomized to erlotinib. For vandetanib treated patients, the causes of death that occurred in > 3 patients were sudden death, cardiac failure, dyspnea, pulmonary hemorrhage, pneumonia, pulmonary embolism, respiratory failure, and aspiration pneumonia.

- The most common (≥5%) grade 3-4 adverse reactions in the vandetanib-treated patients were diarrhea, QTc prolongation, hypertension, and fatigue.

- Adverse reactions of interest in the vandetanib-treated patients included diarrhea and other gastrointestinal toxicities, rash and other skin toxicities, hypertension, ocular toxicity, pulmonary-respiratory toxicity, headache, QTc prolongation and cardiac toxicity.

- Treatment discontinuations due to adverse drug reactions occurred in 12.1% of patients who received vandetanib and 3% of patients on placebo. The most common adverse reactions leading to treatment discontinuation on the

vandetanib arm were asthenia and fatigue (2.6%); gastrointestinal disorders (3.0%) which included diarrhea (0.9%), dyspagia (0.4%), nausea (0.4%), pancreatitis (0.4%), peritonitis (0.4%), small intestinal perforation (0.4%) and vomiting (0.4%); skin and subcutaneous disorders (1.7%) including rash (1.3%), excema (0.4%), photosensitivity reactions (0.4%) and pruritis (0.4%); QTc prolongation (0.9%); elevated creatinine (0.9%); and hypertension (0.9%).

- Dose reductions were reported in 49.4% of vandetanib-treated patients and 15.2% of placebo patients. 81 patients (35.1%) on the vandetanib arm were dose reduced to 200mg and further dose reductions to 100mg was required in an additional 32 patients (13.9%). The most common reasons for dose reductions were diarrhea, QTc prolongation and rash. Dose delays were reported in 47.2% of vandetanib treated patients and 15.2% of placebo treated patients. Of the 81 patients who had their dose reduced to the 200mg dose, 24 remained on the dose until data cut-off, 15 stopped due to disease progression, 8 stopped for AE's and 4 for other reasons. Of 32 patients who had their dose reduced further to 100mg, 17 remained on therapy until data cut-off, 5 stopped due to disease progression and 7 stopped for AEs and 3 for other reasons.

- 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 that have been treated thus far.

7.1 Methods

The phase 3 trial Study 58 included safety assessments at baseline, weekly for the first two weeks, then at four weeks, 8 weeks and 12 weeks after randomization and then every twelve weeks thereafter. Serious adverse events and study drug related adverse events that had not recovered completely by the end of treatment were to be followed until resolution unless in the investigator's opinion the event is unlikely to resolve due to the subjects underlying condition.

At baseline, safety assessments included medical, oncologic, and surgical history, physical exam, laboratories (hematology, chemistries, liver function, calcitonin and CEA, and 24 hour urinalysis), assessment of WHO PS, 12 lead ECG, and assessment of concomitant medications. Pre-infusion safety assessments were the same as at baseline. At the end of treatment, all patients received an ECG and RECIST tumor measurements. Post-treatment follow-up was to occur at 60 days and then survival data would be collected every 12 weeks from the patient or a patient representative until

death or until >50% of study patients had died. An amendment was made to the protocol and an ophthalmologic evaluation was obtained at baseline and then at visit 9 or at study discontinuation.

Reviewer comment: Of note, calcitonin measurements were obtained and were suppressed by vandetanib in 69.3% of patients and 3% of placebo patients. Similarly, CEA was suppressed in 51.5% of vandetanib treated patients and 2.0% of placebo patients. This, along with the side-effect profile, confounds the premise of a placebo controlled trial, as investigators would not be truly blinded to these values and thus would know those patients who were receiving study drug.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The major study under review in this NDA was study 58, a Phase III, randomized, double-blinded, placebo-controlled, multicentre study to assess the efficacy and safety of vandetanib 300mg daily in 331 patients with unresectable or locally advanced medullary thyroid cancer. Along with study 58, 10 additional studies were submitted by the sponsor to lend supportive safety data for the use of Vandetanib 300 mg as monotherapy in a total of 1839 patients. The majority of patients evaluated in the supplemental clinical trials focus upon different patient populations (such as advanced NSCLC) and have a shorter duration of treatment on the whole. There were an additional three studies that used 100mg of vandetanib in combination with various chemotherapeutic agents that were also included in the overall safety analysis.

Table 25: Pivotal and supportive studies contributing data to the overall safety assessment of vandetanib

Study number	Study Title	Number of patients and number receiving vandetanib	Dose of vandetanib	Control
D4200C00058 Study 58	An international, Phase III, randomized, double-blinded, placebo-controlled, multi-centre study to assess the efficacy of ZD6474 versus placebo in subjects with unresecatble locally advanced or metastatic medullary thyroid cancer	331 total 231 at 300mg 58 patients originally randomized to receive placebo received 300mg in open label phase	300 mg	Placebo
D4200C00001	An open, Phase I, rising	25 at 300mg	300mg	None

Study 1	multiple-dose tolerability study of ZD6474 in patients with malignant tumors.			
D4200C00002 Study 2	An open-label, mulitcentre Phase II study to assess the response of subjects with metastatic breast cancer, previously treated with anthracycline and taxane therapy with or without capcitabine, to ZD6474.	24 at 300mg	300 mg	None
D4200C00003 Study 3	A Phase II, randomized, double-blind, 2-part, multicentre study to compare the efficacy of ZD6474 with the efficacy of ZD1839 (Iressa™) in patients with locally advanced or metastatic (IIIB/IV) NSCLC after failure of either first-line and/or second line platinum-based chemotherapy and to assess the activity of ZD6474 in patients following failure of treatment with ZD1839.	83 as initial treatment 37 after gefitinib	300mg	Gefinitib 250mg
D4200C00007 Study 7	A randomized, partially blinded, Phase II study to assess the safety, tolerability, and efficacy of ZD6474 alone or in combination with paclitaxel and carboplatin in subjects with previously untreated unresectable locally advanced or metastatic.	73 at 300mg monotherapy	300mg	Multiple arms
D4200C00008 Study 8	An open-label, two stage, Phase II study to evaluate the efficacy and tolerability of ZD6474 in patients with unresectable locally advanced or metastatic hereditary medullary thyroid carcinoma.	30 at 300mg	300mg	None
D4200C00039 Study 39 Japan	A randomized, double-blind, parallel-group, Phase IIa dose-finding multicentre study to assess the efficacy (Objective response) and safety of ZD6474 100, 200 and 300mg/day in patients with	18 at 300mg	300mg	None

	advanced or metastatic (Stage IIIb/IV) or recurrent NSCLC who have failed one or two previous chemotherapy regimens at least one of which contained platinum			
D4200C00043 Study 43 (TVE-15-11) Japan	An open, Phase I, rising multiple dose tolerability study of ZD6474 in Japanese patients with solid, malignant tumors	6 at 300mg	300mg	None
D4200C00044 Study 44	A Phase III, international, randomized, double-blind, parallel-group, multicentre study to assess the efficacy of ZD6474 plus best supportive care versus placebo plus best supportive care in patients with unresectable advanced or metastatic (Stage IIIb/IV) NSCLC after prior therapy with an epidermal growth factor receptor tyrosine kinase inhibitor (EGFR TKI)	619 at 300mg	300mg	Placebo
D4200C00050 Study 50	A Phase I, randomized, open-label study to assess the effect of ZD6474 on vascular permeability in patient with advanced colorectal cancer and liver metastases.	12 at 300mg	300mg	None
D4200C00057 Study 57	A Phase III, randomized, double-blind, parallel-group, multicentre study to assess the efficacy of ZD6474 versus erlotinib in patients with unresectable locally advanced or metastatic (Stage IIb/IV) NSCLC after failure of at least one prior cytotoxic chemotherapy	623 at 300mg	300mg	Erlotinib
D4200C00032	A Phase III, Randomized, Double blinded, multi-center study to assess the efficacy and safety of docetaxel in combination with vandetanib versus docetaxel in combination with placeboi in patients with locally advanced	694 at 100mg	100mg	Placebo Docetaxel

	or metastatic (Stage iiib-IV) Non-small cell lung cancer (NSCLC) after failure of 1st line therapy			
D4200C00036	A Phase III, Randomized, Double blinded, Parallel-Group, Multi-center study to assess the efficacy and safety of vandetanib in combination with pemetrexed versus pemetrexed alone in patients with locally advanced or metastatic (Stage iiib-IV) Non-small cell lung cancer (NSCLC) after failure of 1st line therapy.	256 at 100mg	100mg	No control
D4200C00068	An open-label, two-Stage, Phase II Study to evaluate the efficacy and tolerability of ZD6474 in Patients with locally advanced or metastatic hereditary medullary thyroid carcinoma.	19 at 100mg	100mg	No control
D4200C00079	An international, Phase III, randomized, double-blinded, placebo-controlled, multi-centre study to assess the efficacy of ZD6474 versus placebo in subjects with unresecatble locally advanced or metastatic differentiated thyroid cancer	72 at 300mg	300mg	Placebo

7.1.2 Categorization of Adverse Events

MedDRA terminology (version 13.0) was used to characterize all adverse events in the phase 3 trial Study 58. Adverse event grading was done according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 3.0.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Adverse event data from 10 trials was included in the integrated safety database (see Section 7.1.1, Table 25 above). The rates of the most common (>10% of patients)

treatment-emergent adverse events in vandetanib-treated patients on study 58 were compared to event rates in the entire ISS database. This analysis is presented in Table 26 below.

Table 26: Incidence of Most Common (>10%) Treatment Emergent Adverse Events in ISS Database

Preferred Term	Study 58 N=231		ISS Database N= 1839	
	Grade 1-4	Grade 3-4	Grade 1-4	Grade 3-4
Diarrhea[1]	132 (57%)	26 (11%)	907 (49%)	90 (5%)
Rash[2]	123 (53%)	11 (5%)	968 (53%)	98 (5%)
Dermatitis Acneiform[3]	81 (35%)	2(1%)	294 (16%)	14 (0.8%)
Nausea	77 (33%)	2 (1%)	466 (25%)	19 (1%)
Hypertension[4]	76 (33%)	20 (9%)	400 (22%)	76 (4%)
Headache	59 (26%)	2 (1%)	223 (12%)	11 (0.6%)
Fatigue	55 (24%)	13 (6%)	408 (22%)	78 (4%)
Decreased Appetite	49 (21%)	10 (4%)	236 (13%)	27 (1%)
Abdominal Pain[5]	48 (21%)	6 (3%)	116 (6%)	15 (0.8%)
Dry Skin	35 (15%)	0	181 (10%)	4 (0.3%)
Vomiting	34 (15%)	2 (1%)	247 (13%)	19 (1%)
Asthenia	34 (15%)	6 (3%)	194 (11%)	50 (3%)
Electrocardiogram Qt Prolonged	33 (14%)	18 (8%)	121 (7%)	59 (3%)
Photosensitivity Reaction	31 (13%)	4 (2%)	87 (5%)	14 (0.7%)
Insomnia	30 (13%)	0	198 (11%)	2 (0.1%)
Nasopharyngitis	26 (11%)	0	80 (4%)	0
Dyspepsia	25 (11%)	0	90 (5%)	0
Hypocalcaemia	25 (11%)	4 (2%)	62 (3%)	9 (0.4%)
Cough	25 (11%)	0	282 (15%)	13 (0.7%)
Pruritus	25 (11%)	3 (1%)	156 (8%)	11 (0.6%)
Weight Decreased	24 (10%)	2 (1%)	134 (7%)	8 (0.4%)
Proteinuria	23 (10%)	0	124 (7%)	12 (0.7%)
Depression	22 (10%)	4 (2%)	76 (4%)	8 (0.4%)
Anorexia	NR	NR	185 (10%)	10 (0.5%)
Constipation	0	0	219 (12%)	6 (0.3%)

R_AE dataset w/ at least 10% of patients experiencing an AE in the Vandetanib arm
[1] Includes diarrhea, hemorrhagic diarrhea and colitis
[2] Includes rash, rash erythematous, generalized, macular, maculo-papular, papular, pruritic, exfoliative, dermatitis, dermatitis bullous, generalized erythema and eczema.
[3] Includes acne and dermatitis Acneiform

[4] Includes hypertension and hypertensive crisis
[5] Includes abdominal pain, abdominal pain upper and abdominal discomfort

In general, the toxicities were similar between the two safety datasets. Notable difference include grade 1-4 headache which was two times higher in study 58 as compared to the ISS safety database. Aceniform deramatitis was almost three times higher in the phase three study as compared to the ISS database, the cause for this is unclear as rash appears similar across both treatment groups. Photosensitivity reaction was higher in the Phase 3 study as well.

Abdominal pain and QT prolongation were two times higher in the Phase 3 MTC study, most likely due to the underlying disease being treated in Study 58. Medullary thyroid cancer patients have an increased incidence of diarrhea, cholelithiasis and electrolyte abnormalities that could have potentially exacerbated these two adverse events. Similarly, hypocalcemia was seen more than three times as frequently in study 58 when compared to the ISS dataset. MTC patients often are hypocalcemic at baseline given prior parathyroid removal and GI losses.

Depression, Nasopharyngitis and dyspepsia were also seen in higher frequency in the Phase 3 study as compared to the ISS database. No conclusions can be drawn from these numbers.

Alternatively, constipation and anorexia were seen more frequently in the ISS dataset. There were very few medullary thyroid cancer patients treated in this group of patients, made up of primarily non small cell lung patients.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The overall mean duration of exposure for the Phase 3 Study 58 was longer for patients treated with vandetanib than for placebo (607 days vs 279 days) and the exposure data can be seen in Table 27 below.

Dose reductions and interruptions were permitted in the Phase 3 study. The number of patients with dose reductions and interruptions that occurred during the randomized treatment are displayed in Tables 4 below.

Table 27: Median Duration of Exposure in the Phase 3 Study 58

	Vandetanib N=231	Placebo N=99
Duration of Exposure	607 days (15-929)	279 days (14-904)
Duration of exposure to 300 mg	187.5 days (1-929)	218 days (3-904)
Duration of exposure to 200 mg	148.5 days (3-801)	153, 158, 462
Duration of exposure to 100 mg	145 days (1-723)	0
Duration of exposure to 0mg	12 days (1-49)	0

Median duration of exposure: Used R_EX, TRTP = Y, EXDOSE not 0,ACTARM = placebo Median = 279

Table 28: Dose Interruptions and Reductions in the Phase 3 Study 58

	Vandetanib N=231	Placebo N=99
Dose Interruptions	109 (47%)	15 (15%)
Median Duration of Interruption	19 days (1-101)	9 days (2-30 days)
Median # Interruptions	1 (1-8)	1 (1-3)
Dose Reductions		
Any	83	3
Dose Reduced 1 Level	81	3
Dose Reduced 2 Levels	32	0

Used R_EX and TRTP = Y, Used EXDOSE = 0 for dose interruption then EXDURAZ for # days, EXDOSE = 300, 200, 100 for median duration of exposure

Median duration of interruption: Used R_EX, TRTP = Y, EXDOSE = 0, EXPID = dose interruption, ACTARM = placebo, Used EXDURAZ, 19 rows for placebo, added together durations for the same pt (N = 15) and Median = 9 (2-30)

Information pertaining to vandetanib dosing and dose reductions is summarized below.

In evaluating the Vandetanib treated population:

1. 231 patients received the 300 mg dose.

2. 81 patients received the 200 mg dose.

3. 1 patient received 200 mg every other day and 32 patients received 100 mg/d. The patient taking 200 mg every other day was changed to 100/d so in essence, 32 patients received 100 mg/d.

4. Dose was interrupted in 109 patients. The median duration of interruption was 23 days (1-101 d).

5. Looking at the 32 pts who received 100 mg/d and the 1 pt who received 200 every other day (total 32).
    a. 31 underwent dose interruption. The median # of interruptions was 2 (1-4).
    b. 30 patients had been dose reduced to 200 mg, leaving 1 patient who proceeded straight to 100 mg.
    c. The 1 pt who was dose reduced to 200 every other day was interrupted, dose reduced to 200 /d, then dose reduced to 200 every other day, then given 100 /d.

6. Looking at the 81 patients who received 200 mg/d
    a. 76 underwent dose interruption, with the median number of interruptions being 1, with a range of 1-4.
    b. 30 patients were later reduced to 100 mg

7. Interestingly, patient E3003001 was dose reduced for 101 days. This patient's dose was interrupted 9 times. The patient was not dose reduced, but maintained on 300 mg. All dose interruptions were due to grade 3-4 AE.

8. Overall, the reasoning for dose interruption was for the following reasons: AE < gr 3 (42), AE $\geq$ gr 3 (46), diarrhea (16), non-compliance (2), other (9), QT prolongation (19), rash (15).

9. Similarly, reasons for dose reduction were as follows: AE < gr 3 (23), AE $\geq$ gr 3 (21), diarrhea (12), other (6), QT prolongation (19), rash (15).

In evaluating the placebo patient population:

2. 99 pts received the 300 mg placebo dose.

3. Dose was interrupted once in 14 pts, twice in 1 pt, and 4 times in 1 pt. The median duration of interruption was 14.5 days with a range (2-30).

4. Dose was restarted at the same level in 11 pts.

5. Dose was restarted at a reduced dose in 3 pts

6. There is one additional patient not accounted for with a dose interruption. In this particular patient, the dose was interrupted on day 547 and permanent discontinuation occurred on day 556. This should have been listed as a permanent discontinuation rather than interruption because it does not appear that the dose was restarted, because of this, there is a discrepancy between the FDAs calculations and the applicants.

7. Reasons for dose interruptions include: AE < gr 3 (7 pts), AE ≥ gr 3 (4 pts), diarrhea (3), other (4). Diarrhea and AEs are counted separately and the pts don't overlap (for example, pts are not counted as both an AE and diarrhea).

8. Reasons for dose reductions include: diarrhea (1), AE < gr 3 (1), other (1).

7.2.2 Explorations for Dose Response

Please refer to the clinical pharmacology review for further details (sections 2.2.3-2.2.4.2).

Briefly, the major circulating metabolites, N-desmethyl vandetanib and vandetanib-N-oxide, were measured in healthy volunteers and NSCLC patients (Study 57), but not in MTC patients. N-desmethyl vandetanib had a similar potency for inhibition of VEGF-induced proliferation, EGF- and basic Fibroblast Growth Factor compared with vandetanib itself. The IC_{50} values of metabolites for RET is not reported. Vandetanib-N-oxide had relatively weak activity in cells ((b) (4) Both metabolites were shown to prolong QTc using the human ether-a-go-go gene (hERG) assay. However, the IC_{50} values were 3- and 10-fold greater, respectively, than that for vandetanib, which indicates they are less likely to cause QT prolongation compared to the parent.

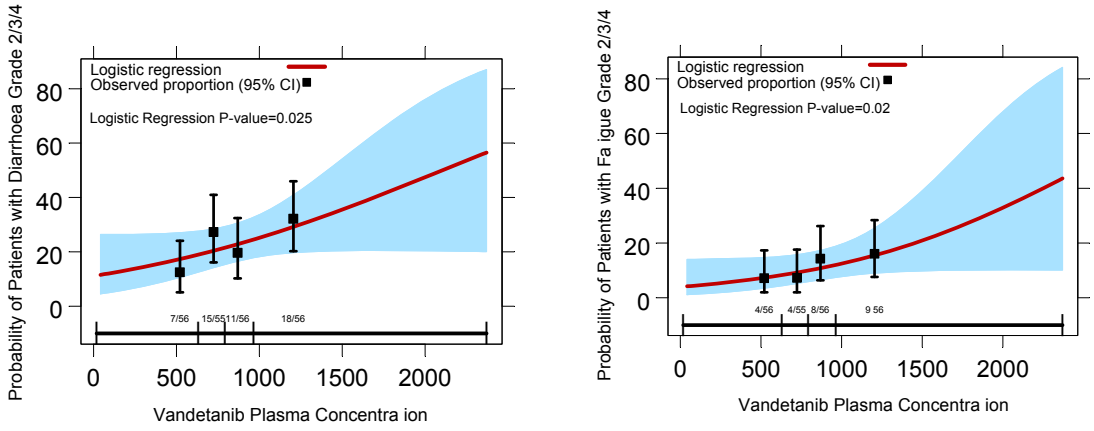


Figure 10. The relationship between $C_{ss,}$ Day 56 and the incidence of grade 2 or higher diarrhea (left) and fatigue (right). Solid black symbols represent the observed proportion of patients experiencing ≥ grade 2 AEs in each quartile of $C_{ss,}$ Day 56. The vertical black bars represent the 95% confidence interval. The solid red line and shaded area represent the predicted mean and 95% confidence interval for the probability of ≥ grade 2 adverse events. The exposure range in each quartile of $C_{ss,}$ Day 56 is denoted by the horizontal black line along with the number of patients with AEs/total number of patients in each quartile.

Significant exposure-response relationships were identified for diarrhea and fatigue, but not for hypertension or rash.

Figure 11: Relationship of Css with Diarrhea and Fatigue

The probability of diarrhea grade 2 or higher is significantly associated with $C_{ss,}$ Day 56 ($p = 0.025$) (Figure 10, left). Similarly, the probability of fatigue grade 2 or higher is significantly associated with $C_{ss,}$ Day 56 ($p = 0.02$) (Figure 10, right), whereas no significant exposure-response relationships were identified for either hypertension or rash. The shallow slopes of the logistic regression models for diarrhea and fatigue project a minimal decrease in AE incidence for dose reductions at the population level, which is consistent with the relatively low incidence of these AEs in the pivotal trial.

7.2.3 Special Animal and/or In Vitro Testing

See the pharmacology/toxicology review for details.

7.2.4 Routine Clinical Testing

See sections 7.4.2-7.4.4.

At baseline, safety assessments included medical, oncologic, and surgical history, physical exam, laboratories (hematology, chemistries, liver function, calcitonin and CEA, and 24 hour urinalysis), assessment of WHO PS, 12 lead ECG, and assessment of concomitant medications. Pre-infusion safety assessments were the same as at baseline. At the end of treatment, all patients received an ECG and RECIST tumor measurements. Post-treatment follow-up was to occur at 60 days and then survival data would be collected every 12 weeks from the patient or a patient representative until death or until >50% of study patients had died. An amendment was made to the protocol and an ophthalmologic evaluation was obtained at baseline and then at visit 9 or at study discontinuation.

7.2.5 Metabolic, Clearance, and Interaction Workup

See the summary of the clinical pharmacology review in section 4.4.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Vandetanib is a tyrosine kinase inhibitor that inhibits vascular endothelial growth factor (VEGF)-stimulated VEGF receptor-2 tyrosine kinase activity in endothelial cells. In

addition, vandetanib inhibits epidermal growth factor (EGF)-stimulated EGF receptor tyrosine kinase in tumor cells and endothelial cells. In vitro studies have also shown that vandetanib inhibits the activity of other tyrosine kinases, including rearranged during transfection (RET) and VEGF receptor-3 (Flt-4).

Sunitinib, sorafenib, erlotinib, gefitinib and pazopanib are FDA approved drugs currently in use that target similar receptors.

Sorafenib: Warnings and precautions include cardiac ischemia and infarction, hemorrhage, hypertension, gastrointestinal perforation. Temporary interruption is recommended in patients undergoing major surgery. Caution is recommended when co-administering substances metabolized/eliminated predominanatly by the UGT1A1 pathway (e.g. irinotecan), and also with docetaxel and doxorubicin. Common adverse reactions include fatigue, weight loss, rash/desquamation, hand-foot skin reaction, diarrhea, hair thinning, anorexia, nausea or vomiting, and abdominal pain.

Erlotinib: Warnings include pulmonary toxicity, myocardial infarction and ischemia, cerbrovascular accidents, microagniopathic hemolytic anemia and thrombocytopenia. As asymptomatic increases in liver transaminases have been noted, periodic monitoring is advised. Common adverse events include rash, diarrhea, anorexia, fatigue, dyspnea, cough, nausea, infection, vomiting, stomatitis, pruritis, dry skin, conjunctivitis, keratoconjunctivitis sicca, and abdominal pain.

Gefitinib: Warnings and precautions include pulmonary toxicity and hepatoxicity. Similar to erlotinib INR elevations were noted in people taking Coumadin. There is Phase II clinical data to suggest gefitinib increases the myelosuppressive effects of vinorelbine. The most common adverse reactions include diarrhea, rash, acne, dry skin, nausea,vomiting, pruritis, anorexia, asthenia, and weight loss. Similar to erlotinib there have been cases of interstitial lung disease noted.

Sunitinib: Precautions include left ventricular dysfunction, noting 15% of patients in 2 MRCC studies had decreases in left ventricular ejection fraction. Patients should be carefully monitored for clinical signs of CHF while receiving sunitinib. Hemorrhagic events occurred ion 26% of patients receiving sunitinib with metastatic renal cell carcinoma (MRCC) and 18% of GIST patients. Hypertension and adrenal toxicity are also listed as precautions. Adverse reactions include gastrointestinal disorders such as diarrhea, nausea, stomatitis, dyspepsia and vomiting. Skin discoloration and skin and hair depigmentation may occur. As well as rash and hand-foot syndrome. fatigue, anorexia, asthenia and bleeding were also commonly seen.

Pazopanib: A black box warning is in place for hepatotoxicity. Increases in serum transaminase levels and bilirubin have been observed as well as severe and fatal hepatotoxicity. Prolonged QT intervals and torsades de pointe have been observed. Fatal hemmorhagic events have been reported. Arterial thrombotic events have been

observed and can be fatal. Gastrointestinal perforation or fistula has occurred as well as fatal perforation events. Hypertension has been observed. Hyporthyroidism may occur and proteinuria can be seen. The most common adverse reactions are diarrhea, hypertension, hair color changes, nausea, anorexia and vomiting.

Class Concerns: All of the above drugs have a recommendation to avoid use of strong CYP3A4 inhibitors and inducers and all are Pregnancy Class D drugs. Interestingly, there was no clinically significant effect on exposure to vandetanib in the presence of the potent CYP3A4 inhibitor itraconazole in healthy volunteers. However, the potent CYP3A4 inducer rifampicin reduced exposure to vandetanib by 48% but increased exposure to the active N-desmethyl metabolite. Therefore, the effect of CYP3A4 inducers on the QTc effect is unclear. Patients receiving vandetanib should avoid the use of potent inducers of CYP3A4.

Tyrosine kinase inhibitors that inhibit VEGF and EGFR, including vandetanib are metabolized and excreted via the hepatic route. Single dose pharmacokinetic data from volunteers with hepatic impairment receiving 800mg suggested that there were no difference in pharmacokinetics compared to patients with normal hepatic function. After administration of radio-labeled vandetanib in healthy male subjects, both urine (25%) and fecal (44%) excretion are the major routes of elimination of vandetanib. Data from a single dose pharmacokinetic study in healthy volunteers with renal impairment resulted in a 40% increase in the mean AUC of vandetanib in patients with moderate and severe renal impairment. A dose reduction to 200 mg for patients with moderate and severe renal impairment is recommended. Single dose pharmacokinetic data from healthy volunteers with hepatic impairment suggests that there were no differences in pharmacokinetics compared to subjects with normal hepatic function. There is limited data in patients with hepatic impairment (serum bilirubin greater than 1.5 times the upper limit of normal). Vandetanib is not recommended for use in patients with hepatic impairment, as safety and efficacy have not been established.

7.3 Major Safety Results

7.3.1 Deaths

Table 29 below reports the causes of death in the major MTC study, as reported by the investigators, and classified as to whether the death was due to progression of disease and by the stage of the treatment study that the patient was in (randomized, open-label, during the safety follow up period of 60 days post discontinuation of treatment, or after the safety follow up. There were a total of 47 deaths reported. 21 of these deaths occurred after the 60 day safety follow up period. 18 of these deaths were thought to be

due to disease progression, 14 (6.1%) on the vandetanib arm and 4 (4.0%) on the placebo arm. 3 patient deaths were deemed not to be due to disease progression, 2 (.9%) on the vandetanib arm and 1 (1%) on placebo.

During the active stages of the study (randomized, open-label and safety follow up), there were a total of 26 deaths. 16 were in the vandetanib arm and 10 in the placebo arm. 6 (2.5%) of these deaths were deemed to be due to other causes besides disease progression in the vandetanib arm and 0 (0%) in the placebo arm.

Table 29: Summary of deaths in Study 58

	Vandetanib N=231	Placebo N=99	Total N=330
Total Deaths	32	15[2]	47
TEAEs	10	1	11
Progression	18	12	30
Other[4] Unknown Other Events	 3 1	 0 1	 3 2
Deaths within 30 days of Last Dose			
TEAEs	5	1	6
Progression	5	8	13
Other Unknown Other Events	 1 0	 0 0	 1 0
Deaths within 60 days of Last Dose			
TEAEs	7	1	8
Progression	8	9	17
Other Unknown Other Events	 1 0	 0 0	 1 0

1. Derived from R_DS dataset
2. All figures extend up to data cut off time is 7/31/2009
3. Patient E2501032 was randomized to placebo and died of progressive disease as per the sponsor, and was not included in the safety analysis set
4. One patient in the vandetanib group died from euthanasia and another in the placebo group died from a self-inflicted gunshot wound to head

At the time of the safety update, there were 2 additional deaths that occurred after the study cut off date that were attributable to sudden death (one AE listed as sudden death, the other as cardio-respiratory arrest).

In the absence of any contradictory evidence, in a drug that has the propensity to prolong the QT interval, one has to question whether the sudden death events could be directly attributable to QT prolongation.

Table 30 below contains a listing of the SAE's that were not due to disease progression. The listing also includes a patient with an SAE of disseminated intravascular coagulation 78 days after receiving his last dose of vandetanib. There was one patient who was excluded from study who was randomized to the placebo arm but who died before receiving his first dose of medication. This patient was excluded from the safety set. The case report narratives have been described below for the 6 patients who were on the vandetanib arm. Patient E2601003 is included in the table despite having died 78 days after the last day of treatment.

Table 30: Listing of key information for SAEs with outcome of death in Study 58 (randomized phase, Safety analysis set)

Treatment Received	AE Preferred Term	Time from start of randomized treatment to onset of AE	Sex/Age	Time from last dose to death
Vandetanib 300mg	Arrhythmia	439	M/42	(b) (6)
Vandetanib 300mg	Cardiac Failure Acute	431		
Placebo	Gastrointestinal Haemorrhage	80	M/52	
Vandetanib 300mg	Staphylococcal Sepsis	99	M/60	
Vandetanib 300mg	Pneumonia Aspiration	372	M/51	
Vandetanib 300mg	Respiratory Arrest	107	F/58	
Vandetanib 300mg	Respiratory Failure	174	M/83	
Vandetanib 300mg	DIC	677	M/31	
Vandetanib 300mg	Sepsis	678	M/31	

1. R_AE dataset
2. Patient E2601003 died at day 78 following last dose of treatment which was after the 60 day follow up time. The investigator deemed that his death from sepsis was not attributable to the study drug.

Reviewer comment: There were 2 deaths attributable to pneumonia or aspiration pneumonia in the phase 3 study. The majority of patients on study have undergone prior thyroidectomies (one or multiple) prior to being initiated on study drug. As vandetanib can increase asthenia and fatigue, it is postulated that this may increase weakness in the neck musculature and increase the propensity to develop aspiration pneumonia.

7.3.2 Nonfatal Serious Adverse Events

In Study 58, SAEs occurred in 30.7% of patients on the vandetanib and 13.1% of patients on the placebo arm. Serious adverse events in > 2% of patients in the vandetanib arm included diarrhea, pneumonia, and hypertension. During open label treatment, 26.5% of patients experienced a SAE. These events were similar to those that occurred during randomized therapy.

Grade 3-4 adverse events > 2% of patients are shown in the table below. Grade 3-4 adverse events were seen in 55.4% of patients in the vandetanib arm. This is greater than the 33% grade 3-4 adverse events that are expected at the maximum tolerated dose. During the open label phase, 45.1% of patients had a grade 3-4 adverse event.

Table 31: Serious Adverse Events in > 2% of Patients in Study 58

	Vandetanib N = 231	Placebo N = 99
All	30.7%	13.1%
Gastrointestinal Disorders		
Diarrhea	2.2%	0
Infections and Infestations		
Pneumonia	2.2%	0
Vascular Disorders		
Hypertension[1]	3.0%	0

From R_AE in section 5.3.5.1.25.3.1 using AESER = Y and AESTFLS = During, After

[1.] Includes accelerated hypertension, hypertensive crisis

No SAEs were reported in ≥ 2% of patients during open label vandetanib.

Table 32: Serious Adverse Events in > 2% of Patients in the 300mg monotherapy group

Serious Adverse Event	Vandetanib 300 mg Monotherapy N = 1550
All	364 (23.5%)
Infections and Infestations	
Pneumonia1	78 (5%)
Diarrhea2	32 (2%)

From R_AE in section 5.3.5.3.25.3.1 selecting on AESER = Y
1. Includes bronchopneumonia, lobar pneumonia, lower respiratory tract infection, lung infection
2. Includes diarrhea, enteritis, and gastroenteritis clostridial

7.3.3 Dropouts and/or Discontinuations

Reasons for treatment discontinuation are summarized in Table 33. Disease progression was the most common reason for treatment discontinuation in the vandetanib group. More patients discontinued treatment due to adverse events on the vandetanib arm than on the placebo arm (12.5% vs. 3%, respectively).

Treatment discontinuations due to adverse drug reactions occurred in 12.5% of patients who received vandetanib and 3% of patients on placebo. The most common adverse reactions leading to treatment discontinuation on the vandetanib arm of the Phase 3 study were skin disorders (2.5%), asthenia and fatigue (2.6%); gastrointestinal disorders (3.0%) which included diarrhea (0.9%), dysphagia (0.4%), nausea (0.4%), pancreatitis (0.4%), peritonitis (0.4%), small intestinal perforation (0.4%) and vomiting (0.4%); QTc prolongation (0.9%); elevated creatinine (0.9%); and hypertension (0.9%). These are summarized in the table below.

Table 33: Permanent Discontinuations due to Adverse Events in the randomized treatment phase

	Vandetanib N=231	Placebo N=99
Any Adverse Event[1]	29 (12.5%)	3 (3.0%)
Skin Disorders[2]	6 (2.5%)	0
Asthenia	4 (1.7%)	0
Fatigue	2 (0.9%)	0
Pyrexia	2 (0.9%)	0
Diarrhea	2 (0.9%)	1 (1.0%)
Elevated creatinine	2 (0.9%)	0

	Vandetanib N=231	Placebo N=99
QTc prolongation	2 (0.9%)	0
Hypertension	2 (0.9%)	0
General Physical Health Deterioration	1 (0.4%)	0
Dysphagia	1 (0.4%)	0
Nausea	1 (0.4%)	0
Pancreatitis	1 (0.4%)	0
Peritonitis	1 (0.4%)	0
Small Intestinal Performation	1 (0.4%)	0
Vomiting	1 (0.4%)	0
Gastrointestinal Hemmorrhage	0	1 (1.0%)
Reduced systolic function	1 (0.4%)	0
Cylothorax	1 (0.4%)	0
Cough	1 (0.4%)	0
Dysphonia	1 (0.4%)	0
Dysonea	1 (0.4%)	0
Pneumonitis	1 (0.4%)	0
Peripheral Ischemia	1 (0.4%)	0
Peripheral Sensorimotor Neuropathy	1 (0.4%)	0
Syncope	0	1 (1.0%)
Vision Blurred	1 (0.4%)	0
Arthralgia	1 (0.4%)	0
Germ Cell Cancer	1 (0.4%)	0
Left Bundle Branch Block	0	1 (1.0%)
Jaw Fracture	0	1 (1.0%)

Verified using R_AE dataset (TRTP & TRTP2, AECN)
When the open label portion of the study is included in the analysis, there were 2 discontinuations due to patients reporting blurred vision, and 2 patients reporting peripheral sensorimotor neuropathy.

1. The discrepancy between the number of individual adverse events and the total number of discontinuations is due to individual patients having any number of adverse events that caused discontinuation, i.e. one patient might have had diarrhea, fatigue and asthenia that led to discontinuation.

2. Skin disorders includes include rash, eczema, pruritis, and photosensitivity reaction.

Reviewer comment: There were several toxicities that were graded by CTC as Grade 1 and Grade 2. For instance, 2 patients discontinued due to grade 1 and grade 2 diarrhea. This highlights that even low grade toxicity is significant enough to disrupt a patient's life and lead to discontinuation. Similarly, there were 6 patients that discontinued due to grade 1 and 2 asthenia or fatigue. Given the toxicity profile of the untreated disease state, any additional toxicity could potentially make the treatment regimen intolerable.

Table 34: Permanent Discontinuations due to AEs in the ISS 300mg monotherapy group in >1 patient

Adverse Event	Vandetanib N=1550
Any Adverse Event	206 (13%)
Skin Disorders[1]	50 (3%)
Pneumonia[2]	14 (0.9%)
Diarrhea	10 (0.6%)
Dyspnea	10 (0.6%)
Asthenia and Fatigue	8 (0.5%)
Myocardial Infarction[3]	8 (0.5%)
Arrhythmic Events [4]	6 (0.4%)
Hemoptysis [5]	6 (0.4%)
Pulmonary Embolism	5 (0.3%)
QTc prolongation	4 (0.3%)
Hypertension[6]	4 (0.3%)
Nausea	3 (0.2%)
Cardiac failure	3 (0.2%)
Cerebrovascular Accident	3 (0.2%)
Pneumonitis & ILD	3 (0.2%)
Arterial Thrombotic Event [7]	3 (0.2%)
Vomiting	2 (0.1%)
Cerebral ischemia	2 (0.1%)
Cognitive disorder	2 (0.1%)
Dehydration	2 (0.1%)
Drug hypersensitivity	2 (0.1%)
Proteinuria	2 (0.1%)
Respiratory Failure	2 (0.1%)
Respiratory Tract Infection	2 (0.1%)

1. Skin disorders include acne, dermatitis aceneiform, dermatitis (allergic, bullous, and exfoliative), erythema, erythema multiforme, rash (exfoliative, erythematous,

generalized, maculo-papular, pruritic), pruritis, palmar-plantar erythrodesia, photosensitivity reaction, and Steven Johnson Syndrome.
2. Includes pneumonia and "lung infection"
3. Includes myocardial infarct, cardiac arrest, cardio-respiratory arrest, cardio-pulmonary failure
3. Includes myocardial infarct, cardiac arrest, cardio-respiratory arrest, cardio-pulmonary failure
4. Includes Ventricular Fibrillation, T wave Inversion and Atrial Fibrilliation, and Supraventricular Tachycardia
5. Includes hemoptysis, pulmonary hemorrhage and bronchial hemorrhage
6. Including hypertensive crisis
7. Includes Pulmonary Artery Thrombosis, Arterial Thrombosis Limb, Peripheral Arterial Occlusive Disease

Reviewer Comment: Two cases of "drug hypersensitivity" led to discontinuation of the study drug. After closer review of these two patient cases, it appears they were more in keeping with Grade 4 Stevens Johnson Syndrome (SJS). Interestingly, they both occurred in the same center in two different Chinese patients. Due to the low number of patients involved, it is impossible to draw any conclusions with regards to whether there is an ethnic pre-disposition to developing SJS.

7.3.4 Significant Adverse Events

Vandetanib at a dose of 300 mg is associated with a substantial (mean effect 35 ms) and concentration dependent prolongation in QTc. This increase in mean QTc does not lessen over time and the half-life of vandetanib (19 days) makes this prolongation in QTc interval particularly problematic. In addition to QTc prolongation, the majority of the severe adverse events seen with both EGFR and VEGFR inhibitors have been reported with vandetanib. This includes Stevens-Johnson syndrome, some ischemic arterial events, and interstitial lung disease. While Stevens-Johnson syndrome or toxic epidermal necrolysis is uncommon, it has resulted in death. Risk factors for evolution of rash into Stevens-Johnson syndrome are unclear with 8 of 21 patients receiving radiation prior to development of Stevens-Johnson syndrome (unknown if initial rash was in the area of prior radiation).

Cerebrovascular events may be increased while cardiac events do not appear to be increased with vandetanib. For example, during the randomized portion of Study 58, a cerebrovascular event (cerebral ischemia, TIA) occurred in 1.3% patients in the vandetanib and in no patients in the control arm while coronary occlusion was reported in 1 (0.4%) patient in the vandetanib and in no patients in the control arm. This increase in cerebrovascular events appears to be consistent among the randomized trials.

However, it is very dependent upon which terms are included as a cerebrovascular event.

Interstitial lung disease and pneumonitis have also been reported more frequently in patients receiving vandetanib. In a large study of patients with non-small cell lung cancer, interstitial lung disease/pneumonitis was reported in 3.5% of patients receiving 100mg vandetanib + docetaxel and in 2.0% of those treated with docetaxel alone. Overall, 23 patients have been reported to have grade 3-4 interstitial lung disease or pneumonitis, with at least 8 patients receiving prior radiation to the chest. While the overall number of patients is small, the number of patients with dyspnea or hypoxia is much larger. For example, while grade 3-5 interstitial lung disease/pneumonitis was reported in 23 patients, dyspnea/hypoxia was reported in 392 (13.0%) patients in the vandetanib safety database and was grade 3-4 in 108 (3.6%) patients. In addition to the events listed in Table 35, 3 additional patients (not on Astra-Zeneca studies) have been reported to have RPLS. Finally, vortex keratopathy has also been reported in patients on vandetanib. This continues to be examined.

Table 35: Significant Adverse Events in the Vandetanib Safety Database

Significant Adverse Events in the Vandetanib Safety Database (Data Cutoff 7/31/09 and 10/19/09)	
	N=3019
Grade 3-4 Interstitial Lung Disease or Pneumonitis	23 (0.8%)
Ischemic Cerebrovascular Events	26 (0.9%)
Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis	21 (0.7%)
Cardiac Failure/ Cardiomyopathy	15 (0.5%)
Hypertensive Crisis or Grade 4 hypertension	11 (0.4%)
Pancreatitis[1]	7 (0.2%)
Intestinal Perforation	6 (0.2%)
Torsades de Pointes/ Sudden Death[2]	3 (0.1%)/9 (0.3%)
Reversible Posterior Leukoencephalopathy Syndrome (RPLS)	1 (<0.1%)

[1]Includes acute pancreatitis and hemorrhagic pancreatitis
[2]Includes cardiac arrest, cardiorespiratory arrest, sudden death, acute death, and arrhythmia (if resulted in death).

Intestinal perforation is included in the table above. However, its association with vandetanib is unclear. In 4 large randomized trials, when the number of patients who developed intestinal perforation (or pneumatosis intestinalis) was compared between arms, the number of patients in the vandetanib arm was increased in 2 of the 4 trials.

7.3.5 Submission Specific Primary Safety Concerns

Torsades de Pointes:

Study 58: There were no reported cases of Torsades noted in Study 58. The R_AE database lists "arrhythmia" in two patients, one grade 1 arrhythmia in a placebo patient and one grade 5 arrhythmia in a vandetanib patient. The patient (E2301006) narrative is summarized above. Briefly, there were no ECGs performed at the time of death, however, ventricular tachycardia was noted on the cardiac monitor at the time of death. ECGs performed within the week before death all were read by the central ECG vendor as having prolonged QTc intervals of 547, 556 and 538 ms respectively. The investigator attributed the patient's cause of death likely to be from vandetanib. Ventricular tachycardia Grade 2 was noted in another vandetanib patient, and lastly the term tachycardia was noted in an additional four patients: two grade 1 events in placebo patients and a grade 2 and grade 3 in the vandetanib patients. There are no further details regarding these events.

ISS database: In the ISS database, Grade 2 Torsades de Pointes was reported in one patient in study 57 on the vandetanib arm (E1304012) after 12 weeks of being on study. Additionally, there were four sudden death events reported in Study 57 (patients E1517004, E2705003, E3203010 and E3702012), only one of which was on the vandetanib 300mg arm, the other 3 were on the erlotinib arm.

Grade 4 Ventricular tachycardia occurred in one patient in study 57 treated with Vandetanib 300mg. Additionally, there were 2 patients in study 57 on the vandetanib arm who experienced Grade 4 ventricular fibrillation.

The term arrhythmia was invoked for an additional 9 patients in the ISS database, 7 of which were on vandetanib containing treatment arms in studies 3, 39, 44 and 57. The AEs were not graded in 3 patients. Alternatively, there was one grade 1 toxicity, two grade 2 and one grade 4.

Torsades was also noted in a patient with differentiated thyroid carcinoma in Study 79 after 5 weeks of being on study. The patient is a 79 yo man with an extensive past medical history including hypertension and hypercholesterolemia, right bundle branch block, and transient ischemic attack. The patient presented to clinic for routine examination while on trial and was noted to be bradycardic with a BP of 160/90. The patient was instructed to perform some knee bends in attempts to raise his heart rate

but quickly loss consciousness. Artificial respiration and cardiac massage were started. During defibrillation the patient was noted to be in AV block which led to torsades. Involuntary seizure like activity ensued and the patient was transferred to the ICU. A 2 chamber ICD was implanted due to several episodes of Torsades and ventricular tachycardia. Of note, the patient had a normal baseline ECG with no QTc prolongation. Study drug was stopped on an unspecified day and the patient recovered. The investigator did attribute this event to the study drug in combination with concomitant hydrochlorothiazide and losartan.

Reviewer comment: This patient was also noted to be bradycardic, an issue that many MTC patients have to contend with due to hypothyroidism. This is a known confounding factor that can exacerbate QT prolongation in patients that are on QT prolonging medications.

Overall, serious arrhythmias (including grade 3-4 arrhythmia, grade 3-4 ventricular tachycardia or ventricular fibrillation and Torsades) were seen in 9 patients in the integrated safety summary. An additional 4 patients may have had arrhythmias leading to sudden death, it is unknown. Two of the patients for which we have patient narratives to review did not have any history of cardiac disease, but both had a history of lung lobectomy for lung cancer.

Steven's Johnson Reaction:

The table below provides information on the incidence of skin reactions with the EGFR inhibitor vandetanib in Study 58. This study recommended steroid creams, topical or systemic antibiotics, and topical or systemic antihistamines to manage events ≥ grade 2. For grade 3-4 events, study drug was temporarily discontinued until the reaction resolved to grade 1 or baseline followed by continuation of study drug at a reduced dose. Patients who developed a grade 3-4 reaction despite 2 dose reductions or patients in whom study drug was withheld > 3 weeks permanently discontinued study drug.

Table 36: Skin Adverse Events on the Phase 3 MTC study

Skin Disorders	Vandetanib N = 231		Placebo N = 99	
	Gr 1-4	Gr 3-4	Gr 1-4	Gr 3-4
All	88.3%	7.8%	24.2%	0
Rash[1]	53.2%	3.9%	12.1%	0
Acne[2]	35.5%	0.9%	7.1%	0
Dry Skin/Chapped Skin	15.2%	0	5.1%	0
Photosensitivity Reaction	13.4%	1.7%	0	0
Erythema/Generalized Erythema[3]	10.8%	1.3%	3.0%	0
Nail Disorder[4]	9.1%	0	0	0
Skin Hyperpigmentation[5]	7.4%	0	0	0

Skin Exfoliation/Breakdown/Fissures	4.8%	0.4%	0	0
Folliculitis	3.0%	0	1.0%	0
Dermatitis	2.2%	0	0	0
Skin Discoloration	2.2%	0	0	0
Skin Lesion	2.2%	0	1.0%	0
Palmar-Plantar Erythrodysaesthesia[6]	1.7%	0.4%	0	0
Urticaria	1.7%	0	0	0
Paronychia	1.3%	0	0	0
Skin Ulcer	1.3%	0	0	0
Allergic Dermatitis	0.9%	0	0	0
Cellulitis	0.9%	0	0	0
Dermatitis Bullous	0.9%	0.4%	0	0
Skin Candida	0.9%	0.4%	0	0
Actinic Keratosis	0.4%	0	0	0
Erysipelas	0.4%	0.4%	0	0
Erythema Migrans	0.4%	0	0	0
Palmar Erythema	0.4%	0	0	0
Skin Atrophy	0.4%	0	0	0
Skin Hemorrhage	0.4%	0	0	0
Skin Pain	0.4%	0	0	0
Pigmentation Loss	0	0	1.0%	0
Rosacea	0	0	1.0%	0

[1]Includes rash erythematous, generalized, macular, maculopapular, papular, pruritic, pustular, exfoliative, and butterfly as well as eczema.
[2]Includes acne, acne pustular, and dermatitis acneiform.
[3]Also includes skin irritation with a reported term of erythema
[4]Includes nail bed infection, inflammation, and tenderness, as well as nail disorder and infection. Also includes onychoclasis and yellow nail syndrome.
[5]Often blue or grey spots.
[6]Also includes skin reaction with a reported term of hand foot skin reaction

Table 36 above provides information from the randomized phase of Study 58. During open label treatment, 58.9% of patients reported a skin disorder. This includes 9 patients who reported a grade 3-4 event. In the vandetanib 300 mg monotherapy program, skin disorders occurred in 1177 patients while grade 3-4 events occurred in 334 (22%) of patients.

Patients on vandetanib who developed a rash, acne, or a photosensitivity reaction (N = 121) during randomized therapy were examined more closely. The time to onset of these reactions varied from day 1 to day 749 on treatment. The median duration, for 65 available events, was 101 days suggesting that these events are persistent. Serious adverse events due to any skin disorder, randomized and open label, were also examined to evaluate concomitant medication use. Five of these events had resolved at the time of data cutoff with the use of anti-histamines, antibiotics, and methylprednisolone. In 1 patient surgery was required to treat a skin ulcer.

Reports of Stevens-Johnson syndrome (6 patients), erythema multiforme (3 patients), toxic epidermal necrolysis (4 patients), and toxic skin eruption (5 patients) are included in the safety database (vandetanib monotherapy and combination trials). This includes

one death in a patient with a toxic skin eruption receiving 100 mg vandetanib and docetaxel. Nine of these events occurred on 100 mg vandetanib + docetaxel while 9 occurred on monotherapy. Time of onset varied from day 17 to day 255 and in some patients this event persisted for several months. As in Study 58, patients received either/both topical treatment and systemic steroids and antibiotics. Thus, while the incidence of skin disorders such as rash, acne, photosensitivity is common, a small number of patients do go on to experience Stevens-Johnson syndrome or toxic epidermal necrolysis and these events can result in death.

Gastrointestinal Perforation:

Gastrointestinal perforation is a well known toxicity in drugs that inhibit VEGF. However, it is unclear as to whether there is an association between GI perforation and vandetanib. In 4 large randomized trials, when the number of patients who developed intestinal perforation (or pneumatosis intestinalis) was compared between arms, the number of patients in the vandetanib arm was increased in 2 of the 4 trials. There were 5 cases of gastrointestinal perforation or pneumatosis intestinalis in the vandetanib ISS monotherapy database and two of these were in placebo patients. Given the small number of patients, no conclusions can be made at this time.

Cardiac Failure:

There were 13 cases (0.8%) of cardiac failure noted in the ISS 300mg vandetanib monotherapy group some of which have led to death. Echocardiograms were not monitored regularly throughout most studies so it is unclear whether this number underresresents the true incidence of cardiac failure. Cardiac failure has been associated with other tyrosine kinase inhibitors and in future studies using vandetanib, echocardiograms or other functional cardiac testing should be monitored. As cardiac failure can exacerbate QT prolongation, this is an important consideration for future studies.

Interstitial Lung Disease (ILD):

There were no reported cases of the specific preferred term ILD in the randomized portion of study 58. However, there were 2 (0.9%) cases of pneumonitis of CTCAE Grade 3. Radiographs of the chest did show an interstitial infiltrate, but both cases were regarded by the investigators as unrelated to study therapy. In one patient (E2501011), Grade 2 pneumonitis developed at day 234 and resolved by day 244, followed by a separate event at day 277 which again resolved at day 296. There were no treatments reported as being given for the pneumonitis. The second patient with pneumonitis developed their AE on day 536 and it continued until day 739. The patient was administered cefixime from days 550-554. Therapy was discontinued for this patient. An additional patient in the open-label phase was reported to have had Grade 1 ILD following administration of contrast material during a cardiac catheterization procedure

for myocardial infarction. This was also deemed unrelated to study treatment by the investigator.

The Study 58 R_AE database was queried for the terms pneumonitis, dyspnea, dyspnea exertional, hypoxia, and respiratory failure. 22 patients on the vandetanib arm were identified, 6 of which had grade 3 toxicity. The preferred terms for these patients were dyspnea, pneumonitis and respiratory failure. The median amount of days on treatment was 406.5, the range was from 36 days to 703 days.

Table 37: Respiratory toxicity on Study 58

	Vandetanib Grade 1-4 N=231	Vandetanib Grade 3-4 N=231	Placebo Grade 1-4 N=99	Placebo Grade 3-4 N=99
Pneumonitis	2 (0.8%)	1 (0.4%)	0	0
Dyspnea	18 (7.7%)	4 (1.7%)	9 (9%)	3 (3%)
Respiratory Failure	2 (0.8%)	2 (0.8%)	0	0
Hypoxia	0	0	0	1 (1%)

In the ISS database, there are 6 (1%) cases of interstitial lung disease identified (not including study 58). 4 cases were on study 3, 1 was on study 39 and 1 on study 57. The grade was only available for the patient on study 57 and was listed as Grade 4. All the patients on Study 3 were NSCLC patients. One patient developed the interstitial lung disease while on gefitiinib, prior to receiving vandetanib. Once starting vandetanib, they did not have a recurrence of the ILD. Another patient developed ILD on (b) (6) after an episode of grade 2 pharyngitis. Their lung disease was complicated by pleural effusions. The ILD was reported as having resolved by (b) (6) Patient E0043002 enrolled on study 3 began treatment on (b) (6) and was withdrawn from treatment on (b) (6) due to disease progression. On b) (6) the patient was hospitalized for orthopnea, productive cough and dyspnea. He was treated with cefuroxime, erythromycin, itraconazole, and codeine phosphate/paracetamol for chest infection. A lung biopsy performed on (b) (6) revealed severe interstitial fibrosis without obvious cause. "No obvious causes (silica particles, asbestos bodies, granulomas) can be found histologically. In light of the history, it is possible that the lung fibrosis could be caused by the study medication." The patient was started on prednisilone and oxygen and his condition improved and the patient was discharged, however the patient died one day after discharge. A 43 yo woman was treated on study 57 starting on (b) (6). 9 days later she was diagnosed with ILD and was discontinued off of therapy. The patient was hypoxic requiring 100% oxygen and antibiotics were administered. At the time of the sponsors report, the patient still had not recovered. The investigator considered the event related to therapy.

Table 38: Respiratory toxicity in the ISS safety database

	Vandetanib Grade 1-4 N=1550	Vandetanib Grade 3-5 N=1550
Interstital Lung Disease	5 (4 unknown grade)	1
Pneumonitis	10 (1 unknown grade)	4
Dyspnea [1]	204 (57 unknown grade)	53
Respiratory Failure	9 (3 unknown grade)	6
Hypoxia	12 (7 unknown grade)	4

(Safety, AEANFL, 300mg monotherapy group)
[1]Dyspnea and dyspnea exacerbated

In study 32, ILD was reported more frequently in patients treated with 100mg vandetanib + docetaxel (2.5%) than with docetaxel alone (0.9). Interestingly, that study also reported ILD more frequently in Japanese patients (16.7% in docetaxel +vandetanib group vs. 7.4% docetaxel alone) than in patients from outside Japan (0.8% vandetanib/0.2% docetaxel alone). The other Phase III studies in NSCLC have reported incidences of ILD of less than 1% with vandetanib, however these studies did not include patients from Japan. The sponsor postulates as to whether the ILD frequency seen in Study 32 could have been the effect of the drug on a Japanese population. The overall incidence of ILD in the 300 mg monotherapy pool was 0.2%.

Study 32—Phase III, randomized, double blinded, multi-centre study to assess Safety and Efficacy of docetaxel in combination with vandetanib versus docetaxel plus placebo in patients with advanced NSCLCa after failure of first line therapy

Table 39: Respiratory Toxicity in Study 32

	Vandetanib+ docetaxel Grade 1-4 N=694	Vandetanib + docetaxel Grade 3-4 N=694	Docetaxel + Placebo Grade 1-4 N=697	Docetaxel + Placebo Grade 3-4 N=697
ILD	17 (2.4%)	4 (0.6%)	6 (0.8%)	3 (0.4%)
Pneumonitis	7 (1%)	2 (0.2%)	8 (1%)	4 (0.5%)
Dyspnea	113 (16.3%)	29 (4.0%)	137 (20%)	35 (5%)
Respiratory Failure	5 (0.7%)	5 (0.7%)	7 (1%)	7 (1%)
Hypoxia	10 (1.4%)	3 (0.4%)	5 (0.7%)	2 (0.2%)

Safety, AEANFL, AESTFL(after before/during,during,during after)

Reversible Posterior Leukoencephalopathy (RPLS):

RPLS is a syndrome characterized by headache, confusion, seizures and visual loss. On MRI of the brain, areas of edema are seen. There were no cases of RPLS identified in study 58. 4 cases of RPLS have occurred in the vandetanib treatment program as a whole. One case occurred in Study 32 in a patient who received 100mg daily in combination with chemotherapy for NSCLC. Two cases occurred in pediatric patients with primary brain tumors receiving vandetanib with concomitant radiation therapy in an investigator sponsored study (IRUSZACT0051). One case occurred in another investigator sponsored study in a patient receiving vandetanib in combination with gemcitabine and oxaliplatin for transitional cell cancer. There were no cases seen in any of the 300mg treatment groups.

Because the diagnosis of RPLS is based on characteristic magnetic resonance imaging (MRI) findings, and some patients with seizures or other neurologic signs may not have had MRI imaging, there is a possibility that RPLS has been under diagnosed.

Reviewer comment: RPLS has been noted with other anti-VEGF therapies. No conclusions can be drawn from the cases presented above due to the small number of patients overall. This reviewer believes that besides note of the possibility of RPLS in the package label, there should be language to suggest that the incidence may be higher in patients on treatment with uncontrolled hypertension, as 75% of patients that developed RPLS experienced elevated blood pressure, including one pediatric patient. Strong language should be inserted with respect to controlling HTN. 2 patients had been treated with radiation therapy for brainstem gliomas, it is unclear whether there is any correlation between radiation and RPLS.

Diarrhea

Diarrhea is of particular concern in this patient population for many reasons. First, patients with medullary thyroid carcinoma often have significant diarrhea at baseline. The ability of the tumor to secrete calcitonin, occasionally along with other hormonally active peptides like ACTH or calcitonin-gene related peptide (CGRP), can contribute to the development of diarrhea. These patients, when confronted with grade 1 or grade 2 diarrhea are by CTCv.4 definition, having anywhere between 1-6 stools per day *OVER* their baseline, which can already be quite high. Secondly, in a drug that can elicit QTc prolongation, the propensity of the drug to cause diarrhea can lower a patient's threshold for developing QTc prolongation derived arrhythmias.

In Study 58, 130 (56%) patients randomized to the vandetanib 300mg arm reported diarrhea which made it the most common adverse event reported in the study. This

was compared to 26% of the placebo population. Grade 3 or higher diarrhea was seen in 11% of patients on vandetanib.

The study 58 protocol recommended "standard medications" for the treatment of diarrhea in order to avoid dose interruptions and modifications. No dose modifications were made for Grade 1 or 2 diarrhea. Electrolyte supplementation was encouraged to avoid risk of prolonged QTc. In R_AE dataset, a search for all terms related to diarrhea was performed. Patients with the preferred terms diarrhea, colitis, hemorrhagic diarrhea, frequent bowel movements, fecal incontinence, and malabsorption are evaluated further. The study day of the start of the adverse event ranged from -29 days (highlighting the fact that many of these patients had diarrhea preceding their initiation of therapy) to 794 days on therapy. A similar wide range was seen in the duration of the AE ranging from unknown to 622 days. In the R_AE dataset there were only a handful of patients where there was note of the treatment for diarrhea, primarily in patients whose diarrhea led to an SAE. Immodium was one treatment intervention. IV fluids, Calcium, magnesium, and potassium was listed as another intervention on two patients. IV solumedrol was given with IV fluids to one patient, and cholestyramine was administered to another patient. Another patient required 1.5 L fluids daily, with loperamide and activated charcoal. Levaquin and metronidazole were given to one patient with a diagnosis of colitis. All events resolved in these 8 patients with the exception of one where the AE was listed as on-going.

The concomitant medication dataset listed many drugs as having been taken for the treatment of diarrhea, including loperamide, opium alkaloid, octreotide, paregoric, lomotil, metamucel, opium tincture, dicyclomine hydrochlrodie, motofen, ms contin, laudanum, spasmine, nifuroxazide, dihydrocodeine (DHC), smectite, codeine, mesalazine, granisetron, trimebutine maleate, rifaximin, and attapulgite.

The median day of diarrhea onset was 10 days for patients on Vandetanib during cycle 1. 13 people had grade 3-4 diarrhea on vandetanib during cycle 1 and the median onset was on day 15. Of these 13 patients, 6 patients temporarily stopped therapy, 1 permanently stopped therapy and 2 necessitated a dose decrease.

Cerebrovascular Accident:

Table 40: Cerebrovascular Events reported in randomized studies using vandetanib

	Cerebrovascular Events- Narrow[1]	Cerebrovascular Events- Broad[2]
Study 58		
Vandetanib N=231	1.3%	2.2%
Placebo N=99	0	0
Study 3		

	Cerebrovascular Events- Narrow[1]	Cerebrovascular Events- Broad[2]
Vandetanib N=83	1%	2%
Control N=85	0	2%
Study 32		
Vandetanib N=689	4%	10%
Control N=690	2%	8%
Study 36		
Vandetanib N=260	4%	7%
Control N=273	0	4%
Study 44		
Vandetanib N=619	1.1%	1.9%
Control N=303	1.6%	2.3%
Study 57		
Vandetanib N=623	6%	11%
Control N=614	4%	7%

[1]Includes CVA, TIA, cerebral ischemia, cerebral infarction, ischemic stroke, cerebral thrombosis
[2]Includes cerebral hemorrhage, dysarthria, dysphasia, facial palsy, aphasia, hemiplegia, hemiparesis, brain stem hemorrhage, facial paresis, cerebral artery embolism

- Study 58: Vandetanib vs. Placebo in Medullary Thyroid
- Study 3: Vandetanib vs. **Iressa** in 2nd or 3rd Line NSCLC
- Study 32: Vandetanib + Docetaxel vs. Placebo + Docetaxel in 1st Line NSCLC
- Study 36: Vandetanib + Pemetrexed vs. Placebo + Pemetrexed in 2nd Line NSCLC
- Study 44: Vandetanib vs. Placebo in 3rd Line NSCLC
- Study 57: Vandetanib vs. **Erlotinib** in 2nd Line NSCLC

Patients treated with vandetanib had a higher incidence of cerbrovascular events in the Phase 3 medullary thyroid study as compared to placebo. This also occurred in the majority of the other randomized studies, with the exception of study 44.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events in >10 of treatment group in Phase 3 MTC study

Table 41: Adverse Events in >10 of treatment group in Phase 3 MTC study

Preferred Term	Vandetanib N=231		Placebo N=99	
	Grade 1-4	Grade 3-4	Grade 1-4	Grade 3-4
Diarrhea[1]	132 (57%)	26 (11%)	27 (27%)	2 (2%)
Rash[2]	123 (53%)	11 (5%)	12 (12%)	0

Dermatitis Acneiform[3]	81 (35%)	2 (1%)	7 (7%)	0
Nausea	77 (33%)	2 (1%)	16 (16%)	0
Hypertension[4]	76 (33%)	20 (9%)	5 (5%)	1 (1%)
Headache	59 (26%)	2 (1%)	9 (9%)	0
Fatigue	55 (24%)	13 (6%)	23 (23%)	1 (1%)
Decreased Appetite	49 (21%)	10 (4%)	12 (12%)	0
Abdominal Pain[5]	48 (21%)	6 (3%)	11 (11%)	0
Dry Skin	35 (15%)	0	5 (5%)	0
Vomiting	34 (15%)	2 (1%)	7 (7%)	0
Asthenia	34 (15%)	6 (3%)	11 (11%)	1 (1%)
ECG Qt Prolonged[6]	33 (14%)	18 (8%)	1 (1%)	1 (1%)
Photosensitivity Reaction	33 (13%)	4 (2%)	0	0
Insomnia	30 (13%)	0	10 (10%)	0
Nasopharyngitis	26 (11%)	0	9 (9%)	0
Dyspepsia	25 (11%)	0	4 (4%)	0
Hypocalcaemia	25 (11%)	4 (2%)	3 (3%)	0
Cough	25 (11%)	0	10 (10%)	0
Pruritus	25 (11%)	3 (1%)	4 (4%)	0
Weight Decreased	24 (10%)	2 (1%)	9 (9%)	0
Proteinuria	23 (10%)	0	2 (2%)	0
Depression	22 (10%)	4 (2%)	3 (3%)	0

[1] Includes diarrhea, hemorrhagic diarrhea and colitis
[2] Includes rash, rash erythematous, generalized, macular, maculo-papular, papular, pruritic, exfoliative, dermatitis, dermatitis bullous, generalized erythema and eczema.
[3] Includes acne and dermatitis Acneiform
[4] Includes hypertension and hypertensive crisis
[5] Includes abdominal pain, abdominal pain upper and abdominal discomfort
[6] 69% had QT prolongation >450ms and 7% had grade 3-4 QT prolongation by ECG using Friderica correction.

7.4.2 Laboratory Findings

Laboratory adverse events are summarized in the table below. Bicarbonate levels were decreased in 100% of patients and are not listed in the table. Hematologic indices did not appear to be significantly effected in patients while on vandetanib therapy. Electrolyte disturbances can be seen at baseline in patients with medullary thyroid cancer, so it is unclear given the relatively small numbers whether the changes seen in chemistry values are secondary to drug effect or merely the patients underlying disease.

Table 42: Laboratory Adverse Events

Laboratory Parameter	Vandetanib 300 mg	Placebo

	N = 231		**N = 99**	
	All Grades	**Grade 3-4**	**All Grades**	**Grade 3-4**
Chemistries				
Calcium Decreased	132 (57%)	13 (6%)	25 (25%)	3 (3%)
ALT Increased	118 (51%)	4 (2%)	19 (19%)	0
Glucose Decreased	55 (24%)	0	7 (7%)	1 (1%)
Creatinine Increased	38 (16%)	0	1 (1%)	0
Bilirubin Increased	29 (13%)	0	17 (17%)	0
Magnesium Decreased	17 (7%)	1 (<1%)	2 (2%)	0
Calcium Increased	16 (7%)	2 (1%)	9 (9%)	1 (1%)
Potassium Decreased	15 (6%)	1 (<1%)	3 (3%)	0
Potassium Increased	13 (6%)	1 (<1%)	4 (4%)	2 (2%)
Glucose Increased	12 (5%)	4 (2%)	7 (7%)	0
Magnesium Increased	6 (3%)	0	4 (4%)	0
Hematologic				
WBC Decreased	45 (19%)	0	25 (25%)	0
Hemoglobin Decreased	31 (13%)	1 (<1%)	19 (19%)	2 (2%)
Neutrophils Decreased	21 (10%)	1 (<1%)	5 (5%)	2 (2%)
Platelets Decreased	18 (9%)	0	3 (3%)	0

Calculated using R_LB datasets. Safety=Y, TRTP=Y, LBANFL= Baseline or Analysis, ASSTIME not screening

Alanine aminotransferase elevations occurred in 51% of patients on ZICTIFA. Grade 3-4 ALT elevations were seen in 2% of patients on this study and no patients had a concomitant increase in bilirubin. Elevations in ALT have resulted in temporary discontinuation of ZICTIFA. However, 16/22 patients with a grade 2 elevation in ALT continued 300 mg ZICTIFA. Six patients had a normal ALT at their next assessment and 15 patients had a normal ALT over an extended period. Periodic monitoring of alanine aminotransferase is recommended in patients receiving ZICTIFA.

Table 43: TSH values on Study 58

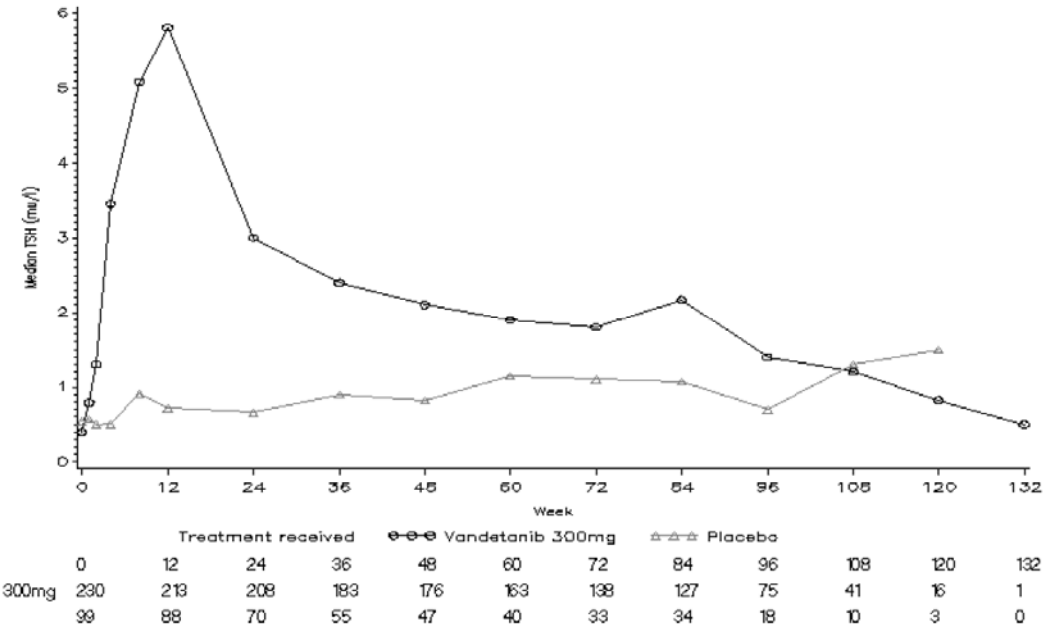
	Vandetanib N = 231		Placebo N = 99	
	Baseline	On Study	Baseline	On Study

Increased TSH				
> ULN	20	180	8	21
> 3xULN	5	88	3	6
> 5xULN	3	48	2	3
> 10xULN	0	14	0	0
Decreased TSH				
< LLN	107	144	36	66

TSH was elevated in 78% of patients receiving Zictifa. 27% of patient had >5x ULN TSH values while on treatment. The majority of patients were noted to have increased TSH at their day 28 visit, however, it was noted as early as day 14 and as late as day 84. It appears that there is a drug-drug interaction with vandetanib and levothyroxine and patients generally require a dose increase of their levothyroxine while on study. This will be an issue for labeling.

Figure 12: (Applicant's Graph): TSH over time

Figure 11 Plot of clinical chemistry - TSH (mu/L) over time (Safety analysis set)



n at weeks	0	12	24	36	48	60	72	84	96	108	120	132
Vandetanib 300mg	230	213	208	183	176	163	138	127	75	41	16	1
Placebo	99	88	70	55	47	40	33	34	18	10	3	0

Derived from Figure 11.3.7.1.3.13.

Table 44: Urinalysis Results on Study 58

	Vandetanib N = 231		Placebo N = 99	
Urinalysis	Baseline	On Study	Baseline	On Study
Blood				
+1/Trace/Small	24	93	12	31
+2/Moderate	6	55	0	11
+3/Large	4	39	1	9
Protein				
+1/Trace	45	222	17	60
+2	8	148	4	9
+3	2	47	2	2
+4	0	0	0	0

7.4.3 Vital Signs

	Vandetanib N = 231	Placebo N = 99
Systolic Blood Pressure		
>140	143 (62%)	28 (28%)
>160	44 (19%)	3 (3%)
Diastolic Blood Pressure		
>95	97 (42%)	8 (8%)

R_VS dataset TRTP, SAFETY, ASSTIME= All except baseline and screening

There is a known class effect with inhibitors of VEGF and elevated blood pressure. Vandetanib has shown the ability of elevate both systolic and diastolic blood pressure and therefore blood pressures should be monitored closely throughout study treatment. Although the overall numbers are small, it is possible there is a correlation between reversible posterior leuokoencephalopathy and hypertension as this was seen in three of four patients being treated with vandetanib, including one pediatric patient.

The number (%) of patients with elevated blood pressure during randomized treatment by antihypertensive drug usage at baseline was performed by the sponsor. For patients with no anti-hypertensive drug usage at baseline, 130 of 212 patients (62%) in the vandetanib arm had elevated BP while on randomized therapy. For patients with anti-hypertensive drug usage at baseline, 13 of 19 patients (68%) in the vandetanib arm had elevated BP while on randomized therapy, compared with 4 of 13 (31%) patients in the placebo arm.

7.4.4 Electrocardiograms (ECGs)

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. The QTc prolongation is concentration dependent. Based on the established exposure-response relationship, the expected mean (90% CI) QTc change from baseline (ΔQTc) at the dose of 300 mg was 35 (33-36) ms. 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 vandentanib in Study D4200C00008.

- 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 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 vandentanib (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). 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 ΔQTc > 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. The increased QTc effect in patients with compromised renal function may be explained by the increased steady-state exposure of vandetanib. 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.

- A slightly larger QTc effect was observed in female patients as compared to male patients.

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, 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. Therefore, we consider Bazett's correction method 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.

- 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.

- The sponsor should submit a REMS plan if the division is considering approval. A med guide and a communication plan is recommended at the present time.

Review Comment: A heavy emphasis was placed on this particular adverse event in the oncologic drug advisory committee safety presentation. With a mean QTc prolongation of 35ms, vandetanib would be considered pro-arrhythmic and a REMS is planned to address this increased risk.

7.4.5 Special Safety Studies/Clinical Trials

Four patients receiving vandetanib 300mg in Study 8 (Phase II study to evaluate the Efficacy and Tolerability of vandetanib in patients with locally advanced or metastatic medullary thyroid carcinoma) reported visual changes and had abnormalities noted on ophthalmologic examination. Given this finding, AZ submitted an amendment on May 30, 2007 to add ophthalmologic examinations as part of study procedures to determine whether vandetanib increases the likelihood of patients developing corneal opacities or other eye abnormalities.

Ophthalmologic examinations were performed at screening and at 9 months after patients began receiving randomized treatment. Patients who were discontinued from study drug before 9 months, or who had already completed their 9 months visit before the amendment was approved, were required to have an ophthalmologic exam performed at discontinuation. Patients who complained of visual symptoms underwent an ophthalmologic exam at the time the symptom was noted. Only 63.7% of randomized patients underwent an examination during randomized treatment.

As shown in Table 45, abnormalities from visual assessment were more common in the vandetanib arm than in placebo with abnormalities in either eye being reported in 133 (83.6%) patients in the vandetanib arm and 32 (61.5%) in the placebo arm. There was slight increase in intraocular pressure (mmHg) in both eyes from baseline to week 36 in both right and left eyes in the vandetanib arm.

Table 45: Abnormalities in Right and/or Left Eye

Test	Vandetanib 300mg	Placebo	Total
Total	133	32	165
Amsler Grid	4 (3%)	1 (3%)	5
Anterior Chamber	3 (2%)	1 (3%)	4
Blood Vessels	11 (8%)	6 (19%)	17
Color vision	12 (9%)	9 (28%)	21
Conjunctiva	12 (9%)	2 (6%)	14
Endothelium	6 (5%)	1 (3%)	7
Intraocular Pressure	79 (59%)	2 (6%)	81
Macula	10 (8%)	3 (9%)	13
Optic Disc	19 (14%)	3 (9%)	22
Periphery	13 (10%)	3 (9%)	16
Pupillary Reactions	6 (5%)	1 (3%)	7
Stroma	28 (21%)	2 (6%)	30
Visual Acuity	3 (2%)	0	3
Visual Cylinder	1 (<1%)	0	1
Visual Fields to Confrontation	15 (11%)	4 (13%)	19
Visual Sphere	3 (2%)	0	3
Other Slit Lamp Abnormalities	37 (29%)	14 (44%)	51

A patient can have more than one abnormality reported under a given test.

Blinded review of the reports was performed by a consultant ophthalmologist procured by Astra-Zeneca (Dr. Alan Laties, MD). This review revealed that 49 of 159 (30.8%) patients in the vandetanib arm who underwent ophthalmologic examinations had vortex keratopathy.

"Vortex keratopathy, also called cornea verticillata, is characterised by the appearance of fine, grayish or brown linear opacities in the epithelial layer of the cornea. The linear opacities typically branch repeatedly to form a distinctive whorl-like pattern. Although the opacities often are asymptomatic, patients can have one or more symptoms such as hazy vision, photophobia, haloes around lights, or, in some instances, glare. Vortex keratopathy is typically innocuous and rarely requires discontinuation of drug therapy."

"The consultant ophthalmologist concluded that the association of study drug to the occurrence of vortex keratopathy can be classified as certain by World Health Organization criteria. This conclusion is strengthened by the fact that the actual

prevalence of vortex keratopathy is decidedly low in the general population. At present, even with partial analysis possible, it appears that at least 3 months of dosing is required for the first appearance of vortex keratopathy. No serious corneal AE has yet been associated with study drug. For this reason, the consultant ophthalmologist indicated that there is no need to stop dosing even in instances where vortex keratopathy develops."

FDA ophthalmology review:
The differential diagnosis for deposits with a bilateral golden-brown whorl pattern include Fabry disease, use of amiodarone, chloroquine and hydroxychloroquine, indomethacin, and phenothiazines. Most studies suggest that all or nearly all patients taking amiodarone will develop verticillata. When depositing drugs are stopped for other reasons, most verticillata will eventually fade away. There is no data currently available to suggest either protective or inducing factors in patients who develop verticillata from medication use.

The potential for these verticillata to fade with discontinuation of drug is unknown because the trial did not evaluate this aspect of the adverse event. If these deposits are located in the basal corneal epithelium, it is likely the corneal deposits would behave similar to other medication-related deposits which fade several months after discontinuation of product. There is not enough information provided from this clinical study report to determine if the corneal changes from vandetanib represent classic vortex keratopathy (cornea verticillata) or if there is some additional corneal stromal abnormality. The clinical study report provides conflicting descriptions of the corneal abnormalities noted.

The majority of subjects with vortex keratopathy are asymptomatic. Some subjects are symptomatic and report halos or other visual disturbances.

There is no treatment for drug-related cornea verticillata except discontinuation of causative medication.

1) ***Please comment on the consultant ophthalmologist's conclusion that there is no need to stop or adjust dosing in instances where vortex keratopathy develops.***

Reviewer's Comments:

If patients are asymptomatic, there is no need to stop or adjust dosing. If a patent is symptomatic, the utility of the study drug would have to be weighed against the level of visual disturbance experienced. See Summary Statement this review.

Although ophthalmologic examinations were added to this protocol after corneal opacities were noted in Study D4200C00008, the level of detail and specificity regarding

the collection of ocular data is scant. No photographs were taken. It appears most investigators did perform visual acuity and posterior segment evaluations as part of their examinations although these were not specified in the protocol. Without adequate protocol instructions to the investigator, it is unclear that the ophthalmic examinations were performed uniformly. It is also unclear who performed the examinations; these examinations should have been performed by individuals with adequate training.

2) Please comment on the clinical significance of the other abnormalities that were increased in the treatment arm compared to placebo as derived from Table 11.3.8.1.17. Specifically:

a. Stromal abnormalities (17.6% v. 2%)

b. Optic disc abnormalities (19% v. 3%)

Reviewer's Comments:

The description of the ophthalmic evaluations in this trial makes it very difficult to determine clinical significance of the stromal abnormalities and optic disc abnormities noted. See response to Question #2 above.

The term "stromal abnormalities" is vague. Table 11.3.8.2 in the Safety Analysis includes stromal haze, stromal whirls/opacities, and stromal edema. Despite the notation of stromal edema, there is no measurement of corneal thickness recorded to evaluate the stromal edema.

The term "optic disc abnormalities" is vague. A review of the adverse event listing by subject (Appendix 12.2.7) mentions optic nerve sheath hemorrhage. Such hemorrhages are usually related to hypertension. Table 11.3.8.2 in the Safety Analysis mentions optic disc cupping.

3) Astra Zeneca's ophthalmology report states that "VK rarely, if ever, needs treatment stopped." What would be the conditions in which treatment should be stopped. The report also went on to say that once stopping therapy, "regression usually follows." If regression does not follow, what is the sequelae, and does the impairment continue to progress?

Reviewer's Comments:

If patients are asymptomatic, there is no need to stop or adjust dosing. The deposits are likely to increase with time with continued dosing. If a patent is symptomatic, the utility of the study drug would have to be weighed against the level of visual disturbance experienced.

Summary Statement/ Recommended Action:

A review of the submitted case report forms for subjects reveals slit lamp exam descriptions consistent with the common presentation of vortex keratopathy (cornea verticillata). However, Table 11.3.8.2 includes listings of abnormalities which include stromal opacities, edema, and whirls. There are no photographs of the corneal changes located in the NDA submission.
There are no photographs of the corneal changes located in the NDA submission.

There is not enough information provided from this clinical study report to determine if the corneal changes from vandetanib represent classic vortex keratopathy (cornea verticillata) or if there is some additional corneal stromal abnormality. The clinical study report provides conflicting descriptions of the corneal abnormalities noted.

Recommend that if any additional trials are conducted with vandetanib, corneal slit lamp photographs should be taken to identify the location of the corneal opacities noted. If subjects develop corneal opacities, the opacities should be followed to determine if they spontaneously resolve off vandetanib treatment.

In the absence of additional trial information, recommend that vandetanib be labeled with a statement that corneal opacities have been observed that may cause a decrease in vision and which may or may not be reversible with discontinuation of product.

7.4.6 Immunogenicity

Two cases of "drug hypersensitivity" led to discontinuation of the study drug. After closer review of these two patient cases, it appears they were more in keeping with Grade 4 Stevens Johnson Syndrome (SJS). Interestingly, they both occurred in the same center in two different Chinese patients. Due to the low number of patients involved, it is impossible to draw any conclusions with regards to whether there is an ethnic pre-disposition to developing SJS.

7.5 Other Safety Exploration

7.5.1 Dose Dependency for Adverse Events

There has been considerable attention on dose dependency for adverse events. Vandetanib has a half life of approximately 19 days, and with >50% of patients experiencing grade 3-4 adverse events, it has been postulated that the dose is potentially too high.

The clinical pharmacology review states the following:

Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

No. The 300 mg daily dose may not be optimal based on the long-half life of the drug.

The sponsor's rationale for the 300 mg dose was based on:

(1) preclinical data, which demonstrated that the greatest benefit (in terms of maximizing inhibition against key targets) is seen when vandetanib is used at the maximum tolerated dose (MTD),
(2) the MTD of 300 mg was concluded from data in the phase 1 ascending-dose in US/Australia and Japanese patients
(3) in phase 2 study of 300 mg vandetanib in hereditary MTC patients, 20% of the patients demonstrated a confirmed partial objective response.

In isolated enzyme assays, vandetanib inhibits VEGFR-2 tyrosine kinase activity (IC_{50} = 40 nM), and shows inhibitory activity against RET receptor tyrosine kinase (IC_{50} = 100 nM), VEGF receptor-3 (IC_{50} = 110 nM), and epidermal growth factor receptor (EGFR) (IC_{50} = 500 nM) tyrosine kinases. The $C_{max,ss}$ in MTC patients following 300 mg daily dose was 857 ng/mL (385 - 2241 ng/mL). Since free drug in plasma is 6% of the total drug, the free drug concentration is about 51 ng/mL (≡ ~100 nM), which is higher than IC_{50} for VEGFR2 inhibition, similar to IC_{50} for RET receptor and VEGFR-3 inhibition, and lower than IC_{50} for EGFR inhibition.

The sponsor selected 300 mg daily dose to maximize the efficacy. However, at the expense of efficacy, patients in vandetanib arm experienced serious adverse events.

7.5.2 Time Dependency for Adverse Events

Significant exposure-response relationships were identified for diarrhea and fatigue, but not for hypertension or rash.

The probability of diarrhea grade 2 or higher is significantly associated with $C_{ss,\ Day\ 56}$ (p = 0.025) (Figure 10, left). Similarly, the probability of fatigue grade 2 or higher is significantly associated with $C_{ss,\ Day\ 56}$ (p = 0.02) (Figure 10, right), whereas no significant exposure-response relationships were identified for either hypertension or rash. The shallow slopes of the logistic regression models for diarrhea and fatigue project a minimal decrease in AE incidence for dose reductions at the population level, which is consistent with the relatively low incidence of these AEs in the pivotal trial.

Figure 13: Relationship of Css with Diarrhea and Fatigue

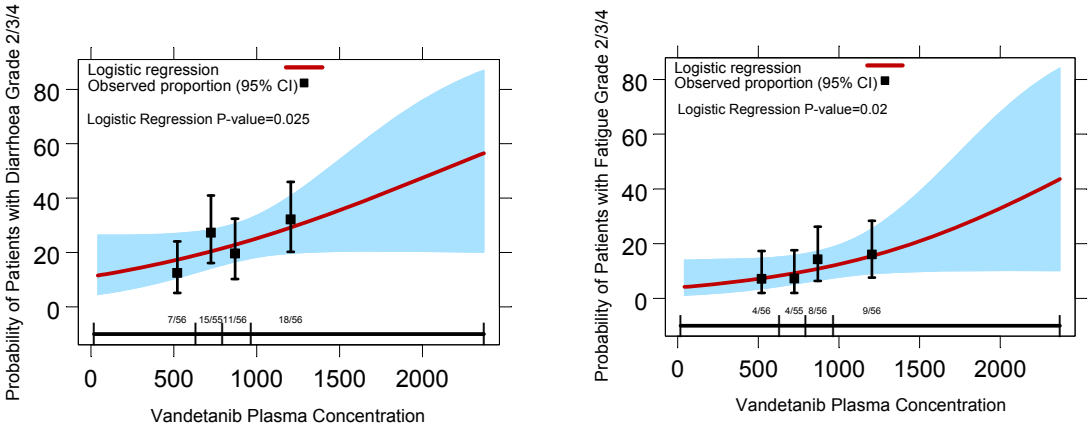
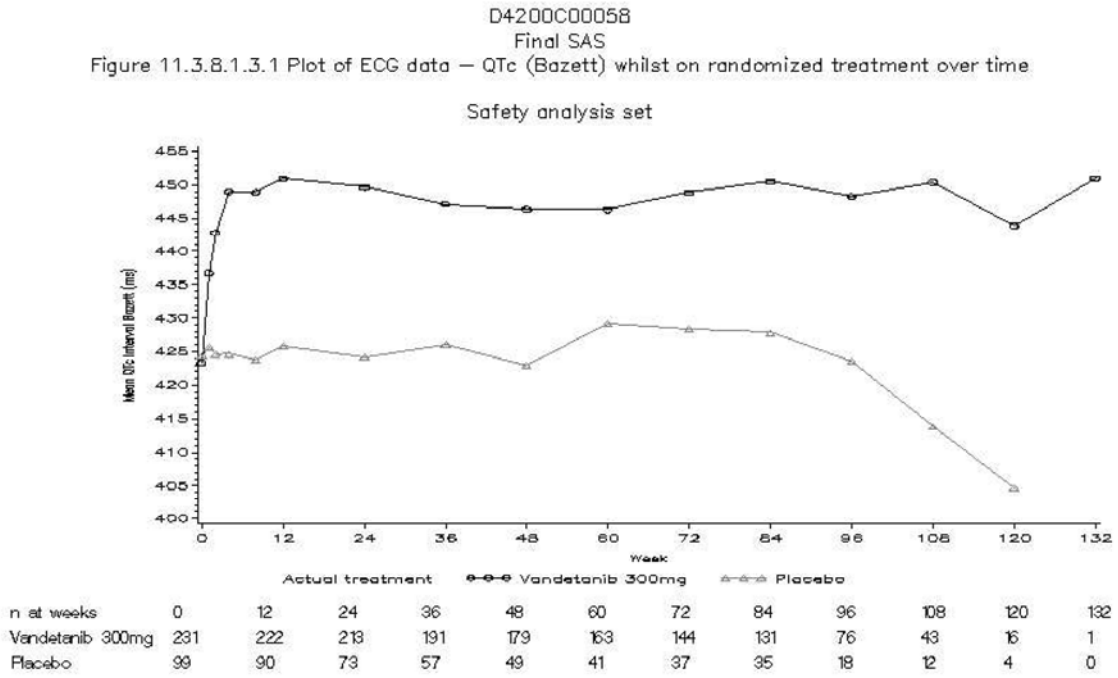


Figure 14. The relationship between $C_{ss,\ Day\ 56}$ and the incidence of grade 2 or higher diarrhea (left) and fatigue (right). Solid black symbols represent the observed proportion of patients experiencing ≥ grade 2 AEs in each quartile of $C_{ss,\ Day56}$. The vertical black bars represent the 95% confidence interval. The solid red line and shaded area represent the predicted mean and 95% confidence interval for the probability of ≥ grade 2 adverse events. The exposure range in each quartile of $C_{ss,\ Day\ 56}$ is denoted by the horizontal black line along with the number of patients with AEs/total number of patients in each quartile.

With regards to the toxicity of QTc prolongation, the toxicity is related to concentration and irrespective of time. The risk of Torsades or other QT prolonging sequelae does not dissipate over time.

Figure 15:QTcB while on randomized treatment as related to time (Applicant's Figure)



n at weeks	0	12	24	36	48	60	72	84	96	108	120	132
Vandetanib 300mg	231	222	213	191	179	163	144	131	76	43	16	1
Placebo	99	90	73	57	49	41	37	35	18	12	4	0

7.5.3 Drug-Demographic Interactions

Rates of common (>10%) grade 1-4 adverse events were examined by age (<65 years of age vs. >=65 years of age) and race (white vs. non-white) and are presented in the tables below.

Overall, grade 1-4 adverse events were similar in patients <65 years old and ≥65 years old. However, a few adverse events did occur more frequently in older patients (>5% difference). The common grade 1-4 events that occurred more frequently in patients ≥65 years old were: rash (49% in <65 yrs vs. 75% in ≥65 yrs), hypertension (32% in <65 yrs vs. 39% in ≥65 yrs), fatigue (21% in <65 yrs vs. 35% in ≥65 yrs), decreased appetite (18% in <65 yrs vs. 33% in ≥65 yrs), pruritis (9% in <65 yrs vs. 16% in ≥65 yrs), and proteinuria (9% in <65 yrs vs. 14% in ≥65 yrs).

Overall, grade 3-4 adverse event rates were similar between the two age comparison groups.

Table 46: Adverse Events by Age in Study 58

	All Grade Toxicity		Grade 3-4 Toxicity	
	<65yrs N=182	**≥65 N=49**	**<65yrs N=182**	**≥65 N=49**
Diarrhea[1]	103 (56%)	28 (57%)	7 (3%)	1 (2%)
Rash[2]	90 (49%)	37 (75%)	3 (1%)	0
Nausea	63 (35%)	14 (29%)	1 (<1%)	1 (2%)
Hypertension[3]	59 (32%)	19 (39%)	10 (5%)	3 (6%)
Headache	49 (27%)	10 (20%)	0	1 (2%)
Fatigue	38 (21%)	17 (35%)	6 (3%)	1 (2%)
Decreased appetite	33 (18%)	16 (33%)	5 (3%)	3 (6%)
Acne	46 (25%)	0	1 (<1%)	0
Dry Skin	27 (15%)	8 (16%)	0	0
Dermatitis Acneiform	29 (16%)	6 (12%)	0	0
Vomiting	27 (15%)	7 (14%)	1 (<1%)	0
Asthenia	25 (14%)	9 (18%)	0	1 (2%)
Abdominal Pain[4]	50 (27%)	12 (24%)	4	1 (2%)
QT Prolongation	27 (15%)	6 (12%)	14 (8%)	3 (6%)
Photosensitivity	26 (14%)	5 (10%)	2 (<1%)	0
Insomnia	25 (14%)	5 (10%)	0	0
Nasopharyngitis	22 (12%)	4 (8%)	0	0
Pruritis	17 (9%)	8 (16%)	0	0
Dyspepsia	22 (12%)	3 (6%)	0	0
Cough	18 (10%)	7 (14%)	0	0
Hypocalcemia	21 (12%)	4 (8%)	2 (<1%)	0
Weight decreased	18 (10%)	6 (12%)	1 (<1%)	1 (2%)
Proteinuria	16 (9%)	7 (14%)	0	0
Depression	16 (9%)	6 (12%)	1 (<1%)	0
Erythema	19 (10%)	4 (8%)	0	0
Vision Blurred	16 (9%)	4 (8%)	0	0
Back Pain	16 (9%)	5 (10%)	0	1 (2%)
Epistaxis	15 (8%)	3 (6%)	0	0
Oropharyngeal pain	16 (9%)	3 (6%)	1 (<1%)	0
Dry Mouth	15 (8%)	5 (10%)	0	0
UTI	15 (8%)	2 (4%)	1 (<1%)	0

	All Grade Toxicity		**Grade 3-4 Toxicity**	
	<65yrs N=182	**≥65 N=49**	**<65yrs N=182**	**≥65 N=49**
URI	15 (8%)	4 (8%)	0	0
Dyspnea	14 (8%)	4 (8%)	1 (<1%)	2 (4%)
Dizziness	12 (7%)	8 (8%)	1 (<1%)	0

Using R_AE dataset.
1. Diarrhea includes diarrhea and hemorrhagic diarrhea.
2. Rash includes the preferred terms rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash popular, rash pruritic, and rash pustular.

3. Hypertension includes hypertension and hypertensive crisis.
4. Abdominal Pain includes abdominal pain upper, lower, and discomfort.

The data for Grade 1-4 toxicity and Grade 3-4 toxicities between white and non-white patients is presented in Table 9. Due to the low number of non-white patients treated on trial, no conclusions can be made regarding the toxicity differential between white and non-white patients.

Table 47: Adverse events by Race in Study 58

	All Grade Toxicity		Grade 3-4 Toxicity	
	White N=218	Other N=13	White N=218	Other N=13
Diarrhea[1]	124 (57%)	7 (54%)	8 (3%)	0
Rash[2]	123 (56%)	9 (69%	3 (1%)	0
Nausea	76 (35%)	1 (8%)	2 (1%)	0
Hypertension[3]	75 (34%)	3 (23%)	13	0
Headache	57	2	1	0
Fatigue	52	3	7	0
Decreased appetite	44	5	7	1
Acne	42	4	1	0
Dry Skin	34	1	0	0
Dermatitis Acneiform	35	0	0	0
Vomiting	33	1	1	0
Asthenia	31	3	1	0
Abdominal Pain[4]	58	4	5	0
QT	32	1	16	1

	All Grade Toxicity		Grade 3-4 Toxicity	
	White N=218	Other N=13	White N=218	Other N=13
Prolongation				
Photosensitivity	29	2	1	1
Insomnia	28	2	0	0
Nasopharyngitis	24	2	0	0
Pruritis	23	2	0	0
Dyspepsia	23	2	0	0
Cough	25	0	0	0
Hypocalcemia	24	1	2	0
Weight decreased	21	3	2	0
Proteinuria	21	2	0	0
Depression	21	1	1	0
Erythema	22	1	0	0
Vision Blurred	18	2	0	0
Back Pain	21	0	1	0
Epistaxis	17	1	0	0
Oropharyngeal pain	19	0	1	0
Dry Mouth	20	0	0	0
UTI	16	1	1	0
URI	19	0	0	0
Dyspnea	16	2	3	0
Dizziness	19	1	1	0
Dysgeusia	19	0	0	0

Using R_AE (adverse events) , R-DS (demographics) and R_LB (laboratory tests).
1. Diarrhea includes diarrhea and hemorrhagic diarrhea.
2. Rash includes the preferred terms rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash popular, rash pruritic, and rash pustular.

3. Hypertension includes hypertension and hypertensive crisis.
4. Abdominal Pain includes abdominal pain upper, lower, and discomfort.

Table 48: Adverse Events by Age in the ISS database

	Vandetanib 300 mg N = 1839	
	< 65 years N = 1227	≥ 65 years N = 623
Gastrointestinal Disorders		
Diarrhea/Colitis	50.5%	54.4%

Nausea	29.2%	24.4%
Vomiting	16.9%	12.0%
Abdominal Pain[1]	14.2%	11.7%
Constipation	12.0%	14.1%
General Disorders		
Fatigue	21.6%	25.2%
Asthenia[2]	10.9%	14.0%
Metabolism and Nutrition Disorders		
Anorexia/Decreased Appetite	23.0%	25.2%
Nervous System Disorders		
Headache/Migraine	14.3%	10.4%
Psychiatric Disorders		
Insomnia/Sleep Disorder	13.4%	9.8%
Respiratory Disorders		
Cough/Productive Cough	17.1%	16.9%
Dyspnea/Exacerbated/Exertional	16.4%	18.5%
Skin Disorders		
Rash[3]	35.5%	34.7%
Acne/Dermatitis Acneiform	20.0%	12.5%
Dry Skin	10.8%	9.8%
Vascular Disorders		
Hypertension[4]	22.9%	21.8%

Includes studies 1, 2, 3, 7, 8, 39, 43, 44, 50, 57, 58
[1]Includes abdominal discomfort, abdominal pain lower, abdominal pain upper
[2]Includes general physical health deterioration, performance status decreased
[3]Includes exfoliative, erythematous, follicular, generalized, macular, maculo-papular, papular, papulosquamous, photosensitive, pruritic, and scaly rash
[4]Includes accelerated hypertension, hypertensive crisis

Table 49: Adverse Events by Sex in the ISS Database

	Vandetanib 300 mg	
	Male N = 1007	Female N = 843
Gastrointestinal Disorders		
Diarrhea/Colitis	47.4%	57.2%
Nausea	21.2%	32.7%
Vomiting	10.6%	19.4%
Abdominal Pain[1]	11.8%	15.2%
Constipation	13.0%	12.3%
General Disorders		

Fatigue	22.5%	23.2%
Asthenia[2]	12.2%	11.6%
Metabolism and Nutrition Disorders		
Anorexia/Decreased Appetite	24.4%	22.9%
Nervous System Disorders		
Headache/Migraine	8.8%	17.9%
Psychiatric Disorders		
Insomnia/Sleep Disorder	11.5%	13.0%
Respiratory Disorders		
Cough/Productive Cough	15.5%	18.9%
Dyspnea/Exacerbated/Exertional	18.2%	15.8%
Skin Disorders		
Rash[3]	31.1%	44.4%
Acne/Dermatitis Acneiform	18.9%	15.8%
Dry Skin	8.8%	12.3%
Vascular Disorders		
Hypertension[4]	19.4%	26.3%

[1]Includes abdominal discomfort, abdominal pain lower, abdominal pain upper
[2]Includes general physical health deterioration, performance status decreased
[3]Includes exfoliative, erythematous, follicular, generalized, macular, maculo-papular, papular, papulosquamous, photosensitive, pruritic, and scaly rash
[4]Includes accelerated hypertension, hypertensive crisis

Table 50: Adverse Events by Race in the ISS Database

	Vandetanib 300 mg			
	White N = 1185	Black N = 27	Asian N = 590	Other N = 47
Gastrointestinal Disorders				
Diarrhea/Colitis	54.5%	29.6%	47.1%	57.4%
Nausea	30.6%	25.9%	18.0%	23.4%
Vomiting	15.1%	3	12.7%	10.6%
Abdominal Pain[1]	14.6%	25.9%	8.6%	17.0%
Constipation	12.2%	11.1%	13.4%	2.1%
General Disorders				
Fatigue	27.2%	33.3%	13.0%	34.0%
Asthenia[2]	14.0%	14.8%	7.6%	12.8%
Metabolism and Nutrition Disorders				
Anorexia/Decreased Appetite	23.7%	44.4%	23.2%	19.1%
Nervous System Disorders				
Headache/Migraine	14.9%	18.5%	9.2%	10.6%
Psychiatric Disorders				

Insomnia/Sleep Disorder	11.6%	7.4%	13.8%	12.8%
Respiratory Disorders				
Cough/Productive Cough	17.3%	18.5%	16.3%	21.3%
Dyspnea/Exacerbated/Exertional	19.9%	18.5%5	10.5%	27.7%
Skin Disorders				
Rash[3]	40.5%	29.6%	52.2%	44.7%
Acne/Dermatitis Acneiform	19.5%	14.8%	13.6%	8.5%
Dry Skin	11.1%	25.9%	8.5%	10.6%
Vascular Disorders				
Hypertension[4]	19.7%	25.9%	28.5%	19.1%

[1]Includes abdominal discomfort, abdominal pain lower, abdominal pain upper
[2]Includes general physical health deterioration, performance status decreased
[3]Includes exfoliative, erythematous, follicular, generalized, macular, maculo-papular, papular, papulosquamous, photosensitive, pruritic, and scaly rash
[4]Includes accelerated hypertension, hypertensive crisis

In study 32, a phase III, randomized, double blinded, multi-centre study to assess Safety and Efficacy of docetaxel in combination with vandetanib versus docetaxel plus placebo in patients with advanced NSCLCa after failure of first line therapy, ILD was reported more frequently in patients treated with 100mg vandetanib + docetaxel (2.5%) than with docetaxel alone (0.9). Interestingly, that study also reported ILD more frequently in Japanese patients (16.7% in docetaxel +vandetanib group vs. 7.4% docetaxel alone) than in patients from outside Japan (0.8% vandetanib/0.2% docetaxel alone). The other Phase III studies in NSCLC have reported incidences of ILD of less than 1% with vandetanib, however these studies did not include patients from Japan. The sponsor postulates as to whether the ILD frequency seen in Study 32 could have been the effect of the drug on a Japanese population. The overall incidence of ILD in the 300 mg monotherapy pool was 0.2%. In one Phase I study performed entirely in Japan (TVE-15-11), there did not appear to be any toxicity related to ILD, however there were only 18 patients in this study and only 6 treated at 300mg so no general conclusions can be made.

7.5.4 Drug-Disease Interactions

There appears to be a higher percentage of pulmonary toxicity in the ISS database as compared to the Phase III MTC study. This finding is most likely due to the majority of patients being treated for non-small cell lung cancer, and is either due to the underlying disease state, or due to the previous treatment regimens given to this cancer population.

Study 58 allowed patients with a CrCl of >30 to be treated with vandetanib. With this lower threshold for creatinine clearance in place, an evaluation of toxicity and creatinine

clearance was performed. The two values that clinical pharmacology cited as having a dependency on renal function, fatigue and diarrhea were examined, as well as QT prolongation.

Table 51: Adverse Events as related to Creatinine Clearance

	CrCl <90		CrCl >90	
	All Grades	Grades 3-4	All Grades	Grades 3-4
Fatigue	39	8	29	5
Diarrhea	83	14	115	19
QT Prolongation	26	15	21	10

The RH_LB and R_AE datasets from Study 58 were joined and used for the randomized portion of the study.

Given the limitations of this small sub-set analysis, no conclusions can be made with regards as to whether lower creatinine clearance negatively impacts toxicity.

7.5.5 Drug-Drug Interactions

Although no *in vivo* drug-drug interaction studies were conducted, *in* vitro data suggests that drug-drug interactions can occur. See section 2.4.2.2 of the clinical pharmacology review.

In study 32, a phase III, randomized, double blinded, multi-centre study to assess Safety and Efficacy of docetaxel in combination with vandetanib versus docetaxel plus placebo in patients with advanced NSCLCa after failure of first line therapy, ILD was reported more frequently in patients treated with 100mg vandetanib + docetaxel (2.5%) than with docetaxel alone (0.9). Interestingly, that study also reported ILD more frequently in Japanese patients (16.7% in docetaxel +vandetanib group vs. 7.4% docetaxel alone) than in patients from outside Japan (0.8% vandetanib/0.2% docetaxel alone). The other Phase III studies in NSCLC have reported incidences of ILD of less than 1% with vandetanib, however these studies did not include patients from Japan. The sponsor postulates as to whether the ILD frequency seen in Study 32 could have been the effect of the drug on a Japanese population. The overall incidence of ILD in the 300 mg monotherapy pool was 0.2%.

Table 52: Study 32 Incidence of ILD/ Pneumonitis

	Vandetanib+ docetaxel Grade 1-4 N=694	Vandetanib + docetaxel Grade 3-4 N=694	Docetaxel + Placebo Grade 1-4 N=697	Docetaxel + Placebo Grade 3-4 N=697
ILD	17 (2.4%)	4 (0.6%)	6 (0.8%)	3 (0.4%)

Pneumonitis	7 (1%)	2 (0.2%)	8 (1%)	4 (0.5%)
Dyspnea	113 (16.3%)	29 (4.0%)	137 (20%)	35 (5%)
Respiratory Failure	5 (0.7%)	5 (0.7%)	7 (1%)	7 (1%)
Hypoxia	10 (1.4%)	3 (0.4%)	5 (0.7%)	2 (0.2%)

Safety, AEANFL, AESTFL(after before/during,during,during after)

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No vandetanib-treated patients developed acute myeloid leukemia or myelodysplastic syndrome. There was one patient who developed a germ-cell tumor while on treatment. Two patients treated in Study 68 at the 100mg dose developed pheochromocytoma. Pheochromocytoma is associated with medullary thyroid cancer as part of the MEN II syndrome.

Given that medullary thyroid cancer patients can have relatively long survival times (up to 40% of patients with 10 years survival according to the SEER database), the pharmacology toxicology reviewers will require a carcinogenicity animal study as a post-marketing requirement.

See pharmacology-toxicology review for further details.

7.6.2 Human Reproduction and Pregnancy Data

Vandetanib is a Pregnancy Category D drug. The following information is from the submitted label pending approval:

7.6.3 Pediatrics and Assessment of Effects on Growth

Vandetanib has not been studied in a pediatric population. A pediatric waiver was granted by the Pediatric Review Committee based on vandetanib's orphan drug status.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Symptoms of overdose have not been established with vandetanib and there is no specific treatment in the event of an over dosage. In phase I trials of vandetanib, a small number of patients were treated at doses higher then 300mg, including daily doses up to 600mg in patients, and 1200mg in healthy volunteers and in patients. The sponsor suggests in their unapproved label to consider the possibility of QTc prolongation and Torsade de pointes. Adverse reactions associated with overdose should be treated symptomatically. In the event of an overdose, the sponsor recommends interrupting further doses and monitoring closely for evidence that an adverse reaction has occurred, e.g. ECG within 24 hours to determine QTc prolongation, anti-diarrheal treatment, monitoring for skin toxicity. Given the long half-life of the drug of approximately 19 days, this would not be adequate. The FDA proposes ECG monitoring for an extended time interval to account for the long half-life. After further consultation with cardio-renal and clinical pharmacology, it does not appear that dialysis would be a possibility in removing the highly protein bound drug. The rationale provided by Astra-Zeneca is as follows: "It is AstraZeneca's belief that dialysis would not be an effective or rapid means of removing vandetanib from patients' circulation. Based on the pharmacokinetic properties of vandetanib (protein binding of 90% and volume of distribution of 7450L) and estimating the fraction of drug that could be dialyzed using the method evaluated by Tang and Mayersohn 2004, we estimate that approximately 0.05% of the drug would be removed in a 6-hour dialysis session."

Substituting into the formula $1/Fr = 1.3Vu + 2.14$, where Vu is (7450L/50 kg)/0.10 and simplifying Fr = 0.05%.

"When using this formula for drugs that are reliably removed by hemodialysis a value for Fr is typically > 30%. Based on the value obtained from this predictive formula, we conclude that there is no additional benefit to experimentally determining (either non-clinically or clinically) whether vandetanib clearance can be increased from the circulation by hemodialysis. Other methods of removal of drug from the circulation, such as hemoperfusion, would also be predicted to be ineffective."

Drug abuse potential, withdrawal, and rebound are not relevant to this application.

7.7 Additional Submissions / Safety Issues

None

8 Postmarket Experience

As this application is for a new molecular entity with no prior approval history, there is no postmarket experience.

9 Appendices

9.1 Literature Review/References

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9.2 Labeling Recommendations

See the final version of the label revised by all of the FDA scientific disciplines.

9.3 Advisory Committee Meeting

Medullary thyroid cancer, even in the metastatic setting, has a relatively long survival time. Due to the toxicity profile of vandetanib, the application was presented at the December 2, 2010 Oncologic Drug Advisory Committee. The members of the committee were asked to discuss whether the indication should be limited to patients with progressive, symptomatic medullary thyroid cancer and to comment on whether there are any other subgroups that may be appropriate for treatment with vandetanib in light of the risk-benefit profile. All of the committee members agreed that treatment with vandetanib is not indicated in patients with low burden or asymptomatic disease. The majority of the committee members agreed with modifying the indication to include only patients with progressive, symptomatic MTC.

The committee was also asked to vote on the following question: If there is a population in which the risk-benefit profile is acceptable, should additional doses of vandetanib be evaluated as a post-marketing requirement to determine the optimal dose? If yes, please discuss potential study designs.

The committee voted 10 to 0 in favor of additional studies to explore alternative doses and dose scheduling. There was no consensus on any particular trial design.

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/s/

GEOFFREY S KIM
03/24/2011

KATHERINE A DELORENZO
03/24/2011

VIRGINIA E MAHER
03/24/2011

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	22405
Priority or Standard	Priority
Submit Date(s)	July 7,2010
Received Date(s)	July 7, 2010
PDUFA Goal Date	January 7, 2011
Division / Office	DDOP/OODP
Reviewer Name(s)	Geoffrey Kim (efficacy) Katherine DeLorenzo (safety)
Review Completion Date	
Established Name	Vandetinib/ ZD6474
(Proposed) Trade Name	(b) (4)
Therapeutic Class	Tyrosine Kinase Inhibitor
Applicant	Astra-Zeneca
Formulation(s)	oral
Dosing Regimen	300mg/ daily
Indication(s)	Advanced medullary thyroid carcinoma
Intended Population(s)	Patients with symptomatic, progressive, unresectable locally advanced or metastatic medullary thyroid carcinoma

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

We recommend a complete response letter.

1.2 Risk Benefit Assessment

The recommendation for approval is based on the single, randomized clinical trial in which vandetanib showed a statistically significant progression free survival advantage compared to placebo in patients with locally advanced or metastatic medullary thyroid cancer (MTC).

The single clinical trial enrolled 331 patients with locally advanced or metastatic MTC. The hazard ratio was 0.35 (95% CI 0.24-0.53); $p<0.0001$, favoring vandetanib. The median progression free survival (PFS) for vandetanib was not yet reached. There were deaths due to toxicity observed on the vandetanib arm in the randomized trial as well as the cumulative clinical experience with vandetanib. Fifty-five percent (55%) of the patients on the vandetanib arm experienced grade 3 or 4 adverse events. Patients receiving vandetanib experienced a mean prolongation of their QT interval of 35 ms, and sudden death and torsades des pointes have been observed with vandetanib. These risks are outweighed by the marked improvement in PFS. However, a Risk Evaluation and Mitigation Strategy (REMS) should be used to decrease the risk of vandetanib.

MTC, even in the metastatic setting, has a relatively long survival time. Due to the toxicity profile of vandetanib, the application was presented at the December 2, 2010 Oncologic Drugs Advisory Committee. The members of the committee were asked to discuss whether the indication should be limited to patients with progressive, symptomatic medullary thyroid cancer and to comment on whether there are any other subgroups that may be appropriate for treatment with vandetanib in light of the risk-benefit profile. All of the committee members agreed that treatment is not indicated in patients with a low burden or asymptomatic disease. The majority of the committee members agreed with modifying the indication to those with progressive, symptomatic MTC. The proposed patient population has no treatment options which offer a progression free survival prolongation and the robust results demonstrated by vandetanib would provide a new treatment option for these patients.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

At the time of this review submission, final recommendations for postmarketing REMS have not been made. Refer to the action letter for final recommendations.

1.4 Recommendations for Postmarket Requirements and Commitments

At the time of this review submission, final recommendations for postmarketing requirements and commitments have not been made. Refer to the action letter for final recommendations.

2 Introduction and Regulatory Background

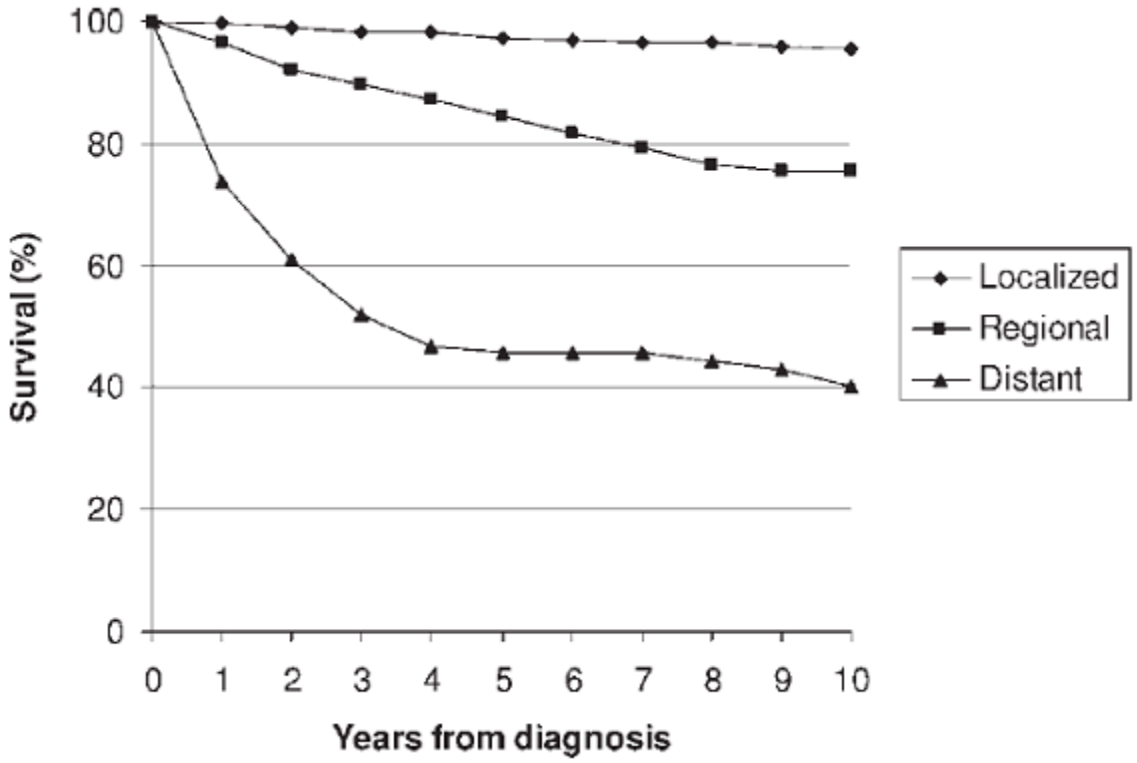
2.1 Medullary Thyroid Cancer

Medullary thyroid cancer (MTC) is a rare tumor arising from the parafollicular C cells of the thyroid. Medullary thyroid cancer represents approximately 5% of all thyroid cancers and the estimated number of new cases of MTC in 2010 is extrapolated to be 1800 (Jemal). Seventy-five (75%) of MTC cases are sporadic, while the remaining 25% are hereditary and are part of the autosomal dominant disorder multiple endocrine neoplasia type 2 (MEN 2). The 3 recognized subtypes of MEN 2 include MEN 2A, characterized by MTC, pheochromocytoma, and hyperparathyroidism; MEN 2B, by MTC and pheochromocytoma; and familial MTC (FMTC), by MTC only. Mutations in the RET proto-oncogene are found in >90% of patients with MEN2A and familial MTC. Somatic mutations in the RET proto-oncogene are found in 40-50% of tumors of patients with sporadic MTC. Mutations in codon 918 which are found in both hereditary and sporadic MTC activate the tyrosine kinase function of the receptor and are associated with poorer outcomes.

There are no hallmark symptoms of medullary thyroid cancer, and patients most often initially present with a thyroid nodule or mass. Patients with localized symptoms, such as dysphagia, dyspnea, or hoarseness, were more likely to have persistent disease following surgery. Systemic symptoms, such as bone pain or diarrhea, most often occur in patients with distant metastases (Kebebew). The etiology of diarrhea may be related to the secretion of calcitonin (CTN), which is produced by the parafollicular C cells of the thyroid (Austin). Calcitonin levels are useful in predicting residual disease after surgery and the doubling time of CTN may have prognostic implications (Barbet). High levels of CTN as seen in patients with disseminated metastases do not usually cause derangements of calcium metabolism (Austin). Hypocalcemia, however, may be seen in patients with MTC as a result of post-surgical hypoparathyroidism (Rosato).

Early stage disease can be treated surgically with curative intent and patients known to be at risk for the hereditary forms of the disease often undergo prophylactic thyroidectomy. The overall prognosis of MTC is favorable with a 10 year overall survival rates for patients with tumors confined to the thyroid gland of approximately 95%, but with distant metastases present at diagnosis, the 10 year overall survival rate is estimated to be 40% (Roman). Surgery is the mainstay of treatment even with the presence of distant metastases. Other modalities that are used for disease control include radiation therapy, radiofrequency ablation, and radiolabelled antibodies (Terezakis).

Figure 1: 10 year, Disease-Specific Survival by SEER Stage for MTC, 1973-2002



To date, there are no approved systemic agents for the treatment of unresectable MTC. Historically, chemotherapy has been used for advanced disease, however the experience has largely been limited to case series or case reports. The best described agent is doxorubicin with response rates reported to be in the range of 10-25% (Matuszczyk; Shimaoka) Other chemotherapy agents that have been reported in the literature include capecitabine, cisplatin, and DTIC (Shimaoka; Gilliam; Nocera). Due to the natural history of the disease and the side effect profile of these cytotoxic agents, it is widely recognized that patients with metastatic disease may survive years without systemic treatment and that systemic therapy is usually reserved for patients with rapidly progressive distant metastasis (Kloos, Pacini)

Recently, there have been several clinical trials reporting the use of small molecule tyrosine kinase inhibitors (TKI) in MTC. Tyrosine kinase inhibitors with in vitro activity against RET and vascular endothelial growth factor (VEGF) receptors have been evaluated in early stage clinical trials. These agents include: (b) (4)

Table 1: Tyrosine Kinase Inhibitors in MTC

Drug Name	Current status	*In Vitro* Inhibitory Kinase Activity	Responses/ number of patients
Vandetanib	Completed Phase 3	RET, VEGFR2, EGFR	103/231 (45%)

(b) (4)

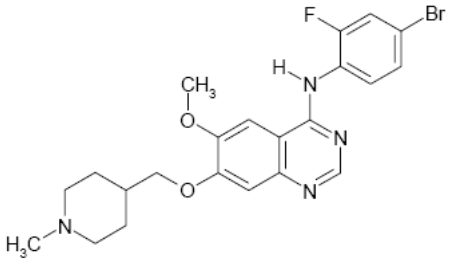
2.1 Product Information

Vandetanib is a new molecular entity and is a kinase inhibitor.

CAS Registry Number	443913-73-3
Generic Name	Vandetanib
Code Name	ZD6474, M382561, AZ11749412
Chemical Name	*N*-(4-bromo-2-fluorophenyl)-6-methoxy-7- [(1-methylpiperidin-4-yl)methoxy]quinazolin-4-amine

Molecular Formula/Molecular Weight $C_{22}H_{24}BRFN_4O_2$/475.36 g/mol

Structure or Biochemical Description



Pharmacologic Class Kinase inhibitor

2.2 Tables of Currently Available Treatments for Proposed Indications

There are no currently available therapies indicated for unresectable locally advanced or metastatic medullary thyroid cancer.

2.3 Availability of Proposed Active Ingredient in the United States

Please refer to CMC review. Vandetanib is not available in the US.

2.4 Important Safety Issues With Consideration to Related Drugs

Both the Sutent and Votrient labels carry boxed warnings for hepatotoxicity. Refer to section 7.2.6.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The development of vandetanib for the treatment of patients with medullary thyroid cancer was discussed during an end of Phase 2 meeting in May 2005. This was followed by a request for Special Protocol Assessment for the key Phase 3 study in this submission. A non-agreement letter was sent, but the FDA did agree PFS by blinded independent review was an acceptable endpoint for full approval. Further, the FDA agreed to the applicant's plan to use co-primary endpoints, PFS in all patients and PFS in patients whose tumor contained the RET mutation. During follow up discussions, the FDA also agreed to the use of modified RECIST criteria in the assessment of PFS, but recommended a series of sensitivity analyses using conventional RECIST criteria. The study was conducted from November 2006 to December 2009 and this NDA was submitted in July 2010 with a data cutoff of July 2009.

2.6 Other Relevant Background Information

None

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission contains all required components of the eCTD. The overall quality and integrity of the application appear reasonable.

3.2 Compliance with Good Clinical Practices

The protocol and its 7 amendments were submitted to Independent Ethics Committees (IEC) and/or Institutional Review Boards (IRB) for review, and the study was conducted after written approval.

The protocol and study conduct complied with recommendations of the 18th World Health Congress (Helsinki, 1964) and all applicable amendments approved by the World Medical Assemblies, and the International Conference for Harmonization (ICH) guidelines for Good Clinical Practice (GCP). The protocol also complied with the laws and regulations, as well as any applicable guidelines, of the countries where the studies were conducted.

Informed consent was obtained prior to the conduct of any study-related procedures. The written informed consent form (ICF) was signed, the names filled in and personally dated by the patient or by the patient's legally acceptable representative, and by the person who conducted the informed consent discussion. The ICF used by the Investigator for obtaining the patient's informed consent was reviewed and approved by the Sponsor prior to submission to the appropriate Ethics Committee (IRB/IEC) for approval/favorable opinion. The patient informed consent form was modified according to the local regulations and requirements.

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. Rosella 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).

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. 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.
In discussions held between the Division of Scientific Integrity (DSI) and the review division medical officers on inspectional findings of Sites 2801 and 2501, it was decided that protocol deviations reported for both of these sites 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 Astra Zeneca revealed that out of 331 subjects randomized into the study 73 failed to meet 1 or more entry criteria. Although regulatory violations were noted as described above, it appears that they are unlikely to significantly impact primary safety and efficacy analyses.

3.3 Financial Disclosures

Disclosure of financial interests of the investigators who conducted the clinical trials supporting this NDA was submitted in the FDA form 3454. The disclosure was certified by Anthony Rodgers, Vice President, Regulatory Affairs for the applicant. Two sub-investigators in the key study supporting this NDA were found to have financial conflict of interest, in the form of significant payments from the applicant. There were 60 sites where patients were enrolled on the pivotal, Phase 3 trial. The number of patients enrolled at each of the 2 sites at which a sub-investigator had a financial conflict of interest did not drive the efficacy or safety data.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

See final CMC review.

Vandetanib is synthesized and mixed with the following excipients: dibasic calcium phosphate dehydrate, microcrystalline cellulose, crospovidone, povidone, and magnesium stearate. Drug product is them formed into 100 mg and 300 mg tablets which are film coated with hypromellose 2910, PEG300, and titanium dioxide. The vandetanib tablets used in the Phase 3 trial were manufactured using the commercial process and the amounts of each excipient and of the components of the film coating are acceptable. Impurities and residual solvents are also acceptable. Thirty-six months of stability has been demonstrated with 3 batches of 100 mg and 3 batches of 300 mg tablets.

4.2 Clinical Microbiology

Vandetanib is taken orally and is not sterile.

4.3 Preclinical Pharmacology/Toxicology

Vandetanib is a multi-kinase inhibitor. Its IC_{50} values against various clinically relevant kinases are shown in Table 1. Vandetanib was not mutagenic or clastogenic in standard assays. Carcinogenicity studies have not been conducted and, given the long natural history of this disease, will be included in the post marketing requirements. Repeat dose toxicity studies in the rat showed damage to the kidneys, adrenal gland, mesenteric lymph nodes, skin, spleen, and thymus. At high doses, mortality secondary to pulmonary toxicity, cholangitis and pancreatitis was seen. Pericarditis and myocardial fibrosis were also seen at high doses. In other studies, vandetanib appeared to impair autonomic and neuromuscular function in the rat. In repeat dose toxicity studies in the dog, target organs included the gastrointestinal tract, kidneys, spleen, and thymus. Results of embryo-fetal development studies in the rat, showed that vandetanib is embryotoxic, fetotoxic, and teratogenic to rats at exposures equivalent to or lower than those expected at the recommended dose of 300 mg/day. The reproductive and developmental toxicology studies suggest that administration of vandetanib may also impair fertility. Vandetanib will be assigned Pregnancy Category D.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Vandetanib is a kinase inhibitor with activity at multiple kinases. Vandetanib was tested in multiple *in vitro* recombinant enzyme assays to evaluate the potency and selectivity of the compound by determining the IC_{50} values for various protein kinases. Based on these assays vandetanib has potency for vascular endothelial growth factor (VEGF), epidermal growth factor receptor (EGFR), and RET kinase. The N-desmethyl metabolite of vandetanib was found to have similar inhibitory activity to vandetanib for inhibition of VEGF (KDR and Flt-1), EGFR, and bFGF.

4.4.2 Pharmacodynamics

In vivo effects of vandetanib were demonstrated using angiogenesis assays and in human tumor xenograft models in nude mice. In a study on the effect of vandetanib on VEGF165-induced angiogenesis with matrigel plugs in athymic nude mice, treatment with vandetanib decreased the number of vessel nodes and vessel length compared to vehicle in mice. Therefore, treatment with vandetanib showed a dose dependent inhibition of VEGF-induced angiogenesis. Vandetanib has also been shown to inhibit tumor growth in a variety of human cancer xenografts including Calc-6 human lung and PC-3 prostate cancer xenografts of various sizes. One study assessed the effects of vandetanib on the expression of pVEGFR-2 and pEGFR levels in paraffin-embedded sections of human lung or colon tumor xenografts from mice treated with vehicle or vandetanib. A dose of 150 mg/m^2 vandetanib inhibited VEGFR2 phosphorylation in the Calu-6 lung xenograft and pEGRF staining in the LoVo human colon tumor xenograft model. These studies provide some evidence that vandetanib has *in vivo* activity against VEGF and EGFR.

In the Phase 3 study, vandetanib concentration in individual patients (at steady state) was compared to patient outcome in terms of PFS and calcitonin level. No exposure-response relationship was seen for PFS. However, a relationship between drug concentration and the decrease in calcitonin level was seen. In the same study, vandetanib concentration was related to adverse events such as diarrhea and fatigue, but was not related to hypertension or rash. Most vascular endothelial growth factor inhibitors exhibit as relationship between hypertension and drug concentration. Vandetanib concentration is closely related to prolongation in the QTc interval. At 300 mg daily, the mean increase in QT interval was 35 ms, with 35.5% of patients showing a > 60 ms increase in QT over baseline (CTCAE v4 grade 4 toxicity). This increase in QT interval will be discussed further in Section 8. Safety.

4.4.3 Pharmacokinetics

The applicant has conducted several Phase 1 studies in healthy volunteers and patients with malignant tumors to evaluate the safety and pharmacokinetics of vandetanib. The Tmax of vandetanib occurs 6 hours (range 4-10 hours) after the dose. The PK of

vandetanib is linear over the range of 100 – 600 mg once daily dosing. A high-fat meal did not change the vandetanib exposure. The pharmacokinetics of vandetanib appear to be affected by race; the area under the curve was increased 2-fold in Japanese and Chinese patients when compared to Caucasians.

In the pivotal study, the clearance was 13 L/h, volume of distribution was 7450 L, and half-life was 19 days. In patients receiving daily vandetanib, steady state is achieved at Day 56. There was high inter-individual variability. Vandetanib is 94% bound to human serum albumin and α1-acid-glycoprotein. Two metabolites – N-desmethyl vandetanib (active) and N-oxide vandetanib (inactive) - were identified in plasma, urine and feces. N-desmethyl vandetanib, which is produced by CYP3A4, is present at concentrations between 7 and 17% of vandetanib. N-desmethyl and N-oxide vandetanib have the potential to prolong QTc based on the human ether-a-go-go gene (hERG) assay with IC50 values that were 3- and 10-fold greater, respectively than that for vandetanib. There was no clinically significant effect on exposure to vandetanib in the presence of the potent CYP3A4 inhibitor itraconazole in healthy volunteers. However, the potent CYP3A4 inducer rifampicin reduced exposure to vandetanib by 48% but increased exposure to the active N-desmethyl metabolite. Therefore, the effect of CYP3A4 inducers on the QTc effect is unclear. Patients receiving vandetanib should avoid the use of potent inducers of CYP3A4.

After administration of radio-labeled vandetanib in healthy male subjects, both urine (25%) and fecal (44%) excretion are the major routes of elimination of vandetanib. Data from a single dose pharmacokinetic study in healthy volunteers with renal impairment resulted in a 40% increase in the mean AUC of vandetanib in patients with moderate and severe renal impairment. A dose reduction to 200 mg for patients with moderate and severe renal impairment is recommended.

Single dose pharmacokinetic data from healthy volunteers with hepatic impairment suggests that there were no differences in pharmacokinetics compared to subjects with normal hepatic function. There is limited data in patients with hepatic impairment (serum bilirubin greater than 1.5 times the upper limit of normal). ZICTIFA is not recommended for use in patients with hepatic impairment, as safety and efficacy have not been established.

Substantial and sustained QTc prolongation was observed. The QTc prolongation is concentration-dependant. Based on the exposure-response relationship, the expected mean (90% CI) ΔQTcF at a dose of 300 mg was 35 (33-36) ms.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 2: Studies in NDA 022405

Study number	Study Title	Number of patients and number receiving vandetanib	Dose of vandetanib	Control
D4200C00058 Study 58	An international, Phase III, randomized, double-blinded, placebo-controlled, multi-centre study to assess the efficacy of ZD6474 versus placebo in subjects with unresecatble locally advanced or metastatic medullary thyroid cancer	331 total 231 at 300 mg 58 patients originally randomized to receive placebo received 300 mg in open label phase	300 mg	Placebo
D4200C00008 Study 8	An open-label, two stage, Phase II study to evaluate the efficacy and tolerability of ZD6474 in patients with unresectable locally advanced or metastatic hereditary medullary thyroid carcinoma.	30 at 300 mg	300 mg	None
D4200C00068 Study 68	An Open-Label, Two-Stage, Phase II Study to Evaluate the Efficacy and Tolerability of ZD6474 in Patients With Locally Advanced or Metastatic Hereditary Medullary Thyroid Carcinoma	19 at 100 mg	100 mg	
D4200C00001 Study 1	An open, Phase I, rising multiple-dose tolerability study of ZD6474 in patients with malignant tumors.	25 at 300 mg	300 mg	None
D4200C00002 Study 2	An open-label, mulitcentre Phase II study to assess the response of subjects with metastatic breast cancer, previously treated with	24 at 300 mg	300 mg	None

	anthracycline and taxane therapy with or without capcitabine, to ZD6474.			
D4200C00003 Study 3	A Phase II, randomized, double-blind, 2-part, multicentre study to compare the efficacy of ZD6474 with the efficacy of ZD1839 (Iressa™) in patients with locally advanced or metastatic (IIIB/IV) NSCLC after failure of either first-line and/or second line platinum-based chemotherapy and to assess the activity of ZD6474 in patients following failure of treatment with ZD1839.	83 as initial treatment 37 after gefitinib	300 mg	Gefinitib 250 mg
D4200C00007 Study 7	A randomized, partially blinded, Phase II study to assess the safety, tolerability, and efficacy of ZD6474 alone or in combination with paclitaxel and carboplatin in subjects with previously untreated unresectable locally advanced or metastatic.	73 at 300 mg monotherapy	300 mg	Multiple arms
D4200C00039 Study 39 Japan	A randomized, double-blind, parallel-group, Phase IIa dose-finding multicentre study to assess the efficacy (Objective response) and safety of ZD6474 100, 200 and 300mg/day in patients with advanced or metastatic (Stage IIIb/IV) or recurrent NSCLC who have failed one or two previous chemotherapy regimens at least one of which contained platinum	18 at 300 mg	300 mg	None
D4200C00043	An open, Phase I, rising	6 at 300 mg	300 mg	None

Study 43 (TVE-15-11) Japan	multiple dose tolerability study of ZD6474 in Japanese patients with solid, malignant tumors			
D4200C00044 Study 44	A Phase III, international, randomized, double-blind, parallel-group, multicentre study to assess the efficacy of ZD6474 plus best supportive care versus placebo plus best supportive care in patients with unresectable advanced or metastatic (Stage IIIb/IV) NSCLC after prior therapy with an epidermal growth factor receptor tyrosine kinase inhibitor (EGFR TKI)	619 at 300 mg	300 mg	Placebo
D4200C00050 Study 50	A Phase I, randomized, open-label study to assess the effect of ZD6474 on vascular permeability in patient with advanced colorectal cancer and liver metastases.	12 at 300 mg	300 mg	None
D4200C00057 Study 57	A Phase III, randomized, double-blind, parallel-group, multicentre study to assess the efficacy of ZD6474 versus erlotinib in patients with unresectable locally advanced or metastatic (Stage IIb/IV) NSCLC after failure of at least one prior cytotoxic chemotherapy	623 at 300 mg	300 mg	Erlotinib

5.2 Review Strategy

The clinical review is based on the clinical study report for Study 58, including the applicant's presentation slides, case report forms, primary data sets for efficacy and toxicity submitted by the applicant, study reports for other vandetanib clinical trials and

literature review of MTC. Efficacy is supported by studies 08 and 68. The other studies were used in the review of safety.

5.3 Discussion of Individual Studies/Clinical Trials

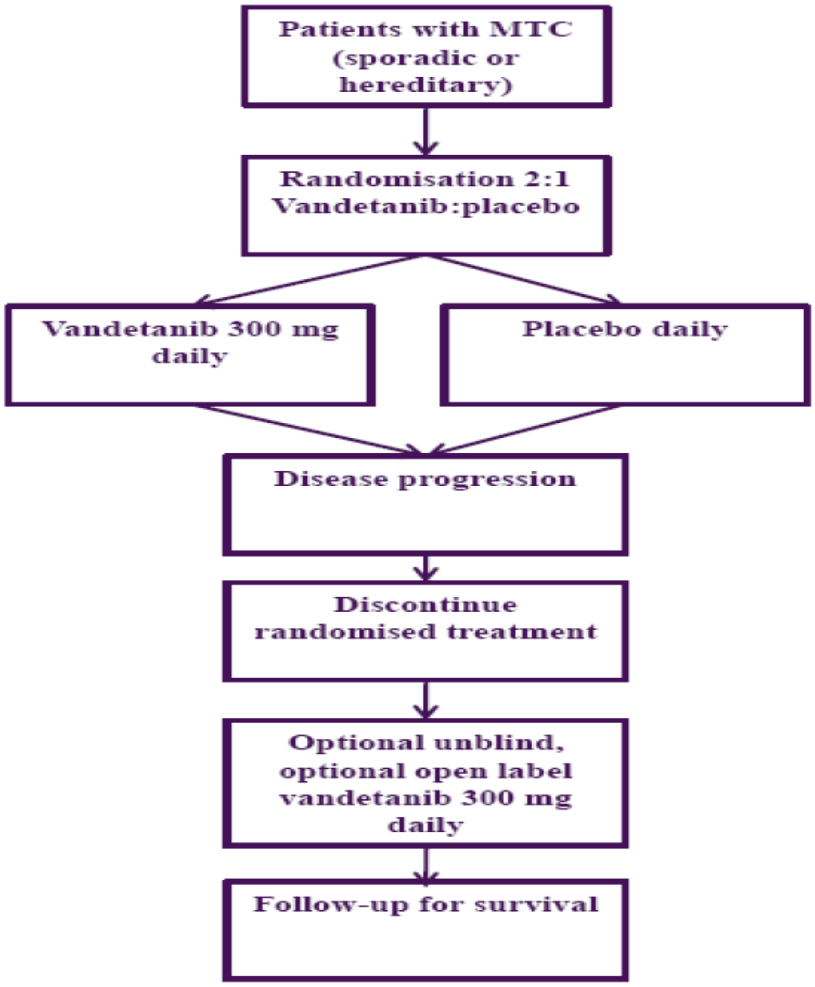
This NDA is based primarily on progression free survival from a single, randomized, double-blinded Phase 3 trial, Study 58

Study Title: An international, Phase III, randomized, double-blinded, placebo-controlled, multi-centre study to assess the efficacy of ZD6474 versus placebo in subjects with unresectable locally advanced or metastatic medullary thyroid cancer.

5.3.1 Study Design

Study 58 was a double-blind, randomized, placebo-controlled Phase 3 trial comparing vandetanib to placebo in patients with unresectable locally advanced or metastatic medullary thyroid cancer.

Figure 2: Study Design Schema



5.3.2 Study Drug Administration and Schedule

Patients were stratified by center to:

1. Vandetanib 300 mg po qd, N = 231
2. Placebo po qd, N = 100

Patients were treated until investigator-determined progression. Patients on both the placebo and vandetanib arm could receive vandetanib after investigator-determined progression.

5.3.3 Study Endpoints

Primary objective
The primary objective of this study was to demonstrate an improvement in progression-free survival (PFS) with ZD6474 as compared to placebo in subjects with unresectable locally advanced or metastatic MTC.

Reviewers Comment: *Conducting a trial with overall survival as the primary endpoint in this patient population would be very difficult to do. Given the long natural history of this disease, it is difficult to determine the clinical benefit of the primary endpoint of progression free survival. In prior meetings, the applicant and the FDA have come to agree that PFS can be used for full approval, provided that the risk/benefit profile favored treatment with vandetanib.*

Secondary objectives

The secondary objectives of the study were:

1. To demonstrate an improvement in the overall objective response rate (ORR), disease control rate (DCR), and duration of response (DOR) with ZD6474 as compared to placebo
2. To demonstrate an improvement in the overall survival (OS) in subjects with MTC who have been treated with ZD6474 as compared to placebo
3. To demonstrate an improvement in biochemical response with ZD6474 as compared to placebo, as measured by CTN and CEA
4. To demonstrate a delay in time to worsening of pain (TWP) among subjects with MTC after treatment with ZD6474 as compared to placebo
5. To determine the pharmacokinetics (PK) of ZD6474 in this subject population and investigate any influence of subject demography and pathophysiology on the PK
6. To assess the relationship between pharmacokinetics (PK) and QTc, safety, efficacy, and biomarkers
7. To determine the safety and tolerability of ZD6474 treatment in MTC subjects
8. To determine the mutational status of the RET proto-oncogene in deoxyribonucleic acid (DNA) extracted from tumor samples.

Exploratory Objectives
The exploratory objectives of the study were:
1. To investigate the effect of treatment with ZD6474 as compared to placebo on diarrhea in subjects with MTC
2. To explore changes in plasma VEGF, VEGFR-2, and bFGF levels in subjects treated with ZD6474 as compared to placebo, and their relationship to efficacy
3. To explore changes in serum protein profiles in subjects treated with ZD6474 as compared to placebo, and their relationship with efficacy and disease progression

4. To measure EGFR expression levels in tumor tissue in subjects treated with ZD6474 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 signalling pathways
6. To demonstrate a delay in time to worsening of pain (TWP) among subjects with MTC who have no pain at baseline (defined as requiring <10mg/day morphine sulfate or equivalent after treatment) with ZD6474 as compared to placebo
7. To demonstrate a delay in time to worsening of pain (TWP) among subjects with MTC who have pain at baseline (defined as requiring ≥ 10mg/day morphine sulfate or equivalent) after treatment with ZD6474 as compared to placebo
8. To demonstrate a reduction in the use of opioid analgesic medication in subjects with MTC who have pain at baseline (defined as requiring ≥ 10mg/day morphine sulfate or equivalent) after treatment with ZD6474 as compared to placebo
9. To demonstrate an improvement in weight in subjects with MTC who have been treated with ZD6474 as compared to placebo
10. To demonstrate a delay in the time to decline in WHO performance status (TDPS) in subjects treated with ZD6474 as compared to placebo.
11. To investigate the effects of ZD6474 as compared to placebo on subject quality of life (QoL) as measured by the FACT-G
12. To determine the relationship between histopathological variables in archival tumor tissue and efficacy of ZD6474
13. To examine the relationship between CTN and CEA expression in archival tumor tissue and plasma
14. To determine the expression status of signaling pathways known to be targets of ZD6474 (VEGFR. EGFR, RET), and their downstream effectors, and the efficacy of ZD6474
15. To determine the mutation status of genes known to play a role in thyroid cancer or other solid tumors

5.3.4 Eligibility Criteria

Inclusion Criteria

For inclusion in the study subjects must have fulfilled all of the following criteria:

1. Provision of written informed consent
2. Female or male aged 18 years and over
3. Previously confirmed histological diagnosis of unresectable, locally advanced or metastatic hereditary or sporadic MTC.
4. Life expectancy of 12 weeks or longer
5. WHO Performance status 0-2
6. Able to swallow study medication

7. Presence of a measurable tumor as defined by:
    a) a solitary lesion measuring ≥2 cm, OR
    b) for multiple lesions
        i. • A technique providing ≤5mm sections: a sum of diameters ≥2cm(no target lesions measuring <1cm and no lymph nodes <1.5cm) OR
        ii. • A technique providing >5mm sections: a sum of diameters ≥4cm(no target lesion measuring <2cm
8. CTN ≥ 500 pg/ml(conventional units) or ≥ 146.3 pmol/L(international standard units)
9. All subjects (other than those with hereditary MTC who have a documented germline RET mutation) must submit a suitable archived tumor collection sample. If an archived tumor sample is not available prior to 2 weeks before 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.
10. Negative pregnancy test for female subjects of childbearing potential

Reviewer's Comments: *Patients were to have measurable, locally advanced or metastatic disease. However, no criteria specifying the pace of disease or whether the patient was in need of treatment were included in the study. This is a particularly important issue in MTC where it is widely recognized that the indolent, natural history of the disease process makes observation of patients an acceptable option, even in the setting of metastatic disease.*

Exclusion Criteria

Any of the following is regarded as a criterion for exclusion from the study:

1. Brain metastases or spinal cord compression, unless treated at least 4 weeks before first dose and stable without steroid treatment for 10 days
2. Any concomitant medications that may affect QTc or induce CYP3A4 function (with the exception of somatostatin or somatostatin analog).
3. Major surgery within 4 weeks before randomization
4. The last dose of prior chemotherapy is received less than 4 weeks prior to randomization
5. Radiation therapy within the last 4 weeks prior to randomization (with the exception of palliative radiotherapy)
6. Serum bilirubin greater than 1.5 x the upper limit of reference range (ULRR)
7. Creatinine clearance <30 ml/min (calculated by Cockcroft-Gault formula)
8. Potassium <4.0 mmol/L despite supplementation, or above the 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 cases where the serum calcium is below the normal range, the

calcium adjusted for albumin is to be obtained and substituted for the measured serum value. Exclusion is to then be based on the calcium adjusted for albumin values falling below the normal limit. Corrected Calcium=Ca + 0.8 X (4-serum albumin)

9. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase (ALP) greater than 2.5 × ULRR, or greater than 5.0 × ULRR if judged by the investigator to be related to liver metastases
10. Significant cardiac event (e.g. myocardial infarction), superior vena cava [SVC] syndrome, New York Heart Association [NYHA] classification of heart disease ≥2, within 12 weeks before randomization, or presence of cardiac disease that in the opinion of the Investigator increases the risk of ventricular arrhythmia
11. History of arrhythmia (multifocal premature ventricular contractions [PVCs], bigeminy, trigeminy, ventricular tachycardia), which is symptomatic or requires treatment (CTCAE grade 3), symptomatic or uncontrolled atrial fibrillation despite treatment, or asymptomatic sustained ventricular tachycardia. Subjects with atrial fibrillation controlled by medication are permitted.
12. Congenital long QT syndrome or 1st degree relative with unexplained sudden death under 40 years of age
13. QT prolongation with other medications that required discontinuation of that medication
14. Presence of left bundle branch block (LBBB)
15. QTc with Bazett's correction unmeasurable or ≥480 msec or greater on screening ECG (Note: If a subject has QTc interval ≥480 msec on screening ECG, the screening ECG may be repeated 2 times [at least 24 hours apart] for a total of 3 ECGs. The average QTc from the three screening ECGs must be <480 msec in order for the subject to be eligible for the study.) If a subject is receiving one of the medications with possible association with Torsades de Pointes prior to study entry, and it cannot be discontinued before study treatment, then the screening QTc must be <460msec.
16. Hypertension not controlled by medical therapy (systolic BP greater than 160 millimeter of mercury [mmHg] or diastolic blood pressure greater than 100 mmHg)
17. Previous or current malignancies of other histologies within the last 5 years, with the exception of tumors associated with MEN2a and MEN2b, in situ carcinoma of the cervix, and adequately treated basal cell or squamous cell carcinoma of the skin
18. Any unresolved chronic toxicity greater than CTCAE grade 2 from previous anticancer therapy
19. Participation in a clinical study and/or receipt of an investigational drug during the last 30 days (participation in the survival follow-up period of a study is not an exclusion)
20. Previous exposure to ZD6474
21. Currently pregnant or breast feeding

22. Involvement in the planning and conduct of the study (applies to both AstraZeneca staff or staff at the investigational site)
23. Previous randomization or treatment in the present study

5.3.5 Duration of Treatment

Subjects could have been discontinued from study treatment and assessments at any time. Subjects continued to receive blinded treatment as long as there was no evidence of tumor progression, they were benefiting from treatment in the opinion of the Investigator, and they did not meet the criteria of discontinuation.

Specific reasons for discontinuing a subject from this study were:

- Disease progression or death
- Voluntary discontinuation by the subject who is at any time free to discontinue his/her participation in the study, without prejudice to further treatment
- Safety reasons as judged by the investigator and/or AstraZeneca
- Severe non-compliance to protocol as judged by the investigator and/or AstraZeneca
- Incorrect enrollment (ie, the subject does not meet the required inclusion/exclusion criteria) of the subject
- Subject lost to follow-up
- Administration of another anti-cancer therapy other than the study medication

Subjects were considered to have withdrawn from the study only if informed consent was withdrawn. In this case, no data was collected after the date of withdrawal of informed consent.

5.3.6 Primary Endpoint Evaluation

Methods of assessment
PFS was determined using data from RECIST assessments performed at baseline, during treatment and during the follow-up period.

Derivation or calculation of outcome variable
Progression free survival was defined from the date of randomization to the date of objective progression or death (by any cause in the absence of progression). Subjects who have not progressed or died at the time of statistical analysis will be censored at the time of their latest objective tumor assessment. This includes subjects who are lost to follow-up or have withdrawn consent. For subjects lost to follow-up without having progressed, death within a further 12 weeks was considered an event; otherwise the subject was censored for PFS at the time of their last tumor assessment date.

The modified RECIST criteria was used to perform the objective tumor assessments and determine a subject's PFS and best overall objective tumor response

Baseline radiological tumor assessments were to be performed no more than 3 weeks before the start of study treatment and at all time points defined in the study plan. All measurable lesions, up to a maximum of 10 lesions and representative of all involved organs (maximum of 5 lesions per organ), were identified as target lesions and were recorded and measured at baseline. Target lesions were selected on the basis of their size (lesions with the LD) and their suitability for accurate repetitive measurements (by either CT or MRI). A sum of the LD for all target lesions was calculated and reported as the baseline sum LD. The baseline sum LD was used as reference to further characterize the objective tumor response of the measurable dimension of the disease.

In order to increase specificity and be able to accurately measure change, only lymph nodes measuring ≥ 1.5 cm in the longest diameter were accepted as a measurable lesion, assuming 5mm imaging section. Most common sites of metastasis in MTC are local regional lymph nodes in the neck and mediastinum. For slice thickness >5 mm, the minimum measurable lesion size was 2 cm for all measurable lesions.

A subject was determined to have progressed if they had progression of target lesions, clear progression of existing non-target lesions or the appearance of one or more new lesions. Progression of target lesions was defined as at least a 20% increase in the sum of the LD of target lesions taking as references the smallest sum of LD recorded. Death was regarded as a progression event in those subjects who die before documented objective disease progression.

All medical images were reviewed at the site and by a centrally appointed CRO. The central review data was used in preference to the local site review data at the time of the data analyses.

Categorization of the objective tumor response assessments were based on the RECIST criteria for target and non-target lesions. Response were assigned as CR, PR, SD, progressive disease (PD), or not evaluable (NE) at each scheduled visit by the Investigator. For the purposes of analysis the applicant determined visit and overall response using the lesion assessments recorded on the eCRF.

Subjects who discontinued from study treatment for toxicity other than objective disease progression continued to have objective tumor assessments every 12 weeks until progression was documented, unless the subject withdrew consent.

Modifications to RECIST criteria

Calcified tumor lesions can occur in MTC subjects and be seen at baseline imaging or during follow up. It is recognized that there is great difficulty in measuring such lesions, and that an increase in size of the calcified component may represent healing rather than progression. As a result, it was recommended that such lesions not be assessed as target lesion at baseline unless no other lesions were available for measurement.

Calcification within the liver or other lesions may occur during the study, as observed in the Phase II study (D4200C00008) in hereditary MTC subjects. Response assessment based upon the presence and potential growth of calcified lesions was modified to recognize that growth in calcified portions of metastases may not represent progression.

As observed in study D4200C00008, (the Phase II study in hereditary MTC subjects), new hypo-dense or hypointense lesions may appear in the liver even as subjects exhibit respond in other target lesions, and demonstrate clinical response with improvement in biomarkers. Visualization of non necrotic/cystic lesions may be difficult at baseline due to near iso-density or iso-intensity with normal liver in terms of contrast enhancement as a documented technical limitation of CT and MRI. If new hypo-dense or hypointense lesions appear in the liver within the first 2 scheduled RECIST follow up assessments, the baseline CT/MRI was re-examined and if in retrospect iso-dense or iso-intense lesions were identified in the same location then these were 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 be identified on retrospective review of the baseline then these lesions were recorded as new lesions.

Reviewer's Comments: *These modifications to the RECIST criteria were not previously validated in any comparison clinical trial and are based on a single arm Phase 2 trial in 30 hereditary MTC patients.*

5.3.7 Secondary Endpoint Evaluation

Overall Response Rate (ORR), Disease Control Rate (DCR), Duration of Response (DOR)

The ORR was calculated as the percentage of subjects with a best response of CR or PR. The DCR was calculated as the percentage of subjects with CR or PR or SD ≥ 24 weeks.

DOR was calculated for those subjects who have a best response of CR or PR only. DOR was defined in two ways:

- from the date of randomization until the date of documented objective disease progression or death from any cause in the absence of documented progression, and
- from the date of first documentation of response until date of documented objective disease progression or death from any cause in the absence of documented progression

Overall survival (OS)

OS was calculated from the date of randomization to the date of death.

After withdrawal from study treatment, subjects were followed up for survival every 12 weeks, unless the subject withdrew consent, or death occurred. This will continue until the survival cut-off timepoint (defined as the time when ≥50% subjects have died). Subjects who had not died at the time of the statistical analysis were censored at the time they were last known to be alive.

Biochemical response

Venous blood (approx. 6 ml) was taken for the analysis of CEA and CTN. All samples were sent to the central laboratory for analysis. The following definitions were used to calculate both the CEA response and the CTN response for each subject:

- **Complete Response (CR):** Complete normalization of CEA/CTN level following treatment, as confirmed with a repeat CEA/CTN level
- **Partial Response (PR):** At least a 50% decrease in the CEA/CTN level (represented by a persistent decrease in CEA/CTN over 4 weeks documented by repeat CEA/CTN serum measurement), taking as reference the baseline (mean) level
- **Progressive Disease (PD):** At least a 50% increase in the CEA/CTN (sustained over weeks), taking as reference the baseline (mean) level
- **Stable disease (SD):** Neither sufficient normalization decrease to qualify for PR nor sufficient normalization increase to qualify for PD, taking as reference the baseline (mean) level

For each subject, their best CEA response and their best CTN response will be calculated from assessments performed at baseline and during treatment. Responders are those subjects with a best biochemical response of CR or PR.

The CEA response rate, the CTN response rate and the associated exact 95% confidence intervals (CI) will be summarized for each treatment group. To be assigned a status of PR or CR, changes in serum tumor marker level were confirmed by repeat assessments, no less than 4 weeks after the criteria for PR or CR were first met. For subjects with biochemical CR, repeat serum tumor marker levels were obtained at least 4 weeks after subjects achieved biochemical CR, and had to remain within normal limits in order to be considered a biochemical CR. In the case of stable disease, follow-up CEA/CTN levels met the stable disease criteria at least once after study entry at a minimum interval defined as 12 weeks.

Opioid Analgesic Use
Baseline opioid analgesic use was established using the average reported opioid medication use assessed during 4 days of the screening period in the week immediately prior to randomization.

In subjects with MTC who used ≥10mg/day of morphine sulphate or equivalent at baseline, a response to opioid analgesic use was defined as a decrease in the use of opioid analgesic medication by >50% from baseline lasting for 14 days and was accompanied by no increase in the worst pain severity item of the Brief Pain Inventory (BPI) . The overall response to opioid analgesic use was calculated as the percentage of subjects with a response. Duration of opioid analgesic use response was calculated for those subjects with opioid analgesic response, from the date of first documented response until the date of the subject no longer met the criteria for response.

Time Worsening of Pain (TWP) and Worst Pain Severity

Methods of assessment
A subject's time to worsening of pain was assessed using the opioid analgesic utilization and responses on the worst pain severity question from the BPI instrument.

Derivation or calculation of variable
Baseline score on the worst-pain item for each subject was established using the average of scores on the worst-pain item from the BPI assessments during 4 days in the screening period in the week immediately prior to randomization. In addition, baseline opioid analgesic use was established using the average reported opioid medication use assessed during 4 days of the screening period in the week immediately prior to randomization. Post-baseline weekly visit responses were established for each subject using the worst pain severity score or the opioid analgesic medication use.

At each visit, worsening of pain severity was considered an increase of ≥ 2 points from baseline on the worst-pain item or an increase in opioid analgesic use from baseline of ≥ 10mg/day of morphine sulphate equivalent. At each visit, an improvement of pain severity was considered a decrease of ≥ 2 point from baseline with no increase from baseline in opioid analgesic use of ≥ 10mg/day of morphine sulphate equivalent or decrease in opioid analgesic use from previous visit of > 50% with no increase of ≥ 2 points from baseline on the worst-pain item. If the visit response could not be categorized as either worsening or improvement of pain severity, then the visit response will be categorized as no change.

5.3.8 Major Protocol Amendments

Table 3: Major Protocol Amendments

Number	Date	Amendment
2	30 May 2007	Ophthalmologic examinations were added to the study plan; Inclusion criteria were updated to indicate that the qualifications for a measurable lesion would include measurements for lymph nodes, sum of diameters, and

		size of target lesion; Exclusion criteria were updated to revise serum creatinine requirement to ≤50 mL/min to ≤30 mL/min.
3	15 May 2008	The study was redefined as a Phase 3 study; DCR was calculated as the percentage of patients with CR, PR, or SD ≥24 weeks;
5	18 May 2009	The objectives for the PRO variables were amended, which affected both the secondary and exploratory objectives of the study. PRO variables and statistical methods for PRO variables were also revised for consistency with changes to study objectives; Patient weight was changed from a secondary to an exploratory objective; (b) (4)
6	13 January 2010	The study plan was updated to provide investigators with the option to unblind patients remaining on blinded, randomized therapy. When unblinded, patients could not remain on blinded therapy; they had to either enter the open-label portion of the study or discontinue blinded therapy and be followed for survival. Patients who were not unblinded had to continue in the study outlined in the study plan.

6 Review of Efficacy

Efficacy Summary

This application is based on the primary endpoint of progression free survival (PFS) in a single, randomized, double-blinded study comparing vandetanib with placebo in 331 patients with unresectable, locally advanced or metastatic medullary thyroid cancer.

- The applicant reports an improvement of PFS in patients treated with vandetanib as compared to placebo, with a hazard ratio of 0.46 95% CI (0.31, 0.69) p = 0.0001. The duration of PFS for vandetanib was not reached.
- The applicant reports an overall response rate of 45% for vandetanib as compared to an ORR of 13% for placebo. The duration of response for vandetanib was not reached.
- There was no statistically significant difference in overall survival seen between arms.
- There were few major protocol violations that could have affected the primary endpoint analysis. The most frequent major protocol violation concerned missing archival tissue for RET mutation analysis (b) (4)

(b) (4) The time to worsening pain endpoint was based on patient opioid use and patient questionnaires. The overall compliance rate with the questionnaires was only 50% with compliance rates of less than 30% seen at multiple timepoints. This large amount of missing data precludes any conclusions being drawn regarding this endpoint. Biochemical responses in CTN and CEA are not validated as clinical endpoints in this disease.

6.1 Indication

The proposed indication is for the treatment of patients with unresectable locally advanced or metastatic medullary thyroid cancer.

6.1.1 Methods

Clinical review is based primarily on the CSR for study 58, the applicant's presentation slides, case report forms, primary data sets for efficacy and toxicity submitted by the applicant and literature review of MTC.

6.1.2 Demographics

There was no substantial imbalance between treatment arms with respect to the demographic characteristics of age, sex, and race. There was a higher percentage of patients in the ≥18 to <40 year age category and a lower percentage of patients in the ≥40 to <65 year age category in the vandetanib arm relative to the placebo arm. A total of 95.2% of patients were Caucasian.

Table 4: Patient Demographics

		Vandetanib (n=231)	Placebo (n=100)	Total (n=331)
Baseline Characteristics:				
Age (years):				
	Mean:	50.7	53.4	51.5
	SD:	14.1	12.0	13.6
	Median:	50.0	52.5	51.0
	Min:	18	26	18
	Max:	83	84	84
Gender:				

Male:	134 (58.0)	56 (56.0)	190 (57.4)
Female:	97 (42.0)	44 (44.0)	141 (42.6)
Race:			
Asian:	8 (3.5)	1 (1.0)	9 (2.7)
Black:	1 (0.4)	1 (1.0)	2 (0.6)
White:	218 (94.4)	97 (97.0)	315 (95.2)
Other:	4 (1.7)	1 (1.0)	5 (1.5)

Enrollment of patients with this rare disease involved 23 countries with 22.1% of patients coming from the US.

Table 5: Country of Enrollment

	Vandetanib (n=231)	Placebo (n=100)	Total (n=331)
Country:			
Australia	5	3	8
Austria	3	1	4
Belgium	6	3	9
Brazil	4	2	6
Canada	9	3	12
Czech Republic	3	1	4
Denmark	3	2	5
France	31	14	45
Germany	19	9	28
Hungary	3	1	4
India	5	1	6
Italy	26	12	38
Netherlands	9	4	13
Poland	22	10	32
Portugal	5	2	7
Republic of Korea	4	1	5
Romania	3	1	4
Russia	5	3	8
Serbia	5	2	7
Spain	1	3	4
Sweden	2	0	2
Switzerland	6	1	7
US	52	21	73

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Stage of disease at entry was balanced between treatment arms. A total of 94.6% of patients in the 2 treatment groups had Stage IVC disease at entry. In terms of sites of disease, there was no imbalance in the distribution of the metastatic sites. Overall, the most common metastatic sites were hepatic (65.9%), lymph nodes (61.3%), and respiratory 56.2%).

Table 6: Baseline Disease Characteristics

		Vandetanib (n=231)		Placebo (n=100)		Total (n=331)	
Primary Tumor:							
	T1	5	(2.2)	1	(1.0)	6	(1.8)
	T2	3	(1.3)	0	(0.0)	3	(0.9)
	T3	2	(0.8)	5	(5.0)	7	(2.1)
	T4a	8	(3.5)	5	(5.0)	13	(3.9)
	T4b	6	(2.6)	1	(1.0)	7	(2.1)
	Tx	207	(89.6)	88	(88.0)	295	(89.1)
Lymph Nodes:							
	N0	29	(12.5)	13	(13.0)	42	(12.7)
	N1a	26	(11.3)	10	(10.0)	36	(10.9)
	N1b	132	(57.1)	59	(59.0)	191	(57.7)
	N2	4	(1.7)	3	(3.0)	7	(2.1)
	N3	0	(0.0)	1	(1.0)	1	(0.3)
	Nx	40	(17.3)	14	(14.0)	54	(16.3)
Metastasis:							
	M0	14	(6.1)	3	(3.0)	17	(5.1)
	M1	216	(93.5)	97	(97.0)	314	(94.9)
	MX	1	(0.4)	0	(0.0)	1	(0.3)
Stage:							
	Stage III	1	(0.4)	2	(2.0)	3	(0.9)
	Stage IVa	8	(3.5)	0	(0.0)	8	(2.4)
	Stage IVb	6	(2.6)	1	(1.0)	7	(2.1)
	Stage IVc	216	(93.5)	97	(97.0)	313	(94.6)

The majority of patients had a history of prior thyroidectomy and lymphadenectomy. Half of the patients had a history of radiation therapy. Twenty percent (20%) of the patients had prior cytotoxic chemotherapy such as doxorubicin and/or cisplatin. Ten percent (10%) of the patients had prior targeted therapy with off-label use of approved agents such as imatinib or use in the context of a different clinical trial.

Table 7: Prior Therapy

	Vandetanib (n=231)	Placebo (n=100)	Total (n=331)
Thyroidectomy	207 (89.6)	92 (92.0)	299 (90.3)
Lymphadenectomy	171 (74.0)	80 (80.0)	251 (75.8)
Prior Systemic Therapy:			
Cytotoxic:	50 (21.6)	18 (18.0)	68 (20.5)
Targeted:	22 (9.5)	11 (11)	33 (10.0)
Radioimmune	10 (4.3)	7 (7.0)	17 (5.1)
Radioisotope	25 (11.0)	9 (9.0)	34 (10.3)
Prior Radiation	117 (51.0)	53 (53.0)	170 (51.3)

The median time from diagnosis of MTC to enrollment on trial was 6 years which underscores the relatively long natural history of this disease.

Table 8: Time from Diagnosis to Enrollment (years)

	Vandetanib (n=231)	Placebo (n=100)	Total (n=331)
Median	6.0	6.0	6.0
Std Error	0.4	0.7	0.4
Range	0-31	0-35	0-35

The median time from last documented progression to enrollment on study was approximately 2 months, but 30% of the patients had last progressed more than 6 months prior to enrolling on trial, and 13 patients had last progressed 3 years before entering the trial. The longest progression free interval was a patient who last progressed almost 9 years before entering the study.

Table 9: Time from last progression (months)

	Vandetanib (n=231)	Placebo (n=98)	Total (n=325)
Median	2.43	1.96	2.14
Std Error	0.92	1.18	0.73
Range	0-107	0-77	0-107
Progressed <6mo	157 (69%)	72 (73%)	229 (70%)
Progressed >6mo	70 (31%)	26 (27%)	96 (30%)

The median sum of the longest diameter of the baseline tumor lesions was 11cm. Eleven percent (11%) of the patients had a baseline sum of less than 4. Fourteen percent (14%) of the patients did not have measurable disease as assessed by independent blinded review of baseline imaging.

Table 10: Baseline sum of lesions (cm)

	Vandetanib (n=211)	Placebo (n=88)	Total (n=299)
Median	12.1	11.1	11.4
Std Error	0.61	1.0	0.53
Range	2.0-45	2.0-47.1	2.0-47.1

Median baseline levels of calcitonin (CTN) and carcinoembryonic antigen are depicted in Table 11. Patients were required to have a CTN level $\geq$ 500 ng/L at entry.

Table 11: Baseline Calcitonin and CEA

	Vandetanib (n=231)	Placebo (n=88)	Total (n=325)
Median CTN ng/L	9620	11696	10242
Std Error	5361	8358	4509
Mean CTN ng/L	29011	35154	30858
Std Dev	80958	82739	81419
Median CEA µg/L	137	194	153
Std Error	248	85	176
Mean CEA µg/L	860	523	759
Std Dev	3749	842	3171

All patients were required to provide an archived tumor sample prior to randomization for RET mutation analysis, although no sample was required for patients with hereditary disease who had a documented germline mutation in RET. Tumor biopsy samples were

obtained using standard core biopsy techniques or by use of fine needle aspiration. RET mutation status was determined by AstraZeneca's Tissue Bank Reception (Alderley Park, Macclesfield, Cheshire UK) by sequencing the 6 most commonly mutated exons in MTC (10, 11, 13, 14, 15, and 16) and by evaluating for the M918T mutation using an amplification refractory mutation system (ARMS) analysis . A RET positive mutation status was defined as having a mutation either observed from the sequencing or ARMS assay. Stringent criteria were chosen to define RET mutation status as negative to minimize the number of patients incorrectly classified in this category. Thus, RET mutation negative status was defined as having the sequencing assay successfully showing wild type sequence at all 6 exons, and the ARMS assay negative for a M918T mutation. Unknown RET mutation status was documented when 1 or more sequencing assay was unsuccessful (non-informative), and none of the successful assays demonstrated a mutation.

Table 12: Genetic Composition

	Vandetanib (n=231)	Placebo (n=100)	Total (n=331)
RET Mutation Positive	137 (59.3)	50 (50.0)	187 (56.5)
RET Mutation Negative	2 (0.9)	6 (6.0)	8 (2.4)
RET Mutation Unknown	92 (39.8)	44 (44.0)	136 (41.1)
Hereditary MTC	28 (12.1)	5 (5.0)	33 (1.0)
Associated Endocrinopathy			
MEN 2a	14 (6.0)	3 (3.0)	17 (5.1)
MEN 2b	7 (3.0)	0 (0.0)	7 (2.1)
Familial MTC	4 (1.7)	1 (1.0)	5 (1.5)
Family History of MTC	12 (5.2)	4 (4.0)	16 (4.8)

6.1.3 Subject Disposition

The first patient was enrolled on 23 November 2006 and the last patient was enrolled in the study on 19 October 2007. The date of data cut-off for the study was 31 July 2009. With 231 patients assigned to the vandetanib arm and 100 patients to the placebo arm, the ratio of the number of patients randomized to vandetanib:placebo exceeded the 2:1 target. Randomization was stratified by site in blocks of 3. If a site did not use all the randomization numbers in a given block, it was expected that the ratio of patients assigned to the vandetanib arm relative to those assigned to the placebo arm would not be equal to 2. 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. All patients received at least 1 dose of randomized treatment except for 1 patient randomized to placebo. Patient E2501032 was randomized to placebo but died of progressive MTC before receiving randomized treatment.

A total of 111 (48.1%) patients in the vandetanib arm continued to receive randomized at the date of data cut-off (31 July 2009), compared with 28 patients (28.0%) in the placebo arm. A total of 120 (51.9%) patients in the vandetanib arm discontinued randomized treatment, compared with 71 (71.0%) patients in the placebo arm. The most common reason for discontinuation was disease progression (71 [30.7%] of patients in the vandetanib arm versus 55 [55.0%] patients in the placebo arm).

Patients who discontinued randomized treatment for disease progression were given the option to be unblinded and receive open label vandetanib or to continue in the study without receiving open label vandetanib.

In the vandetanib arm, 44 patients received open label treatment compared to 58 patients in the placebo arm.

Table 13: Patient Disposition

	Vandetanib	Placebo
Randomized	231	100
Treated	231	99
Ongoing Randomized Treatment	111	28
Discontinued Randomized Treatment	120	71
Permanently Discontinued Study Treatment	76	13
Progressive Disease or Death	41	7
Lost to Follow Up/Patient Decision	23	5
Adverse Event	12	1
Received Open Label Treatment	44	58
Ongoing Open Label Treatment	17	42
Discontinued Open Label Treatment	27	16
Progressive Disease or Death	21	9
Lost to Follow Up/Patient Decision	5	3
Adverse Event	1	4

6.1.4 Analysis of Primary Endpoint(s)

This primary analysis of progression free survival is shown in the table 14. This analysis censors the following patients:

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

Patients with more than 1 censoring-event were censored at the earliest event.

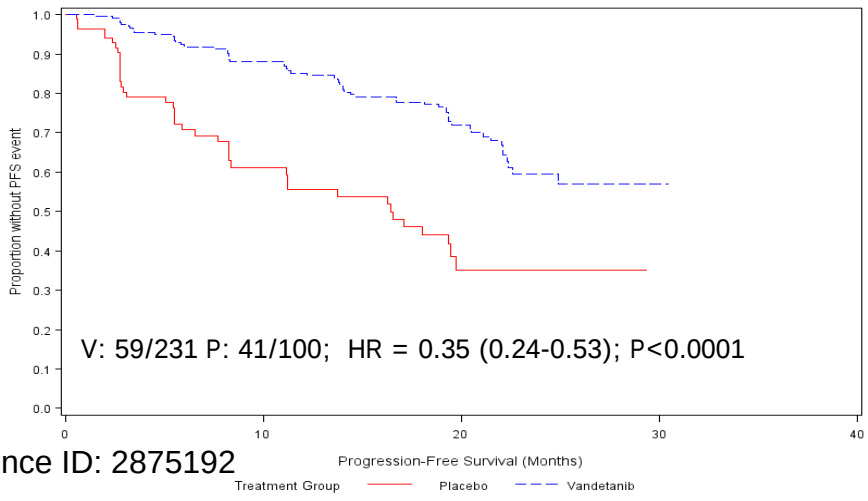
Table 14: Primary Analysis Study 1-FDA (Data Cutoff 7-31-09)

Progression Free Survival	Vandetanib N = 231	Placebo N = 100
Number of Events	59 (25.5%)	41 (41.0%)
Censored	172 (74.5%)	59 (59.0%)
Median PFS	NE (22.6 months, NE)[2]	16.4 months (8.3, 19.7)
Hazard Ratio[1] (95% CI)		0.35 (0.24-0.53)
p-value (logrank test)		<0.0001

[1]Cox proportional hazards model [2]Not estimable

A Kaplan-Meier curve for the comparison of time to PFS, as derived from all available central read RECIST assessments, is presented in Figure 3. As shown in Figure 3, the effects of vandetanib treatment appear to be maintained over time as the curves remain separated and show no appearance of converging through the entire assessment period.

Figure 3: Kaplan-Meier PFS Estimates



The hazard ratio, as calculated by the fda and the applicant, differ due to different censoring criteria, namely differences in handling discordance in progression between the investigator and independent review, the use of additional therapy during randomized treatment, and the absence of baseline disease.

Table 15: FDA and Applicant Primary Analyses

	FDA	Applicant
Events	30%	41%
Censored	70%	59%
Discordance	14%	0
Additional Therapy	2%	0
No Baseline Disease	10%	0
No Event	45%	59%
Hazard Ratio (95% CI)	0.35 (0.24-0.53)	0.46 (0.31-0.69)
p-value	0.0001	0.0001

A summary of the differences between the censoring patterns and calculated hazard ratios as determined by FDA, Investigator assessed, and Independent Radiology Committee readings are depicted in Table 16.

Table 16: FDA, Investigator, and IRC Primary Analysis

	FDA	**Investigator**	**IRC**
Hazard Ratio (95% CI)	0.35[1] (0.24-0.53)	0.40[2] (0.27-0.58)	0.46[2] (0.31-0.69)
Events Resulting in Censoring	Censored at	Censored at	Censored at
No Measurable Disease at Baseline	Day 1	Not Censored	Not Censored
Investigator-Progression Without IRC-Progression	Last RECIST Assessment Prior to Discontinuation of Study Drug	Followed Until IRC-Progression	Followed Until IRC-Progression

Received Radiation Therapy	Last RECIST Assessment Prior to Radiation	Not Censored	Not Censored

In the FDA analysis, 24% of patients were censored in the vandetanib arm and 9% of patients were censored in the placebo arm. Given this evidence of differential censoring, a A sensitivity analysis was conducted in which patient data was handled in the following manner:

- 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; and
- All patients who died without prior documented progression were considered to have progressed 1 day after their last RECIST assessment.

Table 17: Sensitivity Analysis-Primary Endpoint Study 1 (Data Cutoff 7-31-09)

Progression Free Survival	Vandetanib N = 231	Placebo N = 100
Number of Events	109 (47.2%)	44 (44.0%)
Median PFS (95% CI)	20.5 months (19.3, 22.3)	18 months (11.1, NE)
Hazard Ratio[1] (95% CI)		0.83 (0.58, 1.18)
p-value (logrank)		0.29

[1]Cox model

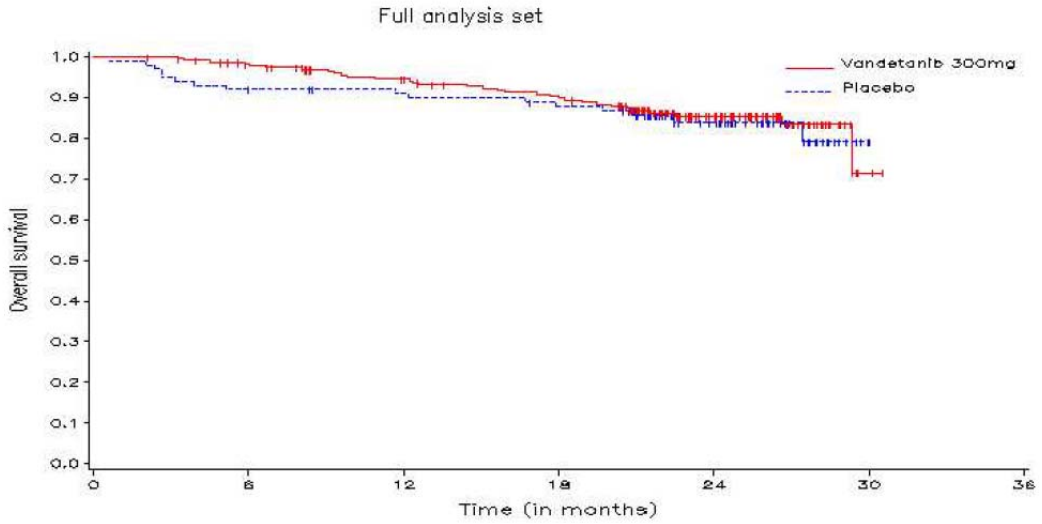
Despite these data handling conventions, the comparison of vandetanib and placebo maintains a hazard ratio < 1.

6.1.5 Analysis of Secondary Endpoints(s)

Overall Survival

Overall survival was a key secondary endpoint, however at the time of the data cutoff, no significant difference between the vandetanib arm and the placebo arm was seen. It is important to note that only 15% of the events have occurred. While this study is not powered for overall survival, a final analysis of this endpoint will occur at 50% of events which currently is anticipated to be in 2012.

Figure 4: Kaplan-Meier OS Estimates



Overall Responses

The table below provides the response rate (RR) and duration of response for patients in Study 58 by the IRC and the investigator-determined RR. It does not include responses which occurred after discontinuation of study drug and crossover to open label vandetanib. It is unusual for the investigator-determined RR to be lower than the IRC-determined RR and the reason for this finding remains unclear. The table also shows the RR in patients with hereditary and sporadic disease. This analysis was performed so that the RR in the Phase 3 study could, in an exploratory manner, be compared to the RR in the Phase 2 studies in hereditary MTC (below). The Phase 2 studies only enrolled patients with hereditary disease.

Table 18: Response Rate Study 58 (Data Cutoff 7-31-09)

Response Rate (CR+PR)	Vandetanib N = 231	Placebo N = 100
Response Rate-IRC	44.6%	1.0%
CR	0	0
PR	44.6%	1.0%
Median Duration of Response	NR	218 days
Response Rate-IRC		
Hereditary	39.0%	0%

Sporadic	44.3%	1.0%
Response Rate-Investigator	39.0%	2.0%

Biochemical Responses

Biochemical response was derived from data collected when patients were receiving randomized treatment. (b) (4)

Table 19: Overall Responses – Calcitonin Levels*

	Vandetanib (n=231)	Placebo (n=100)	Total (n=331)
Complete Responses**	3 (1.3)	0 (0.0)	3 (0.9)
Partial Responses***	157 (68.0)	3 (3.0)	160 (48.0)

* - No correlation between tumor response and calcitonin response.
**-Level of ≤10 pg/ml for men and ≤5pg/ml for women on 2 separate lab measurements at least 4 weeks apart.
*** - A decrease in the CTN level at least 50% from baseline.

Table 20: Overall Responses – CEA Levels*

	Vandetanib (n=231)	Placebo (n=100)	Total (n=331)
Complete Responses**	7 (3.0)	2 (2.0)	9 (2.7)
Partial Responses***	112 (48.5)	0 (0.0)	112 (33.8)

* - No correlation between tumor response and CEA response.
**-Level of ≤2.5 pg/ml on 2 separate lab measurements at least 4 weeks apart.
*** - A decrease in the CEA level at least 50% from baseline.

Time to Worsening Pain

A key secondary endpoint is the time to worsening pain, which is based on patient opioid use and patient questionnaires. Unfortunately, the overall compliance rate with the questionnaires was only 50% with compliance rates of less than 30% seen at multiple timepoints. This large amount of missing data precludes any conclusions being drawn regarding this endpoint.

6.1.6 Other Endpoints

None

6.1.7 Subpopulations

Pre-specified subgroup analyses of PFS conducted by the applicant, are shown below. Note that these data are determined using the applicant's censoring pattern.

Figure 5: Applicant's Prespecified Subgroup Analysis

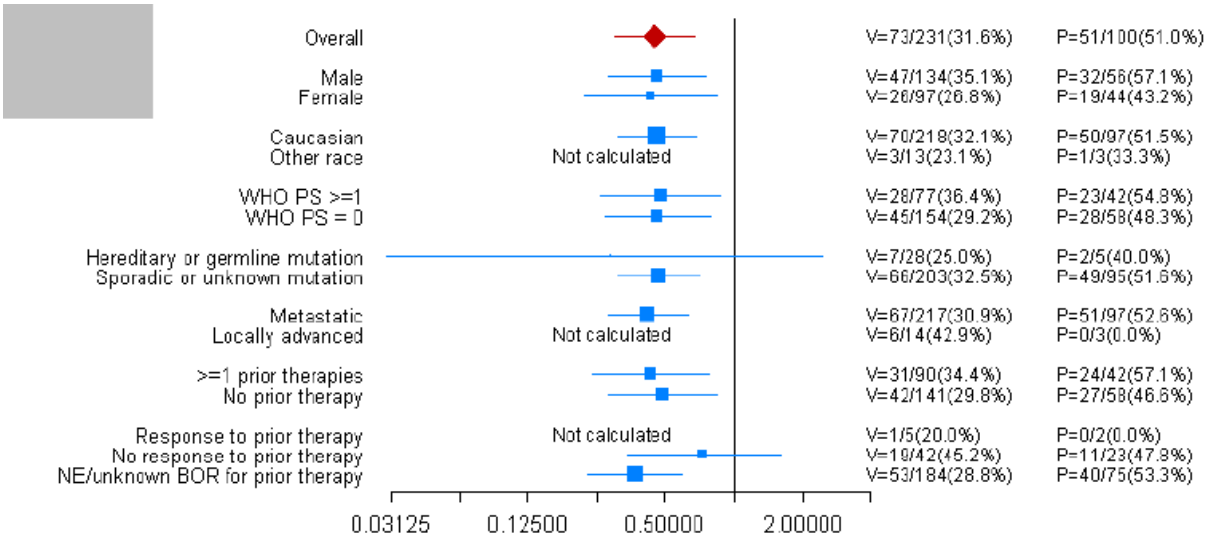
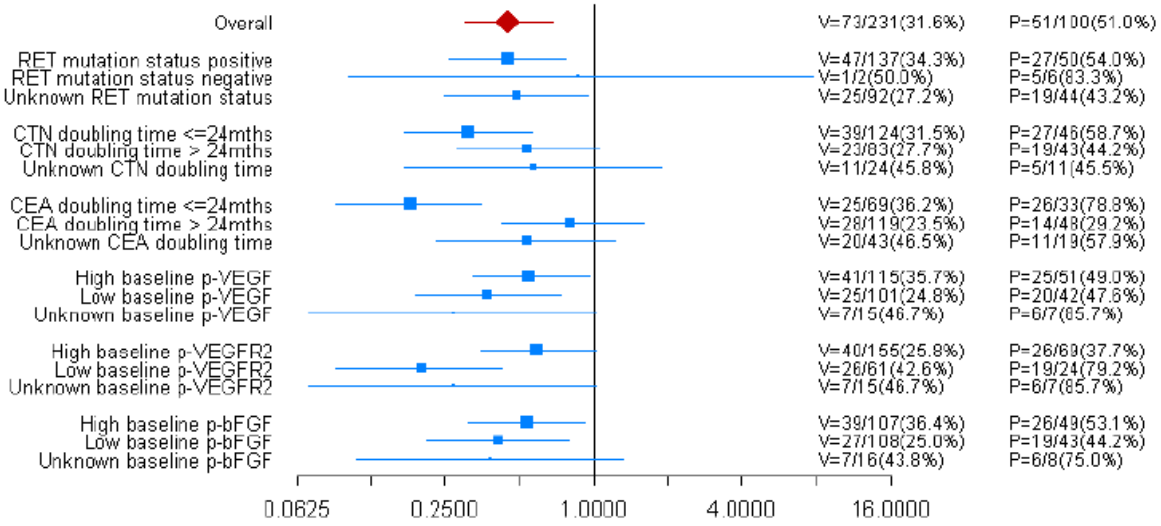


Figure 6: Applicant's Prespecified Subgroup Analysis; Biomarkers



Visual inspection of the forest plots suggest that the PFS benefits observed were generally consistent across all subgroups. However, it appears that patients with a CEA doubling time of <24 months at baseline and patients with low plasma VEGFR2 may have received a greater differential benefit, although the HRs for the complementary subgroups (ie, CEA doubling time >24 months and high plasma VEGFR2) do not suggest a lack of benefit.

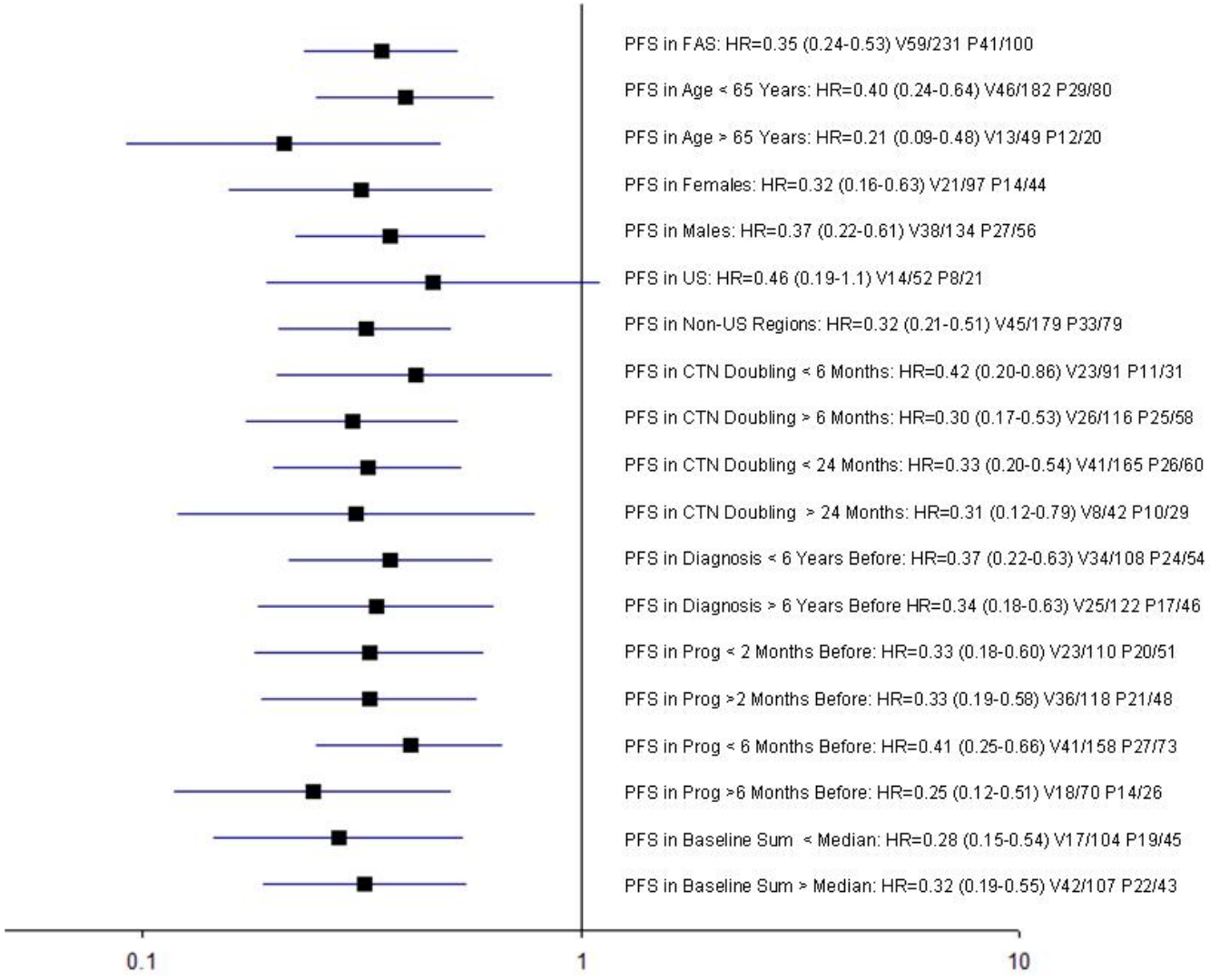
An exploratory subgroup analysis of PFS by age group that was not pre-specified was conducted after unblinding of study data. There was a statistically significant difference in PFS in favor of the vandetanib treatment group in both patients <65 years of age (HR=0.50, 95% CI, 0.32 to 0.80, p=0.0036) and >65 years of age (HR=0.32, 95% CI, 0.14 to 0.74, p=0.0071)

Reviewer's Comment: *CTN and CEA doubling times have not been validated as clinically meaningful subgroups in MTC. Furthermore, the in vitro assays of CTN, CEA, or plasma VEGFR2 have not been validated.*

Post-Hoc Analyses

A series of post-hoc analyses were conducted by the FDA in order to determine whether the improvement in PFS with vandetanib is consistent among the various subsets. The risk ratios were consistent for all subsets including: patients grouped according to last documented progression, time from diagnosis, and baseline tumor burden. The hazard ratio for patients enrolled on trial in the US was 0.46, which was slightly higher than the overall study population, but still suggestive of a benefit for vandetanib among US patients.

Figure 7: FDA Subgroup Analyses

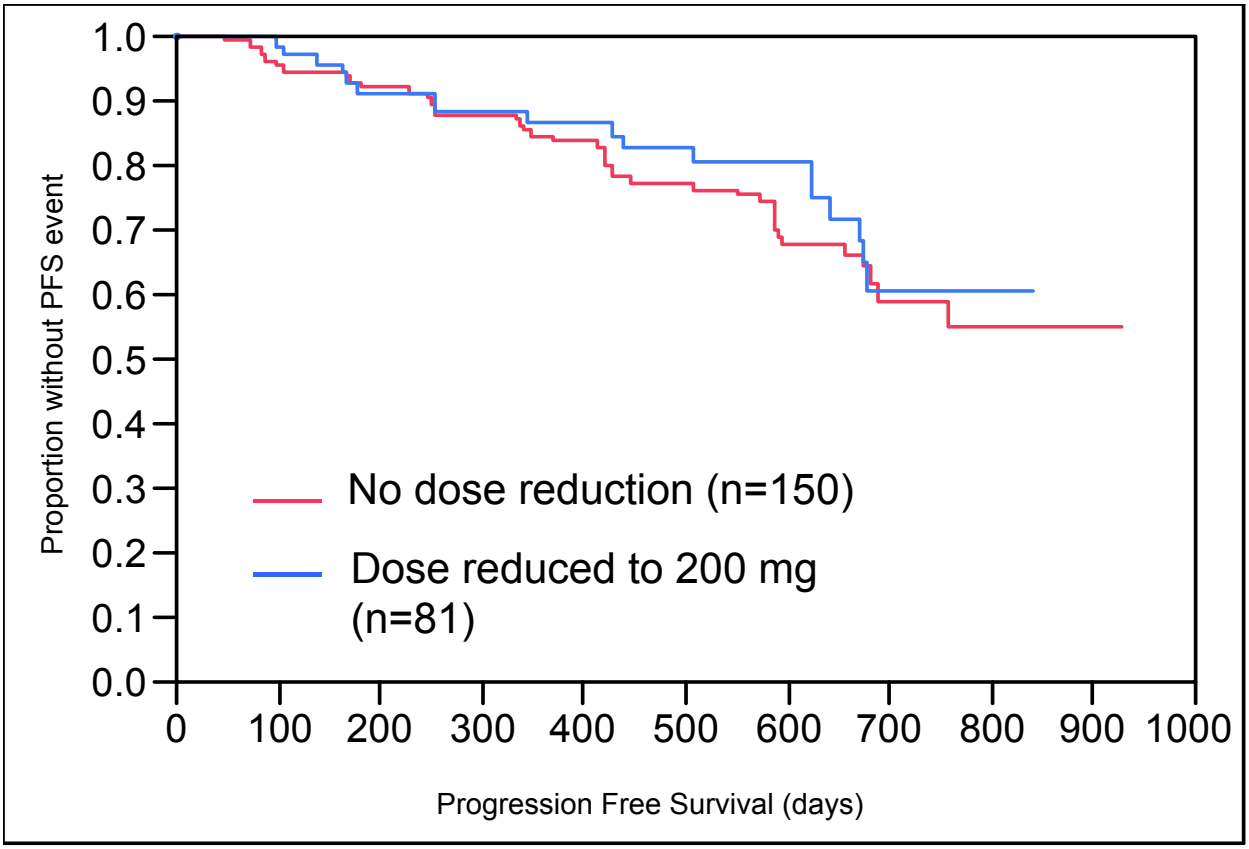


The vast majority of the patients on trial were WHO performance status 0 or 1 (96%); however, there still may be symptoms of pain or diarrhea even among patients with a performance status of 0-1. A post-hoc analysis of symptomatic patients v. asymptomatic patients was performed using a strict definition of asymptomatic, in that, only those patients with a WHO PS of 0 AND a stool frequency less than 4 times per day AND no pain on average at baseline of any type, were considered asymptomatic. The effect of vandetanib on PFS was consistent in both subsets (HR 0.38 95% CI 0.2, 0.75 for asymptomatic v. HR 0.31 95% CI 0.19, 0.53 for symptomatic patients).

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The FDA has performed an exploratory analysis in those patients who required dose reduction to 200 mg and compared them to patients who remained on 300 mg throughout the study. Figure depicts the Kaplan Meier curve comparing PFS for these patients, which demonstrates no clear difference between patient groups. This analysis suggests that patients undergoing dose reduction and those not undergoing a dose reduction benefited equally from treatment with vandetanib.

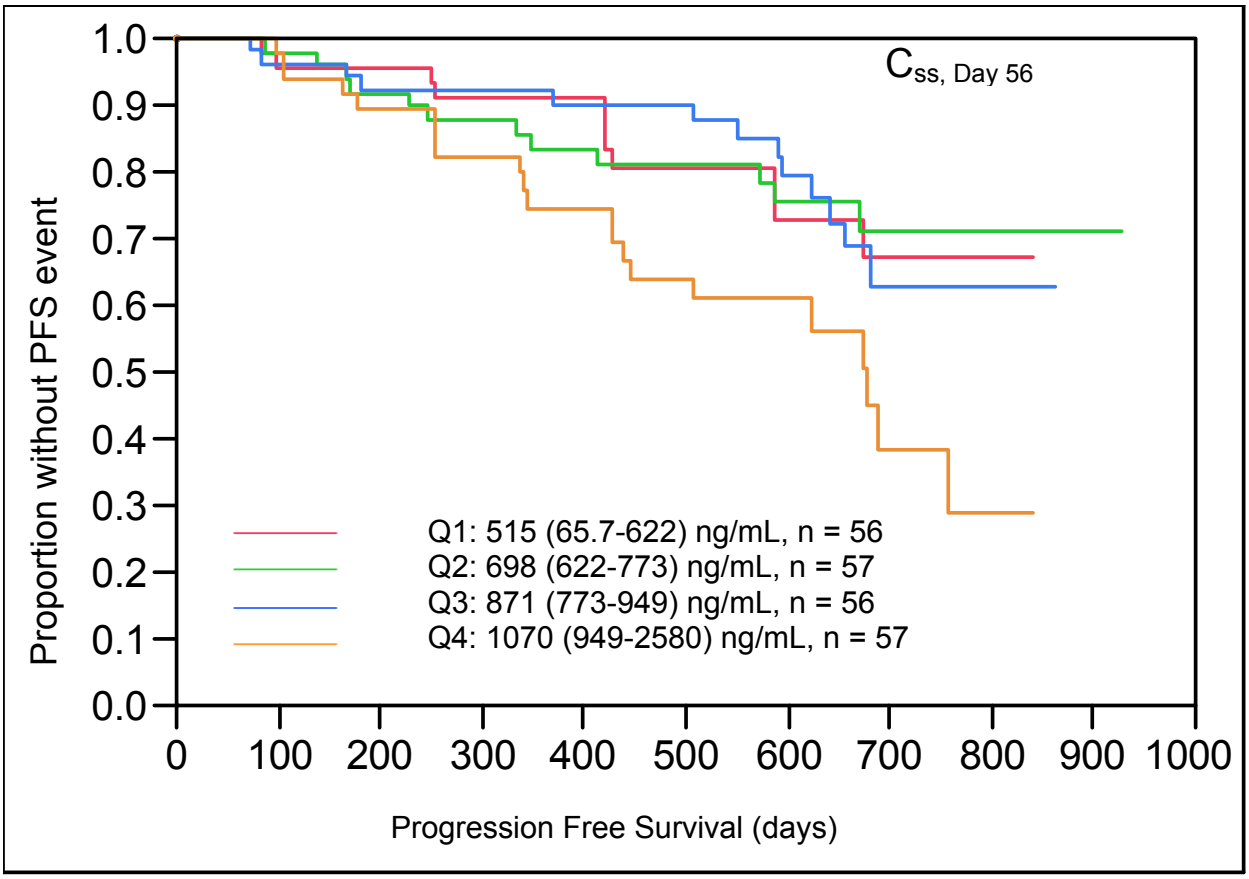
Figure 8: Kaplan Meier PFS Estimates: Dose Reduction v. No Dose Reduction



The FDA has conducted an exploratory analysis on any possible exposure-response relationships seen in Study 58. The trough concentrations at Day 56 were divided into quartiles and a Kaplan-Meier analysis was conducted to assess PFS in patients achieving different concentrations of vandetanib at steady state. The PFS curves of patients in different quartiles were not significantly different from each other, indicating a lack of relationship between steady-state plasma concentrations and PFS over this

range. Administration of lower dosages of vandetanib such as 200 mg or 100 mg would be expected to result in concentrations in the range found in quartile 1.

Figure 9: Exposure-Response Relationship Analysis



6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The median PFS for the vandetanib arm was not met. The median PFS for the placebo arm was 16.4 months (95% CI: 8.3, 19.7).

The median duration of response was not met for either treatment arm at the time of the data cut-off.

6.1.10 Additional Efficacy Issues/Analyses

Two single arm Phase 2 studies have been conducted in patients with hereditary medullary thyroid cancer.

Study 8
Study 8 administered 300 mg of vandetanib to 30 patients with hereditary medullary thyroid cancer. In general, the baseline disease characteristics of patients in Study 8 were more favorable than those in Study 58. However, while treatment was initiated with 300 mg of vandetanib, 80.0% of patients required a dose reduction or interruption. The table below shows the RR by investigator (RECIST criteria without a lower limit for nodal size) and IRC (modified RECIST criteria as in Study 58). While the investigator and IRC RR are similar, only 2 of the 6 patients with an INV response were considered responders by the IRC. Note that this response rate is markedly lower than the 45% RR seen in the Phase 3 trial.

Table 21: Response Rate Study 8 (Data Cutoff 2-22-08)

Response Rate (CR+PR)	Vandetanib 300 mg N = 30	Median Duration of Response (range)
Investigator Response	6 (20.0%)	311 days (137-850)
IRC Response	5 (16.7%)	500 days (337-980)

Study 68
Study 68 administered 100 mg of vandetanib to 19 patients with hereditary medullary thyroid cancer. This dose was chosen because it was estimated that the serum concentration achieved with 100 mg of vandetanib would be comparable to the IC_{50} for the RET gene. Again, the baseline disease characteristics of patients in Study 68 were, in general, more favorable than those in Study 58. Despite initiation of treatment with 100 mg of vandetanib, 21.1% required a dose reduction/interruption. The table below shows the RR by investigator using modified RECIST criteria (as in Study 58). On progression, patients thought to be benefitting could receive 300 mg vandetanib. Four patients choose this option; 3 had SD and 1 had PD.

Table 22: Response Rate Study 68 (Data Cutoff 1-31-08)

Response Rate (CR+PR)	Vandetanib 100 mg N = 19	Median Duration of Response (range)
Investigator Response	3 (15.8%)	168 days (158-245)

Note that while the investigator RR in patients receiving 100 mg of vandetanib in Study 68 appears to be markedly lower than the RR of the hereditary MTC patients in Study 58 (15.8% vs. 39.0%), it is similar to the investigator RR in Study 8 (15.8% vs. 20.0%).

Data Integrity

There were a total of 76 protocol violations. Most of the protocol violations were related to patients with laboratory values outside entry criteria. A large proportion of these patients were enrolled at site 2801. The second most common protocol violation was missing archival tissue for RET mutation analysis. (b) (4) Overall, it is believed that these protocol violations should not impact the overall integrity of site-generated data as related to primary safety and efficacy analyses.

Table 23: Protocol Violations

	Vandetanib (n=231)	Placebo (n=100)	Total (n=331)
All	49	27	76
No measurable tumors at baseline*	9	5	14
Baseline RECIST scan >28 days	2	2	4
Randomized but did not receive treatment	0	1	1
CYP3A4 inducer taken for at least 14 days	0	1	1
No Confirmed Histological Diagnosis	1	0	1
At least 1 dose of incorrect treatment	1	0	1
Previous malignancies within 5 years	1	0	1
Laboratory values outside range	18	11	29
Concomitant medications violation	6	2	8
No serum pregnancy test	3	1	4
QTc unmeasurable or outside specified range	3	1	4
Suitable Archived sample not provided	10	5	15
History of excluded arrhythmia	1	0	1

* - As determined by investigator read.

Overall, there was excellent compliance to protocol mandated imaging assessments. Only 3 imaging assessments were missing and 40 assessments were performed outside the protocol-defined 2 week window.

Table 24: Missing Data

	Vandetanib (n=231)	Placebo (n=100)	Total (n=331)
Missing Time Points	3	0	3
Scans Outside 2wk Window	28	12	40

7 Review of Safety

Safety Summary

The safety of vandetanib was evaluated in 331 patients with advanced or metastatic medullary thyroid cancer in the Phase 3 trial D4200C00058 (Study 58), in which patients were randomized to receive either vandetanib 300mg daily or placebo. A summary of important safety results from this study are included below.

- 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. Two patients died from sudden death and cardio-respiratory failure after the data cut-off, but are included in the safety analysis as they were initially randomized to vandetanib and died within 30 days of last dose. One patient on the placebo arm died due to gastrointestinal hemorrhage. There was an additional placebo death that Astra-Zeneca included in their totals for deaths on placebo, however in the safety database, the primary cause of death for this patient was listed as disease progression, therefore the FDA did not include this patient as a death from adverse event while on placebo.

  In the ISS database, deaths not directly attributed to disease progression were reported in 60 (4%) vandetanib-treated patients. For vandetanib treated patients, the causes of death that occurred in > 3 patients were sudden death, cardiac failure, dyspnea, pulmonary hemorrhage, pneumonia, pulmonary embolism, respiratory failure, and aspiration pneumonia.

- The most common (≥5%) grade 3-4 adverse reactions in the vandetanib-treated patients were diarrhea, QTc prolongation, hypertension, and fatigue.

- Adverse reactions of interest in the vandetanib-treated patients included diarrhea and other gastrointestinal toxicities, rash and other skin toxicities, hypertension, ocular toxicity, pulmonary-respiratory toxicity, headache, QTc prolongation and cardiac toxicity.

- Treatment discontinuations due to adverse drug reactions occurred in 12.1% of patients who received vandetanib and 3% of patients on placebo. The most common adverse reactions leading to treatment discontinuation on the vandetanib arm were asthenia and fatigue (2.6%); gastrointestinal disorders (3.0%) which included diarrhea (0.9%), dysphagia (0.4%), nausea (0.4%), pancreatitis (0.4%), peritonitis (0.4%), small intestinal perforation (0.4%) and vomiting (0.4%); skin and subcutaneous disorders (1.7%) including rash (1.3%),

eczema (0.4%), photosensitivity reactions (0.4%) and pruritis (0.4%); QTc prolongation (0.9%); elevated creatinine (0.9%); and hypertension (0.9%).

- Dose reductions were reported in 49.4% of vandetanib-treated patients and 15.2% of placebo patients. Eighty-one patients (35.1%) on the vandetanib arm were dose reduced to 200mg and further dose reduction to 100mg was required in an additional 32 patients (13.9%). The most common reasons for dose reductions were diarrhea, QTc prolongation and rash. Dose delays were reported in 47.2% of vandetanib treated patients and 15.2% of placebo treated patients. Of the 81 patients who had their dose reduced to 200mg, 24 remained on the dose until data cut-off, 15 stopped due to disease progression, 8 stopped for AE's and 4 for other reasons. Of 32 patients who had their dose reduced further to 100mg, 17 remained on therapy until data cut-off, 5 stopped due to disease progression, 7 stopped for AEs and 3 for other reasons.

- 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 that have been treated thus far.

7.1 Methods

Safety data was primarily derived from the Phase 3 trial, but was supplemented by adverse event information from the safety database. The Phase 3 trial, Study 58 included safety assessments at baseline, weekly for the first two weeks, then at four weeks, 8 weeks and 12 weeks after randomization and then every twelve weeks thereafter. Serious adverse events and study drug related adverse events that had not recovered completely by the end of treatment were to be followed until resolution unless in the investigator's opinion the event is unlikely to resolve due to the subject's underlying condition.

At baseline, safety assessments included medical, oncologic, and surgical history, physical exam, laboratories (hematology, chemistries, liver function, calcitonin and CEA, and 24 hour urinalysis), assessment of WHO PS, 12 lead ECG, and assessment of concomitant medications. Pre-infusion safety assessments were the same as at baseline. At the end of treatment, all patients received an ECG and RECIST tumor measurements. Post-treatment follow-up was to occur at 60 days and then survival data would be collected every 12 weeks from the patient or a patient representative until death or until >50% of study patients had died. An amendment was made to the protocol and an ophthalmologic evaluation was obtained at baseline and then at visit 9 or at study discontinuation.

Reviewer comment: Of note, calcitonin measurements were obtained and were suppressed by vandetanib in 69.3% of patients and 3% of placebo patients. Similarly, CEA was suppressed in 51.5% of vandetanib treated patients and 2.0% of placebo patients. This, along with the side-effect profile, confounds the premise of a placebo controlled trial, as investigators would not be truly blinded to these values and thus would know those patients who were receiving study drug.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The major study under review in this NDA was study 58, a Phase 3, randomized, double-blinded, placebo-controlled, multicenter study to assess the efficacy and safety of vandetanib 300mg daily in 331 patients with unresectable or locally advanced medullary thyroid cancer. Along with study 58, 10 additional studies were submitted by the sponsor to lend supportive safety data for the use of vandetanib 300 mg as monotherapy in a total of 1839 patients. The majority of patients evaluated in the supplemental clinical trials had different underlying tumors (such as advanced NSCLC) and a shorter duration of treatment. There were an additional three studies that used 100mg of vandetanib in combination with various chemotherapeutic agents that were also included in the overall safety analysis.

Table 25: Pivotal and Supportive Studies Contributing Data to the Overall Safety Assessment of Vandetanib

Study number	Study Title	Number of patients and number receiving vandetanib	Dose of vandetanib	Control
D4200C00058 Study 58	An international, Phase III, randomized, double-blinded, placebo-controlled, multi-centre study to assess the efficacy of ZD6474 versus placebo in subjects with unresectable locally advanced or metastatic medullary thyroid cancer	331 total 231 at 300mg 58 patients originally randomized to receive placebo received 300mg in open label phase	300 mg	Placebo
D4200C00001 Study 1	An open, Phase I, rising multiple-dose tolerability study of ZD6474 in patients with malignant tumors.	25 at 300mg	300mg	None
D4200C00002 Study 2	An open-label, multicentre Phase II study to assess the	24 at 300mg	300 mg	None

	response of subjects with metastatic breast cancer, previously treated with anthracycline and taxane therapy with or without capcitabine, to ZD6474.			
D4200C00003 Study 3	A Phase II, randomized, double-blind, 2-part, multicentre study to compare the efficacy of ZD6474 with the efficacy of ZD1839 (Iressa™) in patients with locally advanced or metastatic (IIIB/IV) NSCLC after failure of either first-line and/or second line platinum-based chemotherapy and to assess the activity of ZD6474 in patients following failure of treatment with ZD1839.	83 as initial treatment 37 after gefitinib	300mg	Gefinitib 250mg
D4200C00007 Study 7	A randomized, partially blinded, Phase II study to assess the safety, tolerability, and efficacy of ZD6474 alone or in combination with paclitaxel and carboplatin in subjects with previously untreated unresectable locally advanced or metastatic.	73 at 300mg monotherapy	300mg	Multiple arms
D4200C00008 Study 8	An open-label, two stage, Phase II study to evaluate the efficacy and tolerability of ZD6474 in patients with unresectable locally advanced or metastatic hereditary medullary thyroid carcinoma.	30 at 300mg	300mg	None
D4200C00039 Study 39 Japan	A randomized, double-blind, parallel-group, Phase IIa dose-finding multicentre study to assess the efficacy (Objective response) and safety of ZD6474 100, 200 and 300mg/day in patients with advanced or metastatic (Stage IIIb/IV) or recurrent NSCLC who have failed one or two previous chemotherapy regimens at least one of which	18 at 300mg	300mg	None

	contained platinum			
D4200C00043 Study 43 (TVE-15-11) Japan	An open, Phase I, rising multiple dose tolerability study of ZD6474 in Japanese patients with solid, malignant tumors	6 at 300mg	300mg	None
D4200C00044 Study 44	A Phase III, international, randomized, double-blind, parallel-group, multicentre study to assess the efficacy of ZD6474 plus best supportive care versus placebo plus best supportive care in patients with unresectable advanced or metastatic (Stage IIIb/IV) NSCLC after prior therapy with an epidermal growth factor receptor tyrosine kinase inhibitor (EGFR TKI)	619 at 300mg	300mg	Placebo
D4200C00050 Study 50	A Phase I, randomized, open-label study to assess the effect of ZD6474 on vascular permeability in patient with advanced colorectal cancer and liver metastases.	12 at 300mg	300mg	None
D4200C00057 Study 57	A Phase III, randomized, double-blind, parallel-group, multicentre study to assess the efficacy of ZD6474 versus erlotinib in patients with unresectable locally advanced or metastatic (Stage IIb/IV) NSCLC after failure of at least one prior cytotoxic chemotherapy	623 at 300mg	300mg	Erlotinib
D4200C00032	A Phase III, Randomized, Double blinded, multi-center study to assess the efficacy and safety of docetaxel in combination with vandetanib versus docetaxel in combination with placebo in patients with locally advanced or metastatic (Stage IIIb-IV) Non-small cell lung cancer (NSCLC) after failure of 1st line therapy	694 at 100mg	100mg	Placebo Docetaxel
D4200C00036	A Phase III, Randomized,	256 at 100mg	100mg	No control

	Double blinded, Parallel-Group, Multi-center study to assess the efficacy and safety of vandetanib in combination with pemetrexed versus pemetrexed alone in patients with locally advanced or metastatic (Stage IIIb-IV) Non-small cell lung cancer (NSCLC) after failure of 1st line therapy.			
D4200C00068	An open-label, two-Stage, Phase II Study to evaluate the efficacy and tolerability of ZD6474 in Patients with locally advanced or metastatic hereditary medullary thyroid carcinoma.	19 at 100mg	100mg	No control
D4200C00079	An international, Phase III, randomized, double-blinded, placebo-controlled, multi-centre study to assess the efficacy of ZD6474 versus placebo in subjects with unresectable locally advanced or metastatic differentiated thyroid cancer	72 at 300mg	300mg	Placebo

7.1.2 Categorization of Adverse Events

MedDRA terminology (version 13.0) was used to characterize all adverse events in the Phase 3 trial Study 58. Adverse event grading was done according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 3.0.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Adverse event data from 10 trials were included in the integrated safety database (see Section 7.1.1, Table 25 above). The rates of the most common (>10% of patients) treatment-emergent adverse events in vandetanib-treated patients on study 58 were compared to event rates in the entire ISS database. This analysis is presented in Table 26 below.

Table 26: Incidence of Most Common (>10%) Treatment Emergent Adverse Events in ISS Database

Preferred Term	Study 58 N=231		ISS Database N= 1839	
	Grade 1-4	Grade 3-4	Grade 1-4	Grade 3-4
Diarrhea[1]	134 (58%)	9 (3%)	907 (49%)	90 (5%)
Rash[2]	147 (64%)	13 (6%)	968 (53%)	98 (5%)
Nausea	77 (33%)	2 (1%)	466 (25%)	19 (1%)
Hypertension[3]	78 (34%)	13 (6%)	400 (22%)	76 (4%)
Headache	59 (26%)	2 (1%)	223 (12%)	11 (0.6%)
Fatigue	55 (24%)	13 (6%)	408 (22%)	78 (4%)
Decreased Appetite	49 (21%)	9 (4%)	236 (13%)	27 (1%)
Dermatitis Acneiform[4]	81 (35%)	1 (<1%)	294 (16%)	14 (0.8%)
Dry Skin	35 (15%)	0	181 (10%)	4 (0.3%)
Vomiting	34 (15%)	2 (1%)	247 (13%)	19 (1%)
Asthenia	34 (15%)	6 (3%)	194 (11%)	50 (3%)
Abdominal Pain[5]	33 (14%)	4 (2%)	116 (6%)	15 (0.8%)
Electrocardiogram QT Prolonged	33 (14%)	18 (8%)	121 (7%)	59 (3%)
Photosensitivity Reaction	31 (13%)	4 (2%)	87 (5%)	14 (0.7%)
Insomnia	30 (13%)	0	198 (11%)	2 (0.1%)
Nasopharyngitis	26 (11%)	0	80 (4%)	0
Dyspepsia	25 (11%)	0	90 (5%)	0
Hypocalcaemia	25 (11%)	4 (2%)	62 (3%)	9 (0.4%)
Cough	25 (11%)	0	282 (15%)	13 (0.7%)
Pruritis	25 (11%)	3 (1%)	156 (8%)	11 (0.6%)
Weight Decreased	24 (10%)	2 (1%)	134 (7%)	8 (0.4%)
Proteinuria	23 (10%)	0	124 (7%)	12 (0.7%)
Depression	22 (10%)	4 (2%)	76 (4%)	8 (0.4%)
Anorexia	NR	NR	185 (10%)	10 (0.5%)
Constipation	0	0	219 (12%)	6 (0.3%)

R_AE dataset w/ at least 10% of patients experiencing an AE in the Vandetanib arm
[1] Includes diarrhea, hemorrhagic diarrhea and colitis
[2] Includes rash, rash erythematous, generalized, macular, maculo-papular, papular, pruritic, exfoliative, dermatitis, dermatitis bullous, generalized erythema and eczema.
[3] Includes hypertension and hypertensive crisis
[4] Includes acne and dermatitis Acneiform
[5] Includes abdominal pain, abdominal pain upper and abdominal discomfort

In general, the toxicities were similar between the two safety datasets. Notable difference include grade 1-4 headache which was two times higher in study 58 as compared to the ISS safety database. Acneiform dermatitis was almost three times higher in the Phase three study as compared to the ISS database, the cause for this is unclear as rash appears similar across both treatment groups. Photosensitivity reaction was higher in the Phase 3 study as well.

Abdominal pain and QT prolongation were two times higher in the Phase 3 MTC study, most likely due to the underlying disease being treated in Study 58. Medullary thyroid cancer patients have an increased incidence of diarrhea, cholelithiasis and electrolyte abnormalities that could have potentially exacerbated these two adverse events. Similarly, hypocalcemia was seen more than three times as frequently in Study 58 when compared to the ISS dataset. MTC patients often are hypocalcemic at baseline given prior parathyroid removal and GI losses.

Depression, nasopharyngitis and dyspepsia were also seen in higher frequency in the Phase 3 study as compared to the ISS database. No conclusions can be drawn from these numbers.

Alternatively, constipation and anorexia were seen more frequently in the ISS dataset. There were very few medullary thyroid cancer patients treated in this group of patients, made up of primarily non small cell lung patients.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The overall mean duration of exposure for the Phase 3 Study 58 was longer for patients treated with vandetanib than for placebo (607 days vs 279 days) and the exposure data can be seen in Table 27 below.

Table 27: Median Duration of Exposure in the Phase 3 Study 58

	Vandetanib N=231	Placebo N=99
Duration of Exposure	607 days (15-929)	279 days (14-904)
Duration of exposure to 300 mg	187.5 days (1-929)	218 days (3-904)
Duration of exposure to 200 mg	148.5 days (3-801)	153, 158, 462

Duration of exposure to 100 mg	145 days (1-723)	0
Duration of exposure to 0mg	12 days (1-49)	0

Dose reductions and interruptions were permitted in the Phase 3 study. The number of patients with dose reductions and interruptions that occurred during the randomized treatment are displayed in Table 28 below.

Table 28: Dose Interruptions and Reductions in the Phase 3 Study 58

	Vandetanib N=231	Placebo N=99
Dose Interruptions	109 (47%)	15 (15%)
Median Duration of Interruption	19 days (1-101)	9 days (2-30 days)
Median # Interruptions	1 (1-8)	1 (1-3)
Dose Reductions		
Any	83	3
Dose Reduced 1 Level	81	3
Dose Reduced 2 Levels	32	0

7.2.2 Explorations for Dose Response

Please refer to the clinical pharmacology review for further details (sections 2.2.3-2.2.4.2).

7.2.3 Special Animal and/or In Vitro Testing

See the pharmacology/toxicology review for details.

7.2.4 Routine Clinical Testing

See sections 7.4.2-7.4.4.

At baseline, safety assessments included medical, oncologic, and surgical history, physical exam, laboratories (hematology, chemistries, liver function, calcitonin and CEA, and 24 hour urinalysis), assessment of WHO PS, 12 lead ECG, and assessment of concomitant medications. Pre-infusion safety assessments were the same as at baseline. At the end of treatment, all patients received an ECG and RECIST tumor measurements. Post-treatment follow-up was to occur at 60 days and then survival data would be collected every 12 weeks from the patient or a patient representative until death or until >50% of study patients had died. An amendment was made to the

protocol and an ophthalmologic evaluation was obtained at baseline and then at visit 9 or at study discontinuation.

7.2.5 Metabolic, Clearance, and Interaction Workup

See the summary of the clinical pharmacology review in section 4.4.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Vandetanib is a tyrosine kinase inhibitor that inhibits vascular endothelial growth factor (VEGF)-stimulated VEGF receptor-2 tyrosine kinase activity in endothelial cells. In addition, vandetanib inhibits epidermal growth factor (EGF)-stimulated EGF receptor tyrosine kinase in tumor cells and endothelial cells. In vitro studies have also shown that vandetanib inhibits the activity of other tyrosine kinases, including rearranged during transfection (RET) and VEGF receptor-3 (Flt-4).

Sunitinib, sorafenib, erlotinib, gefitinib and pazopanib are FDA approved drugs currently in use that target similar receptors.

Sorafenib: Warnings and precautions include cardiac ischemia and infarction, hemorrhage, hypertension, gastrointestinal perforation. Temporary interruption is recommended in patients undergoing major surgery. Caution is recommended when co-administering substances metabolized/eliminated predominantly by the UGT1A1 pathway (e.g. irinotecan), and also with docetaxel and doxorubicin. Common adverse reactions include fatigue, weight loss, rash/desquamation, hand-foot skin reaction, diarrhea, hair thinning, anorexia, nausea or vomiting, and abdominal pain.

Erlotinib: Warnings include pulmonary toxicity, myocardial infarction and ischemia, cerebrovascular accidents, microangiopathic hemolytic anemia and thrombocytopenia. Asymptomatic increases in liver transaminases have been noted, periodic monitoring is advised. Common adverse events include rash, diarrhea, anorexia, fatigue, dyspnea, cough, nausea, infection, vomiting, stomatitis, pruritis, dry skin, conjunctivitis, keratoconjunctivitis sicca, and abdominal pain.

Gefitinib: Warnings and precautions include pulmonary toxicity and hepatotoxicity. Similar to erlotinib INR elevations were noted in people taking Coumadin. There is Phase 2 clinical data to suggest gefitinib increases the myelosuppressive effects of vinorelbine. The most common adverse reactions include diarrhea, rash, acne, dry skin, nausea, vomiting, pruritis, anorexia, asthenia, and weight loss. Similar to erlotinib there have been cases of interstitial lung disease noted.

Sunitinib: Precautions include left ventricular dysfunction, with 15% of patients in 2 metastatic renal cell carcinoma (MRCC) studies experiencing a decrease in left ventricular ejection fraction. Patients should be carefully monitored for clinical signs of CHF while receiving sunitinib. Hemorrhagic events occurred in 26% of patients receiving sunitinib with MRCC and 18% of GIST patients. Hypertension and adrenal toxicity are also listed as precautions. Adverse reactions include gastrointestinal disorders such as diarrhea, nausea, stomatitis, dyspepsia and vomiting. Skin discoloration and skin and hair depigmentation may occur, as well as rash and hand-foot syndrome. Fatigue, anorexia, asthenia and bleeding were also commonly seen.

Pazopanib: A black box warning is in place for hepatotoxicity. Increases in serum transaminase levels and bilirubin have been observed as well as severe and fatal hepatotoxicity. Prolonged QT intervals and torsades de pointe have been observed. Fatal hemorrhagic events have been reported. Arterial thrombotic events have been observed and can be fatal. Gastrointestinal perforation or fistula has occurred as well as fatal perforation events. Hypertension has been observed. Hyperthyroidism may occur and proteinuria can be seen. The most common adverse reactions are diarrhea, hypertension, hair color changes, nausea, anorexia and vomiting.

Class Concerns: As shown in the sections below, vandetanib is associated with many of the adverse events reported with these other VEGFR and EGFR tyrosine kinase inhibitors. Prolonged QT intervals have been seen with other tyrosine kinase inhibitors like pazopanib and nilotinib, however, the QTc is higher with vandetanib as will be explained below. The skin toxicity common to EGFR inhibitors is prominent with vandetanib with over 80% of patients experiencing some form of skin toxicity while on study treatment. The incidence of GI perforation does not appear as prominent as has been seen with other VEGF inhibitors. Specific class effect concerns are reviewed in detail in the sections that follow.

7.3 Major Safety Results

7.3.1 Deaths

Table 29 below reports the causes of death in the major MTC study, as reported by the investigators. Here, deaths are classified as to whether the death was due to progression of disease and by the treatment phase (randomized, open-label, 60 day safety follow up, or after the safety follow up). There were a total of 47 deaths reported. Twenty-one (21) of these deaths occurred after the 60 day safety follow up period. Eighteen (18) of these deaths were thought to be due to disease progression, 14 (6.1%) on the vandetanib arm and 4 (4.0%) on the placebo arm. Three patient deaths were deemed not to be due to disease progression, 2 (.9%) on the vandetanib arm and 1 (1%) on placebo. During the active stages of the study (randomized, open-label and safety follow up), there were a total of 26 deaths. Sixteen (16) were in the vandetanib

arm and 10 in the placebo arm. 6 (2.5%) of these deaths were deemed to be due to other causes besides disease progression in the vandetanib arm and 0 (0%) in the placebo arm.

Table 29: Summary of Deaths in Study 58

	Vandetanib N=231	Placebo N=99	Total N=330
Total Deaths	32	15[1]	47
TEAEs	10	1	11
Progression	18	12	30
Other[2]			
Unknown	3	0	3
Other Events	1	1	2
Deaths within 30 days of Last Dose			
TEAEs	5	1	6
Progression	5	8	13
Other			
Unknown	1	0	1
Other Events	0	0	0
Deaths within 60 days of Last Dose			
TEAEs	7	1	8
Progression	8	9	17
Other			
Unknown	1	0	1
Other Events	0	0	0

1. Patient E2501032 was randomized to placebo and died of progressive disease as per the sponsor, and was not included in the safety analysis set
2. One patient in the vandetanib group died from euthanasia and another in the placebo group died from a self-inflicted gunshot wound to head

At the time of the safety update, there were 2 additional deaths that occurred after the study cut off date that were attributable to sudden death (one AE listed as sudden death, the other as cardio-respiratory arrest).

In the absence of any contradictory evidence, in a drug that has the propensity to prolong the QT interval, one has to question whether the sudden death events could be directly attributable to QT prolongation.

Table 30 below contains a listing of the deaths that were not due to disease progression. The listing also includes a patient with an SAE of disseminated

intravascular coagulation 78 days after receiving his last dose of vandetanib. Patient E2601003 is included in the table despite having died 78 days after the last day of treatment.

Table 30: Listing of Key Information for SAEs with Outcome of Death in Study 58 (Randomized Phase, Safety Analysis Set)

Treatment Received	AE Preferred Term	Time from start of randomized treatment to onset of AE	Sex/Age	Time from last dose to death (b) (4)
Vandetanib 300mg	Arrhythmia	439	M/42	
Vandetanib 300mg	Cardiac Failure Acute	431		
Placebo	Gastrointestinal Hemorrhage	80	M/52	
Vandetanib 300mg	Staphylococcal Sepsis	99	M/60	
Vandetanib 300mg	Pneumonia Aspiration	372	M/51	
Vandetanib 300mg	Respiratory Arrest	107	F/58	
Vandetanib 300mg	Respiratory Failure	174	M/83	
Vandetanib 300mg	DIC	677	M/31	
Vandetanib 300mg	Sepsis	678	M/31	

During the open label phase of the Phase 3 study, two patients receiving vandetanib died of causes other than medullary thyroid cancer (aspiration pneumonia, unknown cause of death). In the safety updates which included data collected after the data cut-off, 2 patients who were initially randomized to vandetanib died from sudden death. Technically, these patients are considered open-label as the study was unblinded at the data cut-off date, however, the patient were initially randomized to vandetanib and died within 30 days of their last dose.

Table 31: Adverse Events Resulting in Death (Vandetanib ISS 300 mg Monotherapy, Data Cutoff 10-19-09)

Causes of Death	Vandetanib 300 mg Monotherapy N = 1550
All	58 (3.7%)
Blood and Lymphatic Disorders	
Thrombotic Thrombocytopenic Purpura	1
Cardiac Disorders	
Cardiac Arrest[1] or Cardio-respiratory Arrest	4
Cardiac Failure	3
Myocardial Infarction	2
Cardiopulmonary Failure	1
Gastrointestinal Disorders	

GI Hemorrhage	1
General Disorders	
Death (cause unknown)	5
Infections and Infestations	
Pneumonia or Lung Infection	11
Pneumonia/Respiratory Failure	2
Pneumonia/Cardiac Arrest	1
Respiratory Tract Infection	2
Sepsis/Septic Shock	2
Clostridial Gastroenteritis	1
Injury, Poisonings, Procedural Complications	
Traffic Accident	1
Neurological Disorders	
CVA	3
Psychiatric Disorders	
Suicide/Opioid Overdose	1
Respiratory Disorders	
Dyspnea	3
Hemoptysis/Bronchial Hemorrhage	3
Pulmonary Embolism	2
Pulmonary Embolism/Dyspnea	1
Aspiration Pneumonia	2
Respiratory Arrest/Failure	2
ARDS	1
Bronchospasm	1
Pneumonitis	1
Tracheo-esophageal Fistula/Dyspnea	1

[1]Includes cardio-respiratory arrest, acute death (cause unknown), and sudden death

Reviewer comment: There were 2 deaths attributable to pneumonia or aspiration pneumonia in the Phase 3 study. The majority of patients on study have undergone prior thyroidectomies and multiple neck surgeries prior to initiating study drug. As vandetanib can increase asthenia and fatigue, it is postulated that this may increase weakness in the neck musculature and increase the propensity to develop aspiration pneumonia.

7.3.2 Nonfatal Serious Adverse Events

In Study 58, SAEs occurred in 30.7% of patients on the vandetanib and 13.1% of patients on the placebo arm. Serious adverse events in > 2% of patients in the vandetanib arm included diarrhea, pneumonia, and hypertension. During open label treatment, 26.5% of patients experienced a SAE. These events were similar to those that occurred during randomized therapy.

Grade 3-4 adverse events in > 2% of patients are shown in the table below. Grade 3-4 adverse events were seen in 55.4% of patients in the vandetanib arm. This is greater than the 33% grade 3-4 adverse events that are expected at the maximum tolerated

dose. During the open label phase, 45.1% of patients had a grade 3-4 adverse events. The most common adverse events in the open label portion were similar to those seen in the randomized portion of the trial and include diarrhea, QT prolongation, hypertension, fatigue, and rash.

Table 32: Grade 3-4 AEs in ISS 300mg Monotherapy Group

Preferred Term	ISS Monotherapy Group N= 1550
	Grade 3-4
Rash[1]	80 (5%)
Diarrhea	62 (4%)
Hypertension[2]	56 (4%)
Dyspnea	49 (3%)
Fatigue	47 (3%)
Asthenia	38 (2%)
Pneumonia	37 (2%)

[1] Includes rash, rash erythematous, generalized, macular, maculo-papular, papular, pruritic, exfoliative, dermatitis, dermatitis bullous, generalized erythema and eczema.
[2] Includes hypertension and hypertensive crisis

The grade 3-4 adverse events seen in the monotherapy group were similar to those seen in the Phase 3 study with the exception of a higher incidence of pneumonia and dyspnea. This may be in part due to the large lung cancer population included in the database.

Table 33: Serious Adverse Events in > 2% of Patients in Study 58

	Vandetanib N = 231	Placebo N = 99
All	30.7%	13.1%
Gastrointestinal Disorders		
Diarrhea	2.2%	0
Infections and Infestations		
Pneumonia	2.2%	0
Vascular Disorders		
Hypertension[1]	3.0%	0

[1.] Includes accelerated hypertension, hypertensive crisis

No SAEs were reported in $\geq$ 2% of patients during open label vandetanib. The table below provides information on the SAEs which occurred in patients in the safety database who received 300mg vandetanib. The SAEs reported in this larger population are similar to those in Study 58 despite differences in the patient's underlying cancer.

Table 34: Serious Adverse Events in > 2% of Patients in the 300mg Monotherapy Group

Serious Adverse Event	Vandetanib 300 mg Monotherapy N = 1550
All	364 (23.5%)
Infections and Infestations	
Pneumonia[1]	78 (5%)
Diarrhea[2]	32 (2%)

1. Includes bronchopneumonia, lobar pneumonia, lower respiratory tract infection, lung infection
2. Includes diarrhea, enteritis, and gastroenteritis clostridial

7.3.3 Dropouts and/or Discontinuations

Reasons for treatment discontinuation are summarized in Table 35. Disease progression was the most common reason for treatment discontinuation in the vandetanib group. Treatment discontinuations due to adverse drug reactions occurred in 12.5% of patients who received vandetanib and 3% of patients on placebo. The most common adverse reactions leading to treatment discontinuation on the vandetanib arm of the Phase 3 study were skin disorders (2.5%), asthenia and fatigue (2.6%); gastrointestinal disorders (3.0%) which included diarrhea (0.9%), dysphagia (0.4%), nausea (0.4%), pancreatitis (0.4%), peritonitis (0.4%), small intestinal perforation (0.4%) and vomiting (0.4%); QTc prolongation (0.9%); elevated creatinine (0.9%); and hypertension (0.9%). These are summarized in the table below.

Table 35: Permanent Discontinuations due to Adverse Events in the Randomized Treatment Phase

	Vandetanib N=231	Placebo N=99
Any Adverse Event[1]	29 (12.5%)	3 (3.0%)
Skin Disorders[2]	6 (2.5%)	0
Asthenia	4 (1.7%)	0
Fatigue	2 (0.9%)	0
Pyrexia	2 (0.9%)	0
Diarrhea	2 (0.9%)	1 (1.0%)
Elevated creatinine	2 (0.9%)	0
QTc prolongation	2 (0.9%)	0
Hypertension	2 (0.9%)	0
General Physical Health Deterioration	1 (0.4%)	0
Dysphagia	1 (0.4%)	0

	Vandetanib N=231	Placebo N=99
Nausea	1 (0.4%)	0
Pancreatitis	1 (0.4%)	0
Peritonitis	1 (0.4%)	0
Small Intestinal Perforation	1 (0.4%)	0
Vomiting	1 (0.4%)	0
Gastrointestinal Hemorrhage	0	1 (1.0%)
Reduced systolic function	1 (0.4%)	0
Chylothorax	1 (0.4%)	0
Cough	1 (0.4%)	0
Dysphonia	1 (0.4%)	0
Dyspnea	1 (0.4%)	0
Pneumonitis	1 (0.4%)	0
Peripheral Ischemia	1 (0.4%)	0
Peripheral Sensorimotor Neuropathy	1 (0.4%)	0
Syncope	0	1 (1.0%)
Vision Blurred	1 (0.4%)	0
Arthralgia	1 (0.4%)	0
Germ Cell Cancer	1 (0.4%)	0
Left Bundle Branch Block	0	1 (1.0%)
Jaw Fracture	0	1 (1.0%)

[1]The discrepancy between the number of individual adverse events and the total number of discontinuations is due to individual patients having any number of adverse events that caused discontinuation, i.e. one patient might have had diarrhea, fatigue and asthenia that led to discontinuation.
[2]Skin disorders includes include rash, eczema, pruritis, and photosensitivity reaction.

When the open label portion of the study is included in the analysis, there were 2 discontinuations due to patients reporting blurred vision, and 2 patients reporting peripheral sensorimotor neuropathy.

Reviewer comment: There were several toxicities that were graded by CTC as Grade 1 and Grade 2. For instance, 2 patients discontinued due to grade 1 and grade 2 diarrhea. This highlights that even low grade toxicity is significant enough to disrupt a patient's life and lead to discontinuation. Similarly, there were 6 patients that discontinued due to grade 1 and 2 asthenia or fatigue. Given the toxicity profile of the untreated disease state, any additional toxicity could potentially make the treatment regimen intolerable.

The table below provides information on the causes of treatment discontinuation in the safety database. Note that skin disorders are the most common cause of discontinuation in both groups.

Table 36: Permanent Discontinuations due to AEs in the ISS 300mg Monotherapy Group in >1 Patient

Adverse Event	Vandetanib N=1550
Any Adverse Event	206 (13%)
Skin Disorders[1]	50 (3%)
Pneumonia and Lung Infection	14 (0.9%)
Diarrhea	10 (0.6%)
Dyspnea	10 (0.6%)
Asthenia and Fatigue	8 (0.5%)
Myocardial Infarction[2]	8 (0.5%)
Arrhythmic Events [3]	6 (0.4%)
Hemoptysis [4]	6 (0.4%)
Pulmonary Embolism	5 (0.3%)
QTc prolongation	4 (0.3%)
Hypertension and Hypertensive Crisis	4 (0.3%)
Nausea	3 (0.2%)
Cardiac Failure	3 (0.2%)
Cerebrovascular Accident	3 (0.2%)
Pneumonitis & ILD	3 (0.2%)
Arterial Thrombotic Event [5]	3 (0.2%)
Vomiting	2 (0.1%)
Cerebral Ischemia	2 (0.1%)
Cognitive Disorder	2 (0.1%)
Dehydration	2 (0.1%)
Drug Hypersensitivity	2 (0.1%)
Proteinuria	2 (0.1%)
Respiratory Failure	2 (0.1%)
Respiratory Tract Infection	2 (0.1%)

1. Skin disorders include acne, dermatitis acneiform, dermatitis (allergic, bullous, and exfoliative), erythema, erythema multiforme, rash (exfoliative, erythematous, generalized, maculo-papular, pruritic), pruritis, palmar-plantar erythrodesia, photosensitivity reaction, and Steven Johnson Syndrome.
2. Includes myocardial infarct, cardiac arrest, cardio-respiratory arrest, cardio-pulmonary failure
3. Includes Ventricular Fibrillation, T wave Inversion and Atrial Fibrillation, and Supraventricular Tachycardia
4. Includes hemoptysis, pulmonary hemorrhage and bronchial hemorrhage
5. Includes Pulmonary Artery Thrombosis, Arterial Thrombosis Limb, Peripheral Arterial Occlusive Disease

Reviewer Comment: Two cases of "drug hypersensitivity" led to discontinuation of the study drug. After closer review of these two patient cases, it appears they were more in keeping with Grade 4 Stevens Johnson Syndrome (SJS). Interestingly, they both occurred in the same center in two different Chinese patients. Due to the low number of patients involved, it is impossible to draw any conclusions with regards to whether there is an ethnic pre-disposition to developing SJS.

7.3.4 Significant Adverse Events

Vandetanib at a dose of 300 mg is associated with a substantial (mean effect 35 ms) and concentration dependent prolongation in QTc. This increase in mean QTc does not lessen over time and the half-life of vandetanib (19 days) makes this prolongation in QTc interval particularly problematic. In addition to QTc prolongation, the majority of the severe adverse events seen with both EGFR and VEGFR inhibitors have been reported with vandetanib. This includes Stevens-Johnson syndrome, some ischemic arterial events, and interstitial lung disease. While Stevens-Johnson syndrome or toxic epidermal necrolysis is uncommon, it has resulted in death. Risk factors for evolution of rash into Stevens-Johnson syndrome are unclear with 8 of 21 patients receiving radiation prior to development of Stevens-Johnson syndrome (unknown if initial rash was in the area of prior radiation).

Cerebrovascular events may be increased while cardiac events do not appear to be increased with vandetanib. For example, during the randomized portion of Study 58, a cerebrovascular event (cerebral ischemia, TIA) occurred in 1.3% patients in the vandetanib and in no patients in the control arm while coronary occlusion was reported in 1 (0.4%) patient in the vandetanib and in no patients in the control arm. This increase in cerebrovascular events appears to be consistent among the randomized trials. However, it is very dependent upon which terms are included as a cerebrovascular event.

Interstitial lung disease and pneumonitis have also been reported more frequently in patients receiving vandetanib. In a large study of patients with non-small cell lung cancer, interstitial lung disease/pneumonitis was reported in 3.5% of patients receiving 100mg vandetanib + docetaxel and in 2.0% of those treated with docetaxel alone. Overall, 23 patients have been reported to have grade 3-4 interstitial lung disease or pneumonitis, with at least 8 patients receiving prior radiation to the chest. While the overall number of patients is small, the number of patients with dyspnea or hypoxia is much larger. For example, while grade 3-5 interstitial lung disease/pneumonitis was reported in 23 patients, dyspnea/hypoxia was reported in 392 (13.0%) patients in the vandetanib safety database and was grade 3-4 in 108 (3.6%) patients.

In addition to the events listed in Table 37, 3 additional patients (not on Astra-Zeneca studies) have been reported to have reversible posterior leukoencephalopathy syndrome (RPLS). Finally, vortex keratopathy has also been reported in patients on vandetanib. This continues to be examined.

Table 37: Significant Adverse Events in the Vandetanib Safety Database

Significant Adverse Events in the Vandetanib Safety Database (Data Cutoff 7/31/09 and 10/19/09)	
	N=3019
Grade 3-4 Interstitial Lung Disease or Pneumonitis	23 (0.8%)
Ischemic Cerebrovascular Events	26 (0.9%)
Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis	21 (0.7%)
Cardiac Failure/ Cardiomyopathy	15 (0.5%)
Hypertensive Crisis or Grade 4 Hypertension	11 (0.4%)
Pancreatitis[1]	7 (0.2%)
Intestinal Perforation	6 (0.2%)
Torsades de Pointes/ Sudden Death[2]	3 (0.1%)/9 (0.3%)
Reversible Posterior Leukoencephalopathy Syndrome (RPLS)	1 (<0.1%)

[1]Includes acute pancreatitis and hemorrhagic pancreatitis
[2]Includes cardiac arrest, cardiorespiratory arrest, sudden death, acute death, and arrhythmia (if resulted in death).

7.3.5 Submission Specific Primary Safety Concerns

Torsades de Pointes:

Study 58: There were no reported cases of torsades noted in Study 58. The database lists "arrhythmia" in two patients, one grade 1 arrhythmia in a placebo patient and one grade 5 arrhythmia in a vandetanib patient. In the patient receiving vandetanib, there were no ECGs performed at the time of death, however, ventricular tachycardia was noted on the cardiac monitor at the time of death. All ECGs performed within the week before death were read by the central ECG vendor as having prolonged QTc intervals of 547, 556 and 538 ms. The investigator attributed the patient's cause of death as vandetanib (considered likely). Ventricular tachycardia Grade 2 was noted in another vandetanib patient, and lastly the term tachycardia was noted in an additional four patients: two grade 1 events in placebo patients and a grade 2 and grade 3 event in the vandetanib patients. There are no further details regarding these events.

ISS database: In the ISS database, Grade 2 torsades de pointes was reported in one patient in study 57 on the vandetanib arm (E1304012) after 12 weeks of being on study. Additionally, there were four sudden death events reported in Study 57 (patients

E1517004, E2705003, E3203010 and E3702012), only one of which was on the vandetanib 300mg arm, the other 3 were on the erlotinib arm.

Grade 4 ventricular tachycardia occurred in one patient in study 57 treated with vandetanib 300mg. Additionally, there were 2 patients in study 57 on the vandetanib arm who experienced Grade 4 ventricular fibrillation.

The term arrhythmia was invoked for an additional 9 patients in the ISS database, 7 of which were on vandetanib containing treatment arms in studies 3, 39, 44 and 57. The AEs were not graded in 3 patients. Graded AEs include one grade 1 toxicity, two grade 2 and one grade 4 toxicity.

Torsades was also noted in a patient with differentiated thyroid carcinoma in Study 79 after 5 weeks of being on study. The patient is a 79 yo man with an extensive past medical history including hypertension and hypercholesterolemia, right bundle branch block, and transient ischemic attack. The patient presented to clinic for routine examination while on trial and was noted to be bradycardic with a BP of 160/90. The patient was instructed to perform some knee bends in attempts to raise his heart rate but quickly lost consciousness. Artificial respiration and cardiac massage were started. During defibrillation the patient was noted to be in AV block which led to torsades. Involuntary seizure like activity ensued and the patient was transferred to the ICU. A 2 chamber ICD was implanted due to several episodes of Torsades and ventricular tachycardia. Of note, the patient had a normal baseline ECG with no QTc prolongation. Study drug was stopped on an unspecified day and the patient recovered. The investigator did attribute this event to the study drug in combination with concomitant hydrochlorothiazide and losartan.

Reviewer comment: This patient was also noted to be bradycardic, an issue that many MTC patients have to contend with due to hypothyroidism. This is a known confounding factor that can exacerbate QT prolongation in patients that are on QT prolonging medications.

Overall, serious arrhythmias (including grade 3-4 arrhythmia, grade 3-4 ventricular tachycardia or ventricular fibrillation and torsades) were seen in 9 patients in the integrated safety summary. An additional 4 patients may have had arrhythmias leading to sudden death, it is unknown. Two of the patients for which we have patient narratives to review did not have any history of cardiac disease, but both had a history of lung lobectomy for lung cancer.

Steven's Johnson Reaction:

The table below provides information on the incidence of skin reactions with the EGFR inhibitor vandetanib in Study 58. This study recommended steroid creams, topical or systemic antibiotics, and topical or systemic antihistamines to manage events ≥ grade 2. For grade 3-4 events, study drug was temporarily discontinued until the reaction resolved to grade 1 or baseline followed by continuation of study drug at a reduced dose. Patients who developed a grade 3-4 reaction despite 2 dose reductions or patients in whom study drug was withheld > 3 weeks permanently discontinued study drug.

Table 38: Skin Adverse Events on the Phase 3 MTC study

Skin Disorders	Vandetanib N = 231		Placebo N = 99	
	Gr 1-4	Gr 3-4	Gr 1-4	Gr 3-4
All	88.3%	7.8%	24.2%	0
Rash[1]	53.2%	3.9%	12.1%	0
Acne/Dermatitis Acneiform/Pustular Acne	35.5%	0.9%	7.1%	0
Dry Skin/Chapped Skin	15.2%	0	5.1%	0
Photosensitivity Reaction	13.4%	1.7%	0	0
Erythema/Generalized Erythema	10.8%	1.3%	3.0%	0
Nail Disorder	9.1%	0	0	0
Skin Hyperpigmentation[2]	7.4%	0	0	0
Skin Exfoliation/Breakdown/Fissures	4.8%	0.4%	0	0
Folliculitis	3.0%	0	1.0%	0
Dermatitis	2.2%	0	0	0
Skin Discoloration	2.2%	0	0	0
Skin Lesion	2.2%	0	1.0%	0
Palmar-Plantar Erythrodysaesthesia	1.7%	0.4%	0	0
Urticaria	1.7%	0	0	0
Paronychia	1.3%	0	0	0
Skin Ulcer	1.3%	0	0	0
Allergic Dermatitis	0.9%	0	0	0
Cellulitis	0.9%	0	0	0
Dermatitis Bullous	0.9%	0.4%	0	0
Skin Candida	0.9%	0.4%	0	0
Actinic Keratosis	0.4%	0	0	0
Erysipelas	0.4%	0.4%	0	0
Erythema Migrans	0.4%	0	0	0
Palmar Erythema	0.4%	0	0	0
Skin Atrophy	0.4%	0	0	0
Skin Hemorrhage	0.4%	0	0	0
Skin Pain	0.4%	0	0	0
Pigmentation Loss	0	0	1.0%	0

Rosacea	0	0	1.0%	0

[1]Includes rash erythematous, generalized, macular, maculopapular, papular, pruritic, pustular, exfoliative, and butterfly as well as eczema.
[2]Often blue or grey spots.

Table 38 above provides information from the randomized phase of Study 58. During open label treatment, 58.9% of patients reported a skin disorder. This includes 9 patients who reported a grade 3-4 event. In the vandetanib 300 mg monotherapy program, skin disorders occurred in 1177 patients while grade 3-4 events occurred in 334 (22%) of patients.

Patients on vandetanib who developed a rash, acne, or a photosensitivity reaction (N = 121) during randomized therapy were examined more closely. The time to onset of these reactions varied from day 1 to day 749 on treatment. The median duration, for 65 available events, was 101 days suggesting that these events are persistent. Serious adverse events due to any skin disorder, randomized and open label, were also examined to evaluate concomitant medication use. Five of these events had resolved at the time of data cutoff with the use of anti-histamines, antibiotics, and methylprednisolone. In 1 patient surgery was required to treat a skin ulcer.

Reports of Stevens-Johnson syndrome (6 patients), erythema multiforme (3 patients), toxic epidermal necrolysis (4 patients), and toxic skin eruption (5 patients) are also included in the safety database (vandetanib monotherapy and combination trials). This includes one death in a patient with a toxic skin eruption receiving 100 mg vandetanib and docetaxel. Nine of these events occurred on 100 mg vandetanib + docetaxel while 9 occurred on monotherapy. Time of onset varied from day 17 to day 255 and in some patients this event persisted for several months. As in Study 58, patients received either/both topical treatment and systemic steroids and antibiotics. Thus, while the incidence of skin disorders such as rash, acne, and photosensitivity is common, a small number of patients do go on to experience Stevens-Johnson syndrome or toxic epidermal necrolysis and these events can result in death.

Gastrointestinal Perforation:

Gastrointestinal perforation is a well known toxicity in drugs that inhibit VEGF. However, it is unclear as to whether there is an association between GI perforation and vandetanib. In 4 large randomized trials, when the number of patients who developed intestinal perforation (or pneumatosis intestinalis) was compared between arms, the number of patients in the vandetanib arm was increased in 2 of the 4 trials. There were 5 cases of gastrointestinal perforation or pneumatosis intestinalis in the vandetanib ISS monotherapy database and two of these were in placebo patients. Given the small number of patients, no conclusions can be made at this time.

Cardiac Failure:

There were 13 cases (0.8%) of cardiac failure noted in the ISS 300mg vandetanib monotherapy group some of which have led to death. Echocardiograms were not monitored regularly throughout the studies so it is unclear whether this number under represents the true incidence of cardiac failure. Cardiac failure has been associated with other tyrosine kinase inhibitors and in future studies using vandetanib, echocardiograms or other functional cardiac testing should be monitored. As cardiac failure can exacerbate QT prolongation, this is an important consideration for future studies.

Interstitial Lung Disease (ILD):

There were no reported cases of the specific preferred term ILD in the randomized portion of study 58. However, there were 2 (0.9%) cases of pneumonitis of CTCAE Grade 3. Radiographs of the chest did show an interstitial infiltrate, but both cases were regarded by the investigators as unrelated to study therapy. In one patient (E2501011), Grade 2 pneumonitis developed at day 234 and resolved by day 244, followed by a separate event at day 277 which again resolved at day 296. There were no treatments reported as being given for the pneumonitis. The second patient with pneumonitis developed their AE on day 536 and it continued until day 739. The patient was administered cefixime from days 550-554. Therapy was discontinued for this patient. An additional patient in the open-label phase was reported to have had Grade 1 ILD following administration of contrast material during a cardiac catheterization procedure for myocardial infarction. This was also deemed unrelated to study treatment by the investigator.

The Study 58 R_AE database was queried for the terms pneumonitis, dyspnea, dyspnea exertional, hypoxia, and respiratory failure. Twenty-two (22) patients on the vandetanib arm were identified, 6 of which had grade 3 toxicity. The preferred terms for these patients were dyspnea, pneumonitis and respiratory failure. The median number of days on treatment was 406.5, the range was from 36 days to 703 days until the adverse event was reported.

Table 39: Respiratory Toxicity on Study 58

	Vandetanib Grade 1-4 N=231	Vandetanib Grade 3-4 N=231	Placebo Grade 1-4 N=99	Placebo Grade 3-4 N=99
Pneumonitis	2 (0.8%)	1 (0.4%)	0	0
Dyspnea	18 (7.7%)	4 (1.7%)	9 (9%)	3 (3%)
Respiratory Failure	2 (0.8%)	2 (0.8%)	0	0
Hypoxia	0	0	0	1 (1%)

In the ISS database, there are 6 (1%) cases of interstitial lung disease identified (not including study 58). Four cases were on Study 3, 1 was on Study 39 and 1 on Study 57. The grade was only available for the patient on Study 57 and was listed as Grade 4. All the patients on Study 3 were NSCLC patients. One patient developed interstitial lung disease while on gefitinib, prior to receiving vandetanib. Once started on vandetanib, they did not have a recurrence of the ILD. Another patient developed ILD on (b) (6) after an episode of grade 2 pharyngitis. Their lung disease was complicated by pleural effusions. The ILD was reported as having resolved by (b) (6) Patient E0043002 enrolled on Study 3 began treatment on (b) (6) and was withdrawn from treatment on (b) (6) due to disease progression. On (b) (6) the patient was hospitalized for orthopnea, productive cough and dyspnea. He was treated with cefuroxime, erythromycin, itraconazole, and codeine phosphate/paracetamol for chest infection. A lung biopsy performed on (b) (6) revealed severe interstitial fibrosis without obvious cause. "No obvious causes (silica particles, asbestos bodies, granulomas) can be found histologically. In light of the history, it is possible that the lung fibrosis could be caused by the study medication." The patient was started on prednisilone and oxygen and his condition improved and the patient was discharged, however the patient died one day after discharge. A 43 yo woman was treated on Study 57 starting on (b) (6). 9 days later she was diagnosed with ILD and was discontinued off of therapy. The patient was hypoxic requiring 100% oxygen and antibiotics were administered. At the time of the applicant's report, the patient still had not recovered. The investigator considered the event related to therapy.

Table 40: Respiratory Toxicity in the ISS Safety Database

	Vandetanib Grade 1-4 N=1550	Vandetanib Grade 3-5 N=1550
Interstitial Lung Disease	5 (4 unknown grade)	1
Pneumonitis	10 (1 unknown grade)	4
Dyspnea [1]	204 (57 unknown grade)	53
Respiratory Failure	9 (3 unknown grade)	6
Hypoxia	12 (7 unknown grade)	4

[1]Dyspnea and dyspnea exacerbated

The table below provides additional information on respiratory toxicity in Study 32. Study 32 was a Phase 3 study of docetaxel ± vandetanib in patients with advanced NSCLC after failure of first line therapy. In Study 32, ILD was reported more frequently in patients treated with 100mg vandetanib + docetaxel (2.5%) than with docetaxel alone (0.9%). Interestingly, that study also reported ILD more frequently in Japanese patients (16.7% in docetaxel +vandetanib group vs. 7.4% docetaxel alone) than in patients from outside Japan (0.8% vandetanib/0.2% docetaxel alone). The other Phase 3 studies in NSCLC have reported incidences of ILD of less than 1% with vandetanib, however these studies did not include patients from Japan. The applicant postulates as to

whether the ILD frequency seen in Study 32 could have been the effect of the drug on a Japanese population. The overall incidence of ILD in the 300 mg monotherapy pool was 0.2%.

Table 41: Respiratory Toxicity in Study 32

	Vandetanib+ docetaxel Grade 1-4 N=694	Vandetanib + docetaxel Grade 3-4 N=694	Docetaxel + Placebo Grade 1-4 N=697	Docetaxel + Placebo Grade 3-4 N=697
ILD	17 (2.4%)	4 (0.6%)	6 (0.8%)	3 (0.4%)
Pneumonitis	7 (1%)	2 (0.2%)	8 (1%)	4 (0.5%)
Dyspnea	113 (16.3%)	29 (4.0%)	137 (20%)	35 (5%)
Respiratory Failure	5 (0.7%)	5 (0.7%)	7 (1%)	7 (1%)
Hypoxia	10 (1.4%)	3 (0.4%)	5 (0.7%)	2 (0.2%)

Reversible Posterior Leukoencephalopathy (RPLS):

Reversible Posterior Leukoencephalopathy Syndrome is characterized by headache, confusion, seizures and visual loss. On MRI of the brain, areas of edema are seen. There were no cases of RPLS identified in Study 58. Four cases of RPLS have occurred in the vandetanib treatment program as a whole. One case occurred in Study 32 in a patient who received 100mg daily in combination with chemotherapy for NSCLC. Two cases occurred in pediatric patients with primary brain tumors receiving vandetanib with concomitant radiation therapy in an investigator sponsored study (IRUSZACT0051). One case occurred in another investigator sponsored study in a patient receiving vandetanib in combination with gemcitabine and oxaliplatin for transitional cell cancer. There were no cases seen in any of the 300mg monotherapy treatment groups.

Because the diagnosis of RPLS is based on characteristic magnetic resonance imaging (MRI) findings, and some patients with seizures or other neurologic signs may not have had MRI imaging, there is a possibility that RPLS has been under diagnosed.

Reviewer comment: RPLS has been noted with other anti-VEGF therapies. No conclusions can be drawn from the cases presented above due to the small number of patients overall. This reviewer believes that besides noting the possibility of RPLS in the package label, there should be language to suggest that the incidence may be higher in patients on treatment with uncontrolled hypertension, as 75% of patients that developed RPLS experienced elevated blood pressure, including one pediatric patient. Strong language should be inserted with respect to controlling HTN. 2 patients had been treated with radiation therapy for brainstem gliomas, it is unclear whether there is any correlation between radiation and RPLS.

Diarrhea

Diarrhea is of particular concern in this patient population for many reasons. First, patients with medullary thyroid carcinoma often have significant diarrhea at baseline. The ability of the tumor to secrete calcitonin, occasionally along with other hormonally active peptides like ACTH or calcitonin-gene related peptide (CGRP), can contribute to the development of diarrhea. These patients, when confronted with grade 1 or grade 2 diarrhea are by CTCv.3 definition, having anywhere between 1-6 stools per day *OVER* their baseline, which can already be quite high. Secondly, in a drug that can elicit QTc prolongation, the propensity of the drug to cause diarrhea can lower a patient's threshold for developing QTc prolongation derived arrhythmias.

In Study 58, 130 (56%) patients randomized to the vandetanib 300mg arm reported diarrhea which made it the most common adverse event reported in the study. This was compared to 26% of the placebo population. Grade 3 or higher diarrhea was seen in 11% of patients on vandetanib.

The Study 58 protocol recommended "standard medications" for the treatment of diarrhea in order to avoid dose interruptions and modifications. No dose modifications were made for Grade 1 or 2 diarrhea. Electrolyte supplementation was encouraged to avoid risk of prolonged QTc. In the R_AE dataset, a search for all terms related to diarrhea was performed. Patients with the preferred terms diarrhea, colitis, hemorrhagic diarrhea, frequent bowel movements, fecal incontinence, and malabsorption were evaluated further. The study day of the start of the adverse event ranged from -29 days (highlighting the fact that many of these patients had diarrhea preceding their initiation of therapy) to 794 days on therapy. A similar wide range was seen in the duration of the AE ranging from unknown to 622 days. In the R_AE dataset there were only a handful of patients where there was note of the treatment for diarrhea, primarily in patients whose diarrhea led to an SAE. Imodium was one treatment intervention. Intravenous fluids, calcium, magnesium, and potassium was listed as another intervention in two patients. Intravenous solumedrol was given with IV fluids to one patient, and cholestyramine was administered to another patient. Another patient required 1.5 L fluids daily, with loperamide and activated charcoal. Levaquin and metronidazole were given to one patient with a diagnosis of colitis. All events resolved in these 8 patients with the exception of one where the AE was listed as on-going.

The concomitant medication dataset listed many drugs as having been taken for the treatment of diarrhea, including loperamide, opium alkaloid, octreotide, paregoric, lomotil, metamucil, opium tincture, dicyclomine hydrochloride, motofen, ms contin, laudanum, spasmine, nifuroxazide, dihydrocodeine (DHC), smectite, codeine, mesalazine, granisetron, trimebutine maleate, rifaximin, and attapulgite.

The median day of diarrhea onset was 10 days for patients on vandetanib during cycle 1. Thirteen (13) people had grade 3-4 diarrhea on vandetanib during cycle 1 and the median onset was on day 15. Of these 13 patients, 6 patients temporarily stopped therapy, 1 permanently stopped therapy and 2 necessitated a dose decrease.

Cerebrovascular Accident:

Table 42: Cerebrovascular Events Reported in Randomized Studies Using Vandetanib

	Cerebrovascular Events- Narrow[1]	Cerebrovascular Events- Broad[2]
Study 58		
Vandetanib N=231	1.3%	2.2%
Placebo N=99	0	0
Study 3		
Vandetanib N=83	1%	2%
Control N=85	0	2%
Study 32		
Vandetanib N=689	4%	10%
Control N=690	2%	8%
Study 36		
Vandetanib N=260	4%	7%
Control N=273	0	4%
Study 44		
Vandetanib N=619	1.1%	1.9%
Control N=303	1.6%	2.3%
Study 57		
Vandetanib N=623	6%	11%
Control N=614	4%	7%

[1]Includes CVA, TIA, cerebral ischemia, cerebral infarction, ischemic stroke, cerebral thrombosis
[2]Includes cerebral hemorrhage, dysarthria, dysphasia, facial palsy, aphasia, hemiplegia, hemiparesis, brain stem hemorrhage, facial paresis, cerebral artery embolism

Patients treated with vandetanib had a higher incidence of cerebrovascular events in the Phase 3 medullary thyroid study as compared to placebo. This also occurred in the majority of the other randomized studies, with the exception of Study 44, suggesting that these events are related to vandetanib. A clear increase in cardiac events was not seen with vandetanib. However, future studies and safety updates will be monitored for reports of cardiac arterial events.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Table 43: Adverse Events in >10% of Vandetanib Patients in the Phase 3 MTC Study

Preferred Term	Vandetanib N=231		Placebo N=99	
	Grade 1-4	Grade 3-4	Grade 1-4	Grade 3-4
Diarrhea[1]	134 (58%)	9 (3%)	27 (27%)	2 (2%)
Rash[2]	147 (64%)	13 (6%)	16 (16%)	1 (1%)
Nausea	77 (33%)	2 (1%)	16 (16%)	0
Hypertension[3]	78 (34%)	13 (6%)	5 (5%)	0
Headache	59 (26%)	2 (1%)	9 (9%)	0
Fatigue	55 (24%)	13 (6%)	23 (23%)	1 (1%)
Decreased Appetite	49 (21%)	9 (4%)	12 (12%)	4 (4%)
Dermatitis Acneiform[4]	81 (35%)	1 (<1%)	7 (7%)	0
Dry Skin	35 (15%)	0	5 (5%)	0
Vomiting	34 (15%)	2 (1%)	7 (7%)	0
Asthenia	34 (15%)	6 (3%)	11 (11%)	1 (1%)
Abdominal Pain[5]	57 (25%)	5 (2%)	12 (12%)	0
ECG Qt Prolonged[6]	33 (14%)	18 (8%)	1 (1%)	1 (1%)
Photosensitivity Reaction	33 (13%)	4 (2%)	0	0
Insomnia	30 (13%)	0	10 (10%)	0
Nasopharyngitis	26 (11%)	0	9 (9%)	0
Dyspepsia	25 (11%)	0	4 (4%)	0
Hypocalcaemia	25 (11%)	4 (2%)	3 (3%)	0
Cough	25 (11%)	0	10 (10%)	0
Pruritus	25 (11%)	3 (1%)	4 (4%)	0
Weight Decreased	24 (10%)	2 (1%)	9 (9%)	0
Proteinuria	23 (10%)	0	2 (2%)	0
Depression	22 (10%)	4 (2%)	3 (3%)	0

[1] Includes diarrhea, hemorrhagic diarrhea and colitis
[2] Includes rash, rash erythematous, generalized, macular, maculo-papular, papular, pruritic, exfoliative, dermatitis, dermatitis bullous, generalized erythema and eczema.
[3] Includes hypertension and hypertensive crisis
[4] Includes acne and dermatitis acneiform
[5] Includes abdominal pain, abdominal pain upper and abdominal discomfort
[6] 85% had QT prolongation >450ms and 11% had grade 3-4 QT prolongation by ECG.

7.4.2 Laboratory Findings

Laboratory adverse events are summarized in the table below. Bicarbonate levels were decreased in 100% of patients and are not listed in the table. Hematologic indices did not appear to be significantly effected in patients while on vandetanib therapy. Chemistries were altered when compared to placebo. Baseline laboratory abnormalities were confined to grade 1-2 events. The table below reports the laboratory abnormalities found on study.

Table 44: Laboratory Adverse Events

On Study	Vandetanib N = 231		Placebo N = 99	
	Grade 1-4	Grade 3-4	Grade 1-4	Grade 3-4
Chemistries				
ALT Increased	118 (51%)	4 (2%)	19 (19%)	0
Bilirubin Increased	29 (13%)	0	18 (18%)	0
Calcium Decreased	135 (58%)	18 (6%)	25 (25%)	3 (3%)
Calcium Increased	16 (7%)	2 (9%)	9 (9%)	1 (1%)
Creatinine Increased	41 (18%)	0	1 (1%)	0
Glucose Decreased	55 (24%)	0	7 (7%)	1 (1%)
Glucose Increased	12 (5%)	4 (2%)	7 (7%)	0
Magnesium Decreased	17 (7%)	1 (<1%)	1 (1%)	0
Magnesium Increased	6 (3%)	0	4 (4%)	0
Potassium Decreased	17 (7%)	1 (<1%)	3 (3%)	0
Potassium Increased	13 (6%)	1 (<1%)	4 (4%)	2 (2%)
Hematologic				
Hemoglobin Decreased	22 (10%)	1 (<1%)	20 (20%)	2 (2%)
Neutrophils Decreased	22 (10%)	3 (1%)	5 (5%)	2 (2%)
Platelets Decreased	20 (9%)	0	3 (3%)	0
WBC Decreased	47 (20%)	1 (<1%)	24 (24%)	0

Alanine aminotransferase elevations occurred in 51% of patients on vandetanib. Grade 3-4 ALT elevations were seen in 2% of patients on this study and no patients had a concomitant increase in bilirubin. Elevations in ALT have resulted in temporary discontinuation of vandetanib. However, 16/22 patients with a grade 2 elevation in ALT continued 300 mg vandetanib. Seven patients had a normal ALT within 6 months of the grade 2 elevation. Periodic monitoring of alanine aminotransferase is recommended in patients receiving vandetanib.

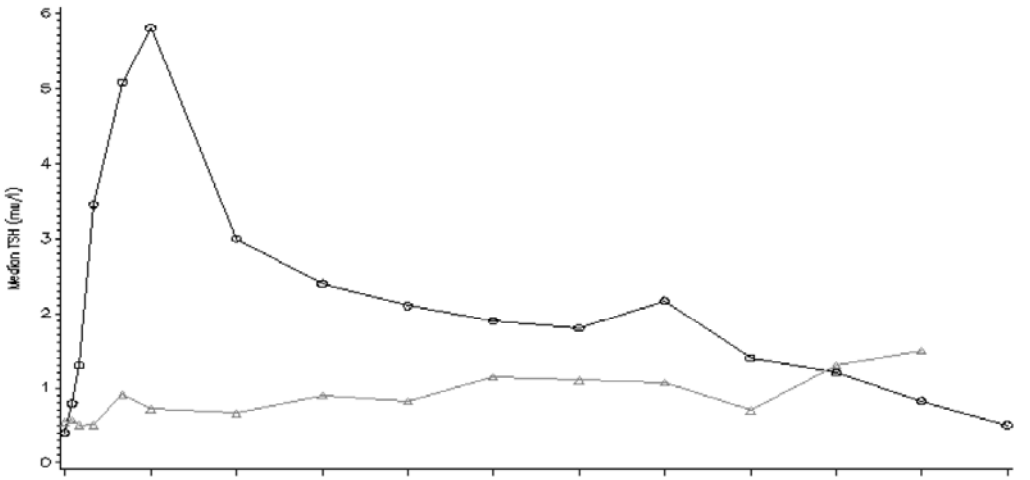
Table 45: TSH values on Study 58

	Vandetanib N = 231		Placebo N = 99	
	Baseline	On Study	Baseline	On Study
Increased TSH				
> ULN	20 (8.7%)	180 (77.9%)	8 (8.1%)	21 (21.2%)
> 3xULN	5 (2.2%)	88 (38.1%)	3 (3.0%)	6 (6.1%)
> 5xULN	3 (1.3%)	48 (20.8%)	2 (2.0%)	3 (3.0%)
> 10xULN	0	14 (6.1%)	0	0
Decreased TSH				
< LLN	107 (46.3%)	144 (62.3%)	36 (36.4%)	66 (66.7%)

Thyroid stimulating hormone was elevated in 78% of patients receiving vandetanib with 21% of patients having a TSH level > 5xULN. The majority of patients were noted to have increased TSH at their day 28 visit, However, it was noted as early as day 14 and as late as day 84. It appears that there is a drug-drug interaction with vandetanib and levothyroxine and patients generally require a dose increase of their levothyroxine while on study. This will be an issue for labeling. Finally, a substantial percentage of patients had a TSH < LLN both at baseline. While this worsened on study, it worsened at a similar rate in the vandetanib and placebo arms.

Figure 10: (Applicant's Graph): TSH over Time

Figure 11 Plot of clinical chemistry - TSH (mu/L) over time (Safety analysis set)



n at weeks	0	12	24	36	48	60	72	84	96	108	120	132
Vandetanib 300mg	230	213	208	183	176	163	138	127	75	41	16	1
Placebo	99	88	70	55	47	40	33	34	18	10	3	0

Derived from Figure 11.3.7.1.3.13.

As with other VEGF inhibitors, patients on Study 58 were noted to have both blood and protein on urinalysis. Importantly, during the randomized phase, 4 patients on the vandetanib arm reported gr 3-4 renal failure or anuria. In 2 patients, this was thought to be due to an infection. In the 1 patient this was thought to be due to pulmonary edema and in the other to hypercalcemia.

7.4.3 Vital Signs

	Vandetanib N = 231	Placebo N = 99
Systolic Blood Pressure		
>140	143 (62%)	28 (28%)
>160	44 (19%)	3 (3%)
Diastolic Blood Pressure		
>95	97 (42%)	8 (8%)

There is a known class effect with inhibitors of VEGF and elevated blood pressure. Vandetanib has shown the ability to elevate both systolic and diastolic blood pressure and therefore blood pressures should be monitored closely throughout study treatment. Although the overall numbers are small, it is possible that there is a correlation between reversible posterior leuokoencephalopathy and hypertension as this was seen in three of four patients being treated with vandetanib, including one pediatric patient.

The number (%) of patients with elevated blood pressure during randomized treatment by antihypertensive drug usage at baseline was performed by the applicant. For patients with no anti-hypertensive drug usage at baseline, 130 of 212 patients (62%) in the vandetanib arm had elevated BP while on randomized therapy. For patients with anti-hypertensive drug usage at baseline, 13 of 19 patients (68%) in the vandetanib arm had elevated BP while on randomized therapy, compared with 4 of 13 (31%) patients in the placebo arm. Thus, baseline anti-hypertensive use does not appear to be a risk factor for the development of hypertension on study.

7.4.4 Electrocardiograms (ECGs)

The focus for the IRT review is to quantify QTc prolongation following the 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 the two-sided 90% confidence intervals (CI) greater than 33 ms. The QTc prolongation is concentration dependent. Based on the established exposure-response relationship, the expected mean (90% CI) QTc change from baseline (ΔQTc) at the dose of 300 mg was 35 (33-36) ms. 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 vandentanib in Study D4200C00008.

- 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 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 interval (together with the 90% CIs) were observed following long-term treatment with vandetanib up to 108 weeks (around 2 years). This contradicts the applicant'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 ΔQTc > 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. The increased QTc effect in patients with compromised renal function may be explained by the increased steady-state exposure of vandetanib. 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.

- A slightly larger QTc effect was observed in female patients as compared to male patients.

QT Interdisciplinary Review Team's Comments

- In the applicant's study reports, QTc effect was evaluated by using QTcB (Bazett's correction) only. As shown in all vandetanib trials we evaluated, 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. Therefore, we consider Bazett's correction method 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 torsades de pointes 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.

- 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.

- The applicant should submit a REMS plan if the division is considering approval.

Review Comment: A heavy emphasis was placed on this particular adverse event in the Oncologic Drug Advisory Committee safety presentation. With a mean QTc prolongation of 35ms, vandetanib would be considered pro-arrhythmic and a REMS is planned to address this increased risk.

7.4.5 Special Safety Studies/Clinical Trials

Four patients receiving vandetanib 300mg in Study 8 (Phase 2 study in patients with medullary thyroid carcinoma) reported visual changes and had abnormalities noted on

ophthalmologic examination. Given this finding, the applicant submitted an amendment on May 30, 2007 to add ophthalmologic examinations as part of study procedures to determine whether vandetanib increases the likelihood of patients developing corneal opacities or other eye abnormalities.

Ophthalmologic examinations were performed at screening and at 9 months after patients began receiving randomized treatment. Patients who were discontinued from study drug before 9 months, or who had already completed their 9 months visit before the amendment was approved, were required to have an ophthalmologic exam performed at discontinuation. Patients who complained of visual symptoms underwent an ophthalmologic exam at the time the symptom was noted. Only 63.7% of randomized patients underwent an examination during randomized treatment.

As shown in Table 46, abnormalities from visual assessment were more common in the vandetanib arm than in placebo with abnormalities in either eye being reported in 133 (83.6%) patients in the vandetanib arm and 32 (61.5%) in the placebo arm. There was a slight increase in intraocular pressure (mmHg) in both eyes from baseline to week 36 in both right and left eyes in the vandetanib arm.

Table 46: Abnormalities in Right and/or Left Eye

Test	Vandetanib 300mg	Placebo
Total	133	32
Amsler Grid	4 (3%)	1 (3%)
Anterior Chamber	3 (2%)	1 (3%)
Blood Vessels	11 (8%)	6 (19%)
Color vision	12 (9%)	9 (28%)
Conjunctiva	12 (9%)	2 (6%)
Endothelium	6 (5%)	1 (3%)
Intraocular Pressure	79 (59%)	2 (6%)
Macula	10 (8%)	3 (9%)
Optic Disc	19 (14%)	3 (9%)
Periphery	13 (10%)	3 (9%)
Pupillary Reactions	6 (5%)	1 (3%)
Stroma	28 (21%)	2 (6%)
Visual Acuity	3 (2%)	0
Visual Cylinder	1 (<1%)	0
Visual Fields to Confrontation	15 (11%)	4 (13%)
Visual Sphere	3 (2%)	0
Other Slit Lamp Abnormalities	37 (29%)	14 (44%)

A patient can have more than one abnormality reported under a given test.

Blinded review of the reports was performed by a consultant ophthalmologist procured by Astra-Zeneca (Dr. Alan Laties, MD). This review revealed that 49 of 159 (30.8%) patients in the vandetanib arm who underwent ophthalmologic examinations had vortex keratopathy.

"Vortex keratopathy, also called cornea verticillata, is characterized by the appearance of fine, grayish or brown linear opacities in the epithelial layer of the cornea. The linear opacities typically branch repeatedly to form a distinctive whorl-like pattern. Although the opacities often are asymptomatic, patients can have one or more symptoms such as hazy vision, photophobia, haloes around lights, or, in some instances, glare. Vortex keratopathy is typically innocuous and rarely requires discontinuation of drug therapy."

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

FDA ophthalmology review:
The differential diagnosis for deposits with a bilateral golden-brown whorl pattern include Fabry disease, use of amiodarone, chloroquine and hydroxychloroquine, indomethacin, and phenothiazines. Most studies suggest that all or nearly all patients taking amiodarone will develop verticillata. When depositing drugs are stopped for other reasons, most verticillata will eventually fade away. There is no data currently available to suggest either protective or inducing factors in patients who develop verticillata from medication use.

The potential for these verticillata to fade with discontinuation of drug is unknown because the trial did not evaluate this aspect of the adverse event. If these deposits are located in the basal corneal epithelium, it is likely the corneal deposits would behave similar to other medication-related deposits which fade several months after discontinuation of product. There is not enough information provided from this clinical study report to determine if the corneal changes from vandetanib represent classic vortex keratopathy (cornea verticillata) or if there is some additional corneal stromal abnormality. The clinical study report provides conflicting descriptions of the corneal abnormalities noted.

The majority of subjects with vortex keratopathy are asymptomatic. Some subjects are symptomatic and report halos or other visual disturbances.

There is no treatment for drug-related cornea verticillata except discontinuation of causative medication.

If patients are asymptomatic, there is no need to stop or adjust dosing. If a patent is symptomatic, the utility of the study drug would have to be weighed against the level of visual disturbance experienced.

FDA Ophthalmology Consult Summary Statement/ Recommended Action:

A review of the submitted case report forms for subjects reveals slit lamp exam descriptions consistent with the common presentation of vortex keratopathy (cornea verticillata). However, Table 11.3.8.2 includes listings of abnormalities which include stromal opacities, edema, and whirls. There are no photographs of the corneal changes located in the NDA submission.

There is not enough information provided from this clinical study report to determine if the corneal changes from vandetanib represent classic vortex keratopathy (cornea verticillata) or if there is some additional corneal stromal abnormality. The clinical study report provides conflicting descriptions of the corneal abnormalities noted.

Recommend that if any additional trials are conducted with vandetanib, corneal slit lamp photographs should be taken to identify the location of the corneal opacities noted. If subjects develop corneal opacities, the opacities should be followed to determine if they spontaneously resolve off vandetanib treatment.

In the absence of additional trial information, recommend that vandetanib be labeled with a statement that corneal opacities have been observed that may cause a decrease in vision and which may or may not be reversible with discontinuation of product.

7.4.6 Immunogenicity

Two cases of “drug hypersensitivity” led to discontinuation of the study drug. After closer review of these two patient cases, it appears they were more in keeping with Grade 4 Stevens Johnson Syndrome (SJS). Interestingly, they both occurred in the same center in two different Chinese patients. Due to the low number of patients involved, it is impossible to draw any conclusions with regards to whether there is an ethnic pre-disposition to developing SJS.

7.5 Other Safety Exploration

7.5.1 Dose Dependency for Adverse Events

There has been considerable attention on dose dependency for adverse events. Vandetanib has a half life of approximately 19 days, and with >50% of patients experiencing grade 3-4 adverse events, it has been postulated that the dose is potentially too high.

Significant exposure-response relationships were identified for diarrhea and fatigue, but not for hypertension or rash.

The probability of diarrhea grade 2 or higher is significantly associated with $C_{ss,\ Day\ 56}$ ($p = 0.025$). Similarly, the probability of fatigue grade 2 or higher is significantly associated with $C_{ss,\ Day\ 56}$ ($p = 0.02$) whereas no significant exposure-response relationships were identified for either hypertension or rash. The shallow slopes of the logistic regression models for diarrhea and fatigue project a minimal decrease in AE incidence for dose reductions at the population level, which is consistent with the relatively low incidence of these AEs in the pivotal trial.

Figure 11: Relationship of Css with Diarrhea and Fatigue

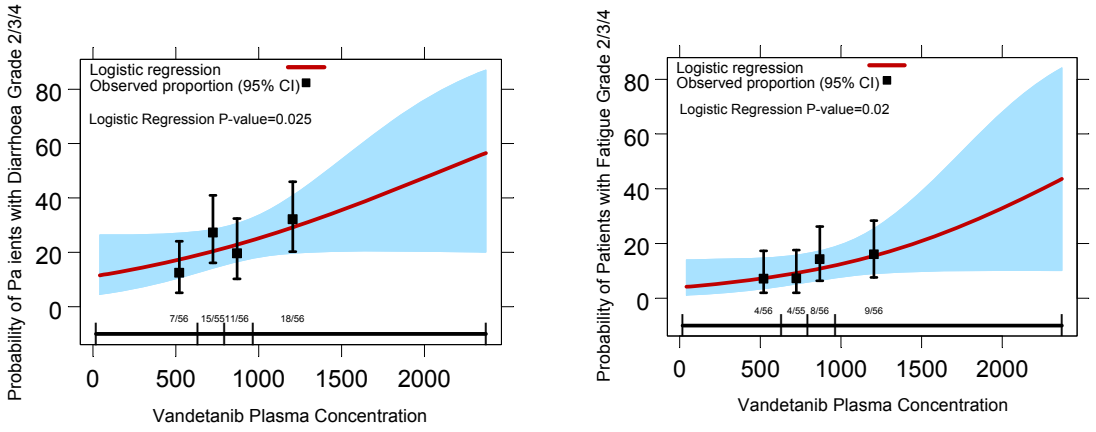
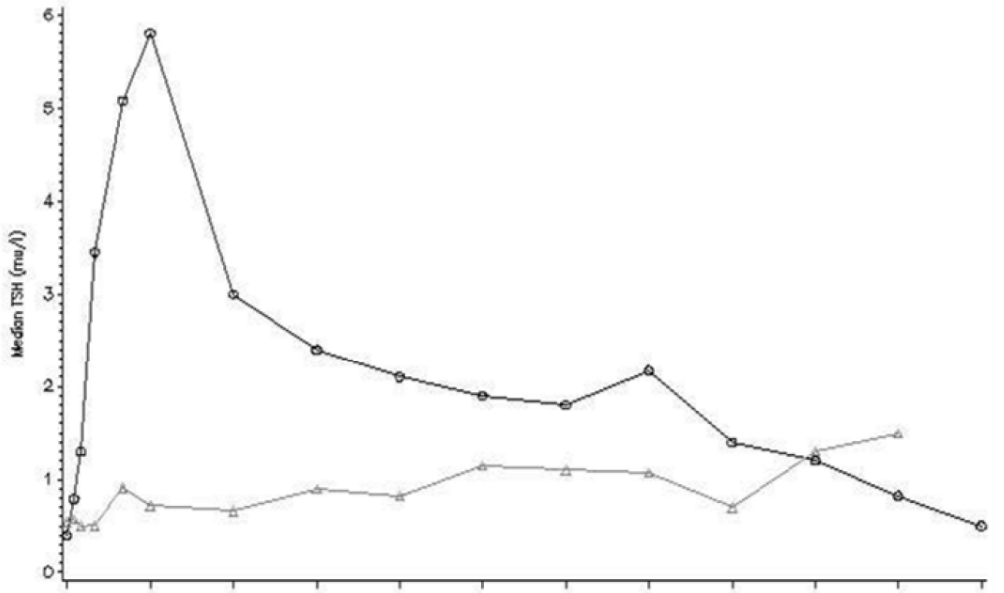


Figure 11. The relationship between $C_{ss,\ Day\ 56}$ and the incidence of grade 2 or higher diarrhea (left) and fatigue (right). Solid black symbols represent the observed proportion of patients experiencing ≥ grade 2 AEs in each quartile of $C_{ss,\ Day56}$. The vertical black bars represent the 95% confidence interval. The solid red line and shaded area represent the predicted mean and 95% confidence interval for the probability of ≥ grade 2 adverse events. The exposure range in each quartile of $C_{ss,\ Day\ 56}$ is denoted by the horizontal black line along with the number of patients with AEs/total number of patients in each quartile.

7.5.2 Time Dependency for Adverse Events

Figure 12: TSH Over Time: (Applicant's Figure)

Figure 12 Clinical chemistry in Study 58 - TSH (mu/L) over time (randomised phase, safety analysis set)



n at weeks	0	12	24	36	48	60	72	84	96	108	120	132
Vandetanib 300mg	230	213	208	183	176	163	138	127	75	41	16	1
Placebo	99	88	70	55	47	40	33	34	18	10	3	0

Css is reached around day 56. Marked accumulation seen on once daily dosing was consistent with a long half-life. In the pivotal study, a total 191 MTC patients were dosed to steady state (Day 56) with 300 mg daily. PK parameters were obtained using population PK modeling. Mean Cmax at steady state was 857 ng/mL (385 - 2241 ng/mL). Cminss on Day 56 was 795 ng/mL and AUCs was 19829 ng-h/mL.

With regards to the toxicity of QTc prolongation, the toxicity is related to concentration and irrespective of time. The risk of torsades or other QT prolonging sequelae does not dissipate over time.

Figure 13: QTcB while on randomized treatment as related to time (Applicant's Figure)

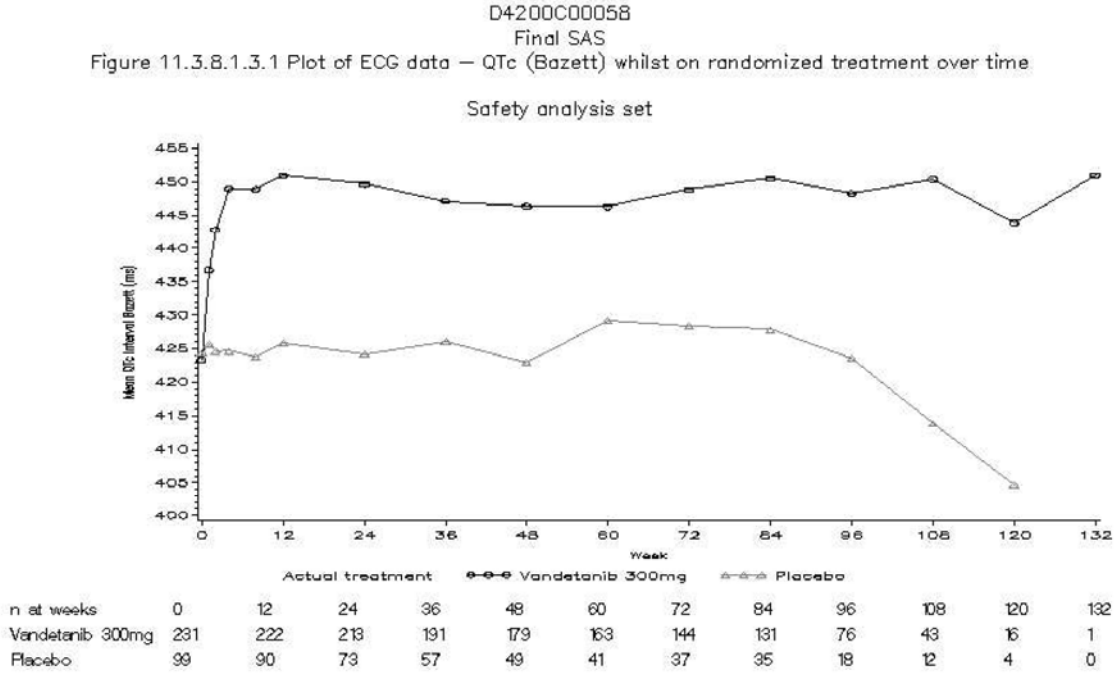
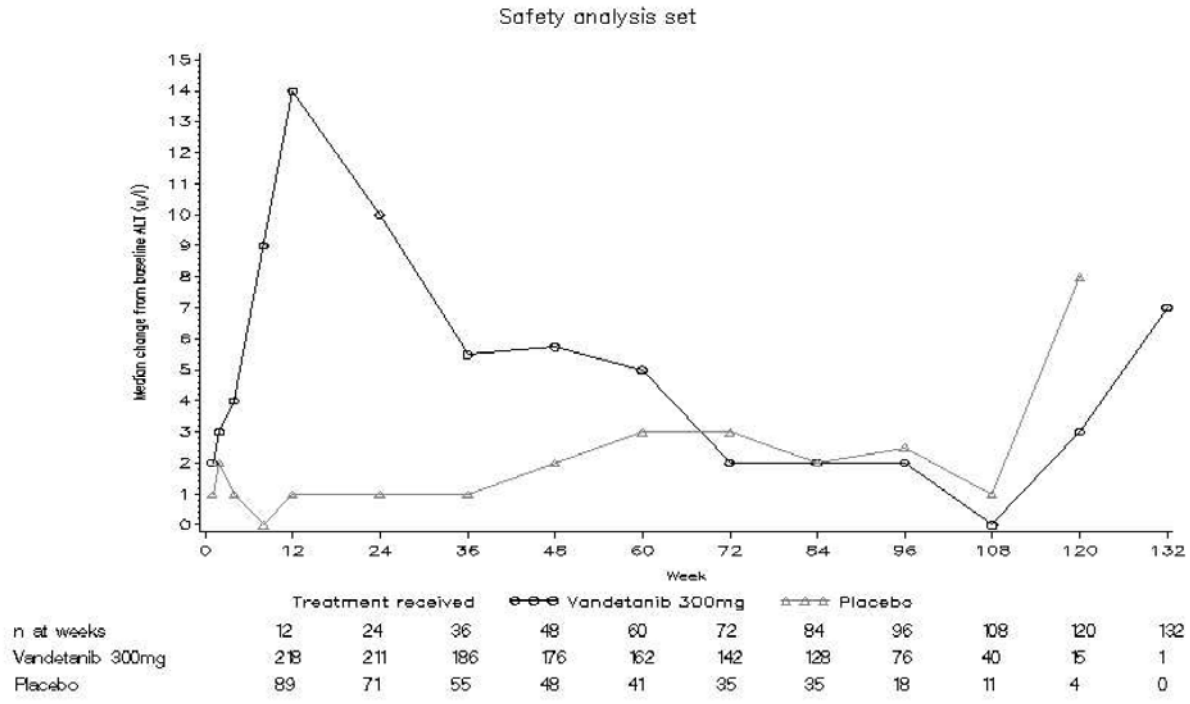


Figure 14: ALT Change from Baseline (Applicant's Figure)



Baseline is defined as the value closest to and preceding the first dose of randomized treatment.

The above graphs depict a similar trend in a sharp upward spike with peak effect occurring around week 12 correlating to vandetanib reaching its steady state concentration.

7.5.3 Drug-Demographic Interactions

Rates of common (>10%) grade 1-4 adverse events were examined by age (<65 years of age vs. >=65 years of age) and race (white vs. non-white) and are presented in the tables below.

Overall, grade 1-4 adverse events were similar in patients <65 years old and ≥65 years old. However, a few adverse events did occur more frequently in older patients (>5% difference). The common grade 1-4 events that occurred more frequently in patients ≥65 years old were: rash (49% in <65 yrs vs. 75% in ≥65 yrs), hypertension (32% in <65 yrs vs. 39% in ≥65 yrs), fatigue (21% in <65 yrs vs. 35% in ≥65 yrs), decreased appetite (18% in <65 yrs vs. 33% in ≥65 yrs), pruritis (9% in <65 yrs vs. 16% in ≥65 yrs), and proteinuria (9% in <65 yrs vs. 14% in ≥65 yrs).

Overall, grade 3-4 adverse event rates were similar between the two age comparison groups.

Table 47: Adverse Events by Age in Study 58

	All Grade Toxicity		Grade 3-4 Toxicity	
	<65yrs N=182	≥65 N=49	<65yrs N=182	≥65 N=49
Diarrhea[1]	103 (56%)	28 (57%)	7 (3%)	1 (2%)
Rash[2]	90 (49%)	37 (75%)	3 (1%)	0
Nausea	63 (35%)	14 (29%)	1 (<1%)	1 (2%)
Hypertension[3]	59 (32%)	19 (39%)	10 (5%)	3 (6%)
Headache	49 (27%)	10 (20%)	0	1 (2%)
Fatigue	38 (21%)	17 (35%)	6 (3%)	1 (2%)
Decreased appetite	33 (18%)	16 (33%)	5 (3%)	3 (6%)
Acne	46 (25%)	0	1 (<1%)	0
Dry Skin	27 (15%)	8 (16%)	0	0
Dermatitis Acneiform	29 (16%)	6 (12%)	0	0
Vomiting	27 (15%)	7 (14%)	1 (<1%)	0
Asthenia	25 (14%)	9 (18%)	0	1 (2%)
Abdominal Pain[4]	50 (27%)	12 (24%)	4	1 (2%)

	All Grade Toxicity		Grade 3-4 Toxicity	
	<65yrs N=182	≥65 N=49	<65yrs N=182	≥65 N=49
QT Prolongation	27 (15%)	6 (12%)	14 (8%)	3 (6%)
Photosensitivity	26 (14%)	5 (10%)	2 (<1%)	0
Insomnia	25 (14%)	5 (10%)	0	0
Nasopharyngitis	22 (12%)	4 (8%)	0	0
Pruritis	17 (9%)	8 (16%)	0	0
Dyspepsia	22 (12%)	3 (6%)	0	0
Cough	18 (10%)	7 (14%)	0	0
Hypocalcemia	21 (12%)	4 (8%)	2 (<1%)	0
Weight decreased	18 (10%)	6 (12%)	1 (<1%)	1 (2%)
Proteinuria	16 (9%)	7 (14%)	0	0
Depression	16 (9%)	6 (12%)	1 (<1%)	0
Erythema	19 (10%)	4 (8%)	0	0
Vision Blurred	16 (9%)	4 (8%)	0	0
Back Pain	16 (9%)	5 (10%)	0	1 (2%)
Epistaxis	15 (8%)	3 (6%)	0	0
Oropharyngeal pain	16 (9%)	3 (6%)	1 (<1%)	0
Dry Mouth	15 (8%)	5 (10%)	0	0
UTI	15 (8%)	2 (4%)	1 (<1%)	0
URI	15 (8%)	4 (8%)	0	0
Dyspnea	14 (8%)	4 (8%)	1 (<1%)	2 (4%)
Dizziness	12 (7%)	8 (8%)	1 (<1%)	0

1. Diarrhea includes diarrhea and hemorrhagic diarrhea.
2. Rash includes the preferred terms rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash popular, rash pruritic, and rash pustular.
3. Hypertension includes hypertension and hypertensive crisis.
4. Abdominal Pain includes abdominal pain upper, lower, and discomfort.

The table below provides information on common adverse events by age in patients receiving vandetanib 300 mg monotherapy. Unlike Study 58, rash and hypertension, were not more common in the older group while acne was more common among those less than 65 years.

Table 48: Adverse Events by Age in the ISS database

	Vandetanib 300 mg N = 1839	
	< 65 years N = 1227	≥ 65 years N = 623

Gastrointestinal Disorders		
Diarrhea/Colitis	50.5%	54.4%
Nausea	29.2%	24.4%
Vomiting	16.9%	12.0%
Abdominal Pain[1]	14.2%	11.7%
Constipation	12.0%	14.1%
General Disorders		
Fatigue	21.6%	25.2%
Asthenia[2]	10.9%	14.0%
Metabolism and Nutrition Disorders		
Anorexia/Decreased Appetite	23.0%	25.2%
Nervous System Disorders		
Headache/Migraine	14.3%	10.4%
Psychiatric Disorders		
Insomnia/Sleep Disorder	13.4%	9.8%
Respiratory Disorders		
Cough/Productive Cough	17.1%	16.9%
Dyspnea/Exacerbated/Exertional	16.4%	18.5%
Skin Disorders		
Rash[3]	35.5%	34.7%
Acne/Dermatitis Acneiform	20.0%	12.5%
Dry Skin	10.8%	9.8%
Vascular Disorders		
Hypertension[4]	22.9%	21.8%

[1]Includes abdominal discomfort, abdominal pain lower, abdominal pain upper
[2]Includes general physical health deterioration, performance status decreased
[3]Includes exfoliative, erythematous, follicular, generalized, macular, maculo-papular, papular, papulosquamous, photosensitive, pruritic, and scaly rash
[4]Includes accelerated hypertension, hypertensive crisis

The table below points out several differences in the incidence of common adverse events between male and female patients in the vandetanib 300 mg monotherapy program. It is unclear if these differences represent an interaction with vandetanib or fluctuations in the reporting of adverse events.

Table 49: Adverse Events by Sex in the ISS Database

	Vandetanib 300 mg	
	Male N = 1007	Female N = 843
Gastrointestinal Disorders		
Diarrhea/Colitis	47.4%	57.2%
Nausea	21.2%	32.7%
Vomiting	10.6%	19.4%

Abdominal Pain[1]	11.8%	15.2%
Constipation	13.0%	12.3%
General Disorders		
Fatigue	22.5%	23.2%
Asthenia[2]	12.2%	11.6%
Metabolism and Nutrition Disorders		
Anorexia/Decreased Appetite	24.4%	22.9%
Nervous System Disorders		
Headache/Migraine	8.8%	17.9%
Psychiatric Disorders		
Insomnia/Sleep Disorder	11.5%	13.0%
Respiratory Disorders		
Cough/Productive Cough	15.5%	18.9%
Dyspnea/Exacerbated/Exertional	18.2%	15.8%
Skin Disorders		
Rash[3]	31.1%	44.4%
Acne/Dermatitis Acneiform	18.9%	15.8%
Dry Skin	8.8%	12.3%
Vascular Disorders		
Hypertension[4]	19.4%	26.3%

[1]Includes abdominal discomfort, abdominal pain lower, abdominal pain upper
[2]Includes general physical health deterioration, performance status decreased
[3]Includes exfoliative, erythematous, follicular, generalized, macular, maculo-papular, papular, papulosquamous, photosensitive, pruritic, and scaly rash
[4]Includes accelerated hypertension, hypertensive crisis

Although 1,839 patients received vandetanib 300 mg, an insufficient number of patients categorized racially as Black or Other were accrued to the various trials to make conclusions about interactions between vandetanib and these racial groups possible. A sufficient number of Asian patients are available to allow a meaningful analysis. However, it is unclear whether differences between Whites and Asians represent a drug interaction or a fluctuation in AE reporting.

Table 50: Adverse Events by Race in the ISS Database

	Vandetanib 300 mg			
	White N = 1185	Black N = 27	Asian N = 590	Other N = 47
Gastrointestinal Disorders				
Diarrhea/Colitis	54.5%	29.6%	47.1%	57.4%
Nausea	30.6%	25.9%	18.0%	23.4%
Vomiting	15.1%	3	12.7%	10.6%
Abdominal Pain[1]	14.6%	25.9%	8.6%	17.0%
Constipation	12.2%	11.1%	13.4%	2.1%

General Disorders				
Fatigue	27.2%	33.3%	13.0%	34.0%
Asthenia[2]	14.0%	14.8%	7.6%	12.8%
Metabolism and Nutrition Disorders				
Anorexia/Decreased Appetite	23.7%	44.4%	23.2%	19.1%
Nervous System Disorders				
Headache/Migraine	14.9%	18.5%	9.2%	10.6%
Psychiatric Disorders				
Insomnia/Sleep Disorder	11.6%	7.4%	13.8%	12.8%
Respiratory Disorders				
Cough/Productive Cough	17.3%	18.5%	16.3%	21.3%
Dyspnea/Exacerbated/Exertional	19.9%	18.5%5	10.5%	27.7%
Skin Disorders				
Rash[3]	40.5%	29.6%	52.2%	44.7%
Acne/Dermatitis Acneiform	19.5%	14.8%	13.6%	8.5%
Dry Skin	11.1%	25.9%	8.5%	10.6%
Vascular Disorders				
Hypertension[4]	19.7%	25.9%	28.5%	19.1%

[1]Includes abdominal discomfort, abdominal pain lower, abdominal pain upper
[2]Includes general physical health deterioration, performance status decreased
[3]Includes exfoliative, erythematous, follicular, generalized, macular, maculo-papular, papular, papulosquamous, photosensitive, pruritic, and scaly rash
[4]Includes accelerated hypertension, hypertensive crisis

7.5.4 Drug-Disease Interactions

There appears to be a higher percentage of pulmonary toxicity in the ISS database as compared to the Phase 3 MTC study. This finding is most likely due to the majority of patients being treated for non-small cell lung cancer, and is either due to the underlying disease state, or due to the previous treatment regimens given to this cancer population.

Study 58 allowed patients with a CrCl of >30 to be treated with vandetanib. With this lower threshold for creatinine clearance in place, an evaluation of toxicity and creatinine clearance was performed. The two values that clinical pharmacology cited as having a dependency on renal function, fatigue and diarrhea were examined, as well as QT prolongation.

Table 51: Adverse Events as related to Creatinine Clearance

	CrCl <90 N=94	CrCl >90 N=130

	All Grades	Grades 3-4	All Grades	Grades 3-4
Fatigue	39 (41%)	8 (9%)	29 (22%)	5 (4%)
Diarrhea	83 (88%)	14 (15%)	115 (88%)	19 (15%)
QT Prolongation	26 (28%)	15 (16%)	21 (16%)	10 (8%)

Given the limitations of this small sub-set analysis, no conclusions can be made with regards as to whether lower creatinine clearance negatively impacts toxicity.

7.5.5 Drug-Drug Interactions

Although no *in vivo* drug-drug interaction studies were conducted, *in* vitro data suggests that drug-drug interactions can occur. See section 2.4.2.2 of the clinical pharmacology review.

In Study 32, a Phase 3, randomized, double blinded, multi-center study to assess the safety and efficacy of docetaxel in combination with vandetanib versus docetaxel plus placebo in patients with advanced NSCLC after failure of first line therapy, ILD was reported more frequently in patients treated with 100mg vandetanib + docetaxel (2.5%) than with docetaxel alone (0.9). Interestingly, that study also reported ILD more frequently in Japanese patients (16.7% in docetaxel +vandetanib group vs. 7.4% docetaxel alone) than in patients from outside Japan (0.8% vandetanib/0.2% docetaxel alone). The other Phase 3 studies in NSCLC have reported incidences of ILD of less than 1% with vandetanib, however these studies did not include patients from Japan. The sponsor postulates as to whether the ILD frequency seen in Study 32 could have been the effect of the drug on a Japanese population. The overall incidence of ILD in the 300 mg monotherapy pool was 0.2%.

Table 52: Study 32 Incidence of ILD/ Pneumonitis

	Vandetanib+ docetaxel Grade 1-4 N=694	Vandetanib + docetaxel Grade 3-4 N=694	Docetaxel + Placebo Grade 1-4 N=697	Docetaxel + Placebo Grade 3-4 N=697
ILD	17 (2.4%)	4 (0.6%)	6 (0.8%)	3 (0.4%)
Pneumonitis	7 (1%)	2 (0.2%)	8 (1%)	4 (0.5%)
Dyspnea	113 (16.3%)	29 (4.0%)	137 (20%)	35 (5%)
Respiratory Failure	5 (0.7%)	5 (0.7%)	7 (1%)	7 (1%)
Hypoxia	10 (1.4%)	3 (0.4%)	5 (0.7%)	2 (0.2%)

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No vandetanib-treated patients developed acute myeloid leukemia or myelodysplastic syndrome. There was one patient who developed a germ-cell tumor while on treatment. Two patients treated in Study 68 at the 100mg dose developed pheochromocytoma. Pheochromocytoma is associated with medullary thyroid cancer as part of the MEN II syndrome.

Given that medullary thyroid cancer patients can have relatively long survival times (up to 40% of patients with 10 years survival according to the SEER database), the pharmacology toxicology reviewers will require a carcinogenicity animal study as a post-marketing requirement.

See pharmacology-toxicology review for further details.

7.6.2 Human Reproduction and Pregnancy Data

Vandetanib is a Pregnancy Category D drug. The following information is from the submitted label pending approval:

(b) (4)

7.6.3 Pediatrics and Assessment of Effects on Growth

Vandetanib has not been studied in a pediatric population. A pediatric waiver was granted by the Pediatric Review Committee based on vandetanib's orphan drug status.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Symptoms of overdose have not been established with vandetanib and there is no specific treatment in the event of an over dosage. In Phase 1 trials of vandetanib, a small number of patients were treated at doses higher then 300mg, including daily doses up to 600mg in patients, and 1200mg in healthy volunteers and in patients. The applicant suggests in their unapproved label to consider the possibility of QTc prolongation and torsade de pointes. Adverse reactions associated with overdose should be treated symptomatically. In the event of an overdose, the sponsor recommends interrupting further doses and monitoring closely for evidence that an adverse reaction has occurred, e.g. ECG within 24 hours to determine QTc prolongation, anti-diarrheal treatment, monitoring for skin toxicity. Given the long half-life of the drug of approximately 19 days, this would not be adequate. The FDA proposes ECG monitoring for an extended time interval to account for the long half-life. After further consultation with cardio-renal and clinical pharmacology, it does not appear that dialysis would be a possibility in removing the highly protein bound drug. The rationale provided by Astra-Zeneca is as follows: "It is AstraZeneca's belief that dialysis would not be an effective or rapid means of removing vandetanib from patients' circulation. Based on the pharmacokinetic properties of vandetanib (protein binding of 90% and volume of distribution of 7450L) and estimating the fraction of drug that could be dialyzed using the method evaluated by Tang and Mayersohn 2004, we estimate that approximately 0.05% of the drug would be removed in a 6-hour dialysis session."

Substituting into the formula 1/Fr = 1.3Vu + 2.14, where Vu is (7450L/50 kg)/0.10 and simplifying Fr = 0.05%.

"When using this formula for drugs that are reliably removed by hemodialysis a value for Fr is typically > 30%. Based on the value obtained from this predictive formula, we conclude that there is no additional benefit to experimentally determining (either non-clinically or clinically) whether vandetanib clearance can be increased from the circulation by hemodialysis. Other methods of removal of drug from the circulation, such as hemoperfusion, would also be predicted to be ineffective."

Drug abuse potential, withdrawal, and rebound are not relevant to this application.

7.7 Additional Submissions / Safety Issues

None

8 Postmarket Experience

As this application is for a new molecular entity with no prior approval history, there is no postmarket experience.

9 Appendices

9.1 Literature Review/References

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9.2 Labeling Recommendations

See the final version of the label revised by all of the FDA scientific disciplines.

9.3 Advisory Committee Meeting

Medullary thyroid cancer, even in the metastatic setting, has a relatively long survival time. Due to the toxicity profile of vandetanib, the application was presented at the December 2, 2010 Oncologic Drug Advisory Committee. The members of the committee were asked to discuss whether the indication should be limited to patients with progressive, symptomatic medullary thyroid cancer and to comment on whether there are any other subgroups that may be appropriate for treatment with vandetanib in light of the risk-benefit profile. All of the committee members agreed that treatment with vandetanib is not indicated in patients with low burden or asymptomatic disease. The majority of the committee members agreed with modifying the indication to include only patients with progressive, symptomatic MTC.

The committee was also asked to vote on the following question: If there is a population in which the risk-benefit profile is acceptable, should additional doses of vandetanib be evaluated as a post-marketing requirement to determine the optimal dose? If yes, please discuss potential study designs.

The committee voted 10 to 0 in favor of additional studies to explore alternative doses and dose scheduling. There was no consensus on any particular trial design.

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/s/

KATHERINE A DELORENZO
12/09/2010

VIRGINIA E MAHER
12/09/2010

GEOFFREY S KIM
12/09/2010

Medical Officer's Review of NDA 22-405
Request for Ophthalmology Consultation from
Division of Anti-Infective and Ophthalmology Products (DAIOP)

NDA 22-405

Submission Date: August 13, 2010
Consultation Date: August 20, 2010
Review Date: November 18, 2010

Applicant: AstraZeneca Pharmaceuticals LP
1800 Concord Pike
PO Box 8355
Wilmington DE 19803-8355

Drug: vandetanib tablets

Proposed Indication: treatment of patients with unresectable locally advanced or metastatic medullary thyroid cancer

Consultation Comments/Special Instructions:

There is an Astra-Zeneca ophthalmologist report that can be found by going to Amendment 7 submitted 8/13/2010.

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

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

Submitted:

Submitted is a Clinical Study Report Addendum to Appendix 12.2.10 of Study D4200C00058. This document contains the final ophthalmology consultant report and the consultant's Curriculum Vitae; the report was inadvertently not included in Appendix 12.2.10 of the D4200C00058 Clinical Study Report which was submitted as part of NDA 22-405.

Ophthalmology exams were added to the Study D4200C00058 protocol with the approval of Amendment 2 on 30 May 2007. Ophthalmologic examinations were included as part of the study examinations to determine whether vandetanib increases the likelihood of patients developing

corneal opacities or other eye abnormalities. These examinations were added to the Study 58 protocol after 4 patients who received vandetanib 300 mg in Study D4200C00008 reported visual changes and had abnormalities noted on ophthalmologic examination. Because patients had begun enrolling in Study 58 for more than 6 months before the requirement to undergo eye examinations, only a limited number of randomized patients had an ophthalmologic examination performed at screening, and 211 (63.7%) of randomized patients underwent an examination during randomized treatment.

AstraZeneca consulted an external ophthalmologist from the University of Pennsylvania, Dr Alan Laties, to review the findings from the reports of all the ophthalmology exams that were performed during the study. Dr Laties also was able to review any clinically relevant patient data that could be related to the health and function of the eye.

BACKGROUND FROM CSR

Study d4200c00058 was an international, Phase 3, randomized, double-blinded, placebo-controlled, multi-center study to assess the efficacy of ZD6474 (vandetanib) versus placebo in subjects with unresectable locally advanced or metastatic medullary thyroid cancer.

Per the clinical study report for D4200C00058:

Vandetanib (ZD6474) is a receptor TKI that, in isolated enzyme assays, potently inhibits vascular endothelial growth factor receptor-2 (VEGFR-2) tyrosine kinase activity (concentration that provides 50% inhibition [IC50] = 40 nM), and shows additional inhibitory activity at sub-micromolar concentrations against RET receptor tyrosine kinase (inhibitory concentration [IC50] = 100 nM), Flt-4 [VEGF] receptor-3: IC50 = 110 nM), and epidermal growth factor receptor (EGF) (IC50 = 500 nM) tyrosine kinases.

The hypothesis was that orally administered vandetanib would inhibit growth and function of MTC cells. A decrease or delay in tumor growth leading to increased progression-free survival (PFS) would serve as a direct marker of therapeutic efficacy.

In the blinded study treatment phase of the trial, 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, color vision, and visual field examinations. The results of the eye examination were to be sent to AstraZeneca.

In the post-progression open label vandetanib treatment phase of the trial, 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, color vision, and visual field examinations. The eye examination was to be sent to AstraZeneca.

From Section 8.5.3, a summary of patients with abnormalities from visual assessment while patients were receiving randomized therapy is shown in Table 55.

Table 55 Summary of patients with abnormalities from visual assessment whilst on randomised treatment (Safety analysis set)

	Abnormality in Right Eye Only _Number(%) of patients_		Abnormality in Left Eye Only _Number(%) of patients_		Abnormality in Right and/or Left Eye _Number(%) of patients_		
Test	Vandetanib 300mg (N=159)	Placebo (N= 52)	Vandetanib 300mg (N=159)	Placebo (N= 52)	Vandetanib 300mg (N=159)	Placebo (N= 52)	Total (N=211)
Total	18 (11.3)	4 (7.7)	28 (17.6)	8 (15.4)	133 (83.6)	32 (61.5)	165 (78.2)
Amsler Grid	1 (0.6)	0 (0.0)	1 (0.6)	1 (1.9)	4 (2.5)	1 (1.9)	5 (2.4)
Anterior Chamber	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.9)	1 (1.9)	4 (1.9)
Blood Vessels	0 (0.0)	0 (0.0)	1 (0.6)	1 (1.9)	11 (6.9)	6 (11.5)	17 (8.1)
Colour Vision	1 (0.6)	1 (1.9)	1 (0.6)	0 (0.0)	12 (7.5)	9 (17.3)	21 (10.0)
Conjunctiva	1 (0.6)	0 (0.0)	3 (1.9)	0 (0.0)	12 (7.5)	2 (3.8)	14 (6.6)
Endothelium	2 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	6 (3.8)	1 (1.9)	7 (3.3)
Epithelium	3 (1.9)	0 (0.0)	1 (0.6)	0 (0.0)	79 (49.7)	2 (3.8)	81 (38.4)
Intraocular Pressure	1 (0.6)	0 (0.0)	5 (3.1)	1 (1.9)	10 (6.3)	3 (5.8)	13 (6.2)
Macula	1 (0.6)	0 (0.0)	4 (2.5)	3 (5.8)	10 (6.3)	3 (5.8)	13 (6.2)
Optic Disc	0 (0.0)	1 (1.9)	6 (3.8)	1 (1.9)	19 (11.9)	3 (5.8)	22 (10.4)
Periphery	4 (2.5)	2 (3.8)	3 (1.9)	1 (1.9)	13 (8.2)	3 (5.8)	16 (7.6)
Pupillary Reactions	1 (0.6)	0 (0.0)	3 (1.9)	0 (0.0)	6 (3.8)	1 (1.9)	7 (3.3)
Stroma	1 (0.6)	1 (1.9)	1 (0.6)	1 (1.9)	28 (17.6)	2 (3.8)	30 (14.2)
Visual Acuity	0 (0.0)	0 (0.0)	2 (1.3)	0 (0.0)	3 (1.9)	0 (0.0)	3 (1.4)
Visual Cylinder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.5)
Visual Fields to Confrontation	2 (1.3)	0 (0.0)	7 (4.4)	1 (1.9)	15 (9.4)	4 (7.7)	19 (9.0)
Visual Sphere	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.9)	0 (0.0)	3 (1.4)
Other Slit Lamp Abnormality					37 (23.3)	14 (26.9)	51 (24.2)

Derived from Table 11.3.8.1.17.
A patient can have one or more abnormality reported under a given test.
Only patients with one or more eye examinations between the first dose of randomised treatment and the earlier of (a) 60 days after last dose of randomised treatment or (b) first dose of open label treatment are included.

The most notable difference between treatment arms was in abnormalities of the corneal epithelium, which were observed in 79 (49.7%) patients in the vandetanib arm compared with 2 (3.8%) patients in the placebo arm. Patients in the vandetanib arm also had a higher frequency of corneal stromal abnormalities (17.6% vs 3.8%) and abnormalities of the conjunctiva (7.5% vs

3.8%). Patients in the vandetanib arm had a lower frequency of abnormalities of blood vessels (6.9% vs 11.5%) and color vision (7.5% vs 17.3%) relative to patients in the placebo arm.

Blinded review of the reports from the ophthalmology examinations was performed by a consultant ophthalmologist (Alan M. Laties, MD, University of Pennsylvania, Philadelphia). This review revealed that 49 of 159 (30.8%) patients in the vandetanib arm who underwent ophthalmologic examinations had vortex keratopathy, compared with no patients in the placebo arm. In addition, another 9 patients in the vandetanib arm could possibly have the same condition and currently remain undiagnosed. The consultant considered the events of vortex keratopathy to be related to vandetanib treatment.

Vortex keratopathy is typically innocuous and rarely requires discontinuation of drug therapy.

The consultant ophthalmologist concluded that the association of study drug to the occurrence of vortex keratopathy can be classified as certain by World Health Organization criteria. The consultant ophthalmologist indicated that there is no need to stop dosing even in instances where vortex keratopathy develops.

BACKGROUND FROM CONSULTANT'S REPORT
Per the ophthalmologist's final consultative report:

In the ongoing clinical trial, 49 out of 331 subjects were diagnosed with vortex keratopathy. In addition, another 9 could possibly have developed the same condition and currently remain undiagnosed. Every diagnosed subject was on study drug.

Vortex keratopathy, also called cornea verticillata, is recognized at slit lamp examination of the eye by the appearance of fine, grayish or brown linear opacities in the epithelial layer of the cornea. The linear opacities typically branch repeatedly to form a distinctive whorl-like pattern. Although the opacities often are asymptomatic, subjects can have one or more of the following complaints: hazy vision, photophobia, haloes around lights or sometimes glare. Most often the finding of vortex keratopathy is innocuous; it rarely if any calls for cessation of drug therapy. Once drug therapy is ended, regression usually follows.

As well as can be told from present information, no serious corneal adverse event has yet been associated with study drug. For this reason there is no need to stop dosing even in instances where vortex keratopathy develops. However, it would be useful to document, a dose-duration relationship to define the threshold dose and duration needed for the development of vortex keratopathy. At present, even with partial analysis possible, it appears that at least three months of dosing is required for its first appearance.

Reviewer's Comments:
Per the CSR, ophthalmic examinations consisted of at least a slit lamp examination, color vision, and visual field. Visual fields were apparently assessed by confrontation. The method of color vision assessment is not specified and cannot be determined from the case report forms provided. There is no additional level of description of the ophthalmologic examinations in protocol Amendment 2 which added the exams.

A review of the submitted case report forms for subjects reveals slit lamp exam descriptions consistent with the common presentation of vortex keratopathy (cornea verticillata). However,

Table 11.3.8.2 includes listings of abnormalities which include stromal opacities, edema, and whirls. There are no photographs of the corneal changes located in the NDA submission.

The outside ophthalmologic consultant for this clinical study, Alan Laties, M.D., is qualified by training and experience.

QUESTIONS

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

1) Please comment on the nature of vortex keratopathy; specifically, the natural history and need for treatment of this condition.

Reviewer's Comments:

The term vortex keratopathy refers to cornea verticillata – a form of corneal deposit which occurs in the basal corneal epithelium, usually inferiorly. Deposits form a faint golden-brown whorl pattern evident in both corneas.

The differential diagnosis for deposits with a bilateral golden-brown whorl pattern include Fabry disease, use of amiodarone, chloroquine and hydroxychloroquine, indomethacin, and phenothiazines. Most studies suggest that all or nearly all patients taking amiodarone will develop verticillata. When depositing drugs are stopped for other reasons, most verticillata will eventually fade away. There is no data currently available to suggest either protective or inducing factors in patients who develop verticillata from medication use.

The potential for these verticillata to fade with discontinuation of drug is unknown because the trial did not evaluate this aspect of the adverse event. If these deposits are located in the basal corneal epithelium, it is likely the corneal deposits would behave similar to other medication-related deposits which fade several months after discontinuation of product. There is not enough information provided from this clinical study report to determine if the corneal changes from vandetanib represent classic vortex keratopathy (cornea verticillata) or if there is some additional corneal stromal abnormality. The clinical study report provides conflicting descriptions of the corneal abnormalities noted.

The majority of subjects with vortex keratopathy are asymptomatic. Some subjects are symptomatic and report halos or other visual disturbances.

There is no treatment for drug-related cornea verticillata except discontinuation of causative medication.

2) Please comment on the consultant ophthalmologist's conclusion that there is no need to stop or adjust dosing in instances where vortex keratopathy develops.

Reviewer's Comments:

If patients are asymptomatic, there is no need to stop or adjust dosing. If a patent is symptomatic, the utility of the study drug would have to be weighed against the level of visual disturbance experienced. See Summary Statement this review.

Although ophthalmologic examinations were added to this protocol after corneal opacities were noted in Study D4200C00008, the level of detail and specificity regarding the collection of ocular data is scant. No photographs were taken. It appears most investigators did perform visual acuity and posterior segment evaluations as part of their examinations although these were not specified in the protocol. Without adequate protocol instructions to the investigator, it is unclear that the ophthalmic examinations were performed uniformly. It is also unclear who performed the examinations; these examinations should have been performed by individuals with adequate training.

3) Please comment on the clinical significance of the other abnormalities that were increased in the treatment arm compared to placebo as derived from Table 11.3.8.1.17. Specifically:
    a. Stromal abnormalities (17.6% v. 2%)
    b. Optic disc abnormalities (19% v. 3%)

Reviewer's Comments:

The description of the ophthalmic evaluations in this trial makes it very difficult to determine clinical significance of the stromal abnormalities and optic disc abnormities noted. See response to Question #2 above.

The term "stromal abnormalities" is vague. Table 11.3.8.2 in the Safety Analysis includes stromal haze, stromal whirls/opacities, and stromal edema. Despite the notation of stromal edema, there is no measurement of corneal thickness recorded to evaluate the stromal edema.

The term "optic disc abnormalities" is vague. A review of the adverse event listing by subject (Appendix 12.2.7) mentions optic nerve sheath hemorrhage. Such hemorrhages are usually related to hypertension. Table 11.3.8.2 in the Safety Analysis mentions optic disc cupping.

4) Astra Zeneca's ophthalmology report states that "VK rarely, if ever, needs treatment stopped." What would be the conditions in which treatment should be stopped. The report also went on to say that once stopping therapy, "regression usually follows." If regression does not follow, what is the sequelae, and does the impairment continue to progress?

Reviewer's Comments:

If patients are asymptomatic, there is no need to stop or adjust dosing. The deposits are likely to increase with time with continued dosing. If a patent is symptomatic, the utility of the study drug would have to be weighed against the level of visual disturbance experienced.

Summary Statement/ Recommended Action:

A review of the submitted case report forms for subjects reveals slit lamp exam descriptions consistent with the common presentation of vortex keratopathy (cornea verticillata). However, Table 11.3.8.2 includes listings of abnormalities which include stromal opacities, edema, and whirls. There are no photographs of the corneal changes located in the NDA submission. There are no photographs of the corneal changes located in the NDA submission.

There is not enough information provided from this clinical study report to determine if the corneal changes from vandetanib represent classic vortex keratopathy (cornea verticillata) or if there is some additional corneal stromal abnormality. The clinical study report provides conflicting descriptions of the corneal abnormalities noted.

Recommend that if any additional trials are conducted with vandetanib, corneal slit lamp photographs should be taken to identify the location of the corneal opacities noted. If subjects develop corneal opacities, the opacities should be followed to determine if they spontaneously resolve off vandetanib treatment.

In the absence of additional trial information, recommend that vandetanib be labeled with a statement that corneal opacities have been observed that may cause a decrease in vision and which may or may not be reversible with discontinuation of product.

William. Boyd, M.D.
Clinical Team Leader
Division of Anti-Infective and Ophthalmology Products

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

/s/

WILLIAM M BOYD
11/30/2010

WILEY A CHAMBERS
11/30/2010

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: N022405 **Applicant: Astra-Zeneca** **Stamp Date: 7-7-2010**

Drug Name: Vandetanib **NDA/BLA Type: NME**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: D4200C00068 Sample Size: 19 Arms: Vandetanib 100 mg qd Location in submission: 5.3.5.2	X			
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1-D4200C00058 Indication: Medullary Carcinoma of the Thyroid	X			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #2-Supportive Studies D4200C00008-hereditary D4200C00068-dose exploration Indication: Medullary Carcinoma of the Thyroid				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		X		
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?		X		e-narratives were submitted per prior agreement

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			X	Orphan Drug
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		X		
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			CRFs contain AEs that occurred beyond the cutoff date while datasets contain AEs up to the cutoff date.
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? _____yes___

If the Application is not fileable from the clinical 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.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Reviewing Medical Officer	Date
Reviewing Medical Officer	Date
Clinical Team Leader	Date

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

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

/s/

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08/27/2010

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