CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	November 30, 2010
From	V. Ellen Maher, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 22405/S000
Applicant	Astra-Zeneca Pharmaceuticals, LP
Date of Submission	July 7, 2010
PDUFA Goal Date	January 7, 2011
Proprietary Name / Established (USAN) names	(b) (4) /vandetanib
Dosage forms / Strength	100 mg, 300 mg tablets
Proposed Indication(s)	Treatment of patients with symptomatic, rapidly progressive, unresectable locally advanced or metastatic medullary thyroid cancer
Recommended:	*Approval*

1. Introduction

iPR Pharmaceuticals and AstraZeneca have submitted a new drug application for the use of vandetanib in patients with unresectable locally advanced or metastatic medullary thyroid cancer. This application is supported by a randomized Phase 3 study and 2 single arm Phase 2 studies in patients with medullary thyroid cancer as well as an extensive safety database.

2. Background

Medullary thyroid carcinoma is a rare malignancy of the parafollicular C-cells of the thyroid. It occurs in both sporadic and hereditary forms. The sporadic form comprises 57.3%-75% of all medullary thyroid carcinomas (Clin Endocrinol 1998 48:265, Cancer Res 1996 56:2167). The hereditary form may occur as a component of multiple endocrine neoplasia type 2A or 2B or as familial medullary thyroid carcinoma (no associated cancers). Both hereditary and sporadic disease are associated with an activating mutation in the RET proto-oncogene. RET mutations occur in most hereditary forms and in the tumors of 50-80% of patients with the sporadic form of the disease (Cancer Res 1996 56:2167, Clin Cancer Res 2009 15:7119).

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. In patients with distant metastases, 10-year survival is approximately 40% (Cancer 2006 107:2134). Metastases may occur to the cervical lymph nodes, liver, lung and bone. Further, diarrhea and flushing have been associated with elevation in calcitonin (produced by C-cells).

Vandetanib is a multi-tyrosine kinase inhibitor and its ability to inhibit various growth factor receptors and the RET oncogene is shown in Table 1. Vandetanib is a potent inhibitor of VEGFR2. As a VEGFR2 inhibitor, it is comparable to pazopanib which has an IC_{50} of 0.03 μM for VEGFR2 and 0.010 μM for VEGFR1 (FDA Pharmacology Review of pazopanib at

www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022465s000_PharmR.pdf) It is able to inhibit EGFR with an IC_{50} of 0.5 µM. This compares to an IC_{50} of 0.0006 µM for erlotinib (FDA Pharmacology Review of erlotinib at www.accessdata.fda.gov/drugsatfda_docs/nda/2004/21-743_Tarceva_PharmR.pdf). The concentration of vandetanib needed for inhibition of these receptor kinases in patients remain unknown. However, in medullary thyroid cancer, vandetanib is able to work through RET, EGFR, and VEGFR2. EGFR is present on the cell surface of 13% of medullary thyroid cancers while VEGFR2 has been found on vessels associated with medullary thyroid cancers (Endocrine-Related Cancer 2010 17:7). Thus, vandetanib may be able to act as a multi-kinase inhibitor in this disease.

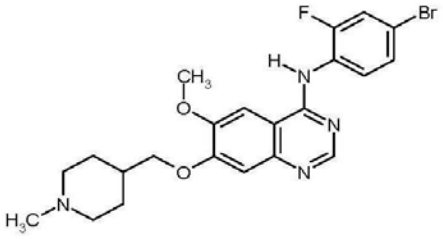
Table 1: In Vitro Inhibition by Vandetanib	
	In Vitro IC_{50}
VEGFR2	0.04 µM
RET	0.1 µM
EGFR	0.5 µM
VEGFR1	1.6 µM

Regulatory History

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 Phase 3 study in this submission. A non-agreement letter was sent, but the FDA did agree that progression free survival (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. The Safety Update was submitted with a data cutoff of June 1, 2010.

3. CMC/Device

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 structure of vandetanib is shown in the figure below.



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. The amount of the 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. Nonclinical 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.

5. Clinical Pharmacology/Biopharmaceutics

Vandetanib is administered orally with a T_{max} of 6 hours (range; 4-10). Absorption is not affected by food. Vandetanib is metabolized by CYP3A4 and concomitant use of strong CYP3A4 inducers should be avoided. It is 94% protein bound in the blood and has a terminal half-life of 19 days. In patients receiving daily vandetanib, steady state is achieved at Day 56. Vandetanib is excreted in the urine (~25%) and feces (~44%). Dose reduction to 200 mg vandetanib daily is recommended in patients with moderate to severe renal impairment. Vandetanib has not been studied in patients with moderate to severe hepatic impairment. However, in a single dose study in subjects with hepatic impairment, no difference was seen in vandetanib pharmacokinetics. The pharmacokinetics of vandetanib do 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 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.

6. Clinical Microbiology

Vandetanib is an oral tablet and is not sterile. Please see CMC review.

7. Clinical/Statistical- Efficacy

The applicant has included the following studies in this submission.

1. **Study 1:** An International, Phase III, Randomized, Double-Blinded, Placebo-Controlled, Multi-Center Study to Assess the Efficacy of ZD6474 versus Placebo in Subjects with Unresectable Locally Advanced or Metastatic Medullary Thyroid Cancer, N = 331
2. **Study 2:** 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, N = 30
3. **Study 3:** A Phase II, Open-Label Study To Assess the Efficacy and Tolerability of ZD6474 (ZACTIMA™) 100 mg Monotherapy In Subjects with Locally Advanced or Metastatic Hereditary Medullary Thyroid Cancer, N = 19

Study Design-Study 1

Eligibility

This study randomized 331 patients with unresectable locally advanced or metastatic medullary thyroid cancer in a roughly 2:1 ratio to vandetanib or placebo. Measurable disease was required and the population included both patients with hereditary medullary thyroid cancer and those with the sporadic form of the disease. There were no requirements concerning prior treatment or the pace of the disease. Only patients with sporadic disease were required to submit archived or fresh tumor samples. These were assessed for the presence of the RET mutation. Patients with hereditary disease were not required to submit tumor samples.

Treatment

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.

Safety Monitoring

EKGs and electrolytes were assessed at weeks 1, 2, 4, and 8 and then every 12 weeks. Blood samples for calcitonin, CEA, and various biomarkers were obtained at baseline, week 4, week 8, and then every 12 weeks. An optional tumor biopsy was performed at week 12.

Imaging

Imaging was performed at baseline and then every 12 weeks. These were assessed by the investigator and by an Independent Review Committee (IRC). The IRC was made up of 2

readers who evaluated each scan. Differences in their findings were adjudicated by a 3rd reader (agreed with 1 of the primary reader's findings). Images were read, by both the investigator and IRC, using the following modifications (made by the applicant) to the RECIST criteria.

1. Liver Lesions: If a new liver lesion manifests at week 12 or 24, its appearance should be compared to the baseline CT. If there is evidence, in retrospect, that the lesion was present at baseline as an isodense focus (although not noted at baseline) and the lesion doesn't progress on subsequent scans, it is not considered progressive disease.

2. Calcified Lesions
    a. The selection of calcified lesions as target lesions should be avoided.
    b. If a target lesion's longest diameter is $\geq$ 80% calcified, the length of the longest diameter should be adjusted. For example, if 80-84% of the longest diameter is calcified, the length of the longest diameter is multiplied by 0.79.

The applicant also provided a plan to impute target lesions measurements if target lesions were missing on subsequent scans.

Statistical Analysis Plan

The primary endpoint, PFS, was defined as the time from randomization to progression, as determined by the IRC, or death due to any cause. Patients who died without prior documented progression were included in this endpoint if their death occurred within 3 months of their last assessment. In the statistical plan, patients who discontinued study drug during the randomized phase due to investigator-determined progression, but without IRC-determined progression were not censored. Instead, patients were followed for progression during subsequent therapy (or off therapy) and this date, if confirmed by the IRC, was used in the primary analysis. Progression-free survival was assessed using an unstratified logrank test. The original statistical plan analyzed PFS in all randomized patients and in all patients whose tumor contained a RET mutation. The final statistical plan changed this to a single analysis of all randomized patients using alpha = 0.05.

Secondary endpoints included response rate, duration of response, disease control rate at 24 weeks, and overall survival as well as an assessment of a variety of biomarkers and patient reported outcomes. In the applicant's analysis of response rate, patients who discontinued study drug during the randomized phase due to investigator-determined progression, but without IRC-determined progression, were followed for response during subsequent therapy. Exploratory endpoints included the effect of treatment on diarrhea, weight, and performance status as well as additional assessments of biomarkers and patient reported outcomes.

Protocol Amendments

Amendment 5 removed the primary endpoint, assessment of PFS in patients whose tumors contained the RET mutation. This was due to difficulties with sample assessment. Amendment 6 allowed all remaining patients to be unblinded and to receive vandetanib.

Patient Disposition

Enrollment of patients with this rare disease involved 23 countries with 22.1% of patients coming from the US. With world-wide recruitment, the applicant was able to enroll 331 patients with medullary thyroid cancer. Patient disposition is shown in the table below. Note that after investigator-determined progression, 58.0% of patients on the placebo and 19% of patients on the vandetanib arm received open label vandetanib.

The patients on the vandetanib arm who discontinued due to patient decision or who were lost to follow up were examined for adverse events which occurred within 30 days of discontinuation. Adverse events were noted in 4 patients.

Table 2: Patient Disposition Study 1 (Data Cutoff 7-31-09)		
	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

Patient Demographics and Disease Characteristics

Patients were well-balanced between arms in terms of age (median 51.5 years), gender (57.4% male), race (95.2% Caucasian), and performance status. The table below provides information on the baseline disease characteristics in each arm. Note that both the time from last progression and the sum of the longest diameter varied widely in each arm. Many of the RET assays were inconclusive and information on the presence/absence of various RET mutations in patients with sporadic disease is not shown in the table below.

Table 3: Baseline Characteristics Study 1 (Data Cutoff 7-31-09)		
	Vandetanib N = 231	Placebo N = 99
Medullary Thyroid Carcinoma		
Hereditary	12.1%	5.0%
Sporadic	87.9%	95.0%
Prior Therapy		
Thyroid Surgery	91.3%	93.0%
Radiation Therapy	51.0%	53.0%
Systemic Therapy	37.2%	39.0%
Median Time from Diagnosis (range)	6.0 years (0-31)	6.0 years (0-35)
Median Time from Last Progression (range)	2.43 months (0-107)	1.96 months (0-77)
Median Sum of the Longest Diameter by IRC (range)	12.1 cm (2.0-45.0)	11.0 cm (1.0-47.1)

Protocol Violations

Protocol violations were seen in 21.2% of patients on the vandetanib and 27.0% of patients on the placebo arm. These included the absence of measurable disease by investigator in 14 patients, the absence of a confirmed histological diagnosis in 1 patient, and 1 patient who received the incorrect treatment.

Primary Endpoint

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

- 51 patients with investigator-determined, but without IRC-determined progression. 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 4: 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

While the hazard ratio is remarkable, the number of censored events and the difference in the percentage of censored events is of concern. Censoring is primarily due to the lack of correlation between investigator and IRC-read scans. Only 88/174 (50.6%) scans were read as progression by both the investigator and IRC. No patients were censored because they missed $\geq$ 2 scans, with only 3 scans not performed at the appropriate time point.

Differences in the pattern of censoring in the FDA analysis (above) and the applicant's analysis are shown in the table below.

Table 5: Differences in the FDA and Applicant Primary Analyses		
	FDA	Applicant
Hazard Ratio (95% CI)	0.35[1] (0.24-0.53)	0.46[2] (0.31-0.69)
Events Resulting in Censoring	Censored at	Censored at
No Measurable Disease at Baseline	Day 1	Not Censored
Investigator-Progression Without IRC-Progression	Last RECIST Assessment Prior to Discontinuation of Study Drug	Followed Until IRC-Progression
Received Radiation Therapy	Last RECIST Assessment Prior to Radiation	Not Censored

[1]Cox proportional hazards [2]Logrank test

The investigator analysis showed a hazard ratio of 0.4 with a $p < 0.001$.

Sensitivity Analyses

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 6: 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

Subgroup Analyses

An analysis of patient subgroups showed that while the hazard ratio was higher in patients with more extensive disease (baseline sum of the longest diameter > the median) than in those with less extensive disease (baseline sum of the longest diameter < the median) that both hazard ratios favored vandetanib. Likewise, while the hazard ratio in patients who progressed within 6 months of study entry was higher than the hazard ratio in those who progressed at a slower rate, both groups appeared to benefit from vandetanib. 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.

Additional Endpoints

Response Rate

The table below provides information on the response rate (RR) and duration of response, by IRC and by investigator, in Study 1. It does not include responses which occurred after discontinuation of study drug and crossover to open label vandetanib. The table also shows the RR in patients with hereditary and sporadic disease. This analysis was performed so that the RR in Study 1 could, in an exploratory manner, be compared to the RR in Studies 2 and 3 (below). Studies 2 and 3 only enrolled patients with hereditary disease.

Table 7: Response Rate Study 1 (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%

Overall Survival

At the time of the final PFS analysis, 14.5% of events had occurred and the analysis of overall survival was not significant. The final analysis will be performed when 50% of events have occurred.

Supportive Studies

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

Study 2

Study 2 administered 300 mg of vandetanib to 30 patients with hereditary medullary thyroid cancer. In general, the baseline disease characteristics of patients in Study 2 were more favorable than those in Study 1. 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 1). While the investigator and IRC RR are similar, only 2 of the 6 patients with an INV response were considered responders by the IRC.

Table 8: Response Rate Study 2 (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 3

Study 3 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 3 were, in general, more favorable than those in Study 1. 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 1). 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 9: Response Rate Study 3 (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 3 appears to be markedly lower than the RR in Study 1 (15.8% vs. 39.0%) that it is similar to the investigator RR in Study 2 (15.8% vs. 20.0%). Study 2 administered 300 mg vandetanib.

8. Safety

Safety Database

Safety data was obtained, primarily, from Study 1, the Phase 3 randomized study of vandetanib vs. placebo in patients with hereditary and sporadic medullary thyroid cancer. This was supported by data from patients treated in the open label portion of the Phase 3 trial, 2 single arm trials in hereditary medullary thyroid cancer, and an extensive safety database of patients with other types of cancer.

Table 10: Safety Database (Data Cutoff 10-19-09)	
	Number of Patients
Vandetanib 300 mg	
Medullary Thyroid Cancer	319
Monotherapy in Other Cancers	1520
Vandetanib 100 mg	
Medullary Thyroid Cancer	19
Other[1]	1161
Total	3019

[1]Includes various doses of vandetanib (50-600 mg) as well as combination studies

Exposure

The table below provides information on exposure to vandetanib during the randomized Phase 3 trial. While the median duration of exposure was markedly longer in the vandetanib arm, a substantial number of patients receiving vandetanib required a dose reduction and/or

interruption. When the causes of reduction/ interruption were evaluated, 31.6% of patients were dose reduced/interrupted for a grade 3-4 and 26.8% for a grade 1-2 event.

Table 11: Patient Exposure During Randomized Treatment Study 1 (Data Cutoff 7-31-09)		
	Vandetanib	Placebo
Median Duration of Exposure		
	607 days (15-929)	279 days (14-904)
Dose Reductions		
Number of Patients	83 patients (35.9%)	3 patients (3.0%)
1 Level Dose Reduction	81 patients (35.1%)	3 patients (3.0%)
2 Level Dose Reduction	32 patients (13.9%)	0
Dose Interruptions		
Number of Patients	109 patients (47.2%)	15 patients (15.2%)
Median Duration (range)	19 days (1-101)	9 days (2-30)
Median Number of Interruptions	1 (1-8)	1 (1-3)

Deaths and Discontinuations

The table below provides information on all deaths due to an adverse event during randomized therapy that occurred within 57 days (3 half-lives) of the last dose of study drug. Several of the patient deaths involved respiratory events.

Table 12: Adverse Events Resulting in Death During Randomized Treatment Study 1 (Data Cutoff 7-31-09)		
	Vandetanib N = 231	Placebo N = 99
All Deaths	6 (2.6%)	1 (1.0%)
Respiratory Failure/Arrest	2	0
Aspiration Pneumonia	1	0
Cardiopulmonary Failure	1	0
Heart Failure with Arrhythmia	1	0
Sepsis	1	0
GI Hemorrhage	0	1

During the open label phase, 2 patients on vandetanib died of a cause other than medullary thyroid cancer (aspiration pneumonia, unknown cause of death). In the safety update, the applicant reported 2 sudden deaths (preferred terms cardiac arrest, sudden death). In the integrated summary of safety (ISS), death due to an adverse event was reported in 4.3% of 1839 patients who received vandetanib 300 mg monotherapy. The most common cause of death in the ISS database was pneumonia.

The table below provides information of the adverse events leading to discontinuation in > 1 patient during randomized therapy in Study 1. There were 21 additional causes of discontinuation which occurred in 1 patient. During open label therapy, adverse events leading to discontinuation in > 1 patient (data cutoff 6-1-10) included blurred vision (3 patients), and peripheral sensorimotor neuropathy (2).

Table 13: Discontinuation Due to an Adverse Event in > 1 Patient in the Vandetanib Arm During Randomized Treatment in Study 1 (Data Cutoff 7-31-09)		
	Vandetanib N = 231	Placebo N = 99
All	28 (12.1%)	3 (3.0%)
Skin Disorders	6 (2.5%)	0
Asthenia/General Physical Health Deterioration	5 (2.2%)	0
Fatigue	2 (0.9%)	0
Pyrexia	2 (0.9%)	0
Diarrhea	2 (0.9%)	0
Elevated Creatinine	2 (0.9%)	0
QT Prolongation	2 (0.9%)	0
Hypertension	2 (0.9%)	0

In the ISS database, 13.8% of patients discontinued due to an adverse event. The most common causes of discontinuation include rash, QT prolongation, pneumonia, and diarrhea.

Serious Adverse Events/Grade 3-4 Adverse Events

In Study 1, SAEs occurred in 30.7% of patients on the vandetanib and 13.1% of patients on the placebo arm. Serious adverse events in $\geq$ 2% of patients in the vandetanib arm included diarrhea, pneumonia, and hypertension. During open label treatment, 23.2% of patients experienced a SAE (data cutoff 6-1-10). These events were similar to those than occurred during randomized therapy. In the ISS database, 30% of patients experienced a SAE with diarrhea and pneumonia reported in at least 2% of patients.

Grade 3-4 adverse events $\geq$ 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, 38.1% of patients had a grade 3-4 adverse event (cutoff 6-1-10). In the ISS database, 51.1% of patients reported a grade 3-4 adverse event with diarrhea and hypertension reported in at least 5% of patients.

Table 14: Grade 3-4 Events in ≥ 2% of Patients in the Vandetanib Arm During Randomized Treatment in Study 1 (Data Cutoff 7-31-09)		
	Vandetanib N = 231	Placebo N = 99
All	55.4%	24.2%
Gastrointestinal Disorders		
Diarrhea/Colitis	11.3%	2.0%
Abdominal Pain/Discomfort[1]	2.6%	0
General Disorders		
Fatigue	5.6%	1.0%
Asthenia/General Physical Health Deterioration	3.0%	2.0%
Investigations		
QT Prolongation	7.8%	1.0%
Metabolism and Nutrition Disorders		
Decreased Appetite	3.9%	0
Skin Disorders		
Rash	3.9%	0
Vascular Disorders		
Hypertension[2]	8.7%	0

[1]Includes upper abdominal pain
[2]Includes hypertensive crisis and accelerated hypertension

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 1, 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 the table, 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.

Table 15: Significant Adverse Events in the Vandetanib Safety Database (Data Cutoff 7-31-09 and 10-19-09)	
	N = 3019
Grade 3-5 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%)
Torsade de Pointes/Sudden Death[2]	2 (<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.

Grade 1-4 Adverse Events

The table below provides information on grade 1-4 adverse events that occurred during randomized therapy in more than 10% of patients in Study 1. Adverse events are ordered by incidence. Although there is a high incidence of diarrhea in patients with medullary thyroid cancer, 27.3% of patients in the placebo arm, this is increased by the use of vandetanib. Further, both QT prolongation and hypocalcemia are increased with vandetanib. While it's interesting to speculate that QT prolongation may be worsened in patients with medullary thyroid cancer due to the patient's difficulties with calcium regulation, it is important to note that QT prolongation has been seen with vandetanib in patients with other types of cancer which are not associated with calcium dysregulation. During the open label portion of Study 1, 79.4% of patients reported a grade 1-4 adverse event with diarrhea, rash, acne, nausea, decreased appetite, and hypertension occurring in > 10% of patients. In the ISS dataset of patients who received 300 mg vandetanib, grade 1-4 adverse events in at least 20% of patients included diarrhea, rash, nausea, decreased appetite, fatigue, and hypertension.

Table 16: Grade 1-4 Adverse Events in > 10% of Patients in the Vandetanib Arm During Randomized Treatment in Study 1 (Data Cutoff 7-31-09)				
	Vandetanib N = 231		Placebo N = 99	
	Grade 1-4	Grade 3-4	Grade 1-4	Grade 3-4
Rash[1]	78.8%	4.8%	19.2%	0%
Diarrhea/Colitis	56.7%	11.3%	27.3%	2.0%
Nausea	33.3%	0.9%	16.2%	1.0%
Hypertension[2]	32.9%	8.7%	5.1%	1.0%
Headache/Migraine	25.5%	0.9%	11.1%	0
Fatigue	23.8%	5.6%	23.2%	1.0%
Decreased Appetite	21.2%	3.9%	12.1%	0
Abdominal Pain[3]	20.8%	2.6%	11.1%	0
Dry Skin	15.2%	0	5.1%	0
Asthenia/General Physical Health Deterioration	15.6%	3.0%	12.1%	2.0%
Vomiting	14.7%	0.9%	7.1%	0
QT Prolongation	14.3%	7.8%	1.0%	1.0%
Photosensitivity Reaction	13.4%	1.7%	0	0
Insomnia	13.0%	0	10.1%	0
Nasopharyngitis	11.3%	0	9.1%	0
Cough	10.8%	0	10.1%	0
Dyspepsia	10.8%	0	4.0%	0
Hypocalcemia	10.8%	1.7%	3.0%	0
Pruritus	10.8%	3	4.0%	0
Weight Decreased	10.4%	2	9.1%	0

[1]Includes rash erythematous, generalized, macular, maculo-papular, papular, pruritic, and pustular as well as acne, acne pustular, and dermatitis acneiform
[2]Includes hypertensive crisis and accelerated hypertension
[3]Includes abdominal pain upper, abdominal pain lower, and abdominal discomfort

9. Advisory Committee Meeting

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 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 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.

10. Pediatrics

A pediatric waiver was granted by the Pediatric Review Committee based on vandetanib's orphan drug status.

11. Other Relevant Regulatory Issues

Establishment inspections are still pending. Three clinical sites were inspected by the Division of Scientific Integrity. The applicant, AstraZeneca Pharmaceuticals LP, and a CRO, (b) (4) were also inspected. A Form 483 was issued at 2 of the clinical sites and at AstraZeneca. However, these findings were not thought to have an impact on overall study outcome.

12. Labeling

Please see final printed label.

March 23, 2011 Addendum to CDTL Review

In the absence of a Risk Evaluation and Mitigation Strategy (REMS) program, we were planning to issue a complete response letter for this application. However, on December 22, 2010, the applicant submitted a REMS plan for vandetanib. This was considered a major amendment and extended the PDUFA date until April 7, 2011. This addendum summarizes the work that took place during this period. Many elements of the Recommendations/Risk Benefit Assessment will be summarized here.

Post-Marketing Requirements

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.

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

Labeling

The package insert, first sent to the applicant on December 16, 2010, was further negotiated with the applicant and finalized on March 23, 2011.

Risk Evaluation and Mitigation Strategy

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.

Establishment Inspections

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

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

Approval

- Risk Benefit Assessment

Risk: Vandetanib causes a marked increase in the QT interval. This is of particular concern in patients with MTC who are also at risk for diarrhea (both as an AE associated with vandetanib and due to their underlying disease) and hypocalcemia. Although uncommon, Stevens-Johnson syndrome, interstitial lung disease, ischemic cerebrovascular events, cardiac failure and hypertensive crisis have been seen with vandetanib. Of further concern, > 55% of patients experienced a grade 3-4 adverse event on vandetanib. Finally, grade 1-4 adverse events in > 20% of patients include: rash, diarrhea, nausea, hypertension, headache, fatigue, anorexia, and abdominal pain.

Benefit: Vandetanib causes a marked prolongation in progression free survival when compared to placebo with a hazard ratio of 0.35, $p < 0.0001$. The results of the analysis of overall survival are not yet mature. However, it is unlikely, given the size of the study and the use of a crossover design, that an improvement in overall survival will be seen. Given the long natural history of this disease it was not feasible to conduct a study in which the primary endpoint was overall survival.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

A risk evaluation and management strategy with elements to ensure safe use will be included in the approval of vandetanib. Please see Addendum just above this section.

- Recommendation for other Postmarketing Requirements and Commitments

Please see addendum just above this section.

- Recommended Comments to Applicant

Please see addendum just above this letter for information about the goals of the REMS program and the post-marketing requirements that will be included in the approval letter.

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/s/

VIRGINIA E MAHER
03/24/2011