Vandetanib for the Treatment of Symptomatic or Progressive Medullary Thyroid Cancer in Patients with Unresectable Locally Advanced or Metastatic Disease: U.S. Food and Drug Administration Drug Approval Summary


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Abstract:

On April 6, 2011, the U.S. Food and Drug Administration approved vandetanib (Caprelsa Tablets, AstraZeneca Pharmaceuticals LP) for the treatment of symptomatic or progressive medullary thyroid cancer in patients with unresectable, locally advanced or metastatic disease. Vandetanib is the first drug approved for this indication and this article focuses on the basis of approval. Approval was based on the results of a double-blind trial conducted in patients with medullary thyroid carcinoma. Patients were randomized 2:1 to vandetanib 300 mg/day orally (n=231) or to placebo (n=100). The primary objective was demonstration of improvement in progression-free survival (PFS) with vandetanib compared to placebo. Other endpoints included evaluation of overall survival (OS) and objective response rate (ORR). The PFS analysis showed a marked improvement for patients randomized to vandetanib (HR=0.35; 95% CI: 0.24-0.53; p<0.0001). The objective response rate for the vandetanib arm was 44% compared to 1% for the placebo arm. The most common grade 3 and 4 toxicities (>5%) were diarrhea/colitis, hypertension and hypertensive crisis, fatigue, hypocalcemia, rash and corrected Q-T interval (QTc) prolongation. This approval was based on a statistically significant and clinically meaningful improvement in progression-free survival. Given the toxicity profile, which includes prolongation of the QT interval and sudden death, only prescribers and pharmacies certified through the Vandetanib Risk Evaluation Mitigation Strategy (REMS) Program, are able to prescribe and dispense vandetanib. Treatment-related risks should be taken into account when considering the use of vandetanib in patients with indolent, asymptomatic or slowly progressing disease.
Background:

Medullary thyroid cancer (MTC) is a rare tumor arising from the parafollicular C cells of the thyroid. MTC represents approximately 3-5% of all thyroid cancers, and the estimated number of new cases of MTC in 2010 is extrapolated to be 1,300-2,200 patients in the U.S. (1). Seventy-five percent 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). Mutations in the rearranged during transfection (RET) proto-oncogene are found in >90% of patients with MEN2A or 2B and in Familial MTC (FMTC), which although inherited, is not associated with other endocrine disorders (2). Somatic mutations in RET are found in 40-50% of tumors of patients with sporadic MTC (3). A range of point mutations have been found in RET with mutations in codon 918, found in both hereditary and sporadic MTC, associated with a poorer outcome (4).

There are no hallmark symptoms of MTC, and patients most often initially present with a thyroid nodule or mass. Patients with localized symptoms, such as dysphagia, dyspnea, or hoarseness, are more likely to have persistent disease following surgery. Systemic symptoms, such as bone pain or diarrhea, most often occur in patients with distant metastases (5). The etiology of diarrhea may be related to the secretion of calcitonin (CTN), which is produced by the parafollicular C cells of the thyroid (6). CTN levels are useful in predicting residual disease after surgery and the doubling time of
CTN may have prognostic implications (7). High levels of CTN, as seen in patients with disseminated metastases, do not usually cause derangements of calcium metabolism (6). Hypocalcemia, however, may be seen in patients with MTC as a result of post-surgical hypoparathyroidism (8).

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 rate for patients with tumors confined to the thyroid gland of approximately 95%. However, for patients with distant metastases present at diagnosis, the 10-year overall survival rate is estimated to be only 40% (9). 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, embolization and radiolabelled antibodies (5, 10).

Until the approval of vandetanib, there were 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% (11, 12). Other chemotherapy agents with reported activity include 5-fluorouracil, capecitabine, cisplatin, and dacarbazine (12-14). Because of the natural history of the disease and the side effect profile of these cytotoxic agents, it is 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 (15, 16).

There have been several clinical trials reporting the use of kinase inhibitors with \textit{in vitro} activity against RET and vascular endothelial growth factor (VEGF) receptors in early phase clinical trials in MTC. These agents include vandetanib, sorafenib, sunitinib, motesanib, and XL184. Phase 2 studies in patients with MTC have shown response rates of 6.3\% for sorafenib (17) and 35\% for sunitinib (18). Also, a relatively large phase 2 study in MTC (91 patients) of motesanib, which inhibits wild-type RET but not mutant RET, demonstrated only a 2\% response rate, while a small study (17 patients) of XL184 showed a 53\% response rate (19, 20). Two single-arm phase 2 studies have been conducted with vandetanib in patients with hereditary MTC with response rates of 20\% and 16\% seen with a 300 mg daily dose and a 100 mg daily dose, respectively. The results of the phase 3 trial of vandetanib in MTC were published following FDA approval (21-23).

\textbf{Chemistry}

Vandetanib is chemically described as N-(4-bromo-2-fluorophenyl)-6-methoxy-7-[(1-methylpiperidin-4-yl) methoxy]quinazolin-4-amine and has a molecular weight of 475.36. Vandetanib exhibits pH-dependent solubility, with increased solubility at lower pH.

\textbf{Pharmacology and Toxicology}

Vandetanib is a multi-kinase inhibitor of the VEGF receptor, epidermal growth factor receptor (EGFR), and RET kinase. Additional kinases identified as targets in these
experiments include protein tyrosine kinase 6 (BRK), TIE2, and members of the EPH kinase and Src family tyrosine kinase families. The N-desmethyl metabolite of vandetanib was found to have similar inhibitory activity to vandetanib for inhibition of VEGF receptors (KDR and Flt-1), EGFR, and bFGF receptor (24).

**In vivo** effects of vandetanib were demonstrated using angiogenesis assays and human tumor xenograft models in nude mice. In a study 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. Vandetanib has also been shown to inhibit tumor growth in a variety of human cancer xenografts. A dose of 150 mg/m² vandetanib inhibited VEGFR2 phosphorylation and pEGFR staining in two distinct tumor xenograft models. These studies provide some evidence that vandetanib has *in vivo* activity against VEGFR and EGFR (24).

Vandetanib was not mutagenic *in vitro* in the bacterial reverse mutation (Ames assay) or clastogenic in the *in vitro* cytogenic assay using human lymphocytes or in the *in vivo* rat micronucleus assay. Given the long natural history of MTC and the potential for prolonged vandetanib use, carcinogenicity studies are being performed as postmarketing requirements.

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. When administered during
organogenesis, vandetanib caused malformations of the heart vessels and delayed ossification of the skull, vertebrae, and sternum at all doses tested. The reproductive and developmental toxicology studies suggest that administration of vandetanib may also impair fertility. Vandetanib was assigned Pregnancy Category D.

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

Repeat dose toxicity studies showed damage to the kidneys, spleen, and thymus in both the rat and dog. Additionally, toxicities were observed in the adrenal gland, bile duct, heart, kidneys, lungs, mesenteric lymph nodes, pancreas, skin, and teeth in the rat and gastrointestinal tract in the dog. Nodular masses were observed in multiple organs in the 6-month toxicology study in the rat. Masses were palpable during clinical assessments and were associated with hemorrhagic or inflammatory findings. Dose-dependent prolongation of the QTc interval and increased blood pressure were observed in dogs after receiving a dose of vandetanib that approximates the clinical dose on a mg/m² basis.

Clinical Pharmacology

A population pharmacokinetic analysis of vandetanib was conducted in 231 patients with MTC following daily oral administration of the 300 mg dose. The pharmacokinetics of vandetanib are characterized by a mean clearance of approximately
13.2 L/h, a mean volume of distribution of approximately 7,450 L, and a median plasma half-life of 19 days.

Absorption of orally administered vandetanib is slow with peak plasma concentrations achieved at a median of 6 hours, range 4-10 hours, after dosing. Vandetanib accumulates approximately 8-fold on multiple dosing with steady state achieved in approximately 3 months. Vandetanib binds to human serum albumin and α1-acid-glycoprotein with \textit{in vitro} protein binding being approximately 90%. \textit{In ex vivo} plasma samples from colorectal cancer patients at steady state exposure after 300 mg once daily, the mean percentage protein binding was 93.7% (range 92.2 to 95.7%).

Both urine and fecal excretion are the major routes of elimination of vandetanib. In the human absorption, distribution, metabolism and excretion (ADME) study, 44% and 25% of the administered radioactive dose (800 mg $^{14}$C-vandetanib) were recovered in feces and urine, respectively.

Vandetanib is a substrate of CYP3A4. Drugs that are CYP3A4 inducers can alter vandetanib plasma concentrations. The concomitant use of known strong CYP3A4 inducers should be avoided while receiving vandetanib therapy. St. John’s Wort may decrease vandetanib exposure unpredictably and should be avoided. In healthy subjects, no clinically significant interaction was shown between vandetanib and the potent CYP3A4 inhibitor, itraconazole. Vandetanib is a weak inhibitor of CYP2D6 and 2C8. It is not an inducer of CYP enzymes.
No effect of mild hepatic impairment was observed on model estimated clearance of vandetanib. However, as there are limited data in patients with moderate and severe hepatic impairment, vandetanib is not recommended for use in patients with moderate and severe hepatic impairment.

For the moderate and severe renal impairment groups, there were increases in AUC of 39% and 41%, respectively. In these subjects, exposure to the N-desmethyl and N-oxide metabolites was increased up to 2-fold and 4-fold, respectively. This increased exposure may be a consequence of a shift to an increased metabolic clearance of vandetanib, which compensates for some of the reduced intrinsic clearance due to renal impairment. A dose reduction to 200 mg for patients with moderate and severe renal impairment is recommended.

Clinical Studies

Study Design

Approval of vandetanib was based primarily on the results of a single double-blind, randomized, placebo-controlled Phase 3 trial (Study 58) comparing vandetanib 300 mg daily administered orally (n = 231) to placebo (n = 100) in patients with unresectable locally advanced or metastatic medullary thyroid cancer. Patients were treated until investigator-determined progression. Eligibility required measurable disease; however,
there were no criteria specifying the pace of disease or the need for treatment. This lack of criteria is an important concern in MTC where it is recognized that the natural history of the disease makes observation an acceptable option, even in the setting of metastatic disease.

**Objectives**

The primary objective of this study was to demonstrate an improvement in PFS with vandetanib as compared to placebo in patients with unresectable, locally advanced or metastatic MTC.

Key secondary endpoints included overall response rate, duration of response, overall survival, calcitonin and carcinoembryonic antigen (CEA) responses, and time to worsening pain. Progression-free survival and response rates were based on centralized, independent review of patient scans.

**Patient Baseline Characteristics**

The treatment arms were balanced with respect to age, sex, and race. This international trial enrolled a total of 331 patients in 23 countries. Almost all patients were Caucasian and 22% of patients were enrolled in the US. A total of 95% of the patients had stage IVc disease at entry. The majority of patients had a history of prior thyroidectomy and lymphadenectomy. Approximately 80% of patients had a history of radiation therapy, and 20% of patients had prior cytotoxic chemotherapy such as doxorubicin and/or cisplatin, while 10% of the patients had prior targeted therapy.
The median time from diagnosis of MTC to enrollment on trial was 6 years. The median time from last documented disease progression was approximately 2 months, but 30% of the patients had a progression-free interval of greater than 6 months prior to entering the trial. No information was available on the pace of disease.

**Study 58 Efficacy Results**

The result of the PFS analysis, based on the independent assessment, showed a statistically significant improvement for patients randomized to vandetanib (Hazard Ratio (HR) = 0.35; 95% Confidence Interval (CI): 0.24, 0.53; p<0.0001). The median PFS was not reached for the vandetanib arm, as compared to a 16 month median PFS for the placebo arm (Fig. 1). Ninety-six percent of the patients on trial were WHO performance status (PS) 0 or 1. Because symptoms of pain or diarrhea may occur, a post-hoc analysis of symptomatic patients vs. asymptomatic patients was performed using the following definition of asymptomatic: 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. The effect of vandetanib on PFS was consistent in both subsets (HR 0.38; 95% CI: 0.2, 0.75 for asymptomatic vs. HR 0.31; 95% CI: 0.19, 0.53 for symptomatic patients). Likewise, the HRs were consistent for all patient subsets: including patients grouped according to last documented progression, time from diagnosis, and baseline tumor burden, and for prespecified subgroup analyses of gender, WHO performance status, and prior therapy.
At the time of the primary analysis of PFS, 15% of the patients had died and there was no significant difference in overall survival between the two treatment groups. While this study is not powered for overall survival, a final analysis of this endpoint will occur at 50% of events which is anticipated to be in 2013. The ORR for patients randomized to vandetanib was 44% compared to 1% for patients randomized to placebo. All objective responses were partial responses. The median duration of response for patients treated with vandetanib was not reached.

A key secondary endpoint is the time to worsening pain, which is based on patient opioid use and patient questionnaires. However, there was a large amount of missing data and thus the results were insufficient to draw any conclusions regarding this endpoint.

Tumors were assessed for RET mutations; however, 41% of tumors were unable to be completely assessed for RET mutations and tumors derived from only 8 patients (2%) could be definitively labeled as RET mutation negative. Due to the limitations of the RET mutation assay, there is insufficient evidence to determine a relationship between the efficacy of vandetanib and RET mutations (25).

The FDA conducted an exploratory analysis of exposure-response relationships 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 exposure and clinical response.
state plasma concentrations and PFS over this range. However, it was noted that the quartile with highest trough concentrations at Day 56 demonstrated the worst PFS among the quartiles (Fig 2.) (26).

Safety

Safety data was primarily derived from the phase 3 trial, but was supplemented by adverse event information from other clinical studies using vandetanib. The phase 3 trial included safety assessments at baseline, weekly for the first two weeks, then at 4, 8 and 12 weeks after randomization and then every twelve weeks thereafter. 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. Ophthalmologic examinations were performed at screening and at 9 months after patients began receiving treatment. Patients who complained of visual symptoms underwent an ophthalmologic exam at the time the symptom was noted. Only 63.7% of patients underwent an examination during randomized treatment.

Adverse reactions resulting in death in patients receiving vandetanib (N=5, 2%) were respiratory failure, respiratory arrest, aspiration pneumonia, cardiac failure with arrhythmia, and sepsis. Adverse reactions resulting in death in patients receiving placebo (2%) were gastrointestinal hemorrhage (1%) and gastroenteritis (1%). In addition, there was one sudden death and one death from cardiopulmonary arrest in patients receiving
vandetanib after data cut-off. Within the vandetanib clinical program, the most common cause of death in patients who received vandetanib was pneumonia.

Treatment discontinuations due to adverse 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 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%); asthenia and fatigue (2.6%); 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 or dose interruption 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 200 mg and further dose reduction to 100 mg 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.

Serious adverse events (SAEs) occurred in 30.7% of patients on the vandetanib arm and 13.1% of patients on the placebo arm. Serious adverse events in ≥ 2% of patients in the vandetanib arm included diarrhea, intestinal perforation, pneumonia, and hypertension. Grade 1-4 adverse events in > 10% of patients are shown in the Table 1. Grade 3-4 adverse events were seen in 55.4% of patients in the vandetanib arm.
Table 2 provides the frequency and severity of laboratory abnormalities reported for patients with MTC. Alanine aminotransferase (ALT) elevations occurred in 51% of patients on vandetanib. Grade 3-4 ALT elevations were seen in 2% of patients and no patients had a concomitant increase in bilirubin. Elevations in ALT have resulted in temporary discontinuation of vandetanib. However, 16 of 22 patients with a grade 2 elevation in ALT continued on a 300 mg dose of vandetanib. Seven patients who continued vandetanib had a normal ALT within 6 months of continued treatment. In the protocol, ALT was monitored every 3 months and more frequently as indicated.

Thyroid stimulating hormone (TSH) was elevated in 78% of patients receiving vandetanib vs. 21% on placebo, and 27% of patients had TSH values greater than 5 times the upper limit of normal while on treatment compared to 3% on placebo. 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. Increases in the dose of the thyroid replacement therapy were required in 49% of the patients randomized to vandetanib compared to 17% of the patients randomized to placebo. Hypocalcemia was seen in 57% of the patients randomized to vandetanib, compared to 25% on placebo.

**QT Prolongation**

Vandetanib is pro-arrhythmic. In the phase 3 clinical trial, vandetanib was associated with sustained plasma concentration-dependent QT prolongation. Based on the exposure-response relationship, the mean (90% CI) QTcF change from baseline ($\Delta$QTcF) was 35 (33-36) ms for the 300-mg dose. The $\Delta$QTcF remained above 30 ms for the duration of the trial (up to 2 years). The sustained, higher QTc prolongation is likely to be
associated with the long half-life of vandetanib (19 days). In addition, about 36% of the patients in the vandetanib arm experienced a greater than 60 ms increase in QTc interval. A higher percentage of patients with changes in QTc greater than 60 ms or with a QTc greater than 480 ms were observed in patients with mild to moderate renal function as compared to patients with normal renal function. Although there were no cases of Torsades de pointes (TdP) in the randomized trial, two cases of TdP were captured in the safety database.

Other Toxicities of Concern

The majority of the severe adverse events seen with both EGFR and VEGFR inhibitors have been reported with vandetanib, such as rash, including Stevens-Johnson syndrome, ischemic arterial events, interstitial lung disease, intestinal perforations, and reversible posterior leukoencephalopathy syndrome. While Stevens-Johnson syndrome is uncommon, lethal reactions have occurred. 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.

Cerebrovascular events appear to be increased with vandetanib. During the randomized portion of the phase 3 study, cerebrovascular events (cerebral ischemia, TIA) occurred in 1.3% of patients in the vandetanib group and in no patients in the control arm while coronary occlusion was reported in 1 (0.4%) patient in the vandetanib arm and in
no patients in the control arm. This increase in cerebrovascular events appears to be consistent across the randomized trials (26).

Interstitial lung disease and pneumonitis have also been reported more frequently in patients receiving vandetanib than in those randomized to placebo. In a large study of patients with non-small cell lung cancer, interstitial lung disease and pneumonitis were reported in 3.5% of patients receiving 100 mg vandetanib + docetaxel and in 2.0% of those treated with docetaxel alone (26). 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.

Blurred vision was more common in patients who received vandetanib versus patients who received placebo for MTC (9% vs. 1%, respectively). Scheduled slit lamp examinations have revealed corneal opacities (vortex keratopathies) in treated patients, which can lead to halos and decreased visual acuity. It is unknown if this will improve after discontinuation.

Discussion
The FDA’s Orphan Drug Designation program provides orphan status to drugs and biologics that are defined as those intended for the safe and effective treatment, diagnosis or prevention of rare diseases/disorders that affect fewer than 200,000 people in the U.S. The FDA remains committed to advancing and evaluating new therapies for small populations. The study in MTC demonstrates the ability to conduct well-designed trials even in small populations.

The recommendation for approval was based on the single, randomized clinical trial in which vandetanib showed a clinically and statistically significant progression-free survival advantage compared to placebo in patients with locally advanced or metastatic MTC. However, treatment with vandetanib was also associated with frequent and serious side effects. Due to the toxicity profile of vandetanib, treatment should be reserved for patients with symptomatic or progressive disease that is not amenable to surgery or other localized therapy. This approach is consistent with the current management strategy and use of systemic agents in the treatment of patients with MTC.

The mean increase in QTcF with 300 mg of vandetanib is 35 ms. This level of increase is consistent with that seen in anti-arrhythmic drugs such as sotalol. Clinical trials infrequently capture TdP, even with drugs known to have significant pro-arrhythmic effects. In a study conducted in Sweden of patients receiving any pro-arrhythmic drug, the incidence of TdP was estimated at approximately 4 cases per 100,000 (27). In the vandetanib clinical development program there were 2 cases in approximately 3000 patients. Few TdP events in a clinical trial do not provide
reassurance of safety and the fact that 2 events were seen in such a limited patient population reveals that there is a significant safety signal.

The pro-arrhythmic potential of vandetanib is a major concern in the MTC population. Patients with MTC are at higher risk of electrolyte imbalances that may predispose them to a prolonged QT interval, TdP, or sudden death. These imbalances may be a result of prior parathyroidectomy, which can lead to hypocalcemia; chronic diarrhea, often a sequela of increased CTN levels; or treatment with vandetanib, which can lead to both hypocalcemia and chronic diarrhea. In addition, bradycardia, which may arise with increases in TSH level, as was seen with vandetanib treatment, may place the patient with MTC at risk of serious cardiac arrhythmias and events. Management of QT prolongation may be complicated by the 19 day half life of vandetanib.

Because of the risk of QT prolongation, Torsades de pointes, and sudden death, and due to the natural history of the disease, vandetanib was approved with a Risk Evaluation and Mitigation Strategy (REMS) to include Elements to Assure Safe Use (ETASU). Only prescribers and pharmacies certified with the Vandetanib REMS Program will be able to prescribe and dispense vandetanib. The goal of the REMS is to reduce the incidence of TdP and sudden death by educating prescribers and patients about the risks of QT prolongation, the appropriate monitoring of the QT interval and of electrolytes, and the management of QT prolongation, given the long half-life of vandetanib. In addition, the applicant has been required to conduct post marketing studies evaluating a lower dosage of vandetanib, ejection fraction, and eye abnormalities.
The relationship between drug concentration, efficacy and toxicity still remain to be explored. For unclear reasons, the highest trough concentrations at day 56 (Css) demonstrated the worst PFS among the various quartiles examined. On the other hand, patients who had their doses reduced to 200 mg or 100 mg by day 84 showed comparable PFS to those consistently dosed with 300 mg of vandetanib, suggesting that lower doses may also provide effective therapy. Given the small number of patients in each quartile, it is impossible to make any sweeping conclusions as to what these findings suggest; however, the concern regarding the use of a lower dose in this patient population will be addressed in a separate postmarketing trial.

FDA’s approval of vandetanib is the first approval for systemic therapy in MTC and is the first molecularly targeted agent approved for this disease. This therapy provides a new treatment option for patients with symptomatic, progressive advanced MTC.
Table 1 - Adverse Reactions in ≥ 10% of Patients on Vandetanib During Randomized Treatment

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Vandetanib 300 mg N=231</th>
<th>Placebo N=99</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>Diarrhea/Colitis</td>
<td>132 (57%)</td>
<td>26 (11%)</td>
</tr>
<tr>
<td>Rash¹</td>
<td>123 (53%)</td>
<td>11 (5%)</td>
</tr>
<tr>
<td>Dermatitis Acneiform/Acne</td>
<td>81 (35%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>77 (33%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Hypertension/Hypertensive Crisis/Accelerated hypertension</td>
<td>76 (33%)</td>
<td>20 (9%)</td>
</tr>
<tr>
<td>Headache</td>
<td>59 (26%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>55 (24%)</td>
<td>13 (6%)</td>
</tr>
<tr>
<td>Decreased Appetite</td>
<td>49 (21%)</td>
<td>10 (4%)</td>
</tr>
<tr>
<td>Abdominal Pain²</td>
<td>48 (21%)</td>
<td>6 (3%)</td>
</tr>
<tr>
<td>Dry Skin</td>
<td>35 (15%)</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>34 (15%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>34 (15%)</td>
<td>6 (3%)</td>
</tr>
<tr>
<td>ECG QT Prolonged³</td>
<td>33 (14%)</td>
<td>18 (8%)</td>
</tr>
<tr>
<td>Photosensitivity Reaction</td>
<td>31 (13%)</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>30 (13%)</td>
<td>0</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>26 (11%)</td>
<td>0</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>25 (11%)</td>
<td>0</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>25 (11%)</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>Cough</td>
<td>25 (11%)</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>25 (11%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Weight Decreased</td>
<td>24 (10%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>23 (10%)</td>
<td>0</td>
</tr>
<tr>
<td>Depression</td>
<td>22 (10%)</td>
<td>4 (2%)</td>
</tr>
</tbody>
</table>

¹ Includes rash, rash erythematous, generalized, macular, maculo-papular, papular, pruritic, and exfoliative rash, dermatitis, dermatitis bullous, generalized erythema and eczema.

² Includes abdominal pain, abdominal pain upper, lower abdominal pain and abdominal discomfort

³ 69% had QT prolongation >450ms and 7% had QT prolongation >500ms by ECG using Fridericia correction.
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<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Vandetanib 300 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td><strong>Chemistries</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium Decreased</td>
<td>132 (57%)</td>
<td>13 (6%)</td>
</tr>
<tr>
<td>ALT Increased</td>
<td>118 (51%)</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>Glucose Decreased</td>
<td>55 (24%)</td>
<td>0</td>
</tr>
<tr>
<td>Creatinine Increased</td>
<td>38 (16%)</td>
<td>0</td>
</tr>
<tr>
<td>Bilirubin Increased</td>
<td>29 (13%)</td>
<td>0</td>
</tr>
<tr>
<td>Magnesium Decreased</td>
<td>17 (7%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Calcium Increased</td>
<td>16 (7%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Potassium Decreased</td>
<td>15 (6%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Potassium Increased</td>
<td>13 (6%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Glucose Increased</td>
<td>12 (5%)</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>Magnesium Increased</td>
<td>6 (3%)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Hematologic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC Decreased</td>
<td>45 (19%)</td>
<td>0</td>
</tr>
<tr>
<td>Hemoglobin Decreased</td>
<td>31 (13%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Neutrophils Decreased</td>
<td>21 (10%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Platelets Decreased</td>
<td>18 (9%)</td>
<td>0</td>
</tr>
</tbody>
</table>
Figure Legends:

Figure 1: Kaplan-Meier curves of progression free survival from study 58.

Figure 2: Kaplan-Meier estimates of progression free survival for the vandetanib arm (N=226) by quartiles of steady state clearance ($C_{ss}$, Day 56) and for the placebo arm (N=100) of the study 58. Quartile of $C_{ss}$, Day 56 was expressed as median (range) in the legend. All patients (N = 100) in the placebo arm are included in the Kaplan-Meier curve, regardless follow-up to Day 56 or not.
Reference List

Progression-free survival (months)

Treatment group

Proportion without PFS event

Hazard ratio = 0.35
95% CI (0.24–0.53)

P < 0.0001
Progression free survival

Q1: 515 (65.7–622) ng/mL, n = 56
Q2: 698 (622–773) ng/mL, n = 57
Q3: 871 (773–949) ng/mL, n = 56
Q4: 1070 (949–2580) ng/mL, n = 57
Vandetanib for the Treatment of Symptomatic or Progressive Medullary Thyroid Cancer in Patients with Unresectable Locally Advanced or Metastatic Disease: U.S. Food and Drug Administration Drug Approval Summary

Katherine Thornton, Geoffrey Kim, Virginia E. Maher, et al.

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